Esophageal emergencies: WSES guidelines


Abstract
The esophagus traverses three body compartments (neck, thorax, and abdomen) and is surrounded at each level by vital organs. Injuries to the esophagus may be classified as foreign body ingestion, caustic ingestion, esophageal perforation, and esophageal trauma. These lesions can be life-threatening either by digestive contamination of surrounding structures in case of esophageal wall breach or concomitant damage of surrounding organs. Early diagnosis and timely therapeutic intervention are the keys of successful management.

Keywords: Esophageal perforation, Caustic ingestion, Emergency management, Foreign body ingestion, Esophageal trauma

Background
Injuries to the esophagus represent a rare but potentially lethal clinical condition. Emergency management is a challenge and mortality remains high. Timely and appropriate treatment of esophageal injuries (EI) is the most important determinant of patient outcomes. Management is multidisciplinary and involves emergency physicians, trauma, general and thoracic surgeons, anesthesiologists, otorhinolaryngologists, gastroenterologists, and radiologists. Due to the rarity of these injuries, most clinicians will have limited personal experience with EI treatment. Therapy of EI is based on the location (neck, thorax, abdomen), the cause, and the extent of esophageal damage. A delay in providing appropriate treatment remains the dominant risk factor for mortality. Associated injuries of surrounding structures require specific treatment and may impact short-term survival.

The aim of the present review is to provide practitioners, who may be called upon to provide emergency management of EI, with a readily accessible comprehensive tool to help in the decision-making process.

Methods
For the purpose of the paper, we used an etiological classification of esophageal injuries: (1) foreign body ingestion, (2) caustic ingestion, (3) esophageal perforations (iatrogenic and spontaneous), and (4) esophageal trauma. Leading specialists in the field were asked to perform a thorough MEDLINE and EMBASE search for relevant papers on each of these topics between 1985 and June 2018. They were asked to focus their search in order to provide evidence-based answers to pertinent questions with immediate practical application. Topics were presented and open to discussion at the 5th WSES congress in Bertinoro, Italy, 28th–30th June, 2018. The level of evidence for each recommendation statement was assigned by using the grading system proposed by the Oxford Centre for Evidence-Based Medicine [1].

Eventually, evidence-based guidelines for the management of EI were developed to outline clinical recommendations.

Foreign body ingestion
In the USA, esophageal foreign body (FB) ingestion accounts for more than 100,000 cases per year. In children, accidental ingestion of coins, batteries, toys, and magnets is common. Accidental ingestions also occur in adults often in association with intoxication or

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in the elderly with cognitive impairment; intentional ingestion by patients with psychiatric disorders or by prisoners is not infrequent [2–4]. Esophageal FB impaction depends on the size and shape of the FB. Impaction usually occurs at the level of the hypopharynx or in the upper thoracic esophagus for anatomical (cricopharyngeus, aortic arch) and physiological reasons (low pressure zone at the transition point between striated and smooth muscle fibers) [5, 6]. Non-impaired adults and older children can typically identify foreign body ingestion and may point to a specific area of discomfort. However, children and mentally impaired adults may not give a history of foreign body ingestion [2]. The typical clinical presentation is the acute onset of dysphagia or inability to swallow saliva. Other related clinical features are odynophagia, neck tenderness, retrosternal pain, sore throat, foreign body sensation, retching, vomiting, and drooling. Choking, stridor, and dyspnea may be present in patients with airway obstruction or aspiration. Physical examination findings include the presence of fever, cervical subcutaneous emphysema or erythema and tenderness in the event of complications [6–8].

**Which are the appropriate biochemical and imaging investigations?**

Initial evaluation should be based on the patient’s history and physical examination. Recommended biochemical investigations are complete blood count (CBC), C-reactive protein (CRP), blood gas analysis for base excess, and lactate (Grade 2C).

Neck, chest, and abdominal radiographs are useful to assess the presence, location, shape, and size of radiopaque or unknown shape objects (Grade 1C). Plain neck, chest, and abdominal radiographs are useful to assess the presence, location, size, shape, and number of ingested objects and possible signs of perforation. Plain radiography is usually employed for the initial screening but the false-negative rate is up to 47%. Biplanar radiography is useful to reduce the false-negative rate and the lateral projection is important to differentiate between tracheobronchial and esophageal FBs. In case of food bolus impaction, thin metal objects, wood and plastic objects, glass fragments, fish or chicken bones, false-negative rates at the X-ray evaluation are up to 85% [9, 10].

Computed tomography (CT) scan should be performed in patients with suspected perforation or other complications that may require interventional endoscopy or surgery (Grade 1B). In a prospective single-center study including 358 adult patients with symptomatic fish bones impaction the sensitivity of plain X-Ray was 32% while the sensitivity of CT scan was 90–100% and the specificity 93.7–100%. For this reason, CT scan should be considered an essential tool in adult patients reporting accidental ingestion or suspected ingestion of bone fragments and negative X-rays. In addition, CT scan is necessary if there is suspicion of FB-related complication (perforation, abscess, mediastinitis, aortic/tracheal fistulas) [11–13].

Contrast swallow is not recommended and should not delay other investigations/interventions (Grade 1B). Oral contrast studies (barium or gastrografin studies) should be avoided in patients with complete esophageal obstruction and inability to swallow saliva because of the increased risk of aspiration. In addition, barium swallow may coat the foreign body and esophageal mucosa impeding endoscopic visualization. In any case, oral contrast studies should not delay other investigations/interventions [14, 15].

**What are the indications for endoscopy?**

Therapeutic flexible endoscopy is recommended as first-line treatment of persistent esophageal foreign bodies (Grade 1B), although 80–90% of ingested foreign bodies pass spontaneously through the gastrointestinal tract. In patients with persistent esophageal symptoms, an endoscopic evaluation should be performed, even if the radiographic examination is negative. In addition, in patients with food bolus impaction and no evidence of complications, endoscopy may be performed first [16–18]. It will depend on local practices but most cases will require anesthetic input and often a general anesthetic with endotracheal intubation will be used to protect the airway.

Emergent flexible endoscopy (preferably within 2 h, at latest within 6 h) is recommended for sharp-pointed objects, batteries, magnets, and for foreign bodies inducing complete esophageal obstruction (Grade 1B). Emergent flexible endoscopy should be performed (a) in case of sharp-pointed objects because of the high risk of full-thickness perforation (up to 35%); (b) in case of button/disk battery ingestion because of the risk of pressure necrosis, electrical burns, and chemical injury (Fig. 1); (c) in case of magnet ingestion due to pressure necrosis; and (d) in case of food bolus ingestion with complete esophageal obstruction because of the risk of aspiration as well as perforation [19–22].

Urgent (< 24 h) flexible endoscopy is recommended for other esophageal foreign bodies without complete obstruction (Grade 1B) [19–22].

Gently pushing the bolus into the stomach is recommended for the treatment of esophageal food bolus impaction. If this procedure is not successful, retrieval should be considered (Grade 1C). It has been shown that in case of food bolus impaction, air insufflation and gentle instrumental pushing (push technique) is associated with a low complication rate and up to 90% success rate. If a large FB is jammed in the lower esophagus, push technique may impact it further; gentle passage of a balloon catheter (ERCP stone extraction catheter) past the FB and inflation of the balloon with withdrawal can be used to try
to disimpact the FB which may then be retrieved in a net. Retrieval techniques using baskets, snares, and grasping forceps should be considered in case of resistant or sharp-pointed objects [18, 23]. A combination of techniques may be required in difficult cases.

In addition to therapeutic endoscopy, diagnostic workup for potential underlying disease including histological evaluation is recommended (Grade 1B). An underlying esophageal disorder can be found in up to 25% of patients. The most commonly associated disorders are esophageal stricture, hiatus hernia, esophageal web or Schatzki ring, eosinophilic esophagitis, achalasia, and tumors. A latent eosinophilic esophagitis may be diagnosed in up to 9% of patients [6, 8, 24–26].

Flexible and rigid endoscopy are complementary/cross-over techniques. Flexible endoscopy remains the “first line” approach to FB; rigid endoscopy has a place as a “second line” therapy (Grade 2B). Rigid endoscopy through rigid endoscopes, should be considered in case of FB located in the upper esophagus (Achilles’ heel of flexible endoscopy) and in case of FB ingestion with concomitant respiratory symptoms or suspicion of FB in the upper airways [26–28]. The use of the bivalved Weerda diverticuloscope is another option as it allows dilation and opening of the upper esophageal sphincter. A combined approach using a flexible endoscope introduced through the Weerda diverticuloscope is also feasible [29, 30]. In addition, through the diverticuloscope, it is possible to use laparoscopic grasping forceps for retrieval. A recent meta-analysis comparing flexible versus rigid endoscopy for retrieval of upper esophageal FB showed that both were effective and safe, with similar success and overall complication rates [31].

Who should undergo surgical treatment and what is the appropriate timing for surgery?
Potential indications for surgical treatment include irretrievable foreign body, perforation, FB close to vital structures (aortic arch), and other complications (Grade 1B). Upfront surgery should be adopted immediately in case of esophageal perforation with extensive pleural/mediastinal contamination (Grade 1B). Up to 1–3% of patients require surgery because of complications (perforation, irretrievable foreign bodies, mediastinitis, pleural empyema, fistula, severe bleeding) [5, 6, 15, 18, 32].

What are the most appropriate surgical procedures?
The surgical approach depends on the location of FB impaction, patient comorbidities, and patient condition (Grade 1B). Minimally invasive techniques should be considered first-line treatment in referral centers (Grade 1C). Esophagotomy with FB extraction and primary closure should be considered in case of limited pleural/mediastinal contamination and vital edges (Grade 1C). Different surgical approaches may be used according to FB location and patient comorbidities (left cervicotomy,
right/left thoracotomy, minimally invasive right/left thoracoscopy, prone thoracoscopy, laparoscopy, and laparotomy) [5, 6, 15]. Open or minimally invasive esophagotomy with primary repair can be used in cases of limited mediastinal contamination and vital edges of the perforation. Rescue esophagotomy with primary or delayed reconstruction should be considered in case of extensive contamination [33–37].

Corrosive ingestion

Corrosive ingestion is a rare but potentially devastating event that can result in patient death. In survivors, it is responsible for swallowing troubles, impaired quality of life, and significant burdens on health systems. The real incidence is currently unknown as the ingestion of corrosive agents is probably largely underreported around the world [38, 39]. In children, ingestion is mostly accidental and severe injuries are rare. Massive suicidal ingestion of strong corrosive agents occurs usually in adults suffering psychiatric disease and requires aggressive emergency management. It is commonly accepted that clinical symptoms do not correlate reliably with the extent of gastrointestinal damage; the absence of pain and of oral lesions does not rule out life-threatening gastrointestinal injuries [38–44]. Appropriate management of corrosive injuries in the emergency setting affects patients’ outcomes [45].

What are the possible etiologies and how do they affect the clinical presentation and the therapeutic options?

Strong acids and alkalis are responsible for most severe caustic injuries to the gastrointestinal tract. Identification of the nature, the physical form, and the quantity of the ingested substance is another major determinant of the damage pattern to the gastrointestinal tract. Solids produce maximum damage to the mouth and the pharynx, while liquids transit rapidly and induce burns of the esophagus and the stomach; concomitant vapor aspiration (ammonia, formaldehyde) may cause airway burns. Caregivers should be aware that specific corrosives may also cause severe systemic effects such as hypocalcemia (phosphoric, hydrofluoric acids), hyponatremia (strong acids/alkalis), hypokalemia, and acidosis [38].

What are the appropriate biochemical and imaging investigations?

Initial laboratory evaluation of caustic injuries should include CBC, serum concentrations of sodium, potassium, chlorine, magnesium, calcium, urea creatinine, liver tests (bilirubin, alanine aminotransferase, aspartate aminotransferase), pH and serum lactate, blood alcohol levels, and measurement of β-HCG in young women (Grade 2A). Laboratory and imaging findings have an important role in identifying patients with transmural necrosis who might benefit from emergency surgical treatment. As initial normal laboratory values do not rule out transmural necrosis, kinetics of laboratory data is useful in patient monitoring and management [47, 48]. Abnormal values such as severe acidosis (low pH, high blood lactate levels) [49], deranged liver function tests [49], leukocytosis, elevated CRP level [39], renal failure [47], and thrombocytopenia [50] are predictive of transmural necrosis and poor outcomes.

Neck, chest, and abdominal radiographs may show the presence of free air in patients with gastrointestinal perforation (Grade 3A). Emergency management of caustic ingestion can be performed safely relying on computed tomographic evaluation (Grade 2A). Recent studies have shown that emergency contrast-enhanced computed tomography (CT) examination outperformed endoscopy in detecting transmural injuries of the gastrointestinal tract after caustic ingestion and in predicting esophageal stricture formation [48, 51, 52]. CT of the neck, the thorax, and the abdomen should be performed 3–6 h after ingestion, before and after intravenous injection (2–3 mL/s) of a nonionic contrast agent (Iomeron 350; 2 mL/kg), with 18- to 25-s acquisition time and a 90-s scan delay. The main sign of transmural digestive necrosis is the absence of post-contrast wall enhancement, and its presence at any level (esophagus, stomach, duodenum, bowel, colon) is an indication for emergency surgery [38]. A four-stage CT classification of esophageal caustic injuries (Fig. 2) can be used in which: Grade I injuries show homogenous enhancement of the esophageal wall while wall edema and mediastinal fat stranding are absent; Grade IIa injuries display internal enhancement of the esophageal mucosa and hypodense aspect of the esophageal wall which appears thickened while concomitant enhancement of the outer esophageal wall may sometimes confer a “target” aspect; Grade IIb injuries present as a fine rim of external wall enhancement; the necrotic mucosa does not enhance and fills the esophageal lumen which shows liquid density.
Reconstructive esophageal surgery should be considered for short (<5 cm) esophageal strictures (Grade 2A). Endoscopy is employed; its ability to predict stricture formation remains controversial [55] and is outperformed by CT [52]. The role of emergency endoscopy evaluation of corrosive injuries is currently reduced to situations in which CT cannot be employed. Endoscopy remains the mainstay of management algorithms following caustic ingestion [45, 53]. The major drawback of endoscopy is its inability to predict accurately transmural necrosis, which may expose patients to either futile surgery or inappropriate “watch and wait” management and risk of death. The use of a CT-based algorithm to select patients for emergency surgery significantly improved patient outcomes when compared to endoscopy-based management [48, 51, 54]. The role of emergency endoscopy evaluation of caustic injuries is currently reduced to situations in which CT cannot be employed. Endoscopy remains the upfront evaluation examination in children as severe injuries are rare and long-term effects of radiation exposure are an important issue [38]. The Zargar endoscopic classification [54] of caustic injuries is most commonly employed; its ability to predict stricture formation remains controversial [55] and is outperformed by CT [52].

Endoscopy is the main diagnostic tool of esophageal/gastric strictures in symptomatic patients (Grade 2A). Stricture formation is the most common and disabling long-term complication of corrosive ingestion. Strictures more frequently involve the esophagus than the stomach and usually occur within 4 months after ingestion [52, 53]. Dysphagia and regurgitation are the main symptoms of corrosive strictures and should prompt immediate upper gastrointestinal evaluation [56].

Endoscopic dilation is the upfront treatment of esophageal strictures. Endoscopic dilation should be attempted 3–6 weeks after ingestion in patients with few (<3) short (<5 cm) esophageal strictures (Grade 2A). Reconstructive esophageal surgery should be considered after recurrent failure of endoscopic dilation (Grade 2A). Corrosive strictures can involve all esophageal segments; are often multiple, long, irregular; and have long stabilization delays [57]. Endoscopic dilation is the first-line management option [39]. Dilation can be started safely after healing of acute injuries, usually between the 3rd and the 6th week and the interval between dilations varies between 1 and 3 weeks. Three to 5 sessions are expected to provide satisfactory results [39], and esophageal reconstruction should be considered after 5–7 failed attempts [58]. The advent of interventional endoscopy has renewed the interest of intraluminal stenting, but solid data supporting this approach is still lacking.

What are the indications for non-operative management?
Patients who do not have full-thickness necrosis of digestive organs should undergo non-operative management (Grade 1C). Patients eligible for non-operative treatment require close clinical and biological monitoring. Any deterioration in the condition of the patient should prompt repeat CT examination and consideration for surgery (Grade 2A). Oral feeding should be reintroduced as soon as patients swallow normally. Enteral feeding by nasogastric tubes or jejunostomy construction is recommended in patients unable to eat. Psychiatric evaluation is mandatory in all patients prior to hospital discharge (Grade 2C). Patients who do not show signs of transmural necrosis of the gastrointestinal tract on emergency CT are eligible for non-operative management [48, 51]. Subsequent deterioration in clinical symptoms and signs (rebound tenderness, increasing abdominal pain, shock, need for ventilator support, etc.) or of laboratory tests (renal failure, acidosis, leukocytosis, etc.) suggest evolution of injuries to transmural necrosis (5% of patients) and should prompt repeat CT evaluation [38]. Patients with Grade I CT injuries can be fed immediately and discharged quickly (24–48 h) from the hospital. Long-term follow-up is not required in these patients as the stricture formation risk is nil. Patients with Grade IIa CT esophageal injuries have a low risk (<20%) of stricture formation [52]. Oral nutrition is usually well tolerated and should be introduced as soon as pain diminishes and patients can swallow. Patients with Grade IIb CT injuries show the absence of post-contrast wall enhancement.
CT esophageal injuries are at high risk (> 80%) of stricture formation [52]. Pain during deglutition, hyper-salivation, and early dysphagia may hinder early oral intake, if symptoms persist, nutritional support by long-term parenteral nutrition or feeding jejunostomy is required. A 4–6 months post-ingestion visit is recommended for patients with Grade II CT injuries as most strictures develop within this delay. Psychiatric evaluation is mandatory in all patients prior to hospital discharge; long-term control of the psychiatric disease is important to avoid recurrence [38].

**What are the indications for surgical treatment?**

Surgery should be performed as soon as possible in patients with caustic necrosis to avoid death (Grade 1C). All obvious transmural necrotic injuries should be resected during the initial operation (Grade 2A). A feeding jejunostomy is indicated at the end of the operation (Grade 2A). Emergency surgery is indicated if the initial evaluation suggests transmural necrosis of the gastrointestinal tract (Grade III CT injuries) [38]. In the absence of appropriate management, necrosis of intraabdominal organs eventually leads to perforation, peritonitis/mediastinitis, and death [59, 60]. The decision to perform an emergency operation after corrosive ingestion is a life-changing event for the patient; in a recent report, the standard mortality ratio of patients operated for caustic necrosis was 21.5 when compared to the general population [45]. Laparotomy remains the standard approach in the emergency setting although successful laparoscopic management has been reported [61, 62]. All obvious transmural necrotic injuries should be resected during the initial procedure; reoperation should be undertaken promptly if ongoing necrosis is suspected [63]. Stripping esophagectomy and gastrectomy, performed through a combined abdominal and cervical approach is indicated in patients with transmural necrosis of both the esophagus and the stomach [45, 59, 60]. Esophageal reconstruction should be prohibited at the time of the emergency procedure because subsequent stricture formation can compromise functional outcomes. If necrosis is confined to the stomach, total gastrectomy with preservation of the native esophagus or esophageal diversion should be considered [38]. Immediate esophageojunostomy reconstruction can be performed safely with low leak rates (5–8%) [64]. Partial gastric resections are not recommended because ongoing necrosis might compromise patient survival. Isolated esophageal necrosis justifying esophagectomy with gastric preservation has been recently challenged [47, 50]; non-operative management may be attempted in these patients in the absence of transmural gastric necrosis. Concomitant necrosis of adjacent organs (spleen, colon, bowel, duodenum, and pancreas) requires extended resections at the time of esophagogastrectomy in up to 20% of patients [45, 63]. If pancreatoduodenectomy is undertaken for corrosive injuries, immediate pancreato-biliary reconstruction is recommended [65]. Preoperative tracheobronchial endoscopy is mandatory to detect tracheobronchial necrosis resulting from mediastinal extension of esophageal necrosis; in this situation pulmonary patch repair through a right thoracotomy approach may be lifesaving [66]. Resection should be abandoned if extensive bowel necrosis is found at laparotomy because of poor survival and compromised nutritional issues [63].

**Esophageal perforations**

Esophageal perforation (EP) covers a large range of conditions characterized by the transmural disruption of the esophagus [67]. Spontaneous esophageal perforation (Boerhaave syndrome) is most often due to an abrupt increase in the esophageal pressure following a vomiting effort in the absence of relaxation of the superior esophageal sphincter. It accounts for 15% of esophageal perforations; the tear is usually located on the left border of the lower third of the thoracic esophagus and the wall defect is large (3–8 cm) [68–70]. The large majority (60%) of esophageal perforations are iatrogenic and occur during diagnostic and therapeutic (esophageal dilation, varices ligation, sclerotherapy, etc.) endoscopic procedures [71]. Other rare causes include operative and external trauma, malignancy, foreign bodies, and caustic ingestion. Forceful retching or vomiting causing perforation has erroneously come to be known as spontaneous esophageal perforation; as it is not spontaneous it may be better to use other terms such as barogenic rupture or Boerhaave syndrome [72].

The common denominator of all these heterogeneous conditions is the contamination of surrounding spaces with digestive contents and the evolution to severe sepsis and death in the absence of timely diagnosis and appropriate treatment. Mortality of esophageal perforation ranges between 10% and 20% and the delay in treatment is the most important survival predictor [73, 74].

**What are the appropriate laboratory and imaging studies?**

Routine blood tests (CBC, serum concentrations of sodium, potassium, chloride, magnesium, calcium, urea creatinine, liver tests (bilirubin, alanine aminotransferase, aspartate aminotransferase), pH and serum lactate) should be performed in patients with suspected EP (Grade 1C). The initial clinical and biological presentation of EP has no specific patterns; late stages are characterized by signs of inflammation and sepsis. To avoid delay in diagnosis (> 50% of cases) and allow timely management, a high degree of suspicion is required at presentation [68, 75, 76].

Contrast-enhanced computed tomography (CT) and CT esophagography is the imaging examination of choice in patients with suspicion of EP (Grade 1C). CT is highly sensitive (92–100%) in detecting EP and helps to asse
extension to adjacent structures (collection of air or fluid in the mediastinum, pleural and intra-peritoneal effusions) and to guide initial therapy. CT can also eliminate other conditions that may mimic EP (aortic dissection, esophageal intramural hematoma, etc.) [13, 67, 77, 78]. In select cases, contrast-enhanced esophagogram (gastrografin/barium) may provide useful information regarding the location and the contained character of EP [78]. Indirect signs of esophageal injury can also be seen on a plain chest radiograph (pleural effusion, pneumomediastinum, subcutaneous emphysema, hydrothorax, pneumothorax, and collapse of the lung) [79].

**What is the role of endoscopy and endoscopic treatment?**

Diagnostic endoscopy is useful in patients with suspected EP and doubtful CT findings. (Grade 1C). Diagnostic endoscopy for EP is reliable and safe in experienced hands; nevertheless, potential risks of enlarging the perforation size and aggravating the contamination of surrounding spaces warrant caution and limit its use as a first-line exam [71].

Endoscopic treatment is the gold standard for closing EP that occur and are recognized during an endoscopic procedure (Grade 2A). New interventional endoscopic techniques, including endoscopic clips, covered metal stents, and endoluminal vacuum therapy, have been developed over the last several years to manage esophageal perforation in an attempt to decrease the related morbidity and mortality [80]. Endoscopic clip placement (through the scope clips, over the scope clips) is currently the standard method for closing small (<2 cm) luminal perforations [81–83]. Endoscopic stents (partially or fully covered self-expandable metal stents, self-expandable plastic stents) can be used to cover larger defects or complete unsatisfactory clip closure [84]. In a recent review, the use of self-expandable stents for the treatment of esophageal leaks (spontaneous, iatrogenic, and postoperative) resulted in 88% success and 7.5% mortality rates. These results compared favorably with outcomes of surgery (83% success and 17% in hospital mortality) leading the authors to conclude that esophageal stenting can be successfully applied as an alternative therapeutic strategy in EP [85]. Minimal 2–4-week duration of stent placement has been advocated to allow sealing of the perforation. Esophageal stent placement is probably just as effective as surgical repair for the treatment of iatrogenic EP [86]. Endoscopy may be used as definitive treatment either alone or in combination with interventional radiology or surgical procedures (drainage of pleural abscess, or compressive pneumothorax, etc.) [71]. Successful closure of esophageal defects by primary or rescue endoluminal vacuum therapy has been recently reported and may represent a promising alternative treatment for EP [87, 88].

In patients with late presentation and in patients with non-endoscopic EP, the use of endoscopy as first-line therapy may be considered (Grade 2C). Although successful endoscopic management has been reported in select Boerhaave [89–91] patients with minimal symptoms and signs of sepsis, concerns on patient safety warrant caution regarding first-line use of endoscopic treatment under such circumstances [71, 89]. Endoscopic stenting is a useful adjunct treatment tool in patients with persistent leakage following surgical treatment of EP [92].

**What are the indications for non-operative treatment?**

Non-operative management (NOM) of EP can be considered in stable patients with early presentation, contained esophageal disruption, and minimal contamination of surrounding spaces if highly specialized surveillance is available (Grade 1C). The criteria developed by Altorjay et al. [93] more than two decades ago are still the mainstay of non-operative management (Table 1). More recently, the Pittsburgh classification has been developed to include an esophageal perforation score based on ten clinical and radiological factors to help decision-making for patients with EP [94]. The score has been validated in a multinational study, and it has been suggested that low score (≤2) patients might be eligible for non-operative management [95].

Patients eligible for NOM should be kept on nil per os, administered broad spectrum antibiotics (aerobic and anaerobic bacteria), and proton pump inhibitor therapy (Grade 1C). Early introduction of nutritional support by enteral feeding or total parenteral nutrition is essential for esophageal healing (Grade 1C). Endoscopic placement of a nasogastric tube is recommended (Grade 2A). Although anti-infective treatment is considered a cornerstone in the management of EP, there is a lack of

**Table 1 Criteria for non-operative management of esophageal perforations**

<table>
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<tr>
<th>Delay in management</th>
<th>Early: less than 24 h</th>
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<td>Clinical presentation</td>
<td>Absence of symptoms and signs of sepsis</td>
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<td>Radiological criteria</td>
<td>Cervical or thoracic location of the esophageal perforation</td>
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<td>Contained perforation by surrounding tissues</td>
<td>- Intramural</td>
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<td>- Minimal peri-esophageal extravasation of contrast material with intra-esophageal drainage</td>
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<td>- Absence of massive pleural contamination</td>
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<td>Esophageal characteristics</td>
<td>No preexistent esophageal disease</td>
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<tr>
<td>Other</td>
<td>Possibility of close surveillance by expert esophageal team</td>
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<td>Availability of round the clock surgical and radiological skills</td>
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consensus regarding the optimal antibiotic regimen and the treatment duration. A recent review of the literature revealed the need for high-quality evidence related to anti-infective treatment in patients diagnosed with EP [96]. Additional measures should target sepsis control by using percutaneous radiology techniques to drain periesophageal and pleural collections [97]. Drainage of pleural collections and pleural decortication by video-thoracoscopy and use of endoscopic techniques (clips, stents, and internal vacuum drainage) are part of an aggressive minimally invasive management of EP. By using such a combined strategy Vogel et al. were able to perform successful NOM in 68% of 47 EP patients with a low mortality rate (6%) [98].

What are the indications for surgery?
Surgery should be undertaken in all patients who do not meet NOM criteria (Grade 1C).

If surgery is indicated for EP, patients should be taken to the operative room as soon as possible (Grade 1C). Even minor delays in surgical treatment may increase morbidity and mortality rates. Mortality of patients managed within 24 h of EP is under 10% compared to 30% after this time [68, 76, 78, 94]. Repair of EP by a minimally invasive surgical (laparoscopy, thoracoscopy) approach may be considered (Grade 1C). Reports are scarce and such an approach should probably be reserved to centers in which highly specialized expertise is available [99, 100].

What are the most appropriate surgical procedures?
General principles of esophageal perforation management include (1) excellent exposure, (2) debridement of non-viable tissue, (3) closure of defect, (4) use of buttress to reinforce esophageal sutures, and (5) adequate tube drainage. The surgical approach should be tailored according to the location of EP.

Cervical EP For EP located in the neck, direct repair of the esophageal defect should be attempted whenever feasible (Grade 1C). The esophagus is approached through a left neck incision along the anterior border of the sternocleidomastoid muscle or by a collar incision if bilateral cervical exploration is required [74, 78]. Surgical treatment includes circumferential esophageal mobilization to facilitate repair, debridement of the perforation site, single- or double-layer tension-free closure of the perforation, buttressing of the repair with vascularized tissue (sternocleidomastoid muscle, digastric muscle), and adequate drainage [74]. Placement of a feeding tube (nasogastric, jejunostomy) at the time of repair allows early nutritional support and favors healing [68].

If direct repair is not feasible (disruption exceeds 50% of the esophageal circumference, delayed surgical exploration), external drainage is recommended (Grade 2A). Construction of a lateral or end esophageal stoma should be considered to decrease contamination of surrounding spaces.

Thoracic EP Primary repair is the treatment of choice for EP with free perforation of the thoracic esophagus (Grade 1C). Management of perforation of the thoracic esophagus relies on immediate interruption of mediastinal and pleural contamination, debridement of the perforation to healthy tissue, tension-free primary repair, and adequate external drainage [101]. These cases demand an individualized approach and it is difficult to be prescriptive about the actual operative steps. Thoracotomy will usually be required and the degree of pleural effusion or visible wall defect on CT may guide the incision side (Fig. 3). A laparotomy or laparoscopy will usually be required in addition to enable construction of a feeding jejunostomy and possibly a decompressive tube gastrostomy. The alternative is a nasogastric tube or combination of tubes to allow decompression and feeding. In general, a diversionary cervical esophagostomy (for saliva) is not recommended. In some patients with suitable body habitus, a transhiatal approach via a midline laparotomy may be used (Fig. 4). Excision of the xiphoid coupled with use of a sternal hook retractor can allow repair of thoracic esophageal perforations without thoracotomy. The fundus will need to be mobilized and the esophagus encircled with a tape to allow full mobilization and dissection high up into the mediastinum. The mucosal defect is often longer than the muscular tear; longitudinal myotomy at both ends of the EP is useful to expose mucosal edges for appropriate repair [68]. Two-layer repair, with separate suturing of the mucosa and muscle has traditionally been recommended. The risk of suture breakdown is generally quoted to be between 25 and 50%. Buttressing the esophageal repair with surrounding viable tissue (intercostal muscle flap, pleural or pericardic patch) has been recommended to decrease the risk of leakage. In cases approached transhiatally, a Nissen fundoplication can be an effective buttress of the repair. Drainage of the mediastinum and pleural cavity is required and enteral nutrition remains an essential component of the treatment plan.

If direct repair of thoracic EP is not feasible (hemodynamic instability, delayed surgical exploration, extensive esophageal damage) esophageal exclusion, diversion, or resection should be performed (Grade 1C). Repair over a large size T-tube can be used to create a controlled esophago-cutaneous fistula and minimize mediastinal and pleural contamination [102]. Complete esophageal diversion or thoracic esophageal resection is required in the presence of large esophageal disruption; creation of a cervical esophagostomy and feeding
Jejunostomy are mandatory in these patients [101]. Resection is the best option in the presence of pre-existing esophageal pathology [68, 103]. If the patient survives, colon interposition or gastric pull-up reconstruction are required 6–12 months after complete diversion or resection of the thoracic esophagus.

**Abdominal EP** Operative repair is the treatment of choice for patients with free perforation of the abdominal esophagus (Grade 1C). Abdominal esophageal perforation should be approached by a midline laparotomy. Following debridement of necrotic tissues, single- or double-layer tension-free closure of the perforation should be performed. It is recommended to buttress the esophageal suture with a gastroplasty using the gastric fundus (i.e., complete or partial fundoplication), position a nasogastric tube, construct a feeding jejunostomy, and perform external drainage of the subphrenic space [78].

**Esophageal trauma**

Injury of the esophagus by external trauma is a rare condition. Traumatic injuries of the esophagus (TIE) account for less than 15% of all esophageal injuries [104, 105]. TIE were recorded in less than 1% of patients managed in 20 Level I trauma centers across a 6-year period [106]. They are classified according to the anatomic location, i.e., cervical, thoracic, or abdominal and according to the mechanism of injury, i.e., penetrating and blunt trauma. An unusual cause of TIE is barotrauma by external air-blast injuries [107]. Due to the anatomic situation of the esophagus, isolated TIE are rare; associated injuries to the spinal cord, airway, major vascular structures, lungs, heart, and abdominal viscera (spleen, pancreas, liver) are common and worsen the prognosis [108, 109]. TIE occurs mostly in young males and the most frequently encountered presentation is that of a penetrating injury to the cervical esophagus. Mortality of TIE is high with most deaths occurring within 24 h because of severe associated injuries [105]. Trauma to the thoracic esophagus is especially associated with high mortality rates [110]. Early diagnosis of TIE is mandatory to improve outcomes and requires a high level of suspicion.

**What is the appropriate diagnostic work-up?**

Physical examination is not reliable for early diagnosis of TIE (Grade 2A). There are no specific symptoms or pathognomonic signs of TIE. Pointers to TIE include thoracic pain (70%), fever (50%), dyspnea (25%), subcutaneous emphysema (19%), and dysphagia (7%). The mechanism of injury outperforms clinical signs in establishing early diagnosis of TIE [109, 111].

Laboratory studies are not useful for early diagnosis of TIE (Grade 2A). Biological modifications such as leukocytosis, increased CRP, and increased procalcitonin are non-specific and are related to the inflammatory response.

![Fig. 3 Axial CT showing a right pleural effusion, mediastinal air and esophageal wall disruption in a patient with spontaneous EP (Boerhaaves). Patient managed by right thoracotomy and laparotomy.](image-url)
response. Similarly, the presence of lactic acidosis, anemia, and coagulopathy are related to shock rather than TIE [104].

Contrast-enhanced CT and CT esophagography should be performed in hemodynamically stable patients with suspicion of TIE (Grade 1C). CT esophagogram has high sensitivity (95%) and specificity (91%) rates in detecting upper digestive tract perforation. Contrast-enhanced CT is useful to identify associated injuries and can provide important information regarding the trajectory of the penetrating agent (bullet, stab wound). CT may also show indirect signs of esophageal perforation (paraesophageal collections, free air, pleural effusions). Over the past years, CT has largely replaced contrast (gastrografin/barium) esophagogram, which was the test of choice for years but provides less information, requires a stable and cooperative patient, and can miss up to 30% of small esophageal perforations [112, 113]. One major drawback of esophageal opacification techniques is the fact that swallowing is only possible in patients who are well; nasogastric tube-administered contrast may miss esophageal perforation.

**What is the role of diagnostic endoscopy?**

Flexible endoscopy should be performed as an adjunct to CT in patients with suspected TIE (Grade 2A). Endoscopy provides direct visualization of the injury site and was shown to be useful in patients with equivocal CT findings. Other advantages include easy availability in most trauma centers and the possibility of use in intubated and unstable patients [114, 115]. In combination with contrast-enhanced CT, flexible endoscopy allows the accurate diagnosis of TIE in more than 90% of cases. The use of endoscopy has been shown to alter surgical management in 69% of patients. In unstable patients rushed to the operative room, intraoperative endoscopy can be employed to rule out esophageal perforation. Under such circumstances triple endoscopy (esophagoscopy, laryngoscopy, and bronchoscopy) is indicated as injury of one of these structures should raise the suspicion of damage to the adjacent organs. Insufflation during the procedure may promote mediastinal contamination by increasing the size of the perforation; for this reason low-flow insufflation and use of CO₂ rather than air are recommended [104, 113].
What are the indications for non-operative management?
Patients with TIE can be offered NOM if they have no esophageal perforation. Patients with esophageal perforation can be offered non-operative management if they meet the previously described NOM criteria (Table 1) (Grade 2A). In these patients, it is mandatory to define the location and the extent of esophageal damage; any delay in the management of overlooked esophageal perforations can impair patient outcomes. It is also essential to detect associated injuries that may affect management and survival [104].

NOM for TIE should be offered only if intense monitoring in an intensive care unit setting, surgical expertise and interventional radiology skills are available around the clock (Grade 1C). NOM requires keeping patients on nil per os status, use of broad spectrum antibiotic coverage, endoscopic placement of a nasogastric tube, and early introduction of nutritional support via the use of either enteral feeding or total parenteral nutrition. Additional measures may target the control of sepsis by using percutaneous radiological drainage of peri-esophageal collections, percutaneous chest tube placement and the drainage of pleural collections and pleural decortication by video-thoracoscopy [78, 104–106, 111].

What are the indications for immediate surgical treatment?
Patients with TIE should undergo immediate surgical treatment if they have hemodynamic instability, obvious non-contained extravasation of contrast material and systemic signs of severe sepsis (Grade 1C). In these patients, surgery should be undertaken as soon as possible; a large body of literature shows that delayed (> 24 h) surgical management of esophageal perforation results in increased morbidity and mortality rates. Recent studies suggested that while delayed surgical treatment does not affect mortality rates, it did nevertheless reduce the odds of successful primary esophageal repair. If emergency surgery was prompted by associated injuries an esophageal perforation should be sought intraoperatively by direct inspection, intraluminal instillation of dye (methylene blue), or endoscopic insufflation [78, 109, 111].

Delayed surgical treatment is indicated in patients with TIE-related esophageal perforation in whom primary repair of the esophagus was not feasible or had failed (Grade 2A). TIE patients with esophageal perforation who are ineligible for primary repair undergo either esophageal resection or exclusion-diversion procedures. If they survive these, patients require a second procedure to restore continuity of the gastrointestinal tract. Esophageal reconstruction by colon or gastric interposition is usually scheduled 6–12 months after TIE [104].

What are the most appropriate surgical procedures?
TIE are rare but highly morbid. Management is dictated by location of the perforation and any concurrent injuries. The majority of cases are amenable to primary repair with flap re-enforcement. Other principles include adequate drainage around the repair, decompression of the esophagus and stomach (via naso-gastric tube or gastrostomy tube), and distal enteral nutrition (feeding jejunostomy) [116].

For TIE located in the neck, direct repair of the esophageal perforation should be attempted whenever feasible (Grade 1C). If direct repair is not feasible, esophagostomy and cervical drainage is recommended (Grade 2A). Appropriate treatment of associated injuries (tracheal, carotid) is essential under these circumstances as these can pose specific problems (tracheo-esophageal fistula, postoperative carotid disruption). Avoiding formation of a tracheotomy, bursing repairs with viable tissue, and drainage through the contralateral neck have all been recommended to prevent such complications [78, 104].

Operative repair is the treatment of choice for TIE with free perforation of the thoracic esophagus (Grade 1C). If primary repair is not feasible, diversion, exclusion, or resection of the thoracic esophagus should be performed (Grade 2A). Severe damage to the spine, the great vessels, the heart, and the lungs may be associated and will determine survival in the short term; their treatment takes priority over esophageal injuries and may require a damage control approach [78, 104].

Operative repair is the treatment of choice for TIE with free perforation of the abdominal esophagus (Grade 1C). Control of potential life-treatment bleeding from associated liver, spleen, or great vessel injuries is essential in patients with abdominal TIE [78, 104].

What is the role of damage control surgery?
Principles of damage control surgery and of damage control reanimation should be applied to hemodynamically unstable patients with TIE (Grade 1C). In one study, mortality of TIE was 44% with 92% of the deaths occurring within 24 h of presentation; mortality was related to the injury severity score (ISS) and not to the esophageal injuries [105]. Thus, abbreviated source control surgery followed by transfer to the intensive care unit for physiological resuscitation is paramount in hemodynamically unstable TIE patients; a second look procedure in the operating room is then required for definitive surgical management of esophageal and other associated injuries. External drainage, esophageal exclusion, or expeditious resection should be undertaken in parallel with bleeding control measures; specific treatment of the esophageal lesions would be undertaken in survivors as previously described [111].
Table 2 Main management principles of esophageal injuries

Foreign body ingestion (FB)

- Computed tomography (CT) is the key exam in patients with suspected perforation or other FB-related complications
- Emergent endoscopy (< 6 h) is recommended for sharp-pointed objects, batteries, magnets and for complete esophageal obstruction
- Indications for surgery include perforation and FB which are irretrievable or close to vital structures
- Esophagotomy with FB extraction and primary closure is the preferred approach.

Caustic ingestion

- The quantity of the ingested agent and the accidental-voluntary ingestion pattern condition outcomes
- Emergency management can be performed safely relying on computed tomographic evaluation alone
- Endoscopy remains the main diagnostic and therapeutic tool for caustic strictures
- Patients who do not have full-thickness necrosis of digestive organs can be offered non-operative management (NOM) under close clinical and biological monitoring. Emergency resection of caustic necrosis can be lifesaving.

Esophageal perforation (EP)

- Contrast-enhanced CT and CT esophagography is the imaging examination of choice
- NOM can be offered to stable patients with early presentation, contained esophageal disruption and minimal contamination of surrounding spaces. Endoscopic (clips, stents) treatment and interventional radiology techniques are useful adjuncts during NOM
- Emergency surgery should be undertaken in patients who do not meet NOM criteria. Direct repair and adequate drainage is the treatment of choice; if repair is not feasible (large disruption, delayed surgery, preexistent esophageal disease), external drainage, esophageal exclusion or resection are possible options.

Esophageal trauma

- Physical examination and laboratory studies are not useful for early diagnosis of TIE
- Contrast-enhanced CT and CT esophagography should be performed in hemodynamically stable patients with suspicion of TIE. Preoperative flexible endoscopy is useful for TIE diagnosis in unstable patients
- Patients with TIE can be offered NOM if they do not have EP or if they meet NOM criteria for EP
- Patients with TIE should undergo immediate surgical treatment if they have hemodynamic instability, obvious non-contained extravasation of contrast material and systemic signs of severe sepsis
- Operative repair is the treatment of choice of TIE. Appropriate management of associate injuries conditions patient survival

Conclusion

The current recommendations rely on extensive review of the literature and expert opinion. Because of the low incidence of esophageal injuries, high-quality evidence is lacking and the majority of publications in the literature are case reports, case series, or literature reviews. Despite these limitations, the value of the consensus conference in Bertinoro was to gather a panel of recognized experts who discussed point by point all the major issues related to esophageal injuries (Table 2). We recommend a high degree of suspicion in clinical situations that might be associated with or secondarily lead to esophageal perforation; starting appropriate treatment within 24 h can be lifesaving under these circumstances. Both CT and endoscopy are reliable diagnostic tools and their use should be tailored to the patient condition. Definitive management of esophageal emergencies should be undertaken in specialized centers in which multispecialty (esophageal surgeons, interventional radiologists, endoscopists, intensive care unit specialists) expertise is available round the clock.

Abbreviations

CBC: Complete blood count; CRP: C-reactive protein; EI: Esophageal injuries; EP: Esophageal perforation; FB: Foreign bodies; NOM: Non-operative management; TIE: Traumatic injuries of the esophagus

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Perforated and bleeding peptic ulcer: WSES guidelines


Abstract

Background: Peptic ulcer disease is common with a lifetime prevalence in the general population of 5–10% and an incidence of 0.1–0.3% per year. Despite a sharp reduction in incidence and rates of hospital admission and mortality over the past 30 years, complications are still encountered in 10–20% of these patients. Peptic ulcer disease remains a significant healthcare problem, which can consume considerable financial resources. Management may involve various subspecialties including surgeons, gastroenterologists, and radiologists. Successful management of patients with complicated peptic ulcer (CPU) involves prompt recognition, resuscitation when required, appropriate antibiotic therapy, and timely surgical/radiological treatment.

Methods: The present guidelines have been developed according to the GRADE methodology. To create these guidelines, a panel of experts was designed and charged by the board of the WSES to perform a systematic review of the available literature and to provide evidence-based statements with immediate practical application. All the statements were presented and discussed during the 5th WSES Congress, and for each statement, a consensus among the WSES panel of experts was reached.

Conclusions: The population considered in these guidelines is adult patients with suspected complicated peptic ulcer disease. These guidelines present evidence-based international consensus statements on the management of complicated peptic ulcer from a collaboration of a panel of experts and are intended to improve the knowledge and the awareness of physicians around the world on this specific topic. We divided our work into the two main topics, bleeding and perforated peptic ulcer, and structured it into six main topics that cover the entire management process of patients with complicated peptic ulcer, from diagnosis at ED arrival to post-discharge antimicrobial therapy, to provide an up-to-date, easy-to-use tool that can help physicians and surgeons during the decision-making process.

Keywords: Peptic ulcer, High-risk patients, Diagnosis, Non-operative management, Surgery, Antibiotics, Peritonitis, Pancreatitis, Intra-abdominal infection, Technique, Timing, Angiography, Embolization, Guidelines
Introduction

Peptic ulcer disease is common with a lifetime prevalence in the general population of 5-10% and an incidence of 0.1–0.3% per year [1]. Peptic ulceration occurs due to acid peptic damage to the gastro-duodenal mucosa, resulting in mucosal erosion that exposes the underlying tissues to the digestive action of gastro-duodenal secretions. This pathology was traditionally related to a hypersecretory acid environment, dietary factors and stress. However, the increasing incidence of the Helicobacter pylori infection, the extensive use of NSAIDs, and the increase in alcohol and smoking abuse have changed the epidemiology of this disease. Despite a sharp reduction in incidence and rates of hospital admission and mortality over the past 30 years [2–8], complications are still encountered in 10–20% of these patients [9, 10]. Complications of peptic ulcer disease include perforation and bleeding and improvement in medical management has made obstruction from chronic fibrotic disease a rare event. A recent review on the epidemiology of complicated peptic ulcer disease [10] found that hemorrhage was by far the most common complication of peptic disease, with a reported annual incidence of hemorrhage in the general population ranging from 0.02 to 0.06%, with sample size-weighted average 30-day mortality of 8.6%. Reported annual incidence of perforation ranges from 0.004 to 0.014%, with sample size-weighted average 30-day mortality of 23.5%. Although perforation is less common, with a perforation:bleeding ratio of approximately 1:6, it is the most common indication for emergency operation and causes about 40% of all ulcer-related deaths [11].

Peptic ulcer disease remains a significant healthcare problem, which can consume considerable financial resources. Management may involve various subspecialties including surgeons, gastroenterologists, and radiologists. Successful management of patients with complicated peptic ulcer (CPU) involves prompt recognition, resuscitation when required, appropriate antibiotic therapy and timely surgical/radiological treatment.

Notes on the use of the guidelines: aims, targets, and limitations

The Guidelines are aimed to present the state-of-the-art regarding diagnosis and therapeutic options for an optimal management of complicated peptic ulcer. These guidelines are thus intended to improve the knowledge and the awareness of physicians around the world on the specific topic of complicated peptic ulcer, providing an up-to-date tool that can help during the decision-making process. For this reason, the Guidelines are evidence-based and the grade of recommendation is provided to summarize the evidences present in literature. The population considered in these guidelines is adult patients with suspected complicated peptic ulcer disease. The practice Guidelines promulgated in this work do not represent a standard of practice. They are suggested plans of care, based on best available evidence and the consensus of experts but they do not exclude other approaches as being within the standard of practice. For example, they should not be used to compel adherence to a given method of medical management, which method should be finally determined after taking account of the conditions at the relevant medical institution (staff levels, experience, equipment, etc.) and the characteristics of the individual patient. However, responsibility for the results of treatment rests with those who are directly engaged therein, and not with the consensus group.

Methods

These consensus guidelines are an update of the 2013 WSES position paper on this topic. To create these guidelines, a panel of experts was designed and charged by the board of the WSES to develop questions on six main topics that thoroughly cover the field of this pathology (diagnosis, resuscitation, nonoperative management, surgery, angiography-angioembolization, antimicrobial therapy). Then, leading specialists in the field were asked to perform a thorough search on each of these topics in different databanks (MEDLINE, SCOPUS, EMBASE) for relevant papers between 1985 and June 2018 and a systematic review of the available literature. They were asked to focus their search in order to provide evidence-based answers to every question with immediate practical application and to summarize them in statements. All the statements were presented and discussed during the 5th WSES Congress held in Bertinoro, Italy in June 28th, 2018. For each statement, a consensus among the WSES panel of experts was reached. All the members contributed to the development of the manuscript; the manuscript was reviewed and approved by all the authors.

The present guidelines have been developed according to the GRADE methodology [12, 13].

Topics and questions

For clarity, we report the six topics together with the questions dividend into each of them.

Diagnosis

1. In patients with a suspected perforated peptic ulcer, which are the appropriate biochemical and imaging investigations that should be requested?
2. In patients with perforated peptic ulcer, what is the clinical value of risk scores such as Boey Score and Pulp score?
3. In patients with suspected bleeding peptic ulcer, which biochemical and imaging investigations should be requested?
4. In patients with suspected bleeding peptic ulcer, what is the diagnostic role of endoscopy?
5. In patients with bleeding peptic ulcer, are the endoscopic findings useful to determine the risk for rebleeding and how do they affect the clinical management?

**Resuscitation**

1. In patients with perforated peptic ulcer, which parameters should be evaluated ad ED referral?
2. In patients with perforated peptic ulcer, which are the appropriate targets for resuscitation (hemoglobin level, blood pressure/heart rate, lactates level, others)?
3. In patients with bleeding peptic ulcer, which parameters should be evaluated at ED referral and which criteria should be adopted to define an unstable patient?
4. In patients with bleeding peptic ulcer, which are the appropriate targets for resuscitation (hemoglobin level, blood pressure/heart rate, lactates level, others)?

**Non-operative management**—endoscopic treatment

1. In patients with perforated peptic ulcer, which are the indications for non-operative management?
2. In patients with perforated peptic ulcer, is there a role for endoscopic treatment?
3. In patients with bleeding peptic ulcer, which are the indications for non-operative management?
4. In patients with bleeding peptic ulcer, which are the indications for non-operative management?
5. In patients with bleeding peptic ulcer, what is the appropriate pharmacological regimen (Erythromycin, PPI, terlipressin, others)?
6. In patients with recurrent bleeding from peptic ulcer, what is the role of non-operative management?

**Angiography—embolization**

1. In patients with bleeding peptic ulcer, which are the indications for angiography?
2. In patients with bleeding peptic ulcer, which are the indications for angioembolization?
3. Should embolization be considered for unstable patients with bleeding peptic ulcer?
4. In patients with recurrent bleeding peptic ulcer, which are the indications for angioembolization?
5. In patients who underwent angioembolization, which are the most appropriate embolization techniques and materials?
6. In patients with bleeding peptic ulcer and non-evident bleeding during angiography is there a role for prophylactic embolization?

**Surgery**

1. In patients with perforated peptic ulcer, which are the indications for surgical treatment and what is the appropriate timing for surgery?
2. In patients with perforated peptic ulcer what is the most appropriate surgical approach (open vs laparoscopy)?
3. In patients with perforated peptic ulcer is there a role for sutureless repair?
4. In patients with perforated peptic ulcer and small perforation (< 2 cm), which surgical procedure should be adopted?
5. In patients with perforated peptic ulcer and large perforation (≥ 2 cm), which surgical procedure should be adopted?
6. In patients with perforated peptic ulcer, what is the role of damage control surgery?
7. In patients with bleeding peptic ulcer, which are the indications for surgical treatment and which is the appropriate timing for surgery?
8. In patients with bleeding peptic ulcer, what is the most appropriate surgical approach (open vs laparoscopy) and what are the most appropriate surgical procedures?
9. In patients with bleeding peptic ulcer, what is the role of damage control surgery?

**Antimicrobial therapy**

1. Should antibiotic therapy be prescribed and should anti-fungal therapy be administrated empirically in patients with perforated peptic ulcer?
2. In patients with perforated peptic ulcer, which antimicrobial regimen should be used and what is its correct duration?
3. In patients with bleeding peptic ulcer, which are the indications for antimicrobial therapy and for *Helicobacter pylori* testing?
4. In patients with bleeding peptic ulcer and positive tests for *H. pylori* infection, which are the therapeutic options?

**Perforated peptic ulcer**

**Diagnosis**

*In patients with a suspected perforated peptic ulcer, which are the appropriate biochemical and imaging investigations that should be requested?*

*In patients with suspected gastroduodenal perforation, we recommend routine laboratory studies and arterial blood gas analysis (strong recommendation based on very low-quality evidences, 1D).*
In patients with acute abdomen from suspected perforated peptic ulcer, we recommend a CT scan imaging (Strong recommendation based on low-quality evidences, 1C).

In patients with acute abdomen from suspected perforated peptic ulcer, we recommend to perform chest/abdominal X-ray as the initial routine diagnostic assessment in case a CT scan is not promptly available (Strong recommendation based on low-quality evidences, 1C).

In patients with acute abdomen from suspected perforated peptic ulcer, when free air is not seen on imaging and there is ongoing suspicion of perforated peptic ulcer, we suggest performing imaging with the addition of water-soluble contrast either oral or via nasogastric tube (weak recommendation based on very low-quality evidences, 2D).

The clinical presentation of gastroduodenal perforation is usually sudden onset of abdominal pain. Localized or generalized peritonitis is typical of perforated peptic ulcer, but may be present in only two-thirds of the patients [14–16]. Thus, physical examination findings may be equivocal and peritonitis may be minimal or absent, particularly in patients with contained and/or sealed leak. Laboratory tests are non-specific, although leukocytosis, metabolic acidosis and elevated serum amylase are usually associated with perforation [17]. The first diagnostic investigation is the radiograph of the abdomen and chest, to detect the presence of free abdominal air. Erect and left lateral decubitus X-rays have similar diagnostic accuracy, the latter being better tolerated by patients presenting with peritonitis. The presence of this radiological sign is highly variable across various studies present in literature and ranges between 30 and 85% of perforations. This high variability and the finding that a negative X-ray does not rule out a possible perforation led multiple authors to state that, in case of clear signs of peritonitis, an abdominal CT scan should be the first radiological examination to be performed. However, in the setting of a peripheral hospital without prompt access to a CT scan, the plain X-ray still has a diagnostic role and free air on X-ray associated with a clear history and signs of peritonitis on physical examination is sufficient to justify surgical exploration [9, 14, 15, 18]. An adjunct to plain X-ray could be the administration through a nasogastric tube (NGT) of water-soluble contrast that can detect the presence of a gastro-duodenal perforation. “Point-of-care” ultrasound could also detect free intra-peritoneal, when performed by a trained operator, with the demonstration of air under the abdominal fascia; anyway, its role in the diagnostic work-up of suspected perforated peptic ulcer still needs to be defined. Suspicious CT scan findings include unexplained intraperitoneal fluid, pneumoperitoneum, bowel wall thickening, mesenteric fat streaking, and presence of extraluminal water-soluble contrast. Indeed, CT scan is increasingly taking the main role in diagnosis of perforation, due to the greater sensitivity in detecting free air and to its ability to characterize the site and size of perforation and to exclude other possible causes [15, 18, 19]. However, up to 12% of patients with perforations may have a normal CT scan; in this scenario, the administration of oral water-soluble contrast or via nasogastric tube and performing triple contrast CT scan may improve diagnostic sensitivity and specificity [17].

In patients with perforated peptic ulcer, what is the clinical value of risk scores such as Boey Score and Pulp score?

In patients with perforated peptic ulcer, we suggest to adopt scoring systems (including the Boey, PULP and ASA score) for risk-stratification of patients and to predict outcomes (weak recommendation, based on low-quality evidences, 2C).

Numerous scoring systems have been designed and validated with the aim of predicting mortality and morbidity in patients with perforated peptic ulcer [20–22]. The Boey score is the most used, followed by the ASA score and the PULP. Boey's score showed an elevated variability in accuracy across the different studies where it was tested. On the other hand, the PULP score is difficult to apply and has not yet been validated outside the initial center. The new PULP score and the ASA score predicted mortality equally well and better than the Boey score, but hypoalbuminemia still remains the strongest single predictor of mortality [20–22].

Resuscitation

In patients with perforated peptic ulcer, which parameters should be evaluated ad ED referral?

We recommend prompt evaluation and early recognition of the patient with perforated peptic ulcer associated sepsis to prevent further organ failure and to reduce mortality (strong recommendation based on moderate-quality evidences, 1B).

We suggest adopting scoring systems (SOFA, qSOFA) to evaluate and assess the severity of the disease in patients with perforated peptic ulcer (Weak recommendation based on low-quality evidences, 2C).

Perforated peptic ulcer, with associated peritonitis and sepsis/septic shock, is a medical/surgical emergency requiring rapid evaluation and management [23]. It is crucial to identify parameters to assess the severity of the disease (i.e., to define if a patient is stable or unstable). The latest
definition of sepsis/septic shock and related debates/controversies are beyond the scope of this manuscript but are covered in recent papers [24, 25]. The timely recognition of sepsis (i.e., before the occurrence of organ dysfunction) is a priority [25, 26]. During the ED evaluation of every septic patient, several elements should be considered to assess the clinical picture. Specifically, several symptoms (i.e., altered mental state, dyspnea), signs (i.e., tachycardia, tachypnea, reduced pulse pressure, decreased urine output) and laboratory findings (hyperlactatemia, arterial hypoxemia, increased creatinine, coagulation abnormalities) must be evaluated. It is important to keep in mind that these findings may be modified by preexisting disease or medications [27]; for this reason, the collection of clinical history needs to be performed carefully.

Scoring systems, i.e., the sequential organ failure assessment (SOFA) [28] or the quick SOFA (qSOFA) [29], with associated limitations [25, 30–33], are available to assess the severity of the disease.

In patients with perforated peptic ulcer, which are the appropriate targets for resuscitation (hemoglobin level, blood pressure/heart rate, lactates level, others)?

In unstable patients with perforated peptic ulcer, we recommend performing rapid resuscitation to reduce mortality (strong recommendation based on low quality evidences, 1C).

In unstable patients with perforated peptic ulcer, we recommend restoring physiological parameters with a mean arterial pressure ≥ 65 mmHg, a urine output ≥ 0.5 ml/kg/h, and a lactate normalization (strong recommendation based on low-quality evidences, 1C).

We suggest utilizing different types of hemodynamic monitoring (invasive or not) to optimize fluids/vasopressor therapy and to individualize the resuscitation strategy (strong recommendation based on low quality evidences, 1C).

Unstable septic perforated peptic ulcer patients need appropriate and rapid (ideally within 1 h) resuscitation to reduce mortality [27, 29]; this must take place simultaneously with surgical consultation, microbiological cultures (blood and other), and antibiotic administration [24, 34]. Primarily, as in any emergency situation, a rapid ABC (airway, breathing, and circulation) evaluation should be done. Secondarily, appropriate targets for resuscitation (the same used for sepsis and septic shock [27, 35]) need to be considered. In general, the most important are:

- Mean arterial pressure (MAP) ≥ 65 mmHg
- Urine output ≥ 0.5 ml/kg/h
- Lactate normalization

Several forms of hemodynamic monitoring (invasive or not) are available to optimize resuscitation and fluid/vasopressors administration. For a more comprehensive approach to sepsis and septic shock, we suggest referring to the last published guidelines of the “Surviving Sepsis Campaign” [35].

Non-operative management—endoscopic treatment

In patients with perforated peptic ulcer, which are the indications for non-operative management?

In patients with perforated peptic ulcer we suggest against a routinely use of non-operative management; non-operative management (NOM) could be considered in extremely selected cases where perforation has sealed as confirmed on water-soluble contrast study (weak recommendation based on low-quality evidences, 2C).

Non-operative management (NOM) of perforated peptic ulcer is attractive as it avoids surgery and its resultant morbidity, e.g., wound-related morbidity, postoperative adhesions, etc. The rationale of NOM is that, in the case of small perforations, the ulcer seals by omental adhesions and can then heal and the peritonitis does not need operation [36]. In 1989 Croft et al. conducted a prospective randomized trial [37] comparing emergency surgery and NOM in patients with a clinical diagnosis of perforated peptic ulcer: 83 patients were entered in the study over a period of 13 months and were randomly assigned to one of the two study groups. In the NOM group, 11 patients (28 percent) had no clinical Improvement after 12 h and required an operation. The overall mortality rates in the two groups were similar (two deaths in each, 5%), and did not differ significantly in the morbidity rates (40% in the surgical group and 50% in the nonsurgical group). The hospital stay was 35% longer in the group treated conservatively and patients over 70 years old were less likely to respond to conservative treatment than younger patients (p < 0.05). Songne et al. in 2004 [38] conducted a prospective trial of 82 consecutive patients with diagnosis of perforated peptic ulcer; they initially underwent NOM and clinical improvement was achieved in 54% of patients after NOM. In multivariate analysis, the factors independently related to NOM failure were size of pneumoperitoneum, heart rate > 94 bpm, and abdominal meteorism (defined as distended bowel loops). In conclusion, the most important factors regarding the feasibility of NOM for perforated peptic ulcer are normal vital signs in a stable patient and whether the ulcer itself has sealed as confirmed by a water-soluble contrast study: if there is a free leak of contrast, surgery is needed. On the other hand, NOM could be considered if no contrast extravasation is present and the patient does not have signs of peritonitis or sepsis.
The essential pre-requisites and components of non-operative management of PPU can be grouped as “R’s” [39]:

- Radiologically undetected leak
- Repeated clinical examination
- Repeated blood investigations
- Respiratory and renal support
- Resources for monitoring and
- Readiness to operate

NOM includes: nil by mouth; intravenous hydration; decompression via nasogastric tube; anti-secretory and PPI therapy; intravenous antibiotics; and follow-up endoscopy at 4–6 weeks. Mortality increases with every hour of delay to surgery, and hence, NOM must be carefully selected. Surapaneni et al. have shown nil mortality in patients who were operated within 24 h of onset of symptoms as compared to surgery beyond 48 h of onset of symptoms [40]. Buck et al. in 2688 Danish patients have shown that every hour of delay from admission to surgery was associated with an adjusted 2.4% decreased probability of survival compared with the previous hour [41]. Elderly patients may experience paradoxical higher mortality if non-operative management fails and caution is advised in patients > 70 years of age.

In patients with perforated peptic ulcer is there a role for endoscopic treatment?

In patients with perforated peptic ulcer, we suggest to avoid endoscopic treatment such clipping, fibrin glue sealing, or stenting (Weak recommendation based on low-quality evidences, 2C)

Closure of acute iatrogenic perforations with endoscopic clips is described [42, 43]; however, clips may not be effective in perforated ulcer cases due to fibrotic tissue with loss of compliance. Combined laparoscopic-endoscopic approaches for perforated ulcer closures have been described [44, 45]. Bergstrom et al. [46] present a case series of eight patients with perforated duodenal ulcers treated with covered self-expandable metal stents and the results indicate that, in very selected patients or in cases where surgical closure will be difficult, gastroscopy with stent placement could be performed during laparoscopy, followed by laparoscopic drain placement. In patients with severe co-morbidity or delayed diagnosis, gastroscopy and stent placement followed by radiologically guided drain placement could be an alternative to more standard treatment. Endoscopic snaring of omentum and pulling is also described as an effective adjunct along with duodenal plication. Furthermore, endoscopy also allows performing a biopsy and rule out gastric outlet obstruction in case of large perforations. In spite of these case series, all the above reported modalities are not recognized as standard approaches to perforated peptic ulcer and need further validation.

Surgery

In patients with perforated peptic ulcer, which are the indications for surgical treatment and what is the appropriate timing for surgery?

In patients with perforated peptic ulcer with significant pneumoperitoneum or extraluminal contrast extravasation or signs of peritonitis, we recommend operative treatment (Strong recommendation based on low-quality evidences, 1C)

We recommend performing surgery as soon as possible, especially in patients with delayed presentation and patients older than 70 years old (strong recommendation based on moderate-quality evidences, 1B)

The feasibility of NOM should be weighed with the evidence that an increase in surgical delay significantly impairs surgical outcome. In fact, a cohort study performed in 2013 from the Danish Clinical Register of Emergency Surgery [41] showed that, over the first 24 h after admission, each hour of surgical delay beyond hospital admission was associated with an adjusted 2.4% decreased probability of survival compared with the previous hour, over the entire observation period. Other studies highlighted the importance of a prompt surgical approach to PPU: a retrospective single-center study by Lunevicious et al. [47] showed an increase in the suture leakage rate after a delay in presentation > 9 h, while a recent prospective single-center study on 101 patients with peritonitis from peptic ulcer perforation who underwent laparotomy and simple closure with omental patch found that a perforation-to-surgery interval longer than 36 h was significantly associated with an increase in postoperative mortality [48]. Furthermore, a systematic review [49] performed in 2010 including fifty studies with 37 prognostic factors comprising a total of 29,782 patients provided strong evidence for an association of older age, co-morbidity, and use of NSAIDs or steroids with mortality; shock upon admission, preoperative metabolic acidosis, tachycardia, acute renal failure, low serum albumin level, high ASA score, and preoperative delay > 24 h were also associated with poor prognosis. Limiting pre-operative delay thus seems to be of great importance.

In patients with perforated peptic ulcer, which is the most appropriate surgical approach (open vs laparoscopy)?

In stable patients with perforated peptic ulcer, we suggest a laparoscopic approach. An open approach is

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recommended in the absence of appropriate laparoscopic skills and equipment (weak recommendation based on moderate-quality evidences, 2B).

In unstable patients with perforated peptic ulcer, we recommend open surgery (strong recommendation based on very low-quality evidences, 1D)

A recent meta-analysis from Cirocchi et al. [50] compared laparoscopic to open surgery for patients with perforated peptic ulcer: their search identified 8 RCTs for a total of 615 patients (307 patients undergoing laparoscopic repair and 308 patients undergoing open repair); however all the included studies were at high risk of bias. The comparison reported a significant advantage of laparoscopic repair with less postoperative pain in the first 24 h after surgery and less postoperative wound infections. No significant differences between laparoscopic and open surgery were found for overall postoperative mortality, leak of the suture repair, intra-abdominal abscesses and reoperation rate. This is the strongest evidence present so far the literature and suggests it is reasonable to pursue a laparoscopic approach for stable patients and in the presence of appropriate surgical skills.

The effects of increased intra-abdominal pressure and hypercarbia due to CO2 insufflation during laparoscopy are well known (increased systemic vascular resistance, mean arterial pressure, afterload, heart rate, caval pressures, respiratory rate, peak airways pressure, PaCO2; reduced stroke volume, venous return, cardiac output, thoracic compliance, pH) [51] and preclude a laparoscopic approach to hemodynamically unstable patients or patients with severe cardiovascular or pulmonary comorbidity.

Is there a role for sutureless repair in patients with perforated peptic ulcer?

Based on the available literature, no recommendation could be made about the sutureless repair.

Sutureless repair was proposed with the rationale to shorten operative time and to simplify the surgical technique, making it easily performed by those who have limited experience with laparoscopic surgery. However, it has not gained a wide acceptance due to its high leakage rate compared to suture repair. A prospective study conducted from January 1992 to December 1998 included 374 patients with perforated peptic ulcer [52]; 219 patients were treated by open suture repair, 109 patients received laparoscopic fibrin glue repair and the remaining 46 patients were treated by laparoscopic suture repair. Laparoscopic fibrin glue repair was initially attempted in 149 patients but 40 required conversion to suture repair. The overall conversion rates for laparoscopic fibrin glue repair and laparoscopic suture repair were 27 and 15%, respectively. The main reasons for conversion were a large (1 cm or more) ulcer perforation and failure to locate the perforation site. The overall leak rates after laparoscopic glue repair and laparoscopic suture repair were 16 and 6% respectively and the reoperation rates for clinical leaks after laparoscopic glue repair and laparoscopic suture repair were 10 and 4% respectively. On the other hand, a retrospective cohort study performed from January 2008 to December 2012 found conflicting results [53]: 107 patients were included, 64 underwent laparoscopic repair with a sutureless onlay omental patch, and 43 were treated by laparoscopic sutured omental patch. High-risk patients with Boey scores of 2 and 3 or those with perforations larger than 10 mm were excluded. The time to water intake was significantly shorter for patients who had repair with a sutureless omental patch (\(p = 0.007\)), as well as the mean hospital stay (\(p = 0.007\)). All patients in both groups survived to the end of the study and no patient experienced leakage after the operation. The evidences listed above are based on low quality studies and do not allow us to make a recommendation for its routine application.

In patients with perforated peptic ulcer and small perforation (< 2 cm), which surgical procedure should be adopted?

In patients with perforated peptic ulcer smaller than 2 cm, we suggest performing primary repair. No recommendation can be made whether the use of an omental patch can provide further protection of the repair (weak recommendation based on low-quality evidences, 2C)

Historically, repair with the adjunct of an omental patch was considered the “standard” laparoscopic procedure for perforated peptic ulcer repair. This belief is a now matter of debate as multiple studies showed the addition of an omental patch does not add benefits to a simple suture repair, but it significantly increases the operation time.

Multiple retrospective single-center studies support these findings. Lin et al. [54] analyzed 118 patients with PPU who underwent laparoscopic repair with simple closure (\(n = 27\)) or omentoplasty (\(n = 91\)) and found Three closure leakage: 1 after simple closure and 2 after omentoplasty, but no patient died. After matching, the simple closure and omentoplasty groups had comparable results regarding leakage rate. Comparison of the operating time in the 4.0- and 5.0–12-mm groups reported that the simple closure took less time than omentoplasty for perforations smaller than 12 mm. Abd Ellatif and colleagues [55] enrolled 179 consecutive patients with PPU who were treated by laparoscopic repair; 108 patients with the omental patch technique and 71 with laparoscopic simple repair. Operative time was significantly
shorter in the non-patch group and no patient was converted to laparotomy. There was no difference in age, gender, ASA score, surgical risk (Boey’s) score, and incidence of co-morbidities between two groups and both groups was comparable in terms of hospital stay, time to resume oral intake, postoperative complications and surgical outcomes. Lo et al. retrospectively identified 73 patients undergoing PPU laparoscopic repair, 26 received simple closure repair and 47 received simple closure plus omental patch. There was no difference in age, gender, ASA score, Boey risk score, incidence of co-morbidities, Mannheim Peritonitis index, median operation time or length of stay. Again, they stated that, in terms of leakage rate and surgical outcome, the maneuver to cover an omental patch on the repaired PPU did not show additional advantage compared to simple closure alone [56]. A multicenter non-randomized retrospective study [57] further strengthens these findings: between 2009 and 2013, 297 patients with PPU underwent a laparoscopic procedure in eight Romanian surgical centers. Primary suture repair was performed in 145 patients (48.8%), primary suture repair with omentopexy in 146 patients (49.2%) and the remaining 6 patients were converted to open surgery. The univariate complications rate analysis they performed found no significant association ($p = 0.634$; Fisher’s exact test) between the type of the repair and the rate of complications. A prospective non-randomized study by Ates et al. compared laparoscopic simple closure with conventional omental patch open repair for perforated peptic ulcer. Of the 35 patients enrolled, none experienced operative complications nor postoperative leak or residual intra-abdominal abscess [58]. On the other hand, multiple retrospective studies highlight low postoperative leak rates with the omental patch technique, even in case of perforations up to 2 cm in diameter [59]. Multiple authors suggest the adjunct of an omental patch in case of large ulcers with friable edges, to reduce the risk of the suture cutting through the edges of the ulcer [60].

In light of the above, we cannot suggest the routine application of the omental patch because of the longer operative time, the need for advanced laparoscopic skills and the similar results after simple closure, but it could be considered a viable option in selected cases.

**In patients with perforated peptic ulcer and large perforation ($\geq 2$ cm), which surgical procedure should be adopted?**

We suggest a tailored approach based upon the location of the ulcer for the treatment of perforated peptic ulcer larger than 2 cm. In case of large gastric ulcers that raise the suspicion of malignancy, we suggest resection with contextual operative frozen pathologic examination whenever possible. In case of large duodenal ulcers, we suggest considering the need of resections or repair plus/minus pyloric exclusion/external bile drainage. We recommend duodenostomy only in extreme circumstances (weak recommendations based on very low-quality evidences, 2D).

While the treatment of a small ulcer is relatively straightforward, the treatment of giant peptic ulcers (diameter $> 2$ cm) poses different challenges according to the anatomical location. Furthermore, large gastric ulcers should always raise the suspicion of malignancy [61]. The spontaneous perforation of gastric cancer is a rare complication, occurring in 1% of patients with gastric cancer, and it has been reported that about 10–16% of all gastric perforations are caused by gastric carcinoma [62]. Besides this, there are no specific surgical treatment recommendations since the site of perforation and the secondary effects on the surrounding anatomical structures must direct the necessary interventions. The gastric location is usually easier to treat when compared to the duodenal location and gastric resection and reconstruction should be the surgical choice for the treatment of perforated gastric ulcers larger than 2 cm. On the other hand, only the first portion of the duodenum can be resected easily without risk of injuring the bile duct or the pancreatic head. Antrectomy plus or minus D1–D2 resection with diversion is the classic and most commonly described intervention, if the ampullary region is not involved [63]. The proximity of the defect and its relation to the common bile duct and ampulla of Vater must also be thoroughly investigated and intraoperative cholangiography may even be necessary to verify common bile duct anatomy. Several different procedures, such as a jejunal serosal patch, Roux en-Y duodenoejunostomy, pyloric exclusion, and several variations of omental plugs [64] have been described for large duodenal defects when the defect is felt too large to perform a primary repair. In large ulcers, leak rates up to 12% have been reported from attempted closure with an omental patch procedure [65]. These patients also frequently present in septic shock when the amount of peritoneal spillage is large. This factor alone should significantly influence the choice of operative intervention, because a definitive resectional approach for ulcers involving the ampullary area (i.e., Whipple procedure or similar) is usually not recommended in patients with peritonitis, because of the high physiological impact of these procedures and the great risk of postoperative complications. In these cases, a damage control procedure (such as pyloric exclusion with gastric decompression via a nasogastric tube or a gastrostomy and an external biliary diversion via T-tube) will likely be the safest and most appropriate operation for the patient [66]. Duodenostomy (e.g., over Petzer tube) should be used only as a last resort, in the presence of giant ulcers with severe tissue inflammation and when mobilization
In patients with perforated peptic ulcer, what is the role of damage control surgery?

In patients with perforated peptic ulcer and signs of severe physiological derangement, we suggest a damage control strategy (Weak recommendation based on very low-quality evidences, 2D)

In severe peritonitis, some patients may experience disease progression to severe sepsis and septic shock experiencing progressive organ dysfunction, hypotension, myocardial depression, and coagulopathy and a staged approach may be required. If the patient is not in a condition to undergo a definitive repair and/or abdominal wall closure, due to mandatory conditions requiring an open abdomen, the intervention should be abbreviated due to suboptimal local conditions for healing and global susceptibility to spiraling organ failure [67]. Such mandatory conditions include physical inability to close the abdominal fascia without tension, a decision to leave intra-abdominal packing, or a decision to leave blind bowel loops to expedite the procedure. Committing a patient to an open abdomen however has significant risks including the most feared enteroatmospheric fistula which has been reported to be more common in emergency general surgery patients than trauma patients. “Source control” of intra-abdominal contamination remains a discretionary reason to leave the abdomen open, recognizing that “inability to achieve source control” is a frequently quoted but poorly objectified concept in emergency general surgery. Although upper gastrointestinal perforations are often less catastrophic than lower gastrointestinal contaminations, when the patient responded with immunological activation and systemic sepsis, they are suffering from severe complicated intra-abdominal sepsis. If these conditions are met, then we suggest participation and potential enrollment in the COOL Trial [68–70] Closed or Open after Laparotomy (COOL) study (https://clinicaltrials.gov/ct2/show/NCT03163095) to help provide better guidance for clinicians in the future treating such challenging patients. In general, anastomoses should be avoided in the presence of hypotension or hemodynamic instability, especially if the patient requires vasopressors. After copious abdominal irrigation, a temporary abdominal closure device can be placed if there are mandatory factors dictating an OA or if the patient is randomized to this therapy in the COOL trial. The patient can then be resuscitated appropriately in the ICU. The surgeon can return to the OR for re-exploration, restoration of continuity and closure of the abdomen once the patient is hemodynamically stable. We refer you to the WSES guidelines on Open Abdomen management for further information [67].

Antimicrobial therapy

Should antibiotic therapy be prescribed and should anti-fungal therapy be administrated empirically in patients with perforated peptic ulcer?

In patients with perforated peptic ulcer, we recommend the administration broad-spectrum antibiotics (strong recommendation based on low-quality evidences, 1C)

We recommend the collection of samples for microbiological analysis for both bacteria and fungi in all patients undergoing surgery with subsequent antibiotic therapy adjustment (strong recommendation based on low-quality evidences, 1C)

We suggest not to administer antifungal agents as standard empiric therapy in patients with perforated peptic ulcer. Antifungal should be administrated in patients at high risk for fungal infection (e.g., immunocompromised, advanced age, comorbidities, prolonged ICU-stay, unresolved intra-abdominal infections) (weak recommendation based on low-quality evidences, 2C)

The perforation of a peptic ulcer almost invariably leads to peritonitis due to the spillage of gastroduodenal content into the peritoneal cavity; this event brings a great burden of morbidity, which ranges from 17% to 63%, and is usually represented by pulmonary and wound infections [66]. Bacteria involved in peritoneal sepsis vary according to the etiology of the peritonitis, including the site of perforation. They are usually represented by gram-positive, gram-negative as well as anaerobic species [71]. Samples of peritoneal fluid should be collected in perforated patients because fungal infections after perforation are common and are associated with longer hospital stay, higher rate of surgical site infections (SSI), and increased mortality, as reported in a prospective study by Shan and coworkers [72]. In the same way, Prakash and coworkers [73] demonstrated in a prospective study on 84 patients undergoing surgery for perforation peritonitis that mortality was higher in patients having positive peritoneal fluid cultures (p < 0.001) compared with those with negative cultures, and in those subjects having mixed bacterial and fungal positive cultures compared with those with isolated bacterial cultures (p < 0.001).

Notwithstanding positive peritoneal fungal culture is a significant risk factor for adverse outcome in patients with PPU [72, 73], the addition of an antifungal therapy to a broad-spectrum antibiotic therapy is still a matter of...
debate [74]. While antifungal therapy is recommended for hospital-acquired infections and in patients critically ill or severely immunocompromised [75], in case of community-acquired fungal infection, it has been suggested that antifungal therapy should be reserved for only clinically severe cases [76].

In a retrospective analysis of 133 patients admitted to the emergency department for abdominal pain due peptic perforation, Li and coworkers [74] demonstrated that there was not a statistically significant difference in survival rate between patients who received antifungal therapy and those who did not and that, on a multivariate analysis, only shock on admission and an APACHE score higher than 20 were independent risk factors for a poor outcome. According to this evidence, antifungal therapy does not benefit patients suffering from PPU peritonitis with *Candida* spp. isolated from peritoneal fluid cultures in general, and antifungal therapy should be reserved for patients who are critically ill and/or severely immunocompromised.

**In patients with perforated peptic ulcer, which antimicrobial regimen should be used and what is its correct duration?**

**In patients with perforated peptic ulcer, we recommend to start as soon as possible an empiric broad-spectrum antibiotic regimen against a mixture of Gram-negative, Gram-positive, and anaerobic bacteria, possibly after peritoneal fluid has been collected (Strong recommendation based on low-quality evidences, 1C).**

**In patients with perforated peptic ulcer, we suggest a short-course (3–5 days or until inflammatory markers normalize) antibiotic therapy (weak recommendation based on low-quality evidences, 2C).**

Perforated peptic ulcer peritonitis is by definition poly-microbial. Gram-negative and Gram-positive as well as anaerobic bacteria and yeasts can be isolated from peritoneal fluid cultures. Antimicrobial therapy, together with adequate source control, plays a pivotal role in the management of patients with peritonitis, especially in those who are immunocompromised. As stated in a previous published paper [71], an empiric broad-spectrum antimicrobial therapy should be started as soon as possible, and possibly after peritoneal fluid sample collection, irrespective of the presence of severe sepsis or septic shock. In these patients, a de-escalation approach is warranted, to avoid the onset of microbial resistances and to promptly treat eventual sepsis. The empiric antimicrobial regimen should be single or combined, according to the range requirements of antimicrobial coverage and the risk factors for major resistance patterns [76].

Modification of the drug regimen becomes possible when cultures are available, and clinical status can be better assessed. If inflammatory markers do not improve, it is mandatory to rule out other extra-abdominal sources of infections or different pathogens [71]. As widely accepted [71], a beta-lactam/beta-lactamase inhibitor can be used as first-line therapy in case of intra-abdominal infections, due to its vigorous in vitro activity against gram-positive, gram-negative, and anaerobic bacteria [77]. The principles of empiric antibiotic treatment should be defined according to the most frequently isolated bacteria, always taking into consideration the local trend of antibiotic resistance. In this era of prevalent drug-resistant microorganisms, the threat of resistance is a source of major concern that cannot be ignored. In the past 20 years, incidence of healthcare-associated IAIs caused by MDROs has risen dramatically [78], probably in correlation with escalating levels of antibiotic exposure and increasing frequency of patients with one or more predisposing conditions, including elevated severity of illness, advanced age, degree of organ dysfunction, low albumin levels, poor nutritional status, immunosuppression, presence of malignancy, and other comorbidities. The first step in determining potential resistance patterns of a given infection is by establishing whether the infection is community-acquired or healthcare-associated (nosocomial). The spectrum of microorganisms involved in nosocomial infections is significantly broader than in community-acquired infections.

Quinolone resistance, prevalence of ESBL-producing bacteria, prevalence and mechanisms of carbapenem resistance in the local environment, and the place of recent traveling should be always taken into account when an antibiotic therapy is administered empirically. Generally, the most important factors in predicting the presence of resistant pathogens in intra-abdominal infections are acquisition in a healthcare setting (particularly if the patient becomes infected in the ICU or has been hospitalized for more than 1 week), corticosteroid use, organ transplantation, baseline pulmonary or hepatic disease, and previous antimicrobial therapy [78]. In patients with IAIs, when patients are not severely ill and when source control is complete, a short course (3–5 days) of postoperative therapy is suggested. In 2015, a prospective study on appropriate duration of antimicrobial therapy was published [79]: the study randomized 518 patients with IAIs and adequate source control to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4 ± 1 calendar days. In patients with intra-abdominal infections who had undergone an adequate source control procedure, the outcomes after fixed-duration antibiotic therapy (approximately 4 days) were similar to those after a longer course of antibiotics.
(approximately 8 days) that extended until after the resolution of physiological abnormalities. In this study, most patients were not severely ill.

If yeast are isolated in the peritoneal fluid culture, the antifungal regimen should be selected according to the clinical and immunological status of the patient, severity of disease, prior exposure to other antifungal therapies, and type of infection (community-acquired vs. hospital-acquired) [80]. The duration of hospital stay is a concern, because prolonged stay is associated with antifungal resistance of Candida strains [81]. Moreover, biofilm formation of fungi usually goes along with significant changes in virulence and resistance because, once embedded into biofilm, fungi become more protected against the fungicidal/fungistatic effect of drugs.

Four classes of antifungal drugs are available [82]:

1) Azoles (fluconazole, itraconazole, vorozonazole, and posaconazole), with fungistatic action against most Candida spp.;
2) Echinocandins (caspofungin, micafungin, anidulafungin), with fungicidal effect;
3) Polyenes (deoxycholate and liposomal formulations of amphotericin B), with fungicidal effect but moderate peritoneal penetration;
4) Flucytosine, only used in combination with another antifungal agent in difficult-to-treat cases, because of the high risk of resistance.

Fungistatic drugs should be used in critically ill patients at low-risk for invasive Candida infections, without prior exposure to azoles, and the therapy should be administered for 7-10 days or until definitive negative fluid cultures. In high-risk patients with or without prior exposure to azoles, echinocandins should be preferred. The duration of treatment depends on the extent of organ involvement. If candidemia is detected, the administration should be prolonged at least 14 days after the end of episode [82].

Following we report the suggested antibiotic regimens according to WSES guidelines on intra-abdominal infections.

**Community-acquired**

1) Empiric antibiotic regimens for non-critically ill patients with IAI and normal renal function:
   - Amoxicillin/clavulanate 1.2-2.2 g 6-hourly or ceftriaxone 2 g 24-hourly + metronidazole 500 mg 6-hourly or cefotaxime 2 g 8-hourly + metronidazole 500 mg 6-hourly
   - In patients with beta-lactam allergy: ciprofloxacin 400 mg 8-hourly + metronidazole 500 mg 6-hourly
   - Patients at risk for infection with community-acquired ESBL-producing Enterobacteriaceae: ertapenem 1 g 24 hourly or tigecycline 100 mg initial dose, then 50 mg 12-hourly

2) Empiric antibiotic regimens for critically ill patients with IAI and Normal renal function:
   - Piperacillin/tazobactam 4.5 g 6-hourly or cefepime 2 g 8-hourly + metronidazole 500 mg 6-hourly
   - Patients at risk for infection with community-acquired ESBL-producing Enterobacteriaceae: meropenem 1 g 8-hourly or doripenem 500 mg 8-hourly or imipenem/cilastatin 1 g 8-hourly

3) If antifungal therapy is indicated:
   - Fluconazole (LD 12 mg/kg BW-800 mg MD 6 mg/kg/day) should be given in critically ill patients, with community-acquired Candida peritonitis, no priorazole exposure, low-risk for infections with fluconazole-resistant Candida spp., as prophylaxis to prevent invasive infections
   - Echinocandin antifungals are recommended as first-line therapy for invasive infections, and candidemia in non-neutropenic critically ill patients
   - Amphotericin B (3–5 mg/day) should be considered if alternative therapy is not available or in case of intolerance to echinocandin or azoles

**Healthcare-associated**

1) Empiric antimicrobial regimens for non-critically ill patients with IAI and normal renal function:
   - Piperacillin/tazobactam 4.5 g 6-hourly
   - In patients at higher risk for infection with MDROs including recent antibiotic exposure, patient living in a nursing home or long-stay care with an indwelling catheter or postoperative infections
     - Meropenem 1 g 8-hourly +/- ampicillin 2 g 6-hourly or
     - Doripenem 500 mg 8-hourly +/- ampicillin 2 g 6-hourly or
     - Imipenem/Cilastatin 1 g 8-hourly or
   - As a carbapenem-sparing regimen piperacillin/tazobactam 4.5 g 6-hourly + tigecycline 100 mg initial dose, then 50 mg 12-hourly

2) Empiric antimicrobial regimens for critically ill patients with IAI and normal renal function:
   - Meropenem 1 g 8-hourly or
   - Doripenem 500 mg 8-hourly or
   - Imipenem/cilastatin 1 g 8-hourly +
     - Vancomycin 25–30 mg/kg loading dose then 15–20 mg/kg/dose 8-hourly or
     - Teicoplanin 12 mg/kg 12-hourly times 3 loading dose then 12 mg/kg 24-hourly

3) In patients at risk for infection with vancomycin-resistant Enterococci (VRE) including patients with...
previous enterococcal infection or colonization, immuno-compromised patients, patients with long ICU stay, or recent vancomycin exposure:

- Linezolid 600 mg 12-hourly or
- Daptomycin 6 mg/kg 24-hourly

**Bleeding peptic ulcer**

**Diagnosis**

In patients with suspected bleeding peptic ulcer, which biochemical and imaging investigations should be requested?

In patients with suspected bleeding peptic ulcer, we recommend blood-typing, determinations of hemoglobin, hematocrit and electrolytes, and coagulation assessment (strong recommendation based on very low-quality evidences, 1D).

In patients with suspected bleeding peptic ulcer, when endoscopy is not available, we suggest performing contrast-enhanced CT scan (weak recommendation based on very low-quality evidences, 2D).

Bleeding peptic ulcer is still the primary cause of non-variceal upper gastrointestinal bleeding and hypovolemic shock or its consequences is a major cause of mortality in acute upper gastrointestinal bleeding [1, 83]. In the acute setting, with the suspicion of bleeding peptic ulcer, blood tests that include blood-typing and cross-matching with determinations of hemoglobin, hematocrit, electrolytes, and coagulation assessment should be performed in all patients. Alteration of coagulation with INR greater than 1.5 is associated with an increased risk of mortality [84].

Data are limited in the literature on the use of CT-scan in the evaluation of gastrointestinal bleeding. Given the assumption that gastroscopy is the first diagnostic step, in patients where it is negative or not feasible, CT-scan may be a valuable tool to detect the site and the degree of the bleeding. Otherwise, CT angiography is the first-line investigation of choice for undifferentiated major gastrointestinal hemorrhage (being particularly useful for the localization of small and large intestinal acute hemorrhage). There are increasing data to suggest that CT-scan should be the “next step” investigative procedure in cases of active GI hemorrhage [85, 86].

In patients with suspected bleeding peptic ulcer, what is the diagnostic role of endoscopy?

In patients with suspected bleeding peptic ulcer, we recommend performing endoscopy as soon as possible, especially in high-risk patients (Strong recommendation based on low-quality evidences, 1C).

Gastroscopy must take place as soon as possible. Many studies, including a meta-analysis of randomized controlled trials [87], have shown the role of gastroscopy in reducing rebleeding, need for surgery, and mortality. Early endoscopy done within 24 h provides both an effective therapy of the bleeding and prognostic information based on endoscopic stigmata [88, 89].

**In patients with bleeding peptic ulcer, are the endoscopic findings useful to determine the risk for rebleeding and how do they affect the clinical management?**

We suggest guiding management decisions according to stigmata of recent hemorrhage during endoscopy because they can predict the risk of further bleeding (strong recommendation based on low-quality evidences, 1C).

The gastroscopy findings can be classified using the modified Forrest classification. With the identification of lesions with high-risk stigmata, it is possible to stratify the risk of rebleeding, the need for intervention, and mortality [89, 90]. Furthermore, gastroscopy is essential in identifying patients with a low risk that may be discharged early [87, 88]. Numerous scores have been tested to predict the need for surgery and gastroscopy, the Glasgow-Blatchford Score (GBS), the Rockall score, and the AIMS65 being the most widely evaluated and adopted. Risk stratification should identify high-risk patients for early intervention and reduce the duration of hospital stay for low-risk patients [91, 92].

**Resuscitation**

In patients with bleeding peptic ulcer, which parameters should be evaluated at ED referral and which criteria should be adopted to define an unstable patient?

We recommend a rapid and careful surgical/medical evaluation of bleeding peptic ulcer disease patients to prevent further bleeding and to reduce mortality (strong recommendation based on very low-quality evidences, 1D).

We recommend evaluating several elements (symptoms, signs, and laboratory findings) to assess the stability/instability of patients with bleeding peptic ulcer at ED referral (strong recommendation based on low quality evidences, 1C).

In patients with bleeding peptic ulcer, we suggest evaluating patients according to Rockall and Glasgow-Blatchford scoring systems to assess the severity of the disease and to guide therapy (weak recommendation based on low-quality evidences, 1C).

Bleeding peptic ulcer disease is a clinical emergency requiring a rapid surgical/medical evaluation to assess the stability of the clinical picture; the approach is
similar to the bleeding trauma patient [93]. In this regard, we suggest referring to the last edition of the European guideline on management of major bleeding and coagulopathy following trauma [94]. The parameters that should be assessed at ER referral are the same as reported in the American College of Surgeons Advanced Trauma Life Support (ATLS) (American College of Surgeons Committee on Trauma. ATLS® Student Manual 10th Edition; 2018) classification of blood loss (heart rate, blood pressure, pulse pressure, respiratory rate, urine output, Glasgow Coma Scale score, and base deficit). Moreover, it is very important to take an accurate medical history [93] especially regarding:

- Drugs and diseases that may affect the coagulation status (i.e., antiplatelets, anticoagulants, hepatic failure)
- Cardiac (i.e., coronary artery disease) and pulmonary diseases that may make patients more susceptible to adverse effects of anemia
- Neurological diseases (i.e., dementia) that may predispose patients to pulmonary aspiration of gastric contents.

Several scoring systems are available for the evaluation of patients with upper gastrointestinal bleeding. The Rockall score [95] can be utilized to identify patients at risk of adverse outcomes where the Glasgow-Blatchford bleeding score [96] identifies patients needing interventions such as blood transfusions or endoscopy.

**In patients with bleeding peptic ulcer, which are the appropriate targets for resuscitation (hemoglobin level, blood pressure/heart rate, lactates level, others)?**

We recommend several resuscitation targets, similar to those of damage control resuscitation in the bleeding trauma patient (weak recommendation based on low-quality evidences, 1C).

**In patients with bleeding peptic ulcer, we recommend to maintain an Hb level of at least > 7 g/dl during the resuscitation phase (strong recommendation based on moderate-quality evidences, 1B).**

Early resuscitation of patients with upper gastrointestinal bleeding is of paramount importance to reduce mortality; this must proceed simultaneously with endoscopic and surgical procedures [97]. A rapid ABC (airway, breathing, and circulation) evaluation should be done immediately. Appropriate targets for resuscitation in bleeding peptic ulcer patients can be considered the same used in bleeding trauma patients (systolic blood pressure of 90–100 mmHg until major bleeding has been stopped; normalization of lactate and base deficit; hemoglobin 7–9 g/dl; correction/prevention of coagulopathy); for this reason, we refer to the abovementioned guideline [94]. Regarding hemoglobin level, a randomized controlled trial comparing the efficacy and safety of a restrictive transfusion strategy (transfusion with an Hb > 7 g/dl) with those of a liberal transfusion strategy (transfusion with an Hb > 9 g/dl) in severe acute gastrointestinal bleeding has been performed [98]. The restrictive strategy, compared with the liberal strategy, has been significantly associated with a better outcome.

**Non-operative management—endoscopic treatment**

**In patients with bleeding peptic ulcer, which are the indications for non-operative management?**

In patients with bleeding peptic ulcer, we recommend non-operative management as the first line of management after endoscopy (strong recommendation based on low-quality evidences, 1C).

Non-operative management of bleeding peptic ulcer incorporates principles of ABCDE [99]:

- Airway control
- Breathing—ventilation and oxygenation
- Circulation—fluid resuscitation and control of bleeding
- Drugs—pharmacotherapy with PPIs, prokinetics, etc.
- Endoscopy (diagnostic and therapeutic) or embolization (therapeutic)

A meta-analysis from Barkun et al. [100] that included forty-one randomized trials showed that all endoscopic therapies decreased rebleeding versus pharmacotherapy alone. Endoscopy is indicated to establish diagnosis and institute therapy for bleeding peptic ulcer [101]. In acutely bleeding ulcers, endoscopy is a part of resuscitation.

**In patients with bleeding peptic ulcer, which are the indications for endoscopic treatment?**

In patients with bleeding peptic ulcer, we recommend endoscopic treatment to achieve hemostasis and reduce re-bleeding, the need for surgery, and mortality (strong recommendation based on low-quality evidences, 1C).

We suggest stratifying patients based on the Blatchford score and adopting a risk-stratified management (weak recommendation based on very low-quality evidences, 2D):

- In the very low-risk group, we suggest outpatient endoscopy (weak recommendation based on low-quality evidences, 2C)
- In the low-risk group, we recommend early inpatient endoscopy (≤ 24 h of admission) (strong recommendation based on low-quality evidences, 1C).
- In the high-risk group, we recommend urgent inpatient endoscopy (≤ 12 h of admission) (strong recommendation based on low-quality evidences, 1C).
In patients with spurting ulcer (Forrest 1a), oozing ulcer (Forrest 1b), and ulcer with non-bleeding visible vessel (Forrest 2a), endoscopic hemostasis is recommended (strong recommendation based on low-quality evidences, 1C).

In patients with bleeding peptic ulcer, we suggest dual modality for endoscopic hemostasis (weak recommendation based on moderate-quality evidences, 2B).

In patients with bleeding peptic ulcer, we suggest considering Doppler probe–guided endoscopic hemostasis if expertise is available (weak recommendation based on very low-quality evidences, 2D).

Endoscopy not only establishes the diagnosis but also treats the bleeding. WSES advocates patients’ risk determination by using Blatchford score, Forrest classification, and clinical judgment. Three levels of risk stratification are proposed:

- Very low risk—safe for outpatient management, low risk of death
- Low risk—need for admission and early endoscopy
- High risk—need for resuscitation and urgent endoscopy

Risk stratification is based on many risk prediction models and Blatchford score is one of the most validated tools. In an international multicenter prospective study including 3012 patients, Stanley et al. [102] has shown that Blatchford score of 1 or less (very low-risk group) had a sensitivity of 98.6%, specificity of 34.6%, positive predictive value of 96.6%, and a negative predictive value of 56.0% for non-intervention and survival both as the combined endpoint. They also reported that a threshold Blatchford score of 7 or more (high-risk group) was best at predicting endoscopic treatment, with a sensitivity of 80.4%, specificity of 57.4%, positive predictive value of 31.3%, and negative predictive value of 92.4%. Endoscopy reassures a safe and early discharge in low-risk patients and assists therapy in high-risk patients. While the timing of endoscopy is determined by local protocols and resources, the sooner the better, WSES advocates to perform endoscopy at the earliest available opportunity regardless of the risk profile and the only limitation would be resources and expertise. Endoscopy by the “clock” is mere guidance, and if endoscopy could be done earlier, then a clinician should do it. Endoscopy is a part of the resuscitative strategy and blood transfusion should not replace early hemostasis. Dual modality of endoscopic hemostasis is advocated in preference to single modality. Marmo et al. has conducted a meta-analysis [103] including 20 randomized controlled trials and 2472 patients comparing dual therapy versus monotherapy in endoscopic treatment of high-risk bleeding ulcers and concluded that dual endoscopic therapy was superior to epinephrine injection alone in improving outcomes of patients with high-risk bleeding ulcers. In a Cochrane review including 19 randomized studies and 2033 patients, Vergara et al. [104] has shown that additional endoscopic treatment after epinephrine injection reduces further bleeding and the need for surgery in patients with high-risk bleeding peptic ulcer; however, they cannot conclude that a particular form of dual-modality treatment is equal or superior to another. Shi et al. have performed a network meta-analysis on dual therapy choices [105] and shown that the addition of mechanical therapy after epinephrine injection significantly reduced the probability of rebleeding (OR 0.19, 95% CI 0.07–0.52) and surgery (OR 0.10, 95% CI 0.01–0.50). Epinephrine with thermal therapy was shown to reduce the rebleeding rate (OR 0.30, 95% CI 0.10–0.91) but not the need for surgical intervention (OR 0.47, 95% CI 0.16–1.20). Hence, it appears that mechanical therapy along with epinephrine injection is adequate. In patients with adherent clot (Forrest 2b), WSES advocates non-aggressive clot irrigation-flushing attempts rather than mechanical dislodgment. The Asia-Pacific Working Group consensus advocates vigorous target irrigation for at least 5 min and dual-modality hemostasis for patients with adherent clots [106]. We advocate a cautious approach for dislodging the adherent clots. If expertise is available, a vigorous approach could be adopted [107]. The individual endoscopist should be at the liberty to make decisions and we propose individual judgment until further evidence is available to support that clot dislodgment improves outcomes. In the event of bleeding, therapy is strongly advocated. Newer modalities such as over the scope clips (OTSC), hemospray, EUS-guided ultrasound angiography, RFA, Endoclot, endoscopic band ligation, cryotherapy, Ankaferd blood stopper, and endoscopic suturing devices are available. Their role needs to be defined. There are six studies that have investigated the role of over the scope clips either as first-line or as second-line therapy for refractory bleeding [108–113]. Doppler probe–guided lesion assessment is more accurate than endoscopic scoring of predicting rebleeding risk. In a prospective cohort study including 163 patients, Jensen et al. showed spurting (Forrest 1a), visible vessel (Forrest 2a), and adherent clot (Forrest 2b) have a higher Doppler flow compared with oozing (Forrest 1b); Doppler assessment improved risk stratification [114]. It is important to note that rebleeding risk prediction is superior to Forrest classification system, i.e., Forrest 1b has low risk of rebleeding compared with Forrest 2a and Forrest 2b lesions. Doppler probe–guided lesion management is shown to reduce rebleeding and further intervention. In a single blinded randomized controlled
study including 148 patients with 125 ulcers, Jensen et al. has shown that Doppler probe–guided endoscopic hemostasis significantly reduced 30-day rates of rebleeding compared with standard, visually guided hemostasis with the number needed to treat of 7 [115].

In patients with bleeding peptic ulcer, what is the appropriate pharmacological regimen (erythromycin, PPI, terlipressin, others)?

In patients with bleeding peptic ulcer, we suggest administering pre-endoscopy erythromycin (weak recommendation based on moderate-quality evidences, 2B).

In patients with bleeding peptic ulcer, we suggest starting PPI therapy as soon as possible (weak recommendation based on moderate-quality evidences, 2B).

In patients with bleeding peptic ulcer, after successful endoscopic hemostasis, we suggest administration of high-dose PPI as continuous infusion for the first 72 h (weak recommendation based on moderate-quality evidences, 2B).

In patients with bleeding peptic ulcer, we recommend PPI for 6–8 weeks following endoscopic treatment. Long-term PPI is not recommended unless the patient has ongoing NSAID use (strong recommendation based on moderate-quality evidences, 1B).

The role of acid suppression in the treatment of peptic ulcer and its complications is well known [116], but the dosage and the duration of PPI administration for the treatment of bleeding peptic ulcer are still a matter of debate. Multiple studies highlighted that high-dose regimens of PPI [117] reduce rebleeding, surgical intervention, and mortality following endoscopic hemostasis. In a randomized placebo-controlled trial of 767 patients with peptic ulcer bleeding treated with endoscopic therapy because of high-risk stigmata, high-dose intravenous PPIs (80 mg of esomeprazole bolus plus 8 mg/h of continuous infusion for 72 h) significantly reduced rebleeding (5.9% vs. 10.3%, p = 0.03) and the need for endoscopic retreatment [118]. Similar results were found by meta-analysis; high-dose intravenous PPIs after endoscopic therapy significantly reduced rebleeding, need for surgery, and mortality compared with placebo/no therapy [119]. On the other hand, a Cochrane review [120] focusing on this topic and including twenty-two RCTs found insufficient evidence to conclude superiority, inferiority, or equivalence of high-dose PPI treatment over lower doses in peptic ulcer bleeding. Another systematic review from the Cochrane Collaboration [121] included six RCTs comprising 2223 patients and showed that PPI treatment initiated before endoscopy for upper gastrointestinal bleeding might reduce the proportion of patients with stigmata of recent bleeding at index endoscopy and significantly reduces the requirement for endoscopic therapy during index endoscopy. However, this study found no evidence that PPI treatment affects clinically important outcomes, namely mortality, rebleeding, or need for surgery. In the light of the above, the administration of high-dose PPI, starting prior to endoscopy and continuing for the first 72 h, seems reasonable and could be suggested, even though further studies are needed to give a strong recommendation. However, the use of proton-pump inhibitors should not replace urgent endoscopy in patients with active bleeding.

A prokinetic drug given before endoscopy helps to empty stomach contents and improves viewing at endoscopy. Only five randomized trials and their pooled analyses have been published: three with the use of erythromycin and two with metoclopramide [122]. Pre-endoscopy erythromycin has been extensively studied and shown to enhance the visualization as well as reduce the need for second endoscopy [123, 124]. However, such practice has not shown to reduce the need for surgical intervention or impact mortality [125].

After initial hemostasis, the risk of rebleeding must be minimized by adjunct therapies. In patients who have PPU complicated by bleeding, there is a 33% risk of rebleeding in 1–2 years. Furthermore, there is a 40–50% rebleeding risk over the subsequent 10 years following the initial episode of bleeding [126]. PPIs are recommended for 6–8 weeks following endoscopic treatment of peptic ulcer bleeding to allow mucosal healing [127]. Once mucosal healing has been achieved, how long PPIs should be continued is still controversial. Randomized prospective trials have demonstrated a benefit to long-term acid-suppression therapy in two settings: chronic NSAID users and H. pylori-infected patients [128]. Testing for H. pylori is recommended in all patients with BPU. This should be followed by eradication therapy for those who are H. pylori positive, with subsequent assessment of the effect of this therapy, and renewed treatment in those in whom eradication fails.

In patients with recurrent bleeding from peptic ulcer, what is the role of non-operative management?

In patients with recurrent bleeding from peptic ulcer, we recommend endoscopy as a first-line treatment (strong recommendation based on low-quality evidences, 1C).

In patients with recurrent bleeding, we suggest transcatheter angioembolization as an alternative option where resources are available (weak recommendation based on very low-quality evidences, 2D).

Emergency endoscopy is the first-line management for rebleeding peptic ulcer [129]. Such endoscopy must be done at the earliest available opportunity. In patients who are hemodynamically stable, angioembolization of the bleeding vessel is an option. However, this should be carefully balanced for its inherent risks of patient transfer, contrast nephropathy, pancreatitis, or cholecystitis.
risk due to embolization material and risks associated with vascular access.

**Angiography, embolization**  
**In patients with bleeding peptic ulcer, which are the indications for angiography?**

In patients with bleeding peptic ulcer, we suggest considering angiography for diagnostic purposes as a second-line investigation after a negative endoscopy (weak recommendation based on low-quality evidences, 2C).

No recommendation can be made regarding the role of provocation angiography.

Angiography may assist both the diagnosis and the treatment of hemorrhage associated with peptic ulcer disease. However, endoscopy remains the first-line investigation of choice for an undifferentiated upper gastrointestinal hemorrhage [130]. Similarly, endoscopy is the first-line diagnostic modality for patients with suspected upper gastrointestinal hemorrhage from ulcer disease [130].

Angiography for diagnostic purposes is a second-line investigation and angiography before endoscopy results in unacceptable rates of negative investigations and is not warranted given the invasive nature of an angiogram. Angiography is useful for the confirmation and localization of the point of hemorrhage and allows treatment by embolization. On occasion, provocation angiography with the use of anticoagulants may be indicated. An inter-specialty consensus should guide this investigation on a case by case basis. Only case reports, case series, and expert opinion are available to guide this decision-making.

**In patients with bleeding peptic ulcer, which are the indications for angioembolization?**

In hemodynamically stable bleeding peptic ulcer patients, where endoscopic hemostasis fails twice or is not possible/feasible, we suggest angiography with angioembolization where technical skills and equipment are available (weak recommendation based on very low-quality evidences, 2D).

Endoscopy is the established first-line therapy for the management of hemorrhage associated with peptic ulcer disease. It is appropriate (high-level evidence), to also conduct a second endoscopic examination with therapeutic intent, in cases of recurrent hemorrhage. However, where this also fails, surgery has been traditionally indicated. These operations are reported to be associated with mortality rates as high as 40% [129, 131]. Because of this high postoperative mortality, other strategies have been sought and angioembolization has become increasingly described during the past two decades.

High-risk surgical patients have been suggested and recommended as the ideal candidates for angioembolization [130, 132]. However, no specific data exist investigating or defining the definition of “high risk.” Interdisciplinary consensus (surgery, gastroenterology, intensive care, anesthesia) is required to guide this decision-making. Low-risk surgical patients are likely to benefit from an operative strategy due to the likely reduced mortality in this group. No specific studies exist to validate this claim.

Furthermore, according to the physiology behind wound repair, it is possible that angioembolization could complicate a subsequent surgical intervention because of the reduction in the blood flow of the operative field, but no specific data exists to validate this claim.

**Should embolization be considered for unstable patients with bleeding peptic ulcer?**

We suggest against a routinely use of angioembolization unstable patients. Angioembolization in unstable patients could be considered only in selected cases and in selected facilities (weak recommendation based on very low-quality evidences, 2D).

There are no specific data to address the relative safety of angioembolization compared with surgery in hemodynamically unstable patients. Variable definitions of hemodynamic stability between studies further complicate meaningful recommendations in this field. Successful reports of angioembolization in patients with hemorrhagic shock are described. A recent retrospective case series describing super-selective angioembolization in 51 patients with active gastrointestinal hemorrhage (with 57% of these upper gastrointestinal in nature), demonstrated the possibility of this approach in patients with physiological shock (defined in this study as a systolic blood pressure of < 90 mmHg) [133].

The appropriateness of angioembolization in hemodynamically unstable patients depends on a number of factors, including the timely availability and skills of the angioembolization service, the quality of the initial and ongoing resuscitation, the quality of the peri-procedural and post-procedural intensive care, and patient variables. Furthermore, the presence of a hybrid OR or strict proximity of OR and the angioembolization facility is mandatory for the angiographic approach to unstable patients. A coordinated, interdisciplinary approach (surgery, interventional radiology, gastroenterology, intensive care, and anesthesia) is likely to benefit these critically ill patients, although there are no specific data to validate this hypothesis.

**In patients with recurrent bleeding peptic ulcer, which are the indications for angioembolization?**

In patients with rebleeding peptic ulcer, we suggest angioembolization as a feasible option (weak recommendation based on low-quality evidences, 2C).

For recurrent bleeding (defined as re-bleeding after 2 endoscopic therapeutic attempts), angioembolization and surgical options should be considered. Multiple reports and case series of successful angioembolization
of hemorrhage from gastroduodenal ulcer disease are reported [134]. However, no high-level studies comparing the outcomes for angioembolization with surgery exist. One prospective and multiple retrospective cohort studies comparing outcomes between patients undergoing angioembolization with those undergoing surgery for rebleeding after failed endoscopic control are available. These studies were summarized in three meta-analysis [135–137]. Kyaw et al. summarized 6 retrospective cohort studies: surgery was found to significantly reduce the likelihood of further (post-intervention) hemorrhage, and was associated with a trend towards a reduced need for further intervention. However, surgery was also associated with a trend to increased mortality. Beggs et al. included 9 cohort studies (8 retrospective and 1 prospective), and similarly concluded that surgery was associated with a significantly lower risk of rebleeding, and only a marginal trend towards increased mortality. Subsequent to these first two meta-analyses, a case-control study comparing angioembolization with surgery [138] reported a trend to higher rebleeding rates following angioembolization, and a trend towards higher mortality after surgery was seen. A significantly lower rate of post-procedural complications was reported in the angioembolization cohort. The latest meta-analysis [137] found similar results, but interestingly found a slight drift toward a lower mortality for the angioembolization group.

**In patients with bleeding peptic ulcer who underwent angioembolization, which are the most appropriate embolization techniques and materials?**

**Varied techniques and materials exist for the use in the embolization of bleeding duodenal ulcer disease. A tailored approach, guided by the multidisciplinary team, incorporating patient, pathology, and environmental factors is suggested (weak recommendation based on low-quality evidences, 2C).**

Successful embolization of gastric and duodenal arteries is complicated by the rich collateral blood supply. Several technical points are raised in various case reports, series, and review articles in this field. There are no high-level articles to guide these technical considerations. Pre-procedural endoscopic localization of the point of hemorrhage could assist guidance of the selective and super-selective angiography and the angiogram can be further guided by the placement of an endoscopic clip at the ulcer if this has been identified. Diagnostic angiography usually commences with a selective coeliac axis and superior mesenteric artery catheterization and angiogram. Where no extravasation is seen, a super-selective approach normally follows. Imaging from both aspects of the bleeding point is ideally obtained (both sides need to be approached).

**In patients with bleeding peptic ulcer and non-evident bleeding during angiography, is there a role for prophylactic embolization?**

**No recommendation can be made on the role of prophylactic embolization.**

Prophylactic embolization may be considered in two situations

- Empirically, at the time of a negative angiogram:
  Several authors have suggested a role for blind embolization for upper gastrointestinal hemorrhage, noting that these patients had similar outcomes to patients who underwent embolization after the demonstration of a point of hemorrhage [134, 139, 140]. A variation on this uses the endoscopic information to guide the area for embolization [141, 142]. However, these approaches are based on retrospective cohorts. There are insufficient high-level data to draw firm conclusions.

- As a planned intervention, in association with endoscopic control: The addition of prophylactic embolization in addition to endoscopic hemostasis has been investigated by several authors, including most recently with two randomized controlled trials [143, 144]. Laursen et al. demonstrated a trend toward improved outcomes in patients who underwent additional prophylactic embolization. However, the second RCT by Lau et al. failed to confirm this observation. This approach was also supported by a retrospective series by Mille et al. [145].

At present, the evidences available in the literature appear to be insufficient to routinely recommend this approach.

**Surgery**

**In patients with bleeding peptic ulcer, which are the indications for surgical treatment and which is the appropriate timing for surgery?**

**In patients with bleeding peptic ulcer, we suggest surgical hemostasis (or angiographic embolization if immediately available and with appropriate skills) after failure of repeated endoscopy. In patients with hypotension and/or hemodynamic instability and/or ulcer larger than 2 cm at first endoscopy, we suggest surgical intervention without repeated endoscopy (strong recommendation based on very low-quality evidences, 1D).**

A renowned RCT conducted in 1999 [129] compared endoscopic retreatment with surgery for peptic ulcer rebleeding after initial endoscopy. Over a 40-month period, 92 patients with recurrent bleeding were enrolled: 48 patients were randomly assigned to undergo immediate endoscopic retreatment and 44 were assigned
to undergo surgery. Of the 48 patients who were assigned to endoscopic retreatment, 35 had long-term control of bleeding. Thirteen underwent salvage surgery, 11 because retreatment failed, and 2 because of perforations resulting from thermocoagulation. Five patients in the endoscopy group died within 30 days, as compared with eight patients in the surgery group ($p = 0.37$). Seven patients in the endoscopy group had complications, as compared with 16 in the surgery group ($p = 0.03$). Duration of hospitalization, need for ICU admission, ICU length of stay, and the number of blood transfusions were similar in the two groups. In multivariate analysis, hypotension at randomization ($p = 0.01$) and an ulcer size of at least 2 cm ($p = 0.03$) were independent factors predictive of the failure of endoscopic retreatment. According to these data, repeated endoscopy is indicated for stable patients with ulcers smaller than 2 cm in diameter, while for patients with a larger ulcer and heavier bleeding, surgery may be taken into account as a first-line therapy.

No evidence is available regarding the impact on clinical outcome of time before surgery for bleeding peptic ulcer. We suggest immediate surgery for unstable patients with bleeding peptic ulcer refractory to endoscopy/angioembolization.

In patients with bleeding peptic ulcer, what is the most appropriate surgical approach (open vs laparoscopy) and what are the most appropriate surgical procedures?

In patients with refractory bleeding peptic ulcer, we suggest surgical intervention with open surgery (weak recommendation based on very low-quality evidences, 2D).

In patients operated for bleeding peptic ulcer, we suggest intra-operative endoscopy to facilitate the localization of the bleeding site (weak recommendation based on very low-quality evidences, 2D).

We suggest choosing the surgical procedure according to the location and extension of the ulcer and the characteristics of the bleeding vessel (weak recommendation based on low-quality evidences, 2C).

An immediate or delayed biopsy is recommended (weak recommendation based on low-quality evidences, 2C).

A refractory bleeding peptic ulcer is defined as an ulcer still bleeding after repeated endoscopy/angioembolization. Open surgery is recommended when endoscopic treatments have failed and there is evidence of ongoing bleeding, plus or minus hemodynamic instability. The choice of the appropriate surgical procedure for bleeding peptic ulcer should be made on the basis of the location and extension of the ulcer and the characteristics of the bleeding vessel. Surgical approach involves ulcer oversew or resection. Bleeding gastric ulcers should be resected or at least biopsied for the possibility of neoplasms. Conversely, most duodenal ulcers requiring surgery for persistent bleeding are usually large and posterior lesions, and the bleeding is often from the gastro-duodenal artery. A recent prospective cohort study conducted in Denmark [146] compared the outcomes of duodenal and gastric bleeding peptic ulcers and found a significantly higher 90-day mortality and re-operation rate for the duodenal location, confirming the greater complexity of surgical management of this ulcer. Via duodenotomy, the bleeding vessel can be seen on the floor of the ulcer and can be rapidly oversewn. It is critical to perform triple-loop suturing of bleeding of the GDA due to the collateral blood supply to the transverse pancreatic arteries. The surgeon may not know pre-operatively where the bleeding originates and intraoperative endoscopic guidance may be helpful. For patients with intractable ulcer bleeding, Schroeder et al. [147] from the analysis of a large database (ACS-NSQIP) have found that the surgical procedure of vagotomy/drainage is associated with significantly lower mortality than simply simple local ulcer oversew. They further suggest that vagotomy/drainage is preferred to local procedures alone for the surgical management of patients with bleeding peptic ulcer disease requiring emergency operation for intractable bleeding ulcers.

In patients with bleeding peptic ulcer, what is the role of damage control surgery?

We suggest considering damage control surgery for patients with hemorrhagic shock and signs of severe physiological derangement, in order to quickly resolve the bleeding and allow a prompt ICU admission (weak recommendation based on very low-quality evidences, 2D).

Indications for damage control surgery in bleeding peptic ulcer are similar to those for perforated peptic ulcer and are reported in the WSES guidelines on Open Abdomen management in non-trauma patients [67].

Antimicrobial therapy

In patients with bleeding peptic ulcer, which are the indications for antimicrobial therapy and for Helicobacter pylori testing?

In patients with bleeding peptic ulcer, empirical antimicrobial therapy is not recommended (strong recommendation based on low-quality evidences, 1C).

We recommend performing Helicobacter pylori testing in all patients with bleeding peptic ulcer (strong recommendation based on low-quality evidences, 1C).

Bleeding peptic ulcer accounts for 75% of patients admitted to ED for peptic ulcer disease [148] and has different etiologies (ulcerogenic medications such as acetylsalicylic acid and NSAIDs, $H. pylori$ infection, etc). $H. pylori$ infection has a variable prevalence of 20–50% among patients with bleeding peptic ulcer in various countries, but its eradication is associated with a significant reduction in ulcer recurrence rate and rebleeding.
In a systematic review, Gisbert et al. showed a 26% rebleeding rate among patients with *H. pylori* infection–associated bleeding ulcers who did not receive eradication therapy [150]. Conflicting results are reported about appropriate timing to start eradication therapy. Empirical eradication therapy immediately after re-feeding has been suggested as the most cost-effective strategy [151], but its real effectiveness can vary by regional prevalence of the bacteria. Therefore, confirming the result of *H. pylori* test and initiating eradication therapy in *H. pylori*-positive patients prior to discharge would appear to be a more appropriate strategy than to apply empirical therapy to all patients with BPU [66, 152].

For this reason, all patients having BPU should undergo *H. pylori* testing. Different tests are available to confirm *H. pylori* infection. The urea breath test (UBT) and stool antigen testing are acceptable non-invasive tests with a sensitivity of 88–95% for UBT and 94% for stool antigen testing, respectively. Specificity is 95–100% for UBT and 92% for stool antigen testing, respectively [151]. In cases of bleeding peptic ulcer, *H. pylori* testing on endoscopic tissue biopsy may be available [151].

**In patients with bleeding peptic ulcer and positive tests for HP infection, which are the therapeutic options?**

In *H. pylori*-positive BPU patients, eradication therapy is recommended to avoid recurrent bleeding (strong recommendation based on low-quality evidences, 1C).

In patients with *HP* positive tests, standard triple therapy (*amoxicillin, clarithromycin, and PPI*) regimen is recommended as first-line therapy if low clarithromycin resistance is present (strong recommendation based on moderate-quality evidences, 1B).

10 days of sequential therapy with four drugs (*amoxicillin, clarithromycin, metronidazole, and PPI*) is recommended in selected cases, if compliance to the scheduled regimen can be maintained, and if clarithromycin high resistance is detected (strong recommendation based on low-quality evidences, 1C).

In patients with *HP* positive tests, a 10-day levofloxacin-amoxicillin triple therapy is recommended as second-line therapy if first-line therapy failed (strong recommendation based on moderate-quality evidences, 1B).

We recommend to start standard triple therapy (STT) after 72–96 h of intravenous administration of PPI and to administer it for 14 days (strong recommendation based on low-quality evidences, 1C).

The worldwide prevalence of *H. pylori* infections is approximately 50%, with the highest being in developing countries [153]. Standard treatments for *H. pylori* infections have been endorsed by Western scientific societies, and by regulatory authorities relying on clarithromycin, metronidazole, or amoxicillin in conjunction with PPI [154].

As the response to eradication therapy is significantly related to the prevalence of primary resistance in the population, the choice of treatment regimen should be based on the knowledge of the underlying prevalence of resistant strains in the community [151–154].

Several international guidelines [151, 152] and available meta-analysis [153, 154] recommend that standard triple therapy (amoxicillin, clarithromycin, and PPI) regimen should be used as first-line therapy if low clarithromycin resistance is present. The suggested doses are:

- PPI standard dose twice a day;
- Clarithromycin 500 mg twice a day;
- Amoxicillin 1000 mg twice a day, or
- Metronidazole 500 mg twice a day.

Sequential therapy with four drugs (amoxicillin, clarithromycin, metronidazole, and PPI) should be considered in selected cases, if compliance to the scheduled regimen can be maintained, and if clarithromycin high resistance is detected. It is defined as the use of one PPI and amoxicillin for the first 5 days followed by PPI plus clarithromycin and metronidazole for the next 5 days [155]. Recommended doses are as follows:

- PPI standard dose twice a day;
- Amoxicillin 1000 mg twice a day;
- Clarithromycin 500 mg twice a day;
- Metronidazole 500 mg twice a day.

If any of these regimens failed, a second-line therapy is represented by a 10-day levofloxacin-amoxicillin triple therapy. The suggested doses are:

- PPI standard dose twice a day;
- Levofloxacin 500 mg once a day or 250 twice a day;
- Amoxicillin 1000 mg twice a day.

**Conclusions**

Peptic ulcer disease is still common among the world population and its incidence pattern is evolving in relation to the rise of new risk factors, i.e., the increasing incidence of the *Helicobacter pylori* infection, the extensive use of NSAIDs and the increase in alcohol and smoking abuse. Despite the tremendous improvement in preventive therapies, the rate of complication of this disease is still high and is burdened by high morbidity and mortality. Prompt recognition and treatment of the complications lead invariably to a better outcome, especially in elderly and frail patients. For this reason, these guidelines present evidence-based international consensus statements on the management of complicated
Peptic ulcer from a collaboration of a panel of experts and are intended to improve the knowledge and the awareness of physicians around the world on this specific topic. We divided our work into two main topics, bleeding and perforated peptic ulcer, and structured it into six main topics that cover the entire management process of patients with complicated peptic ulcer, from diagnosis at ED arrival to post-discharge antimicrobial therapy, to provide an up-to-date and easy-to-use tool that can help physicians and surgeons during the decision-making process.

Abbreviations
ACS-NSQIP: American college of surgeon National Surgical Quality Improvement Program; APACHE score: Acute Physiology and Chronic Health Evaluation score; ASA: American Society of Anesthesiologists score; ASA: Acetylsalicylic acid; ATLS: Advanced trauma life support; AXR: Abdominal X-ray; BPU: Bleeding peptic ulcer; COOL: trial; Closed or Open after Laparotomy trial; CT: Computed tomography; ED: emergency department; EUS: Endoscopic ultrasound; GBS: Glasgow-Blanchford score; GI: Gastrointestinal; GRADE: Grading of Recommendations Assessment, Development and Evaluation; Hb: Hemoglobin; IAI: intra-abdominal infection; ICU: Intensive care unit; INR: International normalized ratio; MAP: Mean arterial pressure; MDRO: Multi-drug resistant organism; NGT: Nasogastric tube; NOM: Nonoperative management; NSAIDs: Non-steroidal anti-inflammatory drugs; OA: Open abdomen; OTSC: Over the scope clip; PPU: Perforated peptic ulcer; PULP score: Peptic ulcer perforation score; qSOFA: Quick sequential organ failure assessment; RCT: randomized controlled trial; RFA: Radiofrequency ablation; SOFA: Sequential organ failure assessment; SSI: Surgical site infection; UBT: Urea breath test; WSES: World Society of Emergency Surgery

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Ethics approval and consent to participate
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Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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References


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Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2017 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group


Abstract

Background: Adhesive small bowel obstruction (ASBO) is a common surgical emergency, causing high morbidity and even some mortality. The adhesions causing such bowel obstructions are typically the footprints of previous abdominal surgical procedures. The present paper presents a revised version of the Bologna guidelines to evidence-based diagnosis and treatment of ASBO. The working group has added paragraphs on prevention of ASBO and special patient groups.

Methods: The guideline was written under the auspices of the World Society of Emergency Surgery by the ASBO working group. A systematic literature search was performed prior to the update of the guidelines to identify relevant new papers on epidemiology, diagnosis, and treatment of ASBO. Literature was critically appraised according to an evidence-based guideline development method. Final recommendations were approved by the workgroup, taking into account the level of evidence of the conclusion.

(Continued on next page)
Adhesive small bowel obstruction (ASBO) is one of the leading causes of surgical emergencies and in particular of surgical emergencies that require an emergent operation [1–4]. In the UK, small bowel obstruction was the indication for 51% of all emergency laparotomies [2]. Scott et al. reported on seven emergency surgical procedures that account for 80% of all general surgery emergency admissions, morbidity, deaths, and healthcare expenditures in the USA [3]. Adhesive small bowel obstruction was the most common diagnosis for both the top 2 (small bowel resection) and top 5 (adhesiolysis) procedures [3]. Post-operative adhesions are the leading cause of small bowel obstructions, accounting for 60% of cases [1].

ASBO causes considerable harm, resulting in 8 days of hospitalization on average and an in-hospital mortality rate of 3% per episode [5–8]. Between 20 and 30% of patients with adhesive small bowel obstruction require operative treatment [1, 9–11]. Length of hospitalization and morbidity depend on the need for surgical intervention. Average hospitalization after surgical treatment of ASBO is 16 days, compared to 5 days following non-operative treatment [12]. Associated costs in a Dutch study in 2016 were estimated at €16,305 for surgical and €2227 for non-operative treatment [12].

Although adhesive small bowel obstruction is a common condition, the prevention and treatment is often characterized by surgeons’ personal preferences rather than standardized evidence-based protocols. There is a large amount of conflicting and low-quality evidence in publications regarding treatment of adhesive small bowel obstruction.

Therefore, the World Society of Emergency Surgery (WSES) working group on ASBO has developed evidence-based guidelines to support clinical decision making in diagnosis and management of ASBO [11, 13]. In the present revision of these guidelines, all recommendations were updated according to the latest evidence available from the medical literature. Further, we have introduced two new sections: prevention of ASBO and special patient groups.

Methods
The guideline was written under the auspices of the WSES by the ASBO working group. Systematic searches of the MEDLINE and Embase databases were carried out in October 2016 using the keywords relevant to each section. Terms relevant to each section of the guideline were mapped to MEDLINE Medical Subjects Headings (MeSH) terms, as well as searched for as text items. Articles describing randomized controlled trials and systematic reviews were searched for using the methodological filters of the Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk/methodological-principles.html). The bibliographies of included articles were subsequently hand-searched for other relevant references, and experts in the field were asked if they found any relevant reports missing.

Critical appraisal
Articles selected to support recommendations were assessed using the levels of evidence as published by the Centre for Evidence-Based Medicine of the University of Oxford (www.cebm.net; Table 1). Articles were classified according to the type of article and individually assessed for methodological quality using the GRADE method as proposed by the GRADE working group. That working group has developed a common, sensible, and transparent approach to grading the quality of evidence and strength of recommendations (http://www.gradingworkinggroup.org). The main literature on which the conclusion for each relevant topic is based is stated with the conclusion, accompanied by the level of evidence (Table 2) [14, 15].
Conclusion and recommendations are graded according to the level of evidence from strong (“there is strong evidence for,” level A) to weak (“we cannot be confident,” level D). Recommendations were graded as strong recommendations (level I) or weak recommendation or suggestions (level II). Recommendations were considered strong recommendations if there is sufficient evidence (level A or B) demonstrating that the benefits of an intervention are of clinical importance and clearly outweigh the harm of the intervention. A concept guideline was sent to all involved for comment and approval after which internal consensus was reached between the members of the working group. Amendments were made based upon these comments, leading to the final version of this updated guideline.

Definitions

Peritoneal adhesions

The term “peritoneal adhesions” or simply “adhesions” is defined as fibrous tissue that connects surfaces or organs within the peritoneal cavity that are normally separated. Such adhesions are the results of a pathological healing response of the peritoneum upon injury, as opposed to the normal “ad integrum” repair [16]. Typical adhesions form after peritoneal injury from abdominal surgery. Other conditions that may cause peritoneal injury resulting in adhesion formation include radiotherapy, endometriosis, inflammation, and local response to tumors. Adhesions from a non-operative etiology are often part of a more complex pathology that can cause chronic pain and complications as the result of adhesions and other mechanisms [17]. Management of chronic abdominal complications by adhesiolysis is controversial [18, 19]. The scope of the present guideline is limited to diagnosis and management of acute bowel obstructions.

Adhesive small bowel obstruction

Small bowel obstruction is a surgical emergency in which the obstruction of the small intestine hinders passage of intestinal contents. Small bowel obstruction is characterized by abdominal pain, vomiting, distention, and constipation. Adhesions are the single most common cause for small bowel obstruction [1, 20]. Nonadhesive etiologies of bowel obstruction include incarcerated hernias, obstructive lesions (malignant and benign), and a number of infrequent causes for bowel obstruction such as bezoars, inflammatory bowel disease, and volvulus [21–25]. Definitive confirmation of the adhesive etiology of bowel obstruction is made during operative treatment. Methods to confirm the adhesive etiology of bowel obstruction non-invasively include a history of previous episodes of bowel obstruction by adhesions or exclusion of other causes of bowel obstruction by imaging (often CT scan).

Adhesiolysis

Adhesiolysis refers to releasing adhesions either by blunt or sharp dissection during surgery. It can be the primary indication for an operation, as in a reoperation for small bowel obstruction caused by adhesions. Adhesiolysis is also performed during reoperations for indications not

Table 1  Classification of evidence per article

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Interventional research</th>
<th>Studies concerning diagnostic accuracy</th>
<th>Studies on complications or side effects, etiology, prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Systematic review/meta-analysis of at least 2 independently performed level A2 studies</td>
<td>Diagnostic test compared to reference test; criteria and outcomes defined in advance; assessment of test results by independent observers; independent interpretation of test results; adequate number of consecutive patients enrolled; all patients subjected to both tests</td>
<td>Prospective cohort with sufficient amount of study participants and follow-up, adequately controlled for confounders; selection in follow-up has been successfully excluded</td>
</tr>
<tr>
<td>A2</td>
<td>Double-blind controlled randomized comparative clinical trial of good study quality with an adequate number of study participants</td>
<td>Diagnostic test compared to reference test; criteria and outcomes defined in advance; assessment of test results by independent observers; independent interpretation of test results; adequate number of consecutive patients enrolled; all patients subjected to both tests</td>
<td>Prospective cohort study, but without all the features mentioned for level A2 or retrospective cohort study or case-control study</td>
</tr>
<tr>
<td>B</td>
<td>Comparative studies, but without all the features mentioned for level A2 (including patient-control studies, cohort studies)</td>
<td>Diagnostic test compared to reference test, but without all the features mentioned in A2</td>
<td>Prospective cohort study, but without all the features mentioned for level A2 or retrospective cohort study or case-control study</td>
</tr>
<tr>
<td>C</td>
<td>Noncomparative studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Expert opinion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2  Grading of the conclusions and recommendations according to the level of evidence and strength of recommendation

<table>
<thead>
<tr>
<th>Level</th>
<th>Conclusion based on</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Systematic review (A1) or at least 2 independent studies with evidence level A2 (&quot;there is evidence that…&quot;)</td>
</tr>
<tr>
<td>B</td>
<td>One study with evidence level A2 or at least 2 independent studies with evidence level B (&quot;it is likely that…&quot;)</td>
</tr>
<tr>
<td>C</td>
<td>One study with evidence level B or level C (&quot;there are indications that…&quot;)</td>
</tr>
<tr>
<td>D</td>
<td>Expert opinion (&quot;the working group recommends…&quot;)</td>
</tr>
<tr>
<td>Level</td>
<td>Recommendation</td>
</tr>
<tr>
<td>I</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>II</td>
<td>Weak recommendation (suggestion)</td>
</tr>
</tbody>
</table>
related to adhesions in order to obtain sufficient access to the operative field. Complicated adhesiolysis refers to the event of inadvertent injury while performing adhesiolysis. Injuries during adhesiolysis are most frequently made to the bowel. These bowel injuries are classified as:

- **Seromuscular injury**: injury to the visceral peritoneum (serosa) and smooth muscle layer of the bowel. The lumen of the bowel or leakage of bowel contents is not visible.
- **Enterotomy**: a full thickness injury to the bowel. The mucous layer or lumen of the bowel is visible, or there may be leakage of intestinal contents.
- **Delayed diagnosed perforation**: bowel injuries made during surgery that initially go unrecognized. Typically, the abdomen is closed at the end of procedure with the bowel injury still in place, causing patients to deteriorate during the postoperative course.

### Results

#### Epidemiology

The risk of SBO is highest following colorectal, oncologic gynecological, or pediatric surgery [1, 26–28]. One in ten patients develops at least one episode of SBO within 3 years after colectomy [7]. Reoperations for ASBO occur in between 4.2 and 12.6% of patients after pediatric surgery patients, and 3.2% of colorectal patients [1, 29]. Recurrence of ASBO is also frequent; 12% of non-operatively treated patients are readmitted within 1 year, rising to 20% after 5 years. The risk of recurrence is slightly lower after operative treatment: 8% after 1 year and 16% after 5 years [30].

#### Classification of adhesions

The most frequently used classification of adhesions in general surgery is the adhesion score according to Zühlke et al. (Table 3) [31]. The score is based on the tenacity and some morphologic aspects of the adhesions. The merits of this score are that it is easy to use and classifications are self-explanatory to most surgeons and gynecologists. The major drawback to the score is that it does not measure the extent of adhesions and that tenacity of adhesions can vary between different parts of the abdomen. The most used grading system in gynecological surgery is the American Fertility Society (AFS) score [32]. The score is designed for grading adhesions in the small pelvis. Adhesions are scored for extent and severity at four sites: right ovary, right tube, left ovary, and left tube. The scores for the right and left side are summed, and the final AFS score is the score for the side with the lowest summed score while discarding the score for the other side. Thus, a patient with an AFS score of 0 can still have adhesions. Further critiques for this score include a relatively low inter-observer reproducibility [33]. A modified AFS has therefore gained popularity in more recent studies [34].

A recently introduced score by the ASBO working group is the peritoneal adhesion index (PAI), which measures tenacity on a 1–3 scale at 10 predefined sites, to integrate tenacity and extent of adhesions in a single score (Fig. 1) [35]. This score is the only score that has been validated to be prognostic for convalescence after surgery for ASBO and the risk of injuries during adhesiolysis [36]. A limitation to all these adhesion scores is that they are only applicable to operative cases because they require operative assessment. Furthermore, none of them has yet been validated to correlate with the long-term risk for (recurrence of) adhesion-related complications.

A different type of classification in the field of ASBO is risk stratification that predicts the need for surgery. Zielinski reported on three radiological and clinical signs that correlate with the need for surgical exploration:

### Table 3 Classification of adhesions according to Zühlke et al.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No adhesions or insignificant adhesions</td>
</tr>
<tr>
<td>1</td>
<td>Adhesions that are filmy and easy to separate by blunt dissection</td>
</tr>
<tr>
<td>2</td>
<td>Adhesions where blunt dissection is possible but sharp dissection necessary, beginning vascularization</td>
</tr>
<tr>
<td>3</td>
<td>Lysis of adhesions possible by sharp dissection only, clear vascularization</td>
</tr>
<tr>
<td>4</td>
<td>Lysis of adhesions possible by sharp dissection only, organs strongly attached with severe adhesions, damage of organs hardly preventable</td>
</tr>
</tbody>
</table>

### Fig. 1 Peritoneal adhesion index. Reproduced with permission from [35]
mesenteric edema, absence of the small-bowel feces sign, and obstipation. The score was validated in 100 cases of ASBO and predicted the risk with a concordance index of 0.77 [37]. A more accurate model was reported by Baghdadi et al. This score comprises radiological findings, sepsis criteria, and comorbidity index. Although the score is somewhat complex to assess, it correlates with an area under the curve of 0.80 in a validation study of 351 cases [38].

Prevention

Surgical technique

The main principles of prevention of adhesion and related complications are minimizing surgical trauma and the use of adjuvants to reduce adhesion formation. Laparoscopy is often believed to reduce adhesion formation and the risk for ASBO. In a systematic review of cohort studies, the incidence of reoperation for ASBO was 1.4 (95% CI 1.0–1.8%) after laparoscopic and 3.8% (95% CI 3.1–4.4%) after open surgery. However, there were differences in both the type and indications for surgery [1]. In a recent meta-analysis of SBO after colorectal operations, the incidence of ASBO after laparoscopic surgery was somewhat lower than after open colorectal procedures (OR 0.62, 95% CI 0.54 to 0.72). However, no significant difference was found in the three randomized trials included in this review (OR 0.50, 95% CI 0.20 to 1.2) [39]. In summary, there is some evidence that the incidence of ASBO is lower after laparoscopy. However, the effect seems modest when correcting for type and indication of surgery. Thus, performing (colorectal) surgery by laparoscopy is not a complete solution to preventing adhesive SBO.

Many other aspects of surgical technique have been associated with adhesion formation, although there are little or no epidemiological data concerning their impact on the incidence of ASBO. Nevertheless, a number of important risk factors for aggravated adhesion formation are worth considering. One of the most important risk factors is the foreign body reaction, for example as seen with starch-powdered gloves, and meshes used for abdominal wall reconstruction [40, 41]. The choice of energy device might also impact adhesion formation. Peritoneal injury is lower in bipolar electrocautery and ultrasonic devices as compared to monopolar electrocautery [42, 43]. Animal data suggest that both systemic and intraperitoneal application of antibiotics, and metronidazole in particular, can reduce adhesion formation in septic conditions [44, 45].

Adhesion barriers

Adhesion barriers are adjuvants for peritoneal administration that can effectively reduce adhesion formation. Adhesion barriers are produced in several forms: solid membranes, gels, and liquids. The concept behind barriers is that they do not actively interfere with inflammation and wound healing. Rather, they act as a spacer which separates injured surfaces of the peritoneum, allowing these surfaces to heal without forming fibrinous attachments which eventually lead to adhesions. In order to accomplish this task, such barriers should ideally be inert to the human immune system and be slowly degradable.

There is moderate evidence that a hyaluronate carboxymethylcellulose adhesion barrier can reduce the incidence of reoperations for ASBO in colorectal surgery. In three trials involving 1132 patients undergoing colorectal surgery, hyaluronate carboxymethylcellulose reduced the incidence of reoperations for adhesive small bowel obstruction (RR 0.49, 95% CI 0.28–0.88) [46–48]. The use of such barriers seems cost-effective in open colorectal surgery [49]. An overview of common used adhesion barriers and their efficacy is found in Table 4.

### Table 4

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Marketed as</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronate carboxymethylcellulose</td>
<td>Seprafilm®</td>
<td>Solid barrier most suitable for open surgery although laparoscopic placement has been described</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Studies in both general surgery and gynecological procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces adhesion formation as well as the risk for reoperations for adhesive small bowel obstruction (relative risk 0.49, 95% CI 0.28–0.88)</td>
</tr>
<tr>
<td>Oxidized regenerated cellulose</td>
<td>Interceed®</td>
<td>Solid barrier most suitable for open surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only studied in gynecological procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces incidence of adhesion formation relative risk 0.51, 95% CI 0.31–0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No studies available on subsequent risk of ASBO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This workgroup does not recommend the use of this barrier to prevent ASBO in general surgery</td>
</tr>
<tr>
<td>Icodextrin</td>
<td>Adept®</td>
<td>Liquid barrier, easy to apply in both open and laparoscopic surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Good safety record in both general surgery and gynecological surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces recurrence of ASBO following surgery for ASBO in one trial (relative risk 0.20, 95% CI 0.04–0.88)</td>
</tr>
<tr>
<td>Polyethylene glycol</td>
<td>Sprayshield*/Spraygel*</td>
<td>Gel barrier, easy to apply in both open and laparoscopic surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces adhesion score in both general surgery and gynecological trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Relative few and small studies, impact on long-term adhesion-related complications not described</td>
</tr>
</tbody>
</table>

Adapted from [52]
Secondary prevention
Adhesion barriers might also be useful to prevent recurrence after surgical treatment of ASBO. One randomized trial with an adhesion barrier included patients undergoing surgery for ASBO [20]. In this trial, patients were randomized to a liquid 4% icodextrin adhesion barrier or standard operative treatment without an adhesion barrier. The ASBO recurrence rate was 2.19% (2/91) in the icodextrin groups versus 11.11% (10/90) in the control group after a mean follow-up period of 41.4 months ($p < 0.05$) [20]. In this trial, the barrier was applied in patients treated for ASBO by laparotomy. However, the icodextrin 4% adhesion barrier can also be administered in laparoscopic surgery. Other trials with icodextrin as an adhesion barrier indicated that it actually might not be the most potent barrier to prevent adhesion reformation, which is typically more challenging than prevention of de novo adhesions [50]. Favoring the use of icodextrin are its low costs and good safety record [51]. From the results of other trials, we suggest that a hyaluronate carboxymethylcellulose might be more efficacious, but this barrier is less practical in laparoscopic surgery [46–48, 52].

Approach to the patient with ASBO
An algorithm for the diagnostic and therapeutic approach to the patient with ASBO is presented in Fig. 2. The initial diagnosis of ASBO is of utmost importance. Failure to diagnose or having a delayed diagnosis represents 70% of malpractice claims in ASBO [53, 54].

The primary goals in the initial evaluation of patients in whom adhesive small bowel obstruction is suspected are:

- Differentiating between adhesive small bowel obstruction and other causes of bowel obstruction
- Assessing the need for urgent surgical exploration
- Identifying and preventing complications from bowel obstruction

History taking and physical examination
History taking in a patient suspected for ASBO includes assessment of potential causes of bowel obstruction (previous operations, radiotherapy) and nutritional status. Signs of dehydration should also be assessed. Traditionally, ASBO is clinically diagnosed in a patient with intermittent colicky abdominal pain, distention, and nausea (with or without vomiting), with or without absence of stools. Although diagnosis of small bowel obstruction is fairly certain in a patient in whom all of these symptoms are present, there are some specific pitfalls that can result in delayed or misdiagnosis of bowel obstruction upon initial presentation. In patients with incomplete obstruction, watery diarrhea may be present. The presence of watery diarrhea can cause an episode of ASBO to be mistaken for gastro-enteritis. Stools might also be present in patients with a relatively high obstruction who are admitted early after onset of symptoms. Moreover, not all of these symptoms may be present, especially in the elderly in whom pain is often less prominent [55, 56].

During physical examination, signs of peritonitis that might reveal strangulation or ischemia should be evaluated. Differential diagnostic considerations that can be assessed during physical examination include the presence of any abdominal wall or groin hernias. The evaluation of ASBO by history taking and physical examination has a low sensitivity for detecting bowel strangulation and ischemia. Sensitivity of physical examination for detection of strangulation is only 48%, even in experienced hands [57].

Laboratory tests
The minimum of laboratory tests include blood count, lactate, electrolytes, CRP, and BUN/creatinine. Laboratory values that might indicate peritonitis are a CRP $> 75$ and white blood cell count $> 10.000/mm^3$, although sensitivity and specificity of these tests are relatively low [6, 57, 58]. Electrolytes are often disturbed in patients with a bowel obstruction; in particular, low values of potassium are frequently found and need to be corrected. BUN/creatinine needs to be assessed as patients with ASBO are frequently dehydrated which could result in acute kidney injury.

Imaging studies
Plain X-rays
The value of plain X-rays complementary to physical examination is limited. In high-grade obstruction, a triad of multiple air-fluid levels, distention of small bowel loops, and absence of gas in the colon are pathognomonic for small bowel obstruction, but overall sensitivity and specificity of plain x-rays are low (sensitivity approximately 70%) [59, 60]. A large volume pneumoperitoneum secondary to bowel perforation in ASBO can also be detected on plain X-rays, preferably by an erect chest X-ray. Plain X-rays, however, do not detect the more early signs of peritonitis or strangulation [59–61]. Furthermore, a plain abdominal X-ray does not provide anatomical information that helps differentiate between the various causes of bowel obstruction.

Water-soluble contrast studies
Several systematic reviews and meta-analyses have established the usefulness of water-soluble contrast agents in the diagnostic work-up of ASBO [62–64]. If the contrast has not reached the colon on an abdominal X-ray taken 24 h following administration of the contrast, this is highly indicative of failure of non-operative management. Multiple studies have shown that the use of water-soluble contrast agents accurately predicts the need for surgery and reduces hospital stay [62, 63]. Some authors also suggest that water-soluble contrast studies reduce the need for
surgery, which is attributed to an active therapeutic role of the contrast [62, 63].

**CT scans**

Current helical CT scans not only have good test characteristics for diagnosing small bowel obstruction but also have approximately 90% accuracy in predicting strangulation and the need for urgent surgery [37, 60, 65–68]. Diagnostic value of CT scan can be enhanced with the use of water-soluble contrast. As with water-soluble contrast studies, progress of the contrast can be evaluated by X-ray at 24 h after CT scan.

Although adhesions are not directly visible even on CT scan, a CT scan can differentiate accurately between different causes of bowel obstruction by excluding other causes. The workgroup therefore considers CT scan to be
the preferred imaging technique if there is any doubt about the diagnosis of ASBO, and to assess the need for urgent surgery.

A CT scan should help to differentiate between a complete obstruction of the bowel and help facilitate the decision for a trial of non-operative management versus a decision to proceed to surgery. It may also help to define the location of the obstruction (e.g., high in the jejunum or deep in the pelvis). Signs of a closed loop, bowel ischemia, and free fluid are signs that suggest the need for surgery without delay. In addition, radiological and clinical scores can be used to predict the need for surgery as described above [37, 38].

**Ultrasound and MRI**

Although the working group considered CT scan to be the preferred technique for diagnosis of ASBO, ultrasound and MRI might be useful in specific situations. Ultrasound is operator dependent but in experienced hands can provide more information than plain X-rays, and is also available in most low income settings. Apart from distension of bowel loops, ultrasound enables detection of free fluid (that might indicate the need for urgent surgery) and assessment of the degree of shock in dehydrated patients [61, 69]. Ultrasound can also be of value in situations in which exposure to radiation is undesirable, such as in pregnant patients. In these cases, ultrasound might be complemented with MRI for more anatomical information if the diagnosis of bowel obstruction is confirmed [70].

**Table 5 Overview of conclusions and recommendation**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adhesive small bowel obstruction is a leading cause of morbidity, deaths, and healthcare expenditures in emergency surgery. A2 Scott 2016; NELA project team 2016</td>
</tr>
<tr>
<td>B</td>
<td>Adhesive small bowel obstruction causes high morbidity, with average hospital stay of 8 days and 3% in-hospital mortality per episode. Recurrence of adhesive small bowel obstruction is high. Risk for adhesive small bowel obstruction may be somewhat lower after laparoscopic compared to open colorectal surgery, but that results could not be confirmed in randomized trials. A2 ten Broek 2013; Yamada 2016; B Kielen 2016; Foster 2006</td>
</tr>
<tr>
<td>IA</td>
<td>Hyaluronic carboxymethylcellulose reduces adhesion formation and the risk of subsequent reoperations of adhesive SBO. The use of this barrier seems cost-effective in open colorectal surgery. A1 ten Broek 2014; A2 Fazio 2006; Park 2009; Kusunoki 205</td>
</tr>
<tr>
<td>IIC</td>
<td>In the absence of signs that require emergent surgical exploration (i.e., peritonitis, strangulation, or bowel ischemia), non-operative management is the treatment strategy of choice. C Fevang 2002; Fevang 2004; Ten Broek 2013; Jeppesen 2016</td>
</tr>
<tr>
<td>IB</td>
<td>A trial of non-operative management can be continued safely for 72 h. B Keenan 2014; Sakakibara 2007</td>
</tr>
<tr>
<td>IID</td>
<td>Initial evaluation should be complemented with assessment of nutritional status and laboratory tests evaluating at least blood count, lactate, electrolytes, and BUN/Creat</td>
</tr>
<tr>
<td>IC</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>IIC</td>
<td>Plain X-rays have only limited value in the work-up of patients with small bowel obstruction and are not recommended. B Maglinte 1996</td>
</tr>
<tr>
<td>IB</td>
<td>Optimal diagnostic work-up should include CT scan in the assessment and water soluble oral contrast. In the absence of the need to perform immediate surgery, a follow-up abdominal X-ray should be made after 24 h. If the contrast has reach the colon, this is indicative for resolution of the bowel obstruction. A2 Ceresoli 2016; Branco 2010; Abbas 2005; B Goussous 2013; Zielinski 2011; Zielinski 2010; Daneshmat 1999; Makita 1999; Zalcman 2000</td>
</tr>
<tr>
<td>IIC</td>
<td>Long trilumen naso-intestinal tubes are more efficacious than naso-gastric tubes in non-operative management, but require endoscopic placement. A2 Chen 2012</td>
</tr>
<tr>
<td>IB</td>
<td>Laparoscopic adhesiolysis might reduce morbidity in selected cases of ASBO that require surgery. Results of a randomized trial are awaited. B Sajid 2016; Farinelli 2009; Sallinen 2014</td>
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<td>IIIB</td>
<td>Adhesion barriers reduce the risk of recurrence for ASBO following operative treatment. A2 Catena 2012</td>
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<td>IIC</td>
<td>Younger patients, and pediatric patients in particular, have higher lifetime risk of developing adhesion-related complications and might therefore benefit most from adhesion prevention. A1 ten Broek 2013; A2 Stik 2016; B Fredriksson 2016</td>
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<td>C</td>
<td>More research is needed to the impact of comorbidities in elderly patients on optimal management of adhesive small bowel obstruction. Patients with diabetes might require more early operative intervention. B Karamanos 2016</td>
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</table>
of the contrast should be monitored after 24 h of non-operative treatment by X-ray. If the diagnosis of ASBO is certain (e.g., because other causes have been excluded with recent imaging), and there are no signs that immediate surgery might be warranted, only a water-soluble contrast study is considered sufficient. Ultrasound and MRI can be useful in specific situations, such as pregnancy or (in low income countries) when CT scan is unavailable.

Management

Initial decision making
Non-operative management should always be tried in patients with adhesive small bowel obstruction, unless there are signs of peritonitis, strangulation, or bowel ischemia [71]. Although the risk of recurrence is slightly lower after operative treatment, this is not a reason to opt for a primary surgical approach. Morbidity from emergency surgical exploration is high; there is a considerable risk for bowel injury, and surgical treatment may significantly reduce post-operative quality of life [1, 72–74].

Non-operative management
The cornerstone of non-operative management is nil per os and decompression using a naso-gastric tube or long intestinal tube. Non-operative management is effective in approximately 70–90% of patients with ASBO [1, 75, 76]. There has been some debate in the literature over the use of long intestinal tubes or naso-gastric tubes. In an older trial, no significant difference in failure rates was found between naso-gastric tubes and long intestinal tubes [77]. In a more recent trial, 186 patients were randomized between a newly designed trilumen long tube and a naso-gastric tube. Long tubes seemed more effective in this trial with a failure rate of 10.4% in this group compared with 53.3% in the naso-gastric tube group [78]. Results from this trial should be interpreted with care, because the failure rate of naso-gastric tube compression is much higher than would be expected from other literature. Moreover, a drawback of trilumen tubes is the need for endoscopic placement. Non-operative management should further include fluid resuscitation, correction of electrolyte disturbances, nutritional support, and prevention of aspiration.

Duration of the period in which non-operative management can be tried is subject to debate. Several retrospective series and databases have shown that delays in surgery increase morbidity and mortality [30, 71, 79, 80]. Evidence for the optimal duration of non-operative treatment is absent, but most authors and the panel consider a 72-h period as safe and appropriate [11, 58, 76, 79, 80]. Continuing non-operative treatment for more than 72 h in cases with persistent high output from a decompression tube, but no other signs of clinical deterioration, however, remains subject to debate. Common medical complications in patients with small bowel obstruction are dehydration with kidney injury, electrolyte disturbances, malnutrition, and aspiration.

Non-operative management: summary
The panel recommends a trial of non-operative management in all patients with ASBO, unless there are signs of peritonitis, strangulation, or bowel ischemia. Evidence for the optimal duration of non-operative is absent, but most authors and the panel consider a 72-h period as safe and appropriate. Further recommendations are found in Table 5.

Operative treatment
Historically, abdominal exploration through laparotomy has been the standard treatment for adhesive small bowel obstruction. In recent years, however, laparoscopic surgery for ASBO has been introduced. The potential benefits of laparoscopy include less extensive adhesion (re)formation, earlier return of bowel movements, reduced post-operative pain, and shorter length of stay [81–83]. In a recent systematic review and meta-analysis of 14 non-randomized studies, laparoscopic adhesiolysis reduced risk of morbidity, in-hospital mortality, and surgical infections [84]. However, there also seems strong selection bias in these series allocating mainly the less severe cases to laparoscopy. In a questionnaire among surgeons, 60% of the respondents reported to have performed laparoscopic adhesiolysis for ASBO in their practice, but half of them in less than 15% of cases [11].

Although laparoscopy might provide some benefits to some patients for ASBO, surgeons should carefully select candidates for laparoscopic treatment. Laparoscopy in an abdomen with very distended loops of bowel and multiple complex adhesions could increase the risk of severe complications such as enterotomies and delayed diagnosis of perforations [85, 86]. Indeed, some authors have reported bowel injury in 6.3 to 26.9% of patients treated with laparoscopic adhesiolysis for ASBO [87–89]. In a recent population-based study, bowel resections were significantly more frequent in laparoscopic surgery. Incidence of bowel resection was 53.5 versus 43.4% in laparoscopic versus open procedures [90]. Farinella et al. reported that predictors for a successful laparoscopic treatment of ASBO are the following: ≤2 laparotomies in history, appendectomy as the operation in history, no previous median laparotomy incision, and a single adhesive band [91]. Laparoscopic adhesiolysis also seems more difficult in patients who have previously been treated by radiotherapy [92].

More compelling evidence on the role of laparoscopy in surgery for ASBO is from an ongoing randomized
trial and is still awaited [93]. In this trial, strict inclusion and exclusion criteria have been used to select candidates in whom simple single band adhesions are expected.

**Operative management: summary**

Laparoscopic surgery has been introduced in recent years and might decrease morbidity in subgroups of patients undergoing surgery for ASBO. The risk of bowel injuries seems higher in laparoscopic surgery for ASBO. Therefore, careful selection of patients for laparoscopic surgery is required. Further recommendations are found in Table 5.

**Special patient groups**

**Young patients**

The risk of adhesion-related complications is life-long. Although most small bowel obstructions will occur within the first 2 years after surgery, new cases continue to develop many years after the primary operation [1, 30, 72, 94, 95]. Also, the risk of requiring a future reoperation for unrelated causes is higher in younger patients [96]. Pediatric patients are at the extreme of young age, have a high risk for adhesion-related complications [1]. In a recent cohort of patients who underwent surgery at a pediatric age, the incidence of adhesive small bowel obstruction was 12.6% after a median follow-up of 14.7 years [29]. Young patients therefore might have the highest lifetime benefit from adhesion prevention [49]. No trials with adhesion barriers have been performed in pediatric surgery, but a recent cohort study in pediatric patients showed a significant reduction in ASBO with the use of a hyaluronate carboxymethylcellulose adhesion barrier [97]. After a follow-up of 24 months, 2.0% of pediatric patients operated with adhesion barrier versus 4.5% of patients operated on without adhesion barrier developed ASBO.

**Elderly patients**

In elderly patients, quality of life considerations are extremely important in decision making. Patients with a high frailty index have a prolonged recovery after a surgical procedure and may not be able to return to their previous functional state and quality of life [98, 99]. The principles of treatment for adhesive small bowel obstruction might interfere with comorbidities and medication in the elderly patients. There is a marked paucity of research on the consequences of stopping or withholding oral medications when a patient is put on nil per os for non-operative treatment of small bowel obstruction. A recent cohort showed that patients with diabetes might require earlier intervention although the level of evidence is rather low. Patients with diabetes were shown to suffer from a 7.5% incidence of acute kidney injury and 4.8% incidence of myocardial infarction if the operation was delayed more than 24 h [100]. The incidence of these complications was significantly higher when compared to diabetic patients that were operated within 24 h and non-diabetic patients with delayed operation.

**Pregnancy**

Small bowel obstruction in pregnancy is very rare but represents an important clinical challenge with significant risk of fetal loss. In a recent review, 46 cases of bowel obstruction during pregnancy were found in literature from case series and case reports [101]. Approximately half of cases were attributed to adhesions, most commonly from previous abdominal operations. Imaging studies performed to diagnose SBO in the case reports included ultrasound in ten cases (83%), abdominal X-ray in four patients (33%), MRI in four patients (33%), and a CT scan in three patients (25%). Strikingly, the failure rate of non-operative treatment in pregnant patients with ASBO was high. A total of 23 cases with ASBO were reported, in 17 of whom initial management was by a non-operative trial. Non-operative treatment failed in 16 cases (94%). Risk of fetal loss was 17% (n = 8) and risk of maternal death 2% (n = 1).

**Conclusions**

The conclusions and recommendations of this guideline have been summarized in Table 5. ASBO is a common surgical emergency, causing high morbidity and even some mortality. Surgeons should be aware that the adhesions causing such bowel obstructions are typically the footprints of previous abdominal surgical procedures or disease. Part of the adhesion formation can be prevented by application of minimal invasive surgical techniques and the use of adhesion barriers. Most cases of ASBO can be treated non-operatively. If operative treatment is required, a laparoscopic approach might be beneficial for simple cases. However, there is a considerable risk for conversion to an open laparotomy and care needs to be taken not to make bowel injury.

**Availability of data and materials**

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

**Authors’ contributions**

RtB, PK, and SdS performed the search for relevant literature, graded the level of evidence of available literature, contributed to the conception of the draft, contributed with important scientific knowledge, and gave the final approval of the manuscript. FCo, WB, LA, GV, MS, GF, MK, FM, AB, AL, EM, JJ, YK, MS, AB, CB, JC, RC, MdM, PF, KI, RI, RL, JK, AK, RM, SR, BS, TS, KS, DW, IW, FAZ, NdaA, RP, JM, and FCa contributed to the manuscript draft, critically revised the manuscript, contributed with important scientific knowledge, and gave the final approval of the manuscript. HvG supervised the literature study, contributed to the conception of the draft, critically revised the manuscript, contributed with important scientific knowledge, and gave the final approval of the manuscript. All authors read and approved the final manuscript.
Ethics approval and consent to participate
Not applicable

Competing interests
The authors declare that they have no competing interests.

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References


Acute mesenteric ischemia: guidelines of the World Society of Emergency Surgery

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Abstract

Acute mesenteric ischemia (AMI) is typically defined as a group of diseases characterized by an interruption of the blood supply to varying portions of the small intestine, leading to ischemia and secondary inflammatory changes. If untreated, this process will eventuate in life threatening intestinal necrosis. The incidence is low, estimated at 0.09–0.2% of all acute surgical admissions. Therefore, although the entity is an uncommon cause of abdominal pain, diligence is always required because if untreated, mortality has consistently been reported in the range of 50%. Early diagnosis and timely surgical intervention are the cornerstones of modern treatment and are essential to reduce the high mortality associated with this entity. The advent of endovascular approaches in parallel with modern imaging techniques may provide new options. Thus, we believe that a current position paper from World Society of Emergency Surgery (WSES) is warranted, in order to put forth the most recent and practical recommendations for diagnosis and treatment of AMI. This review will address the concepts of AMI with the aim of focusing on specific areas where early diagnosis and management hold the strongest potential for improving outcomes in this disease process.

Some of the key points include the prompt use of CT angiography to establish the diagnosis, evaluation of the potential for revascularization to re-establish blood flow to ischemic bowel, resection of necrotic intestine, and use of damage control techniques when appropriate to allow for re-assessment of bowel viability prior to definitive anastomosis and abdominal closure.

Keywords: Mesenteric ischemia, Mesenteric arterial occlusion, Mesenteric angiography, Mesenteric artery stenting, Small bowel ischemia, Guidelines, Recommendations

Background

Acute mesenteric ischemia (AMI) may be defined as a sudden interruption of the blood supply to a segment of the small intestine, leading to ischemia, cellular damage, intestinal necrosis, and eventually patient death if untreated [1]. AMI may be non-occlusive (NOMI) or occlusive, with the primary etiology further defined as mesenteric arterial embolism (50%), mesenteric arterial thrombosis (15–25%), or mesenteric venous thrombosis (5–15%) [2, 3]. The overall incidence is low (0.09 to 0.2% of all acute admissions to emergency departments), representing an uncommon cause of abdominal pain [4–6]. Prompt diagnostic and intervention are essential to reduce the high mortality rates (50 to 80%) [7–10].

There are currently no level 1 evidence to guide the evaluation and treatment of suspected AMI, and the published literature contains primarily institutional reviews, case series and personal recommendations with no clearly defined treatment guidelines.

Accordingly, this review aims to provide an update with recommendations based on the most currently accepted concepts in the management of AMI.

The current presentation evolved from the contributions of a group of experts in the field who submitted their evidence-based literature review of key points pertaining to diagnosis and management of AMI. Following preliminary preparation of these key points, a coordinated...
that mesenteric ischemia does not occur until the patient’s mean arterial pressure is <45 mmHg [12]. Consequently, the small intestine is able to compensate for a 75% reduction in mesenteric blood flow for up to 12 h [13].

### Pathophysiology and epidemiology

#### Acute mesenteric arterial embolism

Roughly, 50% of all cases of AMI are due to acute mesenteric embolism [2, 3]. Mesenteric emboli can originate from the left atrium, associated with cardiac dysrhythmias such as atrial fibrillation, left ventricle with global myocardial dysfunction associated with poor ejection fraction, or cardiac valves due to endocarditis. Occasionally emboli generated from an atherosclerotic aorta. Emboli typically lodge at points of normal anatomic narrowing, and the SMA is particularly vulnerable because of its relatively large diameter and low takeoff angle from the aorta. The majority of emboli lodge 3 to 10 cm distal to the origin of the SMA, thus classically sparing the proximal jejunum and colon. More than 20% of emboli to the SMA are associated with concurrent emboli to another arterial bed including the spleen, or kidney.

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
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<tr>
<td>1A</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1B</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses, or imprecise conclusions) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1C</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but subject to change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>2A</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values</td>
</tr>
<tr>
<td>2B</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values</td>
</tr>
<tr>
<td>2C</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
<td>Very weak recommendation; alternative treatments may be equally reasonable and merit consideration</td>
</tr>
</tbody>
</table>
Thus, findings of changes in these organs on CTA suggest a proximal embolic source [14].

**Acute mesenteric arterial thrombosis**
Thrombosis of the SMA (approximately 25% of cases) is usually associated with pre-existing chronic atherosclerotic disease leading to stenosis. Many of these patients have a history consistent with chronic mesenteric ischemia (CMI), including postprandial pain, weight loss, or “food fear”, and thus a systematic history is important when evaluating a patient suspected to have AMI. Thrombosis usually occurs at the origin of visceral arteries, moreover, an underlying plaque in the SMA usually progresses to a critical stenosis over years resulting in collateral beds. Accordingly, symptomatic SMA thrombosis most often accompanies celiac occlusion [15]. SMA thrombosis may also occur due to vasculitis, mesenteric dissection, or a mycotic aneurysm. Involvement of the ileocolic artery will result in necrosis of the proximal colon.

**Pathophysiology of acute non-occlusive mesenteric ischemia**
NOMI occurs in approximately 20% of cases and is usually a consequence of SMA vasoconstriction associated with low splanchnic blood flow [16]. The compromised SMA blood flow often involves the proximal colon as well due to involvement of the ileocolic artery. Patients with NOMI typically suffer from severe coexisting illness, commonly cardiac failure which may be precipitated by sepsis. Hypovolemia and the use of vasoconstrictive agents may precipitate NOMI.

**Mesenteric venous thrombosis**
Mesenteric venous thrombosis (MVT) accounts for less than 10% of cases of mesenteric infarction. Thrombosis is attributed to a combination of Virchow’s triad, i.e., stagnant blood flow, hypercoagulability, and vascular inflammation, but approximately 20% are idiopathic. Hypercoagulability may be due to inherited disease such as Factor V Leiden, prothrombin mutation, protein S deficiency, protein C deficiency, antithrombin deficiency, and antiphospholipid syndrome. Additionally, recent work suggests that fibrinolysis shutdown (resistance to tissue plasminogen activator (tPA)) is a significant risk factor for hypercoagulability [17]. Thrombophilia may also be acquired due to malignancies, hematologic disorders, and oral contraceptives [18].

The additional components altering blood flow include portal hypertension, pancreatitis, inflammatory bowel disease, sepsis, and trauma. In these situations, the consequences of bowel edema and increased vascular resistance secondary to venous thrombosis result in reduced arterial blood flow, leading to bowel ischemia.

**Severe abdominal pain out of proportion to physical examination findings should be assumed to be AMI until disproven. (Recommendation 1B)**
The key to early diagnosis is a high level of clinical suspicion.

The clinical scenario of a patient complaining of excruciating abdominal pain with an unrevealing abdominal exam is classic for early AMI [19]. If the physical exam demonstrates signs of peritonitis, there is likely irreversible intestinal ischemia with bowel necrosis. In a study of AMI, 95% of patients presented with abdominal pain, 44% with nausea, 35% with vomiting, 35% with diarrhea, and 16% with blood per rectum [20]. Approximately one-third of patients present with the triad of abdominal pain, fever, and hemocult-positive stools. Other patients, particularly those with delayed diagnosis, may present in extremis with septic shock. Clinical signs of peritonitis may be subtle. Accordingly, one must have a high index of suspicion, because such findings almost always are predictive of intestinal infarction.

**Clinical scenario differentiates AMI as mesenteric arterial emboli, mesenteric arterial thrombosis, NOMI or mesenteric venous thrombosis. (Recommendation 1B)**

**Phenotypes of AMI**
A careful history is important because distinct clinical scenarios are associated with the pathophysiological form of AMI [21]. Patients with mesenteric arterial thrombosis often have a history of chronic postprandial abdominal pain, progressive weight loss, and previous revascularization procedures for mesenteric arterial occlusion. Patients with NOMI have pain that is generally more diffuse and episodic associated with poor cardiac performance. Patients with MVT present with a mixture of nausea, vomiting, diarrhea, and abdominal cramping. Gastrointestinal bleeding occurs in 10% [22].

Nearly 50% of patients presenting with embolic AMI have atrial fibrillation and approximately one-third of patients have a prior history of arterial embolus [20].

Risk factors for specific phenotypes of AMI presented in Table 2.

**Conventional plain X-ray films have limited diagnostic value in evaluating AMI, although signs of intestinal perforation may be seen. (Recommendation 1B)**
A radiograph is usually the initial test ordered in patients with acute abdominal pain but has a limited role in the diagnosis of mesenteric ischemia, especially in the early setting. A negative radiograph does not exclude mesenteric ischemia [23]. Plain radiography only becomes positive when bowel infarction...
has developed and intestinal perforation manifests as free intraperitoneal air.

**There are no laboratory studies that are sufficiently accurate to identify the presence or absence of ischemic or necrotic bowel, although elevated l-lactate, and D-dimer may assist. (Recommendation 1B)**

Although laboratory results are not definitive, they may help to corroborate clinical suspicion. More than 90% of patients will have an abnormally elevated leucocyte count. The second most commonly encountered abnormal finding is metabolic acidosis with elevated lactate level, which occurred in 88% [24].

Patients may present with lactic acidosis due to dehydration and decreased oral intake. Thus, differentiation of early ischemia versus irreversible bowel injury based upon the lactate level alone is not reliable unless accompanied by other clinical evidence. Elevated serum lactate levels >2 mmol/l was associated in irreversible intestinal ischemia (Hazard Ratio: 4.1 (95% CI: 1.4–11.5; p < 0.01) in established diagnosis of AMI [25].

It should be emphasized that the presence of lactic acidosis in combination of abdominal pain when the patient may not otherwise appear clinically ill should lead to consideration for early CTA.

Based on the current literature, no accurate biomarkers have been identified to date [26, 27]. D-dimer has been reported to be an independent risk factor of intestinal ischemia [27], reflecting ongoing clot formation and endogenous degradation via fibrinolysis. No patient presenting with a normal D-dimer had intestinal ischemia and D-dimer >0.9 mg/L had a specificity, sensitivity, and accuracy of 82, 60, and 79%, respectively [28]. Thus, D-dimer may well be useful in the early assessment. Elevated amylase has been reported in roughly a half of patients with AMI [29]. Other biomarkers reported to assist in the diagnosis of AMI include intestinal fatty acid binding protein (I-FABP), serum alpha-glutathione S-transferase (alpha–GST), and cobalt-albumin binding assay (CABA) [30, 31]. These biomarkers may offer improved diagnostic accuracy of acute mesenteric ischemia, however, further research is required to specify its accuracy and values.

**Computed tomography angiography (CTA) should be performed as soon as possible for any patient with suspicion for AMI. (Recommendation 1A)**

Delay in diagnosis is the dominant factor that accounts for continued mortality rates as high as 30–70% despite vast clinical experience and recognition of this entity [32, 33]. The multi-detector CTA has supplanted formal angiography as the diagnostic study of choice. Multidetector computed tomography (MDCT) scanners are essential for the early diagnosis of AMI, but often require specialized personnel to perform and interpret the findings. 3D reconstruction is frequently helpful (Fig. 1). Volume rendering as in this image is now a semi-automatic workflow component of many CT machines. These can aide remote communities with less experienced staff.

In the presence of advanced AMI, the CTA findings reflect irreversible ischemia (intestinal dilatation and thickness, reduction or absence of visceral enhancement, pneumatosis intestinalis, and portal venous gas) and free intraperitoneal air [34].

Comprehensive biphasic CTA includes the following important steps:

a) Pre-contrast scans to detect vascular calcification, hyper-attenuating intravascular thrombus and intramural hemorrhage.

b) Arterial and venous phases to demonstrate thrombus in the mesenteric arteries and veins, abnormal enhancement of the bowel wall, and the presence of embolism or infarction of other organs.

c) Multi-planar reconstructions (MPR) to assess the origin of the mesenteric arteries [35].

CTA should be performed despite the presence of renal failure, as the consequences of delayed diagnosis, missed diagnosis, or mismanagement are far more detrimental to the kidneys and the patient then exposure to the iodinated contrast agent. A recent study found that in 27 of 28 patients (96.4%) MDCT correctly diagnosed AMI (specificity of 97.9%) [16, 36]. A sensitivity of 93%, specificity of 100%, and positive
and negative predictive values of 100 and 94%, respectively, were achieved [37, 38].

In NOMI CTA may demonstrate bowel ischemia and free fluid in the face of patent mesenteric vessels. In MVT, the most common positive radiological finding on venous phase CTA is thrombus in the superior mesenteric vein on venous phase CTA (Fig. 2). This has been described as the target sign [39].

Associated findings that suggest MVT include bowel wall thickening, pneumatosis, splenomegaly, and ascites [39]. Portal or mesenteric venous gas strongly suggests the presence of bowel infarction. Duplex ultrasonography has a limited role in this entity, but may be helpful if obtained early in chronic cases [22].

**Non-occlusive mesenteric ischemia (NOMI) should be suspected in critically ill patients with abdominal pain or distension requiring vasopressor support and evidence of multi-organ dysfunction. (Recommendation 1B)**

Unexplained abdominal distension or gastrointestinal bleeding may be the only signs of acute intestinal ischemia in NOMI and may be undetectable in sedated patients in the ICU in approximately 25% of cases [40, 41]. Patients surviving cardiopulmonary resuscitation who develop bacteremia and diarrhea (with or without abdominal pain) should be suspected of having NOMI. Right-sided abdominal pain associated with the passage of maroon or bright red blood in the stool is highly suggestive of NOMI in these patients.

Gastrointestinal perfusion is often impaired early in situations of critical illness, major surgery or trauma, all of which are characterized by increased demands on the circulation to maintain tissue oxygen delivery [42]. This relative mesenteric hypoperfusion is often aggravated by an underlying hypovolemic or a low-flow state. In cases of intraabdominal hypertension, all of the structures within the abdominal cavity are compressed, and this will lead to regional hypoperfusion to the organs in the splanchnic bed. Such an effect is most pronounced in the liver due to its size. Animal studies have shown that even with intraabdominal pressure of only 10 mmHg, portal venous blood flow is reduced considerably, and that at 20 mmHg, the portal venous flow and hepatic arterial flow are reduced by 35 and 55%, respectively [43].

**Fig. 1** Selected image from a CTA scan of a patient with acute mesenteric ischemia secondary to occluded SMA from an embolic source (arrow). 3D reconstruction is demonstrates mid occlusion of SMA (arrow)

**Fig. 2** 30-year-old patient with acute superior mesenteric vein a and portal vein thrombosis b due to hypercoagulable state. No signs of bowel ischemia were noted, and the patient was treated successfully with long-term anticoagulation
Most of the symptoms listed in this section are often not clinically apparent in a critically ill ventilated patient on ICU. Accordingly, any negative changes in patient’s physiology, including new onset of organ failure, increase in vasoactive support and nutrition intolerance should raise the suspicion of mesenteric ischemia.

When the diagnosis of AMI is made, fluid resuscitation should commence immediately to enhance visceral perfusion. Electrolyte abnormalities should be corrected, and nasogastric decompression initiated. (Recommendation 1B)

Fluid resuscitation with crystalloid and blood products is essential for the management of the patient with suspected AMI. Preoperatively resuscitation is important to prevent cardiovascular collapse on induction of anesthesia. To guide effective resuscitation, early hemodynamic monitoring should be implemented [44]. Assessment of electrolyte levels and acid–base status should be performed. This is especially true in patients with AMI, where severe metabolic acidosis and hyperkalemia may be present due to underlying bowel infarction and reperfusion [45]. Vasopressors should be used with caution, and only to avoid fluid overload and abdominal compartment syndrome. Dobutamine, low dose dopamine, and milrinone to improve cardiac function have been shown to have less impact on mesenteric blood flow [46, 47]. The fluid volume requirement in these patients may be high, due to extensive capillary leakage, but extensive crystalloid overload should be avoided to optimize bowel perfusion [48]. The endpoints of therapy should address physiologic levels of oxygen delivery with continued monitoring of lactate level as an indication of improvement. Although in the past, supra-physiologic levels were advocated, current evidence does not support this concept [49].

Broad-spectrum antibiotics should be administered immediately. Unless contraindicated, patients should be anticoagulated with intravenous unfractionated heparin. (Recommendation 1B)

The high risk of infection among patients with AMI outweighs the risks of acquired antibiotic resistance, and therefore broad-spectrum antibiotics should be administered early in the course of treatment [50]. Intestinal ischemia leads to early loss of the mucosal barrier, which facilitates bacterial translocation and the risk of septic complications.

Prompt laparotomy should be done for patients with overt peritonitis. (Recommendation 1A)

When physical findings suggestive of an acute intraabdominal catastrophe are present, bowel infarction already occurred, and the chance of survival in this patient population with significant associated comorbidity is dramatically reduced. There is overwhelming evidence in literature that peritonitis secondary to bowel necrosis mandates surgery without delay.

The goal of surgical intervention for AMI includes:

1) Re-establishment blood supply to the ischemic bowel.
2) Resection of all non-viable regions.
3) Preservation of all viable bowel.

Intestinal viability is the most important factor influencing outcome in patients with AMI. Non-viable intestine, if unrecognized, results in multi-system organ dysfunction and ultimately death. Prompt laparotomy allows for direct assessment of bowel viability.

After initial resuscitation, midline laparotomy should be performed followed by assessment of all areas of the intestine with decisions for resection of all clearly necrotic areas. In cases of uncertainty, intraoperative Doppler may be helpful, as the presence of Doppler signals over distal branches of SMA facilitates bowel conservation, avoiding long-term disability. The SMA is easily palpated by placing fingers behind the root of the mesentery. The SMA is identified as a firm tubular structure, which may or may not have a palpable pulse. Otherwise, the SMA can also be reached by following the middle colic artery where it enters the SMA at the mesentery. Direct sharp dissection, exposing the artery from its surrounding mesenteric tissue, is required for proper exposure to perform revascularization. In cases of diagnostic uncertainties, arteriogram is the study of choice. It can be done intraoperatively especially in hybrid suites.

Different techniques of blood flow restoration are used depending on the pathophysiology of the AMI. Embolectomy and either primary or patch angioplasty is a well-established definitive treatment for SMA emboli. On the other hand, thrombosis of the SMA at the origin of aorta (a common pathology in diffuse aterosclerosis) will require a bypass procedure. However, it increases the magnitude of the procedure and may require prosthetics in the presence of contaminated field. One option is a retrograde bypass from the iliac artery to the distal SMA using the femoral vein or a synthetic graft (Fig. 3).

Neither NOMI nor MVT typically require vascular repair. Full dose anticoagulation should be initiated on all patients prior to the surgical procedure. Unfractioned heparin is effective and easy to manage, especially in patients with acute kidney failure.

Endovascular revascularization procedures may have a role with partial arterial occlusion. (Recommendation 1C)

Several case series using endovascular techniques in combination with pharmacologic therapy have been reported.
recently. It should be emphasized, however, that any evidence of bowel ischemia or infarction precludes the use of thrombolytic therapy. At this time, these techniques have been attempted in very early, cases of AMI, and the role of such procedures remains to be determined [51, 52]. Other contraindications to thrombolytic therapy include recent surgery, trauma, cerebrovascular or gastrointestinal bleeding, and uncontrolled hypertension [53].

In recent retrospective series of 679 patients with AMI and vascular intervention (both open and endovascular) endovascular treatment performed in 24% (165 patients). The technique was successful in 87% of the patients, and in-hospital mortality was lower than among those who underwent open procedure (25 vs. 40%) [10]. Again, this report emphasized that only patients who did not require open emergent intervention are suitable for this technical approach to revascularization.

Endovascular embolectomy may be achieved by percutaneous mechanical aspiration or thrombolysis and permits percutaneous transluminal angioplasty, with or without stenting in case series of patients with CTA evidence of acute partial or complete occlusion of the SMA (either the main trunk or branch) and without no clinical or imaging evidence of advanced bowel ischemia. Complete technical success was achieved in 28% of cases; all of these had occlusion of the main SMA trunk [54–57].

There are no randomized controlled trials comparing laparotomy versus endovascular treatment as a first line strategy for the management AMI [10, 58, 59]. The most important argument in favor of the early laparotomy approach is the ability to assess bowel viability directly and thereby, minimizing delays in restoring mesenteric blood flow. In one retrospective series, the authors documented that 1/3 of patients managed with endovascular therapy avoided laparotomy [10]. In cases of endovascular approach, the use of laparoscopy to assess bowel function may be a reasonable addition [60].

Centers of excellence equipped with hybrid operating rooms may provide further data supporting the use of an endovascular strategy [61].

**Damage control surgery (DCS) is an important adjunct for patients who require intestinal resection due to the necessity to reassess bowel viability and in patients with refractory sepsis. Planned re-laparotomy is an essential part of AMI management. (Recommendation 1B)**

Damage control laparotomy strategy (abbreviated laparotomy) was accepted for trauma over 30 years ago and was found to be an important option in the patient with AMI. Damage control is the surgical modality of choice in the critically ill patient with AMI for physiological and technical reasons. The decision to implement the DCS mode should be made early based upon the response to resuscitation and ongoing physiology, as this has been associated with improved mortality [62]. Advanced age is not a contraindication to DCS as good outcomes have been observed in the elderly [63].

Planned second look techniques are required after restoration of SMA flow, with or without resection of ischemic bowel (and no anastomosis or stoma) following resuscitation in intensive care unit [64, 65]. Given frequent uncertainty with regard to bowel viability, the stapled off bowel ends should be left in discontinuity and re-inspected after a period of continued ICU resuscitation to restore physiological balance. Often, bowel which is borderline ischemic at the initial exploration will improve after restoration of blood supply and physiologic stabilization. Of note, however, multiple adjuncts have been suggested to assess intestinal viability, but none have proven to be uniformly reliable [66, 67].

Most often, re-exploration should be accomplished within 48 h and decisions regarding anastomosis, stoma, or additional resection can be made with plans for sequential abdominal closure.

In a review of 43 patients undergoing open mesenteric revascularization, the authors noted that 11 of the 23 patients undergoing a second-look operation required bowel resection [20]. The bowel in these patients is often very swollen and at high risk for anastomotic leak. Recent studies suggest that careful hand sewn techniques are preferable to the use of staples in this group [68, 69].

These patients often suffer from acidosis, hypothermia, and coagulation abnormalities, which require prompt and ongoing correction. Physiologic restoration is multifactorial and includes careful and limited crystalloid infusion to avoid abdominal compartment syndrome, frequent monitoring of lactate clearance and central
venous oxygen saturation as an indication of satisfactory cardiac output, and the use of viscoelastic techniques (TEG, ROTEM) to assess coagulation status and guide ongoing blood product administration. Recent evidence suggests that peritoneal resuscitation techniques may aid in this process [70, 71].

Various techniques of open abdomen have been described. The author’s preferred mechanism is a simple plastic drape over the bowel, covered with a sterile towel and the use of Ioban over the abdomen. After the initial laparotomy, abdominal closure via negative pressure wound therapy is most commonly used. The open abdomen may help reduce the risk of abdominal compartment syndrome in patients requiring prolonged resuscitation. Various abdominal closure techniques have been described, however, the guiding principle is constant traction on the fascia to facilitate closure [72–75].

**Mesenteric venous thrombosis can often be successfully treated with a continuous infusion of unfractionated heparin. (Recommendation 1B)**

MVT has a distinctive clinical finding on CTA scan, and when noted in a patient without findings of peritonitis, non-operative management should be considered. The first-line treatment for mesenteric venous thrombosis is anticoagulation. Systemic thrombolytic therapy is rarely indicated. When clinical signs demand operative intervention, one should resect only obvious necrotic bowel and employ damage control techniques liberally, since anticoagulation therapy may improve the clinical picture over the ensuing 24–48 h. Early use of heparin has been associated with improved survival [76].

Patients with peritonitis require emergency surgery. Intraoperative management is dictated by the surgical findings, which range from a segmental infarction of small bowel to necrosis of the entire bowel, with or without perforation. The aim of resection is to conserve as much bowel as possible. Second-look laparotomy, 24–48 h later, may avoid the resection of bowel that may be viable. A second-look procedure is mandatory in patients who have extensive bowel involvement.

Most published data on interventional radiological treatments for MVT are from small case series. Systemic intravenous tPA has been successfully reported [77]. Trans-jugular intrahepatic portosystemic shunt can be used for MVT with the rationale of decreasing portal pressure, which works as a vacuum of clot fragments and improves the effectiveness of thrombolysis in the case of acute thrombosis [78–80].

Supportive measures include nasogastric suction, fluid resuscitation, and bowel rest.

When NOMI is suspected, the focus is to correct the underlying cause wherever possible and to improve mesenteric perfusion. Infarcted bowel should be resected promptly. (Recommendation 1B)

Management of NOMI is based on treatment of the underlying precipitating cause. Fluid resuscitation, optimization of cardiac output, and elimination of vasopressors remain important primary measures. Additional treatment may include systemic anticoagulation and the use of catheter-directed infusion of vasodilatory and antispasmodic agents, most commonly papaverine hydrochloride [81]. The decision to intervene surgically is based on the presence of peritonitis, perforation, or overall worsening of the patient’s condition [47].

If a patient presents with peritoneal signs, an exploratory laparotomy is required for resection of frankly necrotic bowel. Unfortunately, these patients are often in critical condition and the mortality remains very high (50–85%) [9]. Damage control mode is an important adjunct, given the critical state of these patients.

The finding of massive gut necrosis requires careful assessment of the patients underlying co-morbidities and advanced directives in order to judge whether comfort carries the best treatment. (Recommendation 1C)

In cases of extensive infarction of most of the small bowel with or without a portion of the colon, the surgeon could face with a philosophical decision whether to do anything. Resection of the entire involved bowel will result in short bowel syndrome with its serious associated consequences. This may not be a preferable state, particularly in elderly infirm patients, who may not tolerate long-term parenteral nutrition. A preoperative discussion with the patient and the patient’s family concerning these issues is warranted and often necessary peri-operatively as well so that an agreeable plan can be reached [82].

**Conclusions**

AMI is a true surgical emergency. First and foremost, important evidence is a high index of suspicion based on the combination of history of abrupt onset of abdominal pain, acidosis, and organ failure. This clinical scenario should prompt imaging (CTA) in order to establish the diagnosis. In parallel with rapid resuscitation and after careful assessment of the CTA, the patient should be explored to assess bowel viability, re-establish vascular flow, and resect non-viable bowel. Subsequently, the employment of damage control techniques and continued critical care resuscitation is essential. Planned re-assessment of the bowel with further resection or anastomosis and stoma as needed is integral. Close cooperation between acute care surgeons, radiologists, anesthetists, and the vascular surgeons is essential.
Appendix
Current recommendations:

**Statement 1**
Severe abdominal pain out of proportion to physical examination findings should be assumed to be AMI until disproven. (Recommendation 1B)

**Statement 2**
Clinical scenario differentiates AMI as mesenteric arterial emboli, mesenteric arterial thrombosis, NOMI, or mesenteric venous thrombosis. (Recommendation 1B)

**Statement 3**
Conventional plain X-ray films have limited diagnostic value in evaluating AMI, although signs of intestinal perforation may be seen. (Recommendation 1B)

**Statement 4**
There are no laboratory studies that are sufficiently accurate to identify the presence or absence of ischemic or necrotic bowel, although elevated l-lactate and D-dimer may assist. (Recommendation 1B)

**Statement 5**
Computed tomography angiography (CTA) should be performed as soon as possible for any patient with suspicion for AMI. (Recommendation 1A)

**Statement 6**
Non-occlusive mesenteric ischemia (NOMI) should be suspected in critically ill patients with abdominal pain or distension requiring vasopressor support and evidence of multi-organ dysfunction. (Recommendation 1B)

**Statement 7**
When the diagnosis of AMI is made, fluid resuscitation should commence immediately to enhance visceral perfusion. Electrolyte abnormalities should be corrected, and nasogastric decompression initiated. (Recommendation 1B)

**Statement 8**
Broad-spectrum antibiotics should be administered immediately. Unless contraindicated, patients should be anticoagulated with intravenous unfractionated heparin. (Recommendation 1B)

**Statement 9**
Prompt laparotomy should be done for patients with overt peritonitis. (Recommendation 1A)

**Statement 10**
Endovascular revascularization procedures may have a role with partial arterial occlusion. (Recommendation 1C)

**Statement 11**
Damage control surgery is an important adjunct for patients who require intestinal resection due to the necessity to reassess bowel viability and in patients with refractory sepsis. Planned re-laparotomy is an essential part of AMI management. (Recommendation 1B)

**Statement 12**
Mesenteric venous thrombosis can often be successfully treated with a continuous infusion of unfractionated heparin. (Recommendation 1B)

**Statement 13**
When NOMI is suspected, the treatment focus should be to correct the underlying cause and to restore mesenteric perfusion. Infarcted bowel should be resected promptly. (Recommendation 1B)

**Statement 14**
The finding of massive gut necrosis requires careful assessment of the patients underlying co-morbidities and advanced directives in order to judge whether comfort carries the best treatment. (Recommendation 1C)

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Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines


Abstract

Background and aims: Acute appendicitis (AA) is among the most common causes of acute abdominal pain. Diagnosis of AA is still challenging and some controversies on its management are still present among different settings and practice patterns worldwide. In July 2015, the World Society of Emergency Surgery (WSES) organized in Jerusalem the first consensus conference on the diagnosis and treatment of AA in adult patients with the intention of producing evidence-based guidelines. An updated consensus conference took place in Nijemegen in June 2019 and the guidelines have now been updated in order to provide evidence-based statements and recommendations in keeping with varying clinical practice: use of clinical scores and imaging in diagnosing AA, indications and timing for surgery, use of non-operative management and antibiotics, laparoscopy and surgical techniques, intra-operative scoring, and peri-operative antibiotic therapy.

(Continued on next page)
Background

Acute abdominal pain accounts for 7–10% of all emergency department accesses [1]. Acute appendicitis (AA) is among the most common causes of lower abdominal pain leading patients to attend the emergency department and the most common diagnosis made in young patients admitted to the hospital with an acute abdomen.

The incidence of AA has been declining steadily since the late 1940s. In developed countries, AA occurs at a rate of 5.7–50 patients per 100,000 inhabitants per year, with a peak between the ages of 10 and 30 [2, 3].

Geographical differences are reported, with a lifetime risk for AA of 9% in the USA, 8% in Europe, and 2% in Africa [4]. Moreover, there is great variation in the presentation, severity of the disease, radiological workup, and surgical management of patients having AA that is related to country income [5].

The rate of perforation varies from 16% to 40%, with a higher frequency occurring in younger age groups (40–57%) and in patients older than 50 years (55–70%) [6].

Appendiceal perforation is associated with increased morbidity and mortality compared with non-perforating AA. The mortality risk of acute but not gangrenous AA is less than 0.1%, but the risk rises to 0.6% in gangrenous AA. On the other hand, perforated AA carries a higher mortality rate of around 5%. Currently, growing evidence suggests that perforation is not necessarily the inevitable result of appendiceal obstruction, and an increasing amount of evidence now suggests not only that not all patients with AA will progress to perforation, but even that resolution may be a common event [7].

The clinical diagnosis of AA is often challenging and involves a synthesis of clinical, laboratory, and radiological findings. The diagnostic workup could be improved by using clinical scoring systems that involve physical examination findings and inflammatory markers. Many simple and user-friendly scoring systems have been used as a structured algorithm in order to aid in predicting the risk of AA, but none has been widely accepted [8–10]. The role of diagnostic imaging, such as ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI), is another major controversy [11, 12].

Since surgeons started performing appendectomies in the nineteenth century, surgery has been the most widely accepted treatment, with more than 300,000 appendectomies performed annually in the USA [13]. Current evidence shows laparoscopic appendectomy (LA) to be the most effective surgical treatment, being associated with a lower incidence of wound infection and post-intervention morbidity, shorter hospital stay, and better quality of life scores when compared to open appendectomy (OA) [14, 15].

Despite all the improvements in the diagnostic process, the crucial decision as to whether to operate or not remains challenging. Over the past 20 years, there has been renewed interest in the non-operative management of uncomplicated AA, probably due to a more reliable analysis of postoperative complications and costs of surgical interventions, which are mostly related to the continuously increasing use of minimally invasive techniques [16–18].

The most common postoperative complications, such as wound infection, intra-abdominal abscess, and ileus, vary in frequency between OA (overall complication rate of 11.1%) and LA (8.7%) [19].

In August 2013, the Organizational Board of the 2nd World Congress of the World Society of Emergency
Surgery (WSES) endorsed its president to organize the first Consensus Conference on AA, in order to develop the WSES Guidelines on this topic. The Consensus Conference on AA was held in Jerusalem, Israel, on July 6, 2015, during the 3rd World Congress of the WSES, following which, the WSES Jerusalem guidelines for diagnosis and treatment of AA were published [20].

Over the last 4 years, major issues still open to debate in the management of AA have been reported concerning the timing of appendectomy, the safety of in-hospital delay, and the indications to interval appendectomy following the resolution of AA with antibiotics [21–24]. Therefore, the board of the WSES decided to convene an update of the 2016 Jerusalem guidelines.

**Materials and methods**

These updated consensus guidelines were written under the auspices of the WSES by the acute appendicitis working group.

The coordinating researcher (S. Di Saverio) invited six experienced surgeons (G. Augustin, A. Birindelli, B. De Simone, M. Podda, M. Sartelli, and M. Ceresoli) with high-level experience in the management of AA to serve as experts in this 2020 update of the WSES Jerusalem guidelines. The experts reviewed and updated the original list of key questions on the diagnosis and treatment of AA addressed in the previous version of the guidelines. The subject of AA was divided into seven main topics: (1) diagnosis, (2) non-operative management of uncomplicated AA, (3) timing of appendectomy and in-hospital delay, (4) surgical treatment, (5) intra-operative grading of AA, (6) management of perforated AA with phlegmon or abscess, and (7) antibiotic prophylaxis and postoperative antibiotic treatment.

Both adults and pediatric populations were considered and specific statements and recommendations were made for each of two groups. Pediatric patients were defined as including children and adolescents aged between 1 and 16 years old. Infants were excluded from this review.

Based upon the list of topics, research questions (Patients/Population, Intervention/Exposure, Comparison, Outcome (PICO)) were formulated, reviewed, and adopted as guidance to conduct an exploratory literature search (Table 1).

The searches were conducted in cooperation with a medical information specialist from the University of Bologna (A. Gori). A computerized search of different databases (MEDLINE, Scopus, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials), and new citations were selected and reviewed in detail to define 48 statements and 51 recommendations addressing seven topics and 30 research questions. A summary of the updated 2020 guidelines statements and recommendations has been reported in (Supplementary material file 1).

The search results were selected and categorized to allow comprehensive published abstract of randomized clinical trials, non-randomized studies, consensus conferences, congress reports, guidelines, government publications, systematic reviews, and meta-analyses.

In the 2016 Jerusalem guidelines, the Oxford classification was used to grade the evidence level (EL) and the grade of recommendation (GoR) for each statement. In this updated document, quality of evidence and strength of recommendations have been evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.

The GRADE system is a hierarchical, evidence-based tool, which systematically evaluates the available literature and focuses on the level of evidence based upon the types of studies included. The quality of evidence (QoE) can be marked as high, moderate, low, or very low. This could be either downgraded in case of significant bias or upgraded when multiple high-quality studies showed consistent results. The highest quality of evidence studies (systematic reviews with meta-analysis of randomized controlled trials) was assessed first. If the meta-analysis was of sufficient quality, it was used to answer the research question. If no meta-analysis of sufficient quality was found, randomized controlled trials (RCTs) and non-randomized cohort studies (n-RCS) were evaluated. The strength of the recommendation (SoR) was based on the level of evidence and qualified as weak or strong (Table 2) [25–28].

The first draft of the updated statements and recommendations was commented on by the steering group of the guidelines and the board of governors of the WSES during the 6th WSES congress held in Nijmegen, Holland (26–28 June 2019). Amendments were made based upon the comments, from which a second draft of the consensus document was generated. All finalized statements and recommendations with QoE and SoR were entered into a web survey and distributed to all the authors and the board of governor’s members of the WSES by e-mail. The web survey was open from December 1, 2019, until December 15, 2019. The authors were asked to anonymously vote on each statement and recommendation and indicate if they agreed, (> 70% “yes” was categorized as agreement), leading to the final version of the document.

**Results**

The literature search yielded 984 articles. The titles, abstracts, and full text were reviewed. In total, 157 articles were selected and reviewed in detail to define 48 statements and 51 recommendations addressing seven topics and 30 research questions. A summary of the updated 2020 guidelines statements and recommendations has been reported in Table 3.
<table>
<thead>
<tr>
<th>Topic</th>
<th>Key questions</th>
</tr>
</thead>
</table>
| **1. Diagnosis** | Q.1.1: What is the value of clinical scoring systems in the management of adult patients with suspected appendicitis? Can they be used as a basis for a structured management?  
Q.1.2: In pediatric patients with suspected acute appendicitis could the diagnosis be based only on clinical scores?  
Q.1.3: What is the role of serum biomarkers in evaluating adult patients presenting with clinical features evocative of acute appendicitis?  
Q.1.4: What is the role of serum biomarkers in evaluating pediatric patients presenting clinical features highly suggestive of acute appendicitis?  
Q.1.5: What is the optimum pathway for imaging in adult patients with suspected acute appendicitis?  
Q.1.6: What is the optimum pathway for imaging in pediatric patients with suspected acute appendicitis? |
| **2. Non-operative management of uncomplicated acute appendicitis** | Q.2.1: Is non-operative management with or without antibiotics a safe and effective treatment option for adult patients with uncomplicated acute appendicitis?  
Q.2.2: Is non-operative management with or without antibiotics a safe and effective treatment option for pediatric patients with uncomplicated acute appendicitis?  
Q.2.3: What is the best non-operative management of patients with uncomplicated acute appendicitis? |
| **3. Timing of appendectomy and in-hospital delay** | Q.3.1: Does in-hospital delay increase the rate of complications or perforation for adult patients with uncomplicated acute appendicitis?  
Q.3.2: Does in-hospital delay increase the rate of complications or perforation for pediatric patients with uncomplicated acute appendicitis? |
| **4. Surgical treatment** | Q.4.1: Does laparoscopic appendectomy confer superior outcomes compared with open appendectomy for adult patients with acute appendicitis?  
Q.4.2: Does laparoscopic appendectomy confer superior outcomes compared with open appendectomy for pediatric patients with acute appendicitis?  
Q.4.3: Does laparoscopic single-incision surgery confer any advantage over the three-trocar technique in performing laparoscopic appendectomy for adult patients with acute appendicitis?  
Q.4.4: Does laparoscopic single-incision surgery confer any advantage over the three-trocar technique in performing laparoscopic appendectomy for pediatric patients with acute appendicitis?  
Q.4.5: Is outpatient laparoscopic appendectomy safe and feasible for patients with uncomplicated acute appendicitis?  
Q.4.6: Is laparoscopic appendectomy indicated over open appendectomy in specific patient groups?  
Q.4.7: Does aspiration alone confer clinical advantages over lavage and aspiration for patients with complicated acute appendicitis?  
Q.4.8: Does the type of mesoappendix dissection technique (endoclip, endoloop, electrocoagulation, Harmonic Scalpel, or LigaSure) produce different clinical outcomes for patients with acute appendicitis undergoing appendectomy?  
Q.4.9: Does the type of stump closure technique (stapler or endoloop, ligation or invagination of the stump) produce different clinical outcomes for patients with acute appendicitis undergoing appendectomy?  
Q.4.10: Is the use of abdominal drains recommended after appendectomy for complicated acute appendicitis in adult patients?  
Q.4.11: Is the use of abdominal drains recommended after appendectomy for complicated acute appendicitis in pediatric patients?  
Q.4.12: What are the best methods to reduce the risk of SSI in open appendectomies with contaminated/dirty wounds? |
| **5. Intra-operative grading of acute appendicitis** | Q.5.1: What is the value of scoring systems for intra-operative grading of acute appendicitis?  
Q.5.2: Should the macroscopically normal appendix be removed during laparoscopy for acute right iliac fossa pain when no other explanatory pathology is found? |
| **6. Management of perforated appendicitis with phlegmon or abscess** | Q.6.1: Is early appendectomy an appropriate treatment compared with delayed appendectomy for patients with perforated acute appendicitis with phlegmon or abscess?  
Q.6.2: Is interval appendectomy always indicated for patients with acute appendicitis following successful NOM? |
| **7. Perioperative antibiotic therapy** | Q.7.1: Is preoperative antibiotic therapy recommended for patients with acute appendicitis?  
Q.7.2: Are postoperative antibiotics always indicated in adult patients following appendectomy?  
Q.7.3: Are postoperative antibiotics always indicated in pediatric patients following appendectomy? |
<table>
<thead>
<tr>
<th>Quality of evidence and strength of recommendation</th>
<th>Clarity of balance between desirable and undesirable effects</th>
<th>Methodological quality of supporting evidence</th>
<th>Implications</th>
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<td>High-quality evidence, strong recommendation</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate effect</td>
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<tr>
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<td>Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirectness, imprecision) or exceptionally strong evidence from unbiased observational studies</td>
<td>Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
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<td>Low-quality evidence, strong recommendation</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
<td>Evidence for at least one critical outcome from observational studies, RCTs with serious flaws or indirect evidence</td>
<td>Recommendation may change when higher quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
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<tr>
<td>Very low-quality evidence, strong recommendation</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
<td>Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence</td>
<td>Recommendation may change when higher quality evidence becomes available; any estimate of effect for at least one critical outcome is very uncertain</td>
</tr>
<tr>
<td>High-quality evidence, weak recommendation</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from observational studies</td>
<td>The best action may differ depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate effect</td>
</tr>
<tr>
<td>Moderate quality evidence, weak recommendation</td>
<td>Desirable effects closely balanced with undesirable effects</td>
<td>Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirectness, imprecision) or exceptionally strong evidence from unbiased observational studies</td>
<td>Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Low-quality evidence, weak recommendation</td>
<td>Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced</td>
<td>Evidence for at least one critical outcome from observational studies, RCTs with serious flaws or indirect evidence</td>
<td>Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
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<tr>
<td>Very low-quality evidence, weak recommendation</td>
<td>Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects</td>
<td>Evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence</td>
<td>Other alternatives may be equally reasonable. Any estimate of effect, for at least one critical outcome, is very uncertain</td>
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</table>
Table 3 Summary of the updated 2020 guidelines statements and recommendations

<table>
<thead>
<tr>
<th>Topic</th>
<th>Statement</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1. Diagnosis</td>
<td>Statement 1.1 Establishing the diagnosis of acute appendicitis based on clinical presentation and physical examination may be challenging. As the value of individual clinical variables to determine the likelihood of acute appendicitis in a patient is low, a tailored individualized approach is recommended, depending on disease probability, sex, and age of the patient.</td>
<td>Recommendation 1.1 We recommend to adopt a tailored individualized diagnostic approach for stratifying the risk and disease probability and planning an appropriate stepwise diagnostic pathway in patients with suspected acute appendicitis, depending on age, sex and clinical signs and symptoms of the patient [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td>Statement 1.2 Clinical scores alone, e.g. Alvarado score, AIR score, and the new Adult Appendicitis Score are sufficiently sensitive to exclude acute appendicitis, accurately identifying low-risk patients and decreasing the need for imaging and the negative appendectomy rates in such patients.</td>
<td>Recommendation 1.2.1 We recommend the use of clinical scores to exclude acute appendicitis and identify intermediate-risk patients needing of imaging diagnostics [QoE: High; Strength of recommendation: Strong; 1A]. Recommendation 1.2.2 We suggest not making the diagnosis of acute appendicitis in pregnant patients on symptoms and signs only. Laboratory tests and inflammatory serum parameters should always be requested [QoE: Very Low; Strength of recommendation: Weak; 2C].</td>
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<td>Statement 1.3 The Alvarado score is not sufficiently specific in diagnosing acute appendicitis in adults, seems unreliable in differentiating complicated from uncomplicated acute appendicitis in elderly patients and is less sensitive in patients with HIV.</td>
<td>Recommendation 1.3 We suggest against the use of Alvarado score to positively confirm the clinical suspicion of acute appendicitis in adults [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td>Statement 1.4 The AIR score and the AAS score seem currently to be the best performing clinical prediction scores and have the highest discriminating power in adults with suspected acute appendicitis. The AIR and AAS scores decrease negative appendectomy rates in low-risk groups and reduce the need for imaging studies and hospital admissions in both low and intermediate-risk groups.</td>
<td>Recommendation 1.4 We recommend the use of AIR score and AAS score as clinical predictors of acute appendicitis [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td>Statement 1.5 In pediatric patients with suspected acute appendicitis, the Alvarado score and Pediatric Appendicitis Score are useful tools in excluding acute appendicitis.</td>
<td>Recommendation 1.5 In pediatric patients with suspected acute appendicitis, we suggest against making a diagnosis based on clinical scores alone [QoE: Low; Strength of recommendation: Weak; 2C].</td>
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<td>Statement 1.6 Biochemical markers represent a promising reliable diagnostic tool for the identification of both negative cases or complicated acute appendicitis in adults. However, further high-quality evidence is needed [QoE: Low; No recommendation].</td>
<td>Recommendation 1.6.1 In evaluating children with suspected appendicitis, we recommend to request routinely laboratory tests and serum inflammatory biomarkers [QoE: Very Low; Strength of recommendation: Strong; 1D]. Recommendation 1.6.2 In pediatric patients with suspected acute appendicitis, we suggest adopting both biomarker tests and scores in order to predict the severity of the inflammation and the need for imaging investigation [QoE: Very Low; Strength of recommendation: Weak 2D].</td>
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<td>Statement 1.7 White blood cell count, the differential with the calculation of the absolute neutrophil count, and the CRP are useful lab tests in predicting acute appendicitis in children; moreover, CRP level on admission ≥ 10 mg/L and leucocytosis ≥ 16,000/mL are strong predictive factors for appendicitis in pediatric patients.</td>
<td>Recommendation 1.7 We recommend the routine use of a combination of clinical parameters and US to improve diagnostic sensitivity and specificity and eventually replace the need for a CT scan in adult patients with suspected acute appendicitis.</td>
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<td>Statement 1.8 Combination of US and clinical (e.g. AIR, AAS scores) parameters forming combined clinico-radiological scores may significantly improve diagnostic sensitivity and specificity and eventually replace the need for a CT scan in adult patients with suspected acute appendicitis.</td>
<td>Recommendation 1.8 We suggest proceeding with timely and systematic diagnostic imaging in patients with intermediate-risk of acute appendicitis [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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| | Statement 1.9 Intermediate-risk classification identifies patients likely to benefit from observation and systematic diagnostic imaging. | Recommendation 1.9 We suggest that cross-sectional imaging (i.e., CT scan) in
Table 3 Summary of the updated 2020 guidelines statements and recommendations (Continued)

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<td>1. Appendicitis according to AIR score/Alvarado score/AAS score and younger than 40 years may not require cross-sectional pre-operative imaging (i.e., CT scan).</td>
<td><strong>Statement 1.11</strong> POCUS (Point-of-care Ultrasound) is a reliable initial investigation with satisfactory sensitivity and specificity in diagnosing acute appendicitis, easing swift decision-making by the emergency physicians or surgeons. POCUS, if performed by an experienced operator, should be considered the most appropriate first-line diagnostic tool in both adults and children.</td>
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<td><strong>Recommendation 1.10</strong> We recommend POCUS as the most appropriate first-line diagnostic tool in both adults and children, if an imaging investigation is indicated based on clinical assessment [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td>When it is indicated, contrast-enhanced low-dose CT scan should be preferred over contrast-enhanced standard-dose CT scan. Diagnostic accuracy of contrast-enhanced low-dose CT is not inferior to standard CT in diagnosing AA or distinguishing between uncomplicated and complicated acute appendicitis and enables significant radiation dose reduction.</td>
<td><strong>Statement 1.12</strong> When it is indicated, contrast-enhanced low-dose CT scan should be preferred over contrast-enhanced standard-dose CT scan. Diagnostic accuracy of contrast-enhanced low-dose CT is not inferior to standard CT in diagnosing AA or distinguishing between uncomplicated and complicated acute appendicitis and enables significant radiation dose reduction.</td>
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<td><strong>Recommendation 1.11</strong> We recommend the use of contrast-enhanced low-dose CT scan over contrast-enhanced standard-dose CT scan for adolescents and young adults with suspected acute appendicitis and negative US findings [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td>In patients with normal investigations and symptoms unlikely to be acute appendicitis but which do not settle, cross-sectional imaging is recommended before surgery. Laparoscopy is recommended to establish/exclude the diagnosis of acute appendicitis and eventually treat the disease.</td>
<td><strong>Statement 1.13</strong> In patients with normal investigations and symptoms unlikely to be acute appendicitis but which do not settle, cross-sectional imaging is recommended before surgery. Laparoscopy is recommended to establish/exclude the diagnosis of acute appendicitis and eventually treat the disease.</td>
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<tr>
<td><strong>Recommendation 1.12</strong> We recommend cross-sectional imaging before surgery for patients with normal investigations but non-resolving right iliac fossa pain. After negative imaging, initial non-operative treatment is appropriate. However, in patients with progressive or persistent pain, explorative laparoscopy is recommended to establish/exclude the diagnosis of acute appendicitis or alternative diagnoses [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td>MRI is sensitive and highly specific for the diagnosis of acute appendicitis during pregnancy. However, a negative or inconclusive MRI does not exclude appendicitis and surgery should be still considered if high clinical suspicion.</td>
<td><strong>Statement 1.14</strong> MRI is sensitive and highly specific for the diagnosis of acute appendicitis during pregnancy. However, a negative or inconclusive MRI does not exclude appendicitis and surgery should be still considered if high clinical suspicion.</td>
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<td><strong>Recommendation 1.13.1</strong> We suggest graded compression trans-abdominal ultrasound as the preferred initial imaging method for suspected acute appendicitis during pregnancy [QoE: Very Low; Strength of Recommendation: Weak; 2C]. <strong>Recommendation 1.13.2</strong> We suggest MRI in pregnant patients with suspected appendicitis, if this resource is available, after inconclusive US [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td>The use of US in children is accurate and safe in terms of perforation rates, emergency department re-visits, and negative appendectomy rates. CT use may be decreased by using appropriate clinical and/or staged algorithm with US/MRI. MRI has at least the same sensitivity and specificity as CT and, although higher costs, should be preferred over CT as second-line imaging in children.</td>
<td><strong>Statement 1.15</strong> The use of US in children is accurate and safe in terms of perforation rates, emergency department re-visits, and negative appendectomy rates. CT use may be decreased by using appropriate clinical and/or staged algorithm with US/MRI. MRI has at least the same sensitivity and specificity as CT and, although higher costs, should be preferred over CT as second-line imaging in children.</td>
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<td><strong>Recommendation 2.1.1</strong> We recommend discussing NOM with antibiotics as a safe alternative to surgery in selected patients with uncomplicated acute appendicitis. Patients who wish to avoid surgery must be aware of a risk of recurrence of up to 39% after 5 years. Most recent data from meta-analyses of RCTs showed that NOM with antibiotics achieves a significantly lower overall complication rate at 5 years and shorter sick leave compared to surgery.</td>
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<td><strong>Recommendation 2.1.2</strong> Since in pediatric patients with equivocal CT finding the prevalence of true acute appendicitis is not negligible, we suggest against the routine use of CT as first-line imaging in children with right iliac fossa pain [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td>NOM for uncomplicated acute appendicitis in children is feasible, safe and effective as initial treatment. However, failure rate increases in the presence of appendicolith, and surgery is recommended in such cases.</td>
<td><strong>Statement 2.2</strong> NOM for uncomplicated acute appendicitis in children is feasible, safe and effective as initial treatment. However, failure rate increases in the presence of appendicolith, and surgery is recommended in such cases.</td>
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<td><strong>Recommendation 2.2.1</strong> We suggest discussing NOM with antibiotics as a safe and effective alternative to surgery in children with uncomplicated acute appendicitis in the absence of an appendicolith, advising of the possibility of failure and misdiagnosing complicated appendicitis [QoE: Moderate; Strength of recommendation: Weak; 2C].</td>
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<td><strong>Statement 2.3</strong> Current evidence supports initial intravenous antibiotics with subsequent conversion to oral antibiotics until further evidence from ongoing RCT is available.</td>
<td>Recommendation: Weak; 2B.</td>
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<td><strong>Statement 2.4</strong> Uncomplicated acute appendicitis may safely resolve spontaneously with similar treatment failure rates, shorter length of stay and costs compared with antibiotics. However, there is still limited data for the panel to express in favor of or against the symptomatic treatment without antibiotics [QoE: Moderate; No recommendation].</td>
<td>Recommendation 2.3 In the case of NOM, we recommend initial intravenous antibiotics with a subsequent switch to oral antibiotics based on patient’s clinical conditions [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td>3. Timing of appendectomy and in-hospital delay</td>
<td><strong>Statement 3.1</strong> Short, in-hospital surgical delay up to 24 h is safe in uncomplicated acute appendicitis and does not increase complications and/or perforation rate in adults. Surgery for uncomplicated acute appendicitis can be planned for the next available list minimizing delay wherever possible (better patient comfort, etc.). Short, in-hospital delay with observation and repeated trans-abdominal US in pregnant patients with equivocal appendicitis is acceptable and does not seem to increase the risk of maternal and fetal adverse outcomes.</td>
<td>Recommendation 3.1 We recommend planning laparoscopic appendectomy for the next available operating list within 24 h in case of uncomplicated acute appendicitis, minimizing the delay wherever possible [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 3.2</strong> Delaying appendectomy for uncomplicated acute appendicitis for up to 24 h after admission does not appear to be a risk factor for complicated appendicitis, postoperative surgical site infection or morbidity. Conversely, appendectomies performed after 24 h from admission are related to an increased risk of adverse outcomes.</td>
<td>Recommendation 3.2 We recommend against delaying appendectomy for acute appendicitis needing surgery beyond 24 h from the admission [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 3.3</strong> Appendectomy performed within the first 24 h from presentation in the case of uncomplicated appendicitis is not associated with an increased risk of perforation or adverse outcomes. Early appendectomy is the best management in complicated appendicitis.</td>
<td>Recommendation 3.3 We suggest against delaying appendectomy for pediatric patients with uncomplicated acute appendicitis needing surgery beyond 24 h from the admission. Early appendectomy within 8 h should be performed in case of complicated appendicitis [QoE: Low; Strength of Recommendation: Weak; 2C].</td>
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<tr>
<td>4. Surgical treatment</td>
<td><strong>Statement 4.1</strong> Laparoscopic appendectomy offers significant advantages over open appendectomy in terms of less pain, lower incidence of surgical site infection, decreased length of hospital stay, earlier return to work, overall costs, and better quality of life scores.</td>
<td>Recommendation 4.1 We recommend laparoscopic appendectomy as the preferred approach over open appendectomy for both uncomplicated and complicated acute appendicitis, where laparoscopic equipment and expertise are available [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td><strong>Statement 4.2</strong> Laparoscopic appendectomy is associated with lower postoperative pain, lower incidence of SSI and higher quality of life in children.</td>
<td>Recommendation 4.2 We recommend laparoscopic appendectomy should be preferred over open appendectomy in children where laparoscopic equipment and expertise are available [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 4.3</strong> Single-incision laparoscopic appendectomy is basically feasible, safe, and as effective as conventional three-port laparoscopic appendectomy, operative times are longer, requires higher doses of analgesia, and is associated with a higher incidence of wound infection.</td>
<td>Recommendation 4.3 We recommend conventional three-port laparoscopic appendectomy over single-incision laparoscopic appendectomy, as the conventional laparoscopic approach is associated with shorter operative times, less postoperative pain, and lower incidence of wound infection [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td><strong>Statement 4.4</strong> In children with acute appendicitis, the single incision/transumbilical extracorporeal laparoscopic-assisted technique is as safe as the laparoscopic three-port technique.</td>
<td>Recommendation 4.4 In pediatric patients with acute appendicitis and favorable anatomy, we suggest performing single incision/transumbilical extracorporeal laparoscopic assisted appendectomy or traditional three-port laparoscopic appendectomy based on local skills and expertise [QoE: Low; Strength of recommendation: Weak; 2C].</td>
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<td><strong>Statement 4.5</strong> Outpatient laparoscopic appendectomy for uncomplicated acute appendicitis is feasible and safe without any difference in morbidity and</td>
<td>Recommendation 4.5 We suggest the adoption of outpatient laparoscopic appendectomy for uncomplicated appendicitis, provided that an ambulatory</td>
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<td>readmission rates. It is associated with potential benefits of earlier recovery after surgery and lower hospital and social costs.</td>
<td><strong>Statement 4.6</strong> Laparoscopic appendectomy seems to show relevant advantages compared to open appendectomy in obese adult patients, older patients, and patients with comorbidities. Laparoscopic appendectomy is associated with reduced mortality, reduced overall morbidity, reduced superficial wound infections, shorter operating times and postoperative length of hospital stay in such patients.</td>
<td><strong>Recommendation 4.6</strong> We suggest laparoscopic appendectomy in obese patients, older patients and patients with high peri- and postoperative risk factors [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td><strong>Statement 4.7</strong> Laparoscopic appendectomy during pregnancy is safe in terms of risk of fetal loss and preterm delivery and it is preferable to open surgery as associated to shorter length of hospital stay and lower incidence of surgical site infection.</td>
<td></td>
<td><strong>Recommendation 4.7</strong> We suggest laparoscopic appendectomy should be preferred to open appendectomy in pregnancy patients when surgery is indicated. Laparoscopy is technically safe and feasible during pregnancy where expertise of laparoscopy is available [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 4.8</strong> Peritoneal irrigation does not have any advantage over suction alone in complicated appendicitis in both adults and children. The performance of irrigation during laparoscopic appendectomy does not seem to prevent the development of IAA and wound infections in neither adults nor pediatric patients.</td>
<td></td>
<td><strong>Recommendation 4.8</strong> We recommend performing suction alone in complicated appendicitis patients with intra-abdominal collections undergoing laparoscopic appendectomy [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 4.9</strong> There are no clinical differences in outcomes, length of hospital stay and complications rates between the different techniques described for mesentery dissection (monopolar electrocoagulation, bipolar energy, metal clips, endoloops, LigaSure, Harmonic Scalpel, etc.).</td>
<td></td>
<td><strong>Recommendation 4.9</strong> We suggest the use of monopolar electrocoagulation and bipolar energy as they are the most cost-effective techniques, whereas other energy devices can be used depending on the intra-operative judgment of the surgeon and resources available [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td><strong>Statement 4.10</strong> There are no clinical advantages in the use of endostaplers over endoloops for stump closure for both adults and children in either simple or complicated appendicitis, except for a lower incidence of wound infection when using endostaplers in children with uncomplicated appendicitis. Polymeric clips may be the cheapest and easiest method (with shorter operative times) for stump closure in uncomplicated appendicitis.</td>
<td></td>
<td><strong>Recommendation 4.10</strong> We recommend the use of endostaplers/suture ligation or polymeric clips for stump closure for both adults and children in either uncomplicated or complicated appendicitis whereas endostaplers may be used when dealing with complicated cases depending on the intra-operative judgment of the surgeon and resources available [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 4.11</strong> Simple ligation should be preferred to stump inversion, either in open or laparoscopic surgery, as the major morbidity and infectious complications are similar. Simple ligation is associated with shorter operative times, less postoperative ileus and quicker recovery.</td>
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<td><strong>Recommendation 4.11</strong> We recommend simple ligation over stump inversion either in open and laparoscopic appendectomy [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td><strong>Statement 4.12</strong> In adult patients, the use of drains after appendectomy for perforated appendicitis and abscess/peritonitis should be discouraged. Drains are of no benefit in preventing intra-abdominal abscess and lead to longer length of hospitalization and there is also low-quality evidence of increased 30-day morbidity and mortality rates in patients in the drain group.</td>
<td></td>
<td><strong>Recommendation 4.12</strong> We recommend against the use of drains following appendectomy for complicated appendicitis in adult patients [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 4.13</strong> The prophylactic use of abdominal drainage after laparoscopic appendectomy for perforated appendicitis in children does not prevent postoperative complications and may be associated with negative outcomes.</td>
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<td><strong>Recommendation 4.13</strong> We suggest against the prophylactic use of abdominal drainage after laparoscopic appendectomy for complicated appendicitis in children [QoE: Low; Strength of recommendation: Weak; 2C].</td>
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<td><strong>Statement 4.14</strong> The use of wound ring protectors shows some evidence of surgical site infection reduction in open appendectomy, especially in case of complicated appendicitis with contaminated/dirty wounds.</td>
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<td><strong>Recommendation 4.14</strong> We recommend wound ring protectors in open appendectomy to decrease the risk of SSI [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 4.15</strong> Delayed primary skin closure increases the length of hospital stay and overall costs in open appendectomies with contaminated/dirty wounds and does not reduce the risk of SSI. Subcuticular suture seems preferable in open appendectomy with well-defined ERAS protocols and patient information/consent are locally established [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td><strong>Recommendation 4.15</strong> We recommend primary skin closure with a unique absorbable intradermal suture for open appendectomy wounds [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td>5. Intra-operative grading of acute appendicitis</td>
<td><strong>Statement 5.1</strong> The incidence of unexpected findings in appendectomy specimens is low. The intra-operative diagnosis alone is insufficient for identifying unexpected disease. From the currently available evidence, routine histopathology is necessary.</td>
<td><strong>Recommendation 5.1</strong> We recommend routine histopathology after appendectomy [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 5.2</strong> Operative findings and intra-operative grading seem to correlate better than histopathology with morbidity, overall outcomes, and costs, both in adults and children. Intra-operative grading systems can help the identification of homogeneous groups of patients, determining optimal postoperative management according to the grade of the disease and ultimately improve the utilization of resources.</td>
<td><strong>Recommendation 5.2</strong> We suggest the routine adoption of an intra-operative grading system for acute appendicitis (e.g., WSES 2015 grading score or AAST EGS grading score) based on clinical, imaging and operative findings [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td><strong>Statement 5.3</strong> Surgeon’s macroscopic judgment of early grades of acute appendicitis is inaccurate and highly variable. The variability in the intra-operative classification of appendicitis influences the decision to prescribe postoperative antibiotics and should be therefore prevented/avoided.</td>
<td><strong>Recommendation 5.3</strong> We suggest appendix removal if the appendix appears “normal” during surgery and no other disease is found in symptomatic patients [QoE: Low; Strength of recommendation: Weak; 2C].</td>
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<td>6. Management of perforated appendicitis with phlegmon or abscess</td>
<td><strong>Statement 6.1</strong> Non-operative management is a reasonable first-line treatment for appendicitis with phlegmon or abscess. Percutaneous drainage as an adjunct to antibiotics, if accessible, could be beneficial, although there is a lack of evidence for its use on a routine basis. Laparoscopic surgery in experienced hands is a safe and feasible first-line treatment for appendiceal abscess, being associated with fewer readmissions and fewer additional interventions than conservative treatment, with a comparable hospital stay.</td>
<td><strong>Recommendation 6.1</strong> We suggest non-operative management with antibiotics and—if available—percutaneous drainage for complicated appendicitis with periappendicular abscess, in settings where laparoscopic expertise is not available [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td><strong>Statement 6.2</strong> Operative management of acute appendicitis with phlegmon or abscess is a safe alternative to non-operative management in experienced hands, and may be associated with shorter LOS, reduced need for readmissions and fewer additional interventions than conservative treatment.</td>
<td><strong>Recommendation 6.2</strong> We suggest the laparoscopic approach as treatment of choice for patients with complicated appendicitis with phlegmon or abscess where advanced laparoscopic expertise is available, with a low threshold for conversion [QoE: Moderate; Strength of recommendation: Weak; 2B].</td>
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<td><strong>Statement 6.3</strong> The reported rate of recurrence after non-surgical treatment for perforated AA and phlegmon ranges from 12% to 24%. Interval appendectomy and repeated NOM in case of recurrence of appendiceal phlegmon are associated with similar morbidity. However, elective interval appendectomy is related to additional operative costs to prevent recurrence in only one of eight patients, such as not to justify the routine performance of appendectomy.</td>
<td><strong>Recommendation 6.3</strong> We recommend against routine interval appendectomy after NOM for complicated appendicitis in young adults (&lt; 40 years old) and children. Interval appendectomy is recommended for those patients with recurrent symptoms [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td><strong>Statement 6.4</strong> The incidence of appendicular neoplasms is high (3–17%) in adult patients ≥ 40 years old with complicated appendicitis.</td>
<td><strong>Recommendation 6.4</strong> We suggest both colonic screening with colonoscopy and interval full-dose contrast-enhanced CT scan for patients with appendicitis treated non-operatively if ≥ 40 years old [QoE: Low; Strength of recommendation: Weak; 2C].</td>
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<td>7. Perioperative antibiotic therapy</td>
<td><strong>Statement 7.1</strong> A single dose of broad-spectrum antibiotics given preoperatively (from 0 to 60 min before the surgical skin incision) has been shown to be effective in decreasing wound infection and postoperative intra-abdominal abscess, regardless of the degree of inflammation of the removed appendix.</td>
<td><strong>Recommendation 7.1</strong> We recommend a single preoperative dose of broad-spectrum antibiotics in patients with acute appendicitis undergoing appendectomy. We recommend against postoperative antibiotics for patients with uncomplicated appendicitis [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td><strong>Statement 7.2</strong> In patients with complicated acute appendicitis, postoperative broad-spectrum antibiotics are suggested, especially if complete source control has not been achieved. For adult patients deemed to require them, discontinuation of antibiotics after 24 h seems safe and is associated with shorter length of hospital stay.</td>
<td><strong>Recommendation 7.2</strong> We recommend against prolonging antibiotics longer than 3–5 days postoperatively in case of complicated appendicitis with adequate source-control [QoE: High; Strength of recommendation: Strong; 1A].</td>
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<td>hospital stay and lower costs. In patients with intra-abdominal infections who had undergone an adequate source control, the outcomes after fixed-duration antimicrobial therapy (approximately 3–5 days) are similar to those after a longer course of antibiotics.</td>
<td><strong>Statement 7.3</strong> Administering postoperative antibiotics orally in children with complicated appendicitis for periods shorter than 7 days postoperatively seems to be safe and it is not associated with increased risk of complications. Early transition to oral antibiotics is safe, effective, and cost-efficient in the treatment of complicated appendicitis in the child.</td>
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<td><strong>Recommendation 7.3</strong> We recommend early switch (after 48 h) to oral administration of postoperative antibiotics in children with complicated appendicitis, with an overall length of therapy shorter than 7 days [QoE: Moderate; Strength of recommendation: Strong; 1B].</td>
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<td>Postoperative antibiotics after appendectomy for uncomplicated acute appendicitis in children seems to have no role in reducing the rate of surgical site infection.</td>
<td><strong>Statement 7.4</strong></td>
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<td><strong>Recommendation 7.4</strong> In pediatric patients operated for uncomplicated acute appendicitis, we suggest against using postoperative antibiotic therapy [QoE: Low; Strength of recommendation: Weak; 2C].</td>
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**Topic 1: Diagnosis**

**Q.1.1: What is the value of clinical scoring systems in the management of adult patients with suspected appendicitis?**

Can they be used as basis for a structured management?

RISK stratification of patients with suspected AA by clinical scoring systems could guide decision-making to reduce admissions, optimize the utility of diagnostic imaging, and prevent negative surgical explorations. Clinical scores alone seem sufficiently sensitive to identify low-risk patients and decrease the need for imaging and negative surgical explorations (such as diagnostic laparoscopy) in patients with suspected AA.

The RCT by Andersson et al. demonstrated that, in low-risk patients, the use of an AIR (Appendicitis Inflammatory Response) score-based algorithm resulted in less imaging (19.2% vs 34.5%, *P* = 0.001), fewer admissions (29.5% vs 42.8%, *P* < 0.001), fewer negative explorations (1.6% vs 3.2%, *P* = 0.030), and fewer surgical operations for non-perforated AA (6.8% vs 9.7%, *P* = 0.034). Intermediate-risk patients randomized to the imaging and observation strategies had the same proportion of negative appendectomies (6.4% vs 6.7%, *P* = 0.884), number of hospital admissions, rates of perforation, and length of hospital stay, but routine imaging was associated with an increased proportion of patients treated for AA (53.4% vs 46.3%, *P* = 0.020) [29].

Among the many available clinical prediction models for the diagnosis of AA, the AIR score appears to be the best performer and most pragmatic. The review by Kularatna et al. recently summarized the results from validation studies, showing that the overall best performer in terms of sensitivity (92%) and specificity (63%) is the AIR score [30].

Although the Alvarado score is not sufficiently specific in diagnosing AA, a cutoff score of < 5 is sufficiently sensitive to exclude AA (sensitivity of 99%). The Alvarado score could, therefore, be used to reduce emergency department length of stay and radiation exposure in patients with suspected AA. This is confirmed by a large retrospective cohort study that found 100% of males with Alvarado score of 9 or greater, and 100% of females with an Alvarado score of 10 had AA confirmed by surgical pathology. Conversely, 5% or less of female patients with an Alvarado score of 2 or less and 0% of male patients with an Alvarado score of 1 or less were diagnosed with AA at surgery [31].

However, the Alvarado score is not able to differentiate complicated from uncomplicated AA in elderly patients and seems less sensitive in HIV+ patients [32, 33].

The RIPASA (Raja Isteri Pengiran Anak Saleha Appendicitis) score has shown to achieve better sensitivity and specificity than the Alvarado score in Asian and Middle Eastern population. Malik et al. recently published the first study evaluating the utility of the RIPASA score in predicting AA in a Western population. At a value of 7.5 (a cut of score suggestive of AA in the Eastern population), the RIPASA demonstrated reasonable sensitivity (85.39%), specificity (69.86%), positive predictive value (84.06%), negative predictive value (72.86%), and diagnostic accuracy (80%) in Irish patients with suspected AA and was more accurate than the Alvarado score [34].

The Adult Appendicitis Score (AAS) stratifies patients into three groups: high, intermediate, and low risk of AA. The score has been shown to be a reliable tool for stratification of patients into selective imaging, which results in a low negative appendectomy rate. In a prospective study enrolling 829 adults presenting with clinical suspicion of AA, 58% of patients with histologically confirmed AA had score value at least 16 and were classified as high probability group with 93% specificity. Patients with a score below 11 were classified as low probability of AA. Only 4% of patients with AA had a score below 11, and none of them had complicated AA. In contrast, 54% of non-AA patients had a score below 11. The area under ROC curve was significantly larger with the new score 0.882 compared with AUC of Alvarado score 0.790 and AIR score 0.810 [11].

In the validation study by Sammalkorpi et al., the AAS score stratified 49% of all AA patients into a high-risk group with the specificity of 93.3%, whereas in the low-risk group the prevalence of AA was 7%. The same study group demonstrated that diagnostic imaging has limited value in patients with a low probability of AA according to the AAS [35].

Tan et al. recently performed a prospective data collection on 350 consecutive patients with suspected AA for whom the Alvarado score for each patient was scored at admission and correlated with eventual histology and CT findings. The positive likelihood ratio of disease was significantly greater than 1 only in patients with an Alvarado score of 4 and above. An Alvarado score of 7 and above in males and 9 and above in females had a positive likelihood ratio comparable to that of CT scan [36].

Nearly all clinical signs and symptoms, as isolated parameters, do not significantly discriminate between those pregnant women with and without AA [37–39].

Of 15 validated risk prediction models taken into consideration in a recently published study enrolling 5345 patients with right iliac fossa pain across 154 UK hospitals, the AAS performed best for women (cutoff score 8 or less, specificity 63.1%, failure rate 3.7%), whereas the AIR score performed best for men (cutoff score 2 or less, specificity 24.7%, failure rate 2.4%) [40].

The Alvarado score can be higher in pregnant women due to the higher WBC values and the frequency of nausea and vomiting, especially during the first trimester,
implicating lower accuracy compared to the non-pregnant population. Studies show Alvarado score (cutoff 7 points) sensitivity of 78.9% and specificity of 80.0% in pregnant patients [41, 42]. The RIPASA score has a specificity (cutoff 7.5 points) of 96%, but the score should be validated in larger studies. There are no studies of the Alvarado score discriminating between uncomplicated and complicated AA during pregnancy.

The preoperative distinction between uncomplicated and complicated AA is challenging. Recently, prediction models based on temperature, CRP, presence of free fluids on ultrasound, and diameter of the appendix have been shown to be useful for the identification of “high-risk” patients for complicated AA. Atema et al. found that, with the use of scoring systems combining clinical and imaging features, 95% of the patients deemed to have uncomplicated AA were correctly identified [43].

**Statement 1.1** Establishing the diagnosis of acute appendicitis based on clinical presentation and physical examination may be challenging. As the value of individual clinical variables to determine the likelihood of acute appendicitis in a patient is low, a tailored individualized approach is recommended, depending on disease probability, sex, and age of the patient. **Recommendation 1.1** We recommend to adopt a tailored individualized diagnostic approach for stratifying the risk and disease probability and planning an appropriate stepwise diagnostic pathway in patients with suspected acute appendicitis, depending on age, sex, and clinical signs and symptoms of the patient [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 1.2** Clinical scores alone, e.g., Alvarado score, AIR score, and the new Adult Appendicitis Score are sufficiently sensitive to exclude acute appendicitis, accurately identifying low-risk patients and decreasing the need for imaging and the negative appendectomy rates in such patients. **Recommendation 1.2.1** We recommend the use of clinical scores to exclude acute appendicitis and identify intermediate-risk patients needing of imaging diagnostics [QoE: High; Strength of recommendation: Strong; 1A]. **Recommendation 1.2.2** We suggest not making the diagnosis of acute appendicitis in pregnant patients on symptoms and signs only. Laboratory tests and inflammatory serum parameters (e.g., CRP) should always be requested [QoE: Very Low; Strength of recommendation: Weak; 2C].

**Statement 1.3** The Alvarado score is not sufficiently specific in diagnosing acute appendicitis in adults, seems unreliable in differentiating complicated from uncomplicated acute appendicitis in elderly patients, and is less sensitive in patients with HIV. **Recommendation 1.3** We suggest against the use of Alvarado score to positively confirm the clinical suspicion of acute appendicitis in adults [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Statement 1.4** The AIR score and the AAS score seem currently to be the best performing clinical prediction scores and have the highest discriminating power in adults with suspected acute appendicitis. The AIR and AAS scores decrease negative appendectomy rates in low-risk groups and reduce the need for imaging studies and hospital admissions in both low- and intermediate-risk groups. **Recommendation 1.4** We recommend the use of AIR score and AAS score as clinical predictors of acute appendicitis [QoE: High; Strength of recommendation: Strong; 1A].

Q.1.2: In pediatric patients with suspected acute appendicitis could the diagnosis be based only on clinical scores?

AA is the most common surgical emergency in children, but early diagnosis of AA remains challenging due to atypical clinical features and the difficulty of obtaining a reliable history and physical examination. Several clinical scoring systems have been developed, the two most popular for use in children being the Alvarado score and Samuel’s Pediatric Appendicitis Score (PAS).

PAS includes similar clinical findings to the Alvarado score in addition to a sign more relevant in children: right lower quadrant pain with coughing, hopping, or percussion. Several studies comparing the PAS with the Alvarado score have validated its use in pediatric patients. However, in a systematic review by Kulik et al. both scores failed to meet the performance benchmarks of CRP (C-reactive protein). On average, the PAS would over-diagnose AA by 35%, and the Alvarado score would do so by 32% [44].

If we consider patients of preschool age, AA often presents with atypical features, more rapid progression, and higher incidence of complications. This age group is more likely to have lower PAS and Alvarado score than those of school-aged children [45]. This is the reason why Macco et al. retrospectively analyzed data from 747 children (mean age of 11 years) suspected of AA to evaluate the predictive value of the Alvarado score and PAS compared with the AIR score, which includes fewer symptoms than the Alvarado score and PAS, but adds the CRP value and allows for different severity levels of rebound pain, leukocytosis, CRP, and polymorphonucleocytes. The study showed that the AIR had the highest discriminating power and outperformed the other two scores in predicting AA in children [46].

The use of PAS seems to be useful to rule out or in AA in pediatric female patients. A retrospective observational study demonstrated that at a cutoff of ≥8, the PAS showed a specificity of 89% for adolescent females and 78% for all other patients, although the specificities...
did not differ at a cutoff of \( \geq 7 \). At both cutoffs, the positive predictive values were poor in both groups. At a cutoff of \( \geq 3 \), the PAS showed similar sensitivities in both groups [47].

Recently, the new Pediatric Appendicitis Laboratory Score (PALabS) including clinical signs, leucocyte and neutrophil counts, CRP, and calprotectin levels has been shown to accurately predict which children are at low risk of AA and could be safely managed with close observation. A PALabS \( \leq 6 \) has a sensitivity of 99.2%, a negative predictive value of 97.6%, and a negative likelihood ratio of 0.03 [48].

The preoperative clinical scoring system to distinguish perforation risk with pediatric AA proposed by Bonadio et al., based on the duration of symptoms (\( > 1 \) day), fever (\( > 38.0 \) C), and WBC absolute count (\( > 13,000/mm^3 \)), resulted in a multivariate ROC curve of 89% for perforation (\( P < 0.001 \)), and the risk for perforation was additive with each additional predictive variable exceeding its threshold value, linearly increasing from 7% with no variable present to 85% when all 3 variables are present [49].

In assessing if the clinical scores can predict disease severity and the occurrence of complications, a retrospective study on the Alvarado score validity in pediatric patients showed that a higher median score was found in patients who suffered postoperative complications. The eight items in the scoring system were analyzed for their sensitivities. Fever, right lower quadrant tenderness, and neutrophilia were found to be the three most sensitive markers in predicting complicated AA (88.6%, 82.3%, and 79.7%). On the other hand, rebound tenderness was found to have the highest positive predictive value (65%) among the eight items to predict complicated AA [50].

**Statement 1.5** In pediatric patients with suspected acute appendicitis, the Alvarado score and Pediatric Appendicitis Score are useful tools in excluding acute appendicitis. **Recommendation 1.5** In pediatric patients with suspected acute appendicitis, we suggest against making a diagnosis based on clinical scores alone [QoE: Low; Strength of recommendation: Weak: 2C].

### Q.1.3: What is the role of serum biomarkers in evaluating adult patients presenting with clinical features evocative of acute appendicitis?

The diagnostic accuracy of several biomarker panels has been prospectively validated, showing high sensitivity and negative predictive values for AA in large cohorts of patients with right iliac fossa pain, thereby potentially reducing the dependence on CT for the evaluation of possible AA [51].

The diagnostic value of baseline and early change of CRP concentrations has been evaluated separately or in combination with the modified Alvarado score in patients with clinically suspected AA in the prospective observational study by Msolli et al. Early change of CRP had a moderate diagnostic value in patients with suspected AA, and even combining CRP values to the modified Alvarado score did not improve diagnostic accuracy [52]. Recently, ischemia-modified albumin (IMA) levels have been used to determine the prediction of severity in AA patients. Kilic et al. found a strong positive correlation between IMA levels and CT findings in distinguishing gangrenous/perforated AA from uncomplicated AA [53]. A combination of clinical parameters, laboratory tests, and US may significantly improve diagnostic sensitivity and specificity and eventually replace the need for CT scan in both adults and children [54].

**Statement 1.6** Biochemical markers represent a promising reliable diagnostic tool for the identification of both negative cases or complicated acute appendicitis in adults. However, further high-quality evidence is needed [QoE: Low; No recommendation].

### Q.1.4: What is the role of serum biomarkers in evaluating pediatric patients presenting clinical features highly suggestive of acute appendicitis?

In pediatric patients, routine diagnostic laboratory workup for suspected AA should include WBC, the differential with the calculation of the absolute neutrophil count (ANC), CRP, and urinalysis.

Although not widely available, the addition of procalctinin and calprotectin to the above tests may significantly improve diagnostic discrimination [55].

Biomarkers have also been shown to be useful when used in association with the systematic adoption of scoring systems, as the addition of negative biomarker test results to patients with a moderate risk of AA based on the Pediatric Appendicitis Score (PAS) can safely reclassify many patients to a low-risk group. This may allow surgeons to provide more conservative management in patients with suspected AA and decrease unnecessary resource utilization [56].

Zouari et al. highlighted the value of CRP \( \geq 10 \) mg/L as a strong predictor of AA in children \( < 6 \) years old [57].

Yu et al. reported that PCT had little value in diagnosing AA, with lower diagnostic accuracy than CRP and WBC, but a greater diagnostic value in identifying complicated AA [58]. In a recent meta-analysis, it was confirmed that PCT was more accurate in diagnosing complicated AA, with a pooled sensitivity of 0.89 (95% CI 0.84–0.93), specificity of 0.90 (95% CI 0.86–0.94), and diagnostic odds ratio of 76.73 (95% CI 21.6–272.9) [59].

Zani et al. retrospectively analyzed data from 1197 children admitted for AA and reported that patients with complicated AA had higher CRP and WBC levels...
than normal patients and those with uncomplicated AA. The authors found a CRP > 40 mg/L in 58% of patients with complicated AA and 37% of patients with uncomplicated AA, and WBC > 15 × 10⁹/L in 58% of patients with complicated AA and 43% of patients with uncomplicated AA [60].

One recent study identified a panel of biomarkers, the APPY1 test, consisting of WBC, CRP, and myeloid-related protein 8/14 levels that have the potential to identify, with great accuracy, children and adolescents with abdominal pain who are at low risk for AA. The biomarker panel exhibited a sensitivity of 97.1%, a negative predictive value of 97.4%, and a negative likelihood ratio of 0.08, with a specificity of 37.9% for AA [51].

Benito et al. prospectively evaluated the usefulness of WBC and ANC and other inflammatory markers such as CRP, procalcitonin, calprotectin, and the APPY1 test panel of biomarkers, to identify children with abdominal pain at low risk for AA. The APPY1 test panel showed the highest discriminatory power, with a sensitivity of 97.8, negative predictive value of 95.1, negative likelihood ratio of 0.06, and specificity of 40.6. In the multivariate analysis, only the APPY1 test and ANC > 7500/ mL were significant risk factors for AA [55].

More recently the Appendicitis-Pediatric score (APPE) was developed with the aim of identifying the risk of AA. Patients with an APPE score ≤ 8 were at low risk of AA (sensitivity 94%); those with a score ≥ 15 were at high risk for AA (specificity 93%). Those between 8 and 15 were defined at intermediate-risk [61].

A number of prospective studies of children were conducted to find urinary biomarkers for AA, such as leucine-rich α-2-glycoprotein (LRG), not to be used alone but combined with PAS and routine blood tests. LRG in conjunction with PAS showed 95% sensitivity, 90% specificity, 91% positive predictive value, and 95% negative predictive value for AA in children [62].

Among the new laboratory biomarkers developed, the Appendicitis Urinary Biomarker (AuB—leucine-rich alpha-2-glycoprotein) appears promising as a diagnostic tool for excluding AA in children, without the need for blood sampling (negative predictive value 97.6%) [63].

**Statement 1.7** White blood cell count, the differential with the calculation of the absolute neutrophil count, and the CRP are useful lab tests in predicting acute appendicitis in children; moreover, CRP level on admission ≥ 10 mg/L and leucocytosis ≥ 16,000/mL are strong predictive factors for appendicitis in pediatric patients. **Recommendation 1.6.1** In evaluating children with suspected appendicitis, we recommend to request routinely laboratory tests and serum inflammatory biomarkers [QoE: Very Low; Strength of recommendation: Strong: 1D]. **Recommendation 1.6.2** In pediatric patients with suspected acute appendicitis, we suggest adopting both biomarker tests and scores in order to predict the severity of the inflammation and the need for imaging investigation [QoE: Very Low; Strength of recommendation: Weak: 2D].

**Q.1.5: What is the optimum pathway for imaging in adult patients with suspected acute appendicitis?**

Estimating pre-image likelihood of AA is important in tailoring the diagnostic workup and using scoring systems to guide imaging can be helpful: low-risk adult patients according to the AIR/Alvarado scores could be discharged with appropriate safety netting, whereas high-risk patients are likely to require surgery rather than diagnostic imaging. Intermediate-risk patients are likely to benefit from systematic diagnostic imaging [64]. A positive US would lead to a discussion of appendectomy and a negative test to either CT or further clinical observation with repeated US. A conditional CT strategy, where CT is performed after the negative US, is preferable, as it reduces the number of CT scans by 50% and will correctly identify as many patients with AA as an immediate CT strategy.

Point-of-care ultrasonography (POCUS) has proven to be a valuable diagnostic tool in diagnosing AA and has a positive impact on clinical decision-making. Overall sensitivity and specificity of US is 76% and 95% and for CT is 99% and 84% respectively [65].

The meta-analysis by Matthew Fields et al. found that the sensitivity and specificity for POCUS in diagnosing AA were 91% and 97%, respectively. The positive and negative predictive values were 91% and 94%, respectively [66]. US reliability for the diagnosis of AA can be improved through standardized results reporting. In the study by Sola et al., following the adoption of a diagnostic algorithm that prioritized US over CT and encompassed standardized templates, the frequency of indeterminate results decreased from 44.3% to 13.1% and positive results increased from 46.4% to 66.1% in patients with AA [67].

Recent studies from the Finnish group led by Salminen demonstrated that the diagnostic accuracy of contrast-enhanced low-dose CT is not inferior to standard CT in diagnosing AA or distinguishing between uncomplicated and complicated AA, enabling significant radiation dose reduction. The OPTICAP randomized trial has shown that a low-dose protocol using intravenous contrast media was not inferior to the standard protocol in terms of diagnostic accuracy (79% accurate diagnosis in low-dose and 80% in standard CT by a primary radiologist) and accuracy to categorize AA severity (79% for both protocols). However, the mean radiation dose of low-dose CT was significantly lower compared with standard CT (3.33 and 4.44 mSv, respectively) [12]. The radiation dose of appendiceal CT for adolescents and young adults
can be reduced to 2 mSv without impairing clinical outcomes and reducing the potential risk of exposure to ionizing radiation simultaneously [68]. The recently published Cochrane systematic review on CT scan for diagnosis of AA in adults identified 64 studies including 71 separate study populations with a total of 10280 participants (4583 with and 5697 without AA). Summary sensitivity of CT scan was 0.95, and summary specificity was 0.94. At the median prevalence of AA (0.43), the probability of having AA following a positive CT result was 0.92, and the probability of having AA following a negative CT result was 0.04. In subgroup analyses according to contrast enhancement, summary sensitivity was higher for CT with intravenous contrast (0.96), CT with rectal contrast (0.97), and CT with intravenous and oral contrast enhancement (0.96) than for non-enhanced CT (0.91). Summary sensitivity for low-dose CT (0.94) was similar to summary sensitivity for standard-dose or unspecified-dose CT (0.95). Summary specificity did not differ between low-dose and standard-dose or unspecified-dose CT [69].

The usefulness of CT for determining perforation in AA is limited [70]. Methods to improve precision in identifying patients with complicated AA should be explored, as these may help improve risk prediction for the failure of treatment with antibiotic therapy and guide patients and providers in shared decision-making for treatment options. In cases with equivocal CT features, repeat US and detection of specific US features (presence of non-compressibility and increased vascular flow of the appendix wall) can be used to discriminate AA from a normal appendix [71].

MRI has at least the same sensitivity and specificity as CT and, although has higher costs and issues around availability in many centers, should be preferred over CT as a first-line imaging study in pregnant women.

The American College of Radiology Appropriateness Criteria for pregnant women recommend graded compression grayscale US as a preferred initial method in case of suspected AA. These criteria recommend MRI as a second-line imaging method in inconclusive cases, although MRI can be used as a first-line imaging modality if available [72]. Others also recommend MRI after non-visualization or inconclusive US [73]. Despite some excellent US accuracy findings, the main drawback of US is the rate of non-visualization, which goes from 34.1% up to 71% with positive AA on the pathology reports [74, 75]. Low US accuracy for the diagnosis of AA in pregnant patients beyond the 1st trimester of pregnancy is evident and 30% of pregnant women with suspected AA have potentially avoidable surgery. Given the low yield of US, second-line imaging should be considered in those cases with an inconclusive US before surgery. A high rate (8%) of false-negative US results are positive on MRI [73, 76].

From 2011, there are three meta-analyses reporting on the use of MRI for AA during pregnancy with the following results: sensitivity 90.5%, 94%, and 91.8%; specificity 98.6%, 97%, and 97.9%; positive predictive value 86.3%; and negative predictive value 99.0% [77, 78]. Unfortunately, non-visualization of the appendix is up to 30–43% in some single-center series [79–82]. The rate of non-visualization is higher during the 3rd trimester when the largest degree of anatomic distortion occurs due to the gravid uterus [81]. Although a negative or inconclusive MRI does not exclude AA during pregnancy, many authors suggest MRI as the gold standard in all female patients during their reproductive years, mostly because of its high specificity and sensitivity (100% and 89%, respectively) and the high negative (96–100%) and positive (83.3–100%) predictive values [73, 83, 84].

**Statement 1.8** Combination of US and clinical (e.g., AIR, AAS scores) parameters forming combined clinico-radiological scores may significantly improve diagnostic sensitivity and specificity and eventually replace the need for a CT scan in adult patients with suspected acute appendicitis. **Recommendation 1.7** We recommend the routine use of a combination of clinical parameters and US to improve diagnostic sensitivity and specificity and reduce the need for CT scan in the diagnosis of acute appendicitis. The use of imaging diagnostics is recommended in patients with suspected appendicitis after an initial assessment and risk stratification using clinical scores [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 1.9** Intermediate-risk classification identifies patients likely to benefit from observation and systematic diagnostic imaging. **Recommendation 1.8** We suggest proceeding with timely and systematic diagnostic imaging in patients with intermediate-risk of acute appendicitis [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Statement 1.10** Patients with strong signs and symptoms and high risk of appendicitis according to AIR score/Alvarado score/AAS and younger than 40 years old may not require cross-sectional pre-operative imaging (i.e., CT scan). **Recommendation 1.9** We suggest that cross-sectional imaging (i.e., CT scan) for high-risk patients younger than 40 years old (AIR score 9–12, Alvarado score 9–10, and AAS ≥ 16) may be avoided before diagnostic +/- therapeutic laparoscopy [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Comment:** This statement and recommendation has raised an intense debate among the panel of experts and consensus was difficult to reach, especially in view of the strong opinions from two parties: one advocating the
need of routine imaging with CT scan for all high-risk patients before any surgery and the other advocating the value of the clinical scores and thorough clinical assessment and risk stratification as being enough for proceeding to diagnostic and therapeutic laparoscopy in the subset of patients younger than 40 years old and scoring high in all Alvarado, AIR, and AAS scores.

The results of the first round of the Delphi consensus modified the previous recommendation from 2016 guidelines (see graphs included as Supplementary Material files 2, 3, 4, 5 and 6) as follows: “We suggest appendectomy without pre-operative imaging for high-risk patients younger than 50 years old according to the AIR score”, 8.3% agreement; “We suggest diagnostic +/- therapeutic laparoscopy without pre-operative imaging for high-risk patients younger than 40 years old, AIR score 9–12, Alvarado score 9–10, and AAS ≥ 16”, 70.8% agreement; “Delete recommendation”, 20.8% agreement) were discussed in a further consensus due to the strong opposition by few of the expert panelists who were still not keen to accept the results of the first Delphi and the recommendations despite being already labeled as a weak recommendation (“suggestion” according to GRADE Criteria).

A further revision of the statement was proposed and a second round of Delphi was performed before endorsing the final recommendation “We suggest that cross-sectional imaging i.e. CT scan for high-risk patients younger than 40 years old, AIR score 9–12 and Alvarado score 9–10 and AAS ≥ 16 may be avoided before diagnostic +/- therapeutic laparoscopy” which obtained the 68.0% of agreement, whereas the statement “We suggest diagnostic +/- therapeutic laparoscopy without pre-operative imaging for high-risk patients younger than 40 years old and AIR score 9–12; Alvarado score 9–10; AAS ≥ 16” reached 26% and the option “delete the statement and recommendations reached 6%. Some authors also added that cross-sectional imaging, i.e., CT scan for high-risk patients younger than 40 years old may be skipped or imaging may be avoided at all, before diagnostic +/- therapeutic laparoscopy for young male patients. Some also emphasized that the responsible surgeon (not PGY1 trainee) should examine the patient prior to the decision for CT scanning and recommended a highly value-based surgical care. WSES supports this recommendation of a value-based surgical care and these further comments will be the ground for the next future editions of the guidelines, when hopefully further and stronger evidence will be available from the literature about this challenging subgroup of high-risk scoring patients. All the graphs reporting the results of the additional Delphi are reported within the Supplementary Material files 2, 3, 4, 5 and 6.

Statement 1.11 POCUS (Point-of-care Ultrasound) is a reliable initial investigation with satisfactory sensitivity and specificity in diagnosing acute appendicitis, easing swift decision-making by the emergency physicians or surgeons. POCUS, if performed by an experienced operator, should be considered the most appropriate first-line diagnostic tool in both adults and children. Recommendation 1.10 We recommend POCUS as the most appropriate first-line diagnostic tool in both adults and children, if an imaging investigation is indicated based on clinical assessment [QoE: Moderate; Strength of recommendation: Strong; 1B].

Statement 1.12 When it is indicated, contrast-enhanced low-dose CT scan should be preferred over contrast-enhanced standard-dose CT scan. Diagnostic accuracy of contrast-enhanced low-dose CT is not inferior to standard CT in diagnosing AA or distinguishing between uncomplicated and complicated acute appendicitis and enables significant radiation dose reduction. Recommendation 1.11 We recommend the use of contrast-enhanced low-dose CT scan over contrast-enhanced standard-dose CT scan in patients with suspected acute appendicitis and negative US findings [QoE: High; Strength of recommendation: Strong; 1A].

Statement 1.13 In patients with normal investigations and symptoms unlikely to be acute appendicitis but which do not settle, cross-sectional imaging is recommended before surgery. Laparoscopy is recommended to establish/exclude the diagnosis of acute appendicitis and eventually treat the disease. Recommendation 1.12 We recommend cross-sectional imaging before surgery for patients with normal investigations but non-resolving right iliac fossa pain. After negative imaging, initial non-operative treatment is appropriate. However, in patients with progressive or persistent pain, explorative laparoscopy is recommended to establish/exclude the diagnosis of acute appendicitis or alternative diagnoses [QoE: High; Strength of recommendation: Strong; 1A].

Statement 1.14 MRI is sensitive and highly specific for the diagnosis of acute appendicitis during pregnancy. However, a negative or inconclusive MRI does not exclude appendicitis and surgery should be still considered if high clinical suspicion. Recommendation 1.13.1 We suggest graded compression trans-abdominal ultrasound as the preferred initial imaging method for suspected acute appendicitis during pregnancy [QoE: Very Low; Strength of Recommendation: Weak; 2C]. Recommendation 1.13.2 We suggest MRI in pregnant patients with suspected appendicitis, if this resource is available, after inconclusive US [QoE: Moderate; Strength of recommendation: Weak; 2B].
Q.1.6: What is the optimum pathway for imaging in pediatric patients with suspected acute appendicitis?

US is currently the recommended initial imaging study of choice for the diagnosis of AA in pediatric and young adult patients. US has been shown to have high diagnostic accuracy for AA as an initial imaging investigation and to reduce or obviate the need for further imaging without increased complications or unacceptable increases in length of stay [85].

However, the sensitivity and specificity of US for the diagnosis of pediatric AA varies across studies: it is well known that US is operator dependent and may be dependent on patient-specific factors, including BMI [86].

A retrospective study assessing the ability of US to identify complicated AA or an appendicolith showed that US has a high specificity and negative predictive value to exclude complicated AA and the presence of an appendicolith in children being considered for non-operative management of uncomplicated AA [87].

The study by Bachur et al. found that, among children with suspected AA, the use of US imaging has increased substantially (from 24.0% in 2010 to 35.3% in 2013), whereas the use of CT has decreased (from 21.4% in 2010 to 11.6% in 2013). However, important condition-specific quality measures, including the frequency of appendiceal perforation and readmissions, remained stable, and the proportion of negative appendectomy declined slightly [88].

The study of CT in the pediatric population can be reduced by using appropriate clinical and/or staged algorithm based on US/MRI implementation, with a sensitivity up to 98% and a specificity up to 97% and by applying imaging scoring system, such as the Appy-Score for reporting limited right lower quadrant US exams, that performs well for suspected pediatric AA [89–91].

A systematic literature review was performed to evaluate the effectiveness of abdominal US and abdominal CT in diagnosing AA in adult and pediatric patients. Data reported that for US, the calculated pooled values of sensitivity, specificity, positive predictive value, and negative predictive value were 86%, 94%, 100%, and 92%, respectively. For CT, the calculated pooled values of sensitivity, specificity, positive predictive value, and negative predictive value were 95%, 94%, 95%, and 99%, respectively. These results suggest that US is an effective first-line diagnostic tool for AA and that CT should be performed for patients with inconclusive ultrasonographic finding [92]. Recently, a meta-analysis was carried out to compare the accuracy of US, CT, and MRI for clinically suspected AA in children. The area under the receiver operator characteristics curve of MRI (0.995) was a little higher than that of US (0.987) and CT (0.982) but with no significant difference [93].

Lee et al. compared US and CT in terms of negative appendectomy rate and appendiceal perforation rate in adolescents and adults with suspected appendicitis to evaluate the diagnostic performance as preoperative imaging investigations with a propensity score method. This analysis reported that the use of US instead of CT may increase the negative appendectomy rate but does not significantly affect the rate of perforation [94].

A low dose CT, when indicated, can be an adequate method compared to US and standard dose CT in diagnosing AA in children in terms of sensitivity (95.5% vs 95.0% and 94.5%), specificity (94.9% vs 80.0% and 98.8%), positive-predictive value (96.4% vs 92.7%), and negative-predictive value (93.7% vs 85.7% and 91.3%) [95].

The diagnostic performance of staged algorithms involving US followed by conditional MRI imaging for the diagnostic workup of pediatric AA has proven to be high (98.2% sensitive and 97.1% specific) [90]. MRI is a feasible alternative to CT for secondary imaging in AA in children, and it can differentiate perforated from non-perforated AA with a high specificity [96].

MRI plays a role as an imaging investigation to avoid CT radiation dose in children with inconclusive US findings. Moore et al. reported sensitivity of 96.5%, specificity of 96.1%, positive predictive value of 92.0%, and negative predictive value of 98.3% for MRI [97].

In a prospective study conducted by Kinner et al., when the diagnostic accuracy of MRI was compared to CT, sensitivity and specificity were 85.9% and 93.8% for non-enhanced MRI, 93.6% and 94.3% for contrast-enhanced MRI, and 93.6% and 94.3% for CT [98].

However, the costs and the availability of MRI often prevent its use as the initial imaging investigation in cases of suspected AA.

As second-line imaging modalities after initial US for assessing AA in children and adults, repeated US, CT, and MRI showed comparable and high accuracy in children and adults. These three modalities may be valid as second-line imaging in a clinical imaging pathway for diagnosis of AA. In particular, pooled sensitivities and specificities of second-line US for the diagnosis of AA in children were 91.3% and 95.2%, respectively. Regarding second-line CT, the pooled sensitivities and specificities were 96.2% and 94.6%. Regarding second-line MRI, pooled sensitivities and specificities were 97.4% and 97.1% [99].

Statement 1.15 The use of US in children is accurate and safe in terms of perforation rates, emergency department re-visits, and negative appendectomy rates. CT use may be decreased by using appropriate clinical and/or staged algorithm with US/MRI. MRI has at least the same sensitivity and specificity as CT and, although higher costs, should be preferred over CT as second-line imaging in children. Recommendation 1.14.1 In
pediatric patients with suspected appendicitis, we suggest the use of US as first-line imaging. In pediatric patients with inconclusive US, we suggest choosing the second-line imaging technique based on local availability and expertise, as there are currently no strong data to suggest a best diagnostic pathway due to a variety of options and dependence on local resources [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Recommendation 1.14.2** Since in pediatric patients with equivocal CT finding the prevalence of true acute appendicitis is not negligible, we suggest against the routine use of CT as first-line imaging in children with right iliac fossa pain [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Topic 2: Non-operative management of uncomplicated acute appendicitis**

**Statement 2.1** The antibiotic-first strategy can be considered safe and effective in selected patients with uncomplicated acute appendicitis. Patients who wish to avoid surgery must be aware of a risk of recurrence of up to 39% after 5 years. Most recent data from meta-analyses of RCTs showed that NOM with antibiotics achieves a significantly lower overall complication rate at 5 years and shorter sick leave compared to surgery.
**Recommendation 2.1.1** We recommend discussing NOM with antibiotics as a safe alternative to surgery in selected patients with uncomplicated acute appendicitis and absence of appendicolith, advising of the possibility of failure and misdiagnosing complicated appendicitis [QoE: High; Strength of Recommendation: Strong; 1A].

**Recommendation 2.1.2** We suggest against treating acute appendicitis non-operatively during pregnancy until further high-level evidence is available [QoE: Very Low; Strength of Recommendation: Weak; 2C].

**Q.2.2: Is non-operative management with or without antibiotics a safe and effective treatment option for pediatric patients with uncomplicated acute appendicitis?**

Less than 19% of children have a complicated acute appendicitis; hence, the majority of children with uncomplicated AA may be considered for either a non-operative or an operative management [112].

The antibiotic-first strategy appears effective as an initial treatment in 97% of children with uncomplicated AA (recurrence rate 14%), with NOM also leading to less morbidity, fewer disability days, and lower costs than surgery [113, 114].

A systematic review of all evidence available comparing appendectomy to NOM for uncomplicated AA in children included 13 studies, 4 of which were retrospective studies, 4 prospective cohort studies, 4 prospective non-randomized comparative trials, and 1 RCT. The initial success of the NOM groups ranged from 58 to 100%, with 0.1–31.8% recurrence at 1 year [115].

The meta-analysis by Huang et al. showed that antibiotics as the initial treatment for pediatric patients with uncomplicated AA may be feasible and effective without increasing the risk of complications. However, surgery is preferred for uncomplicated AA with the presence of an appendicolith as the failure rate in such cases is high [116].

The prospective trial by Mahida et al. reported that the failure rate of NOM with antibiotics in children affected by uncomplicated AA with appendicolith was high (60%) at a median follow-up of less than 5 months [117]. The presence of an appendicolith has also been associated with high failure rates in the reports published by Tanaka et al. (failure rate, 47%), Svensson et al. (failure rate, 60%), and Lee et al., concluding that patients with evidence of an appendicolith on imaging had an initial NOM failure rate of more than twice that of patients without an appendicolith [118–120].

Gorter et al. investigated the risk of complications following NOM and appendectomy for uncomplicated AA in a systematic review. Five studies (RCT and cohort studies) were analyzed, including 147 children (NOM) and 173 children (appendectomy) with 1-year follow-up. The percentage of children experiencing complications ranged from 0 to 13% for NOM versus 0–17% for appendectomy. NOM avoided an appendectomy in 62–81% of children after 1-year follow-up. The authors concluded that NOM can avoid an appendectomy in a large majority of children after 1-year follow-up but evidence was insufficient to suggest NOM in all children with uncomplicated AA [121].

In the meta-analysis by Kessler et al. NOM showed a reduced treatment efficacy (relative risk 0.77, 95% CI 0.71–0.84) and an increased readmission rate (relative risk 6.98, 95% CI 2.07–23.6), with a comparable rate of complications (relative risk 1.07, 95% CI 0.26–4.46). Exclusion of patients with appendicoliths improved treatment efficacy in conservatively treated patients. The authors concluded that NOM was associated with a higher readmission rate [122].

Considering these results, NOM can be suggested only for selected pediatric patients presenting with uncomplicated AA.

Minnecci et al. conducted a prospective patient choice cohort study enrolling 102 patients aged 7 to 17 years and showed that the incidence of complicated AA was 2.7% in the NOM group and 12.3% in the appendectomy group. After 1 year, children managed nonoperatively had fewer disability days and lower appendicitis-related health care costs compared with those who underwent appendectomy [114].

**Statement 2.2** NOM for uncomplicated acute appendicitis in children is feasible, safe, and effective as initial treatment. However, the failure rate increases in the presence of appendicolith, and surgery is recommended in such cases. **Recommendation 2.2** We suggest discussing NOM with antibiotics as a safe and effective alternative to surgery in children with uncomplicated acute appendicitis in the absence of an appendicolith, advising of the possibility of failure and misdiagnosing complicated appendicitis [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Q.2.3: What is the best non-operative management of patients with uncomplicated acute appendicitis?**

The implementation of treatment and follow-up protocols based on outpatient antibiotic management and new evidence indicating safety and feasibility of same-day laparoscopic appendectomy for uncomplicated AA may result in optimization of the resource used by reducing inpatient admissions and hospital costs for both NOM and surgical treatment in the future. Although the pilot trial by Talan et al. assessed the feasibility of antibiotics-first strategy including outpatient management (intravenous ertapenem greater than or equal to 48 h and oral cefdinir and metronidazole), the majority of RCTs published to date included 48 h minimum of inpatient administration of intravenous antibiotics,
followed by oral antibiotics for a total length of 7–10 days [123].

The empiric antibiotic regimens for non-critically ill patients with community-acquired intra-abdominal infections as advised by the 2017 WSES guidelines are the following: Amoxicillin/clavulanate 1.2–2.2 g 6-hourly or ceftiraxone 2 g 24-hourly + metronidazole 500 mg 6-hourly or cefotaxime 2 g 8-hourly + metronidazole 500 mg 6-hourly.

In patients with beta-lactam allergy: Ciprofloxacin 400 mg 8-hourly + metronidazole 500 mg 6-hourly or moxifloxacin 400 24-hourly. In patients at risk for infection with community-acquired ESBL-producing Enterobacteriaceae: Ertapenem 1 g 24-hourly or tigecycline 100 mg initial dose, then 50 mg 12-hourly [124].

Currently, the APPAC II trial is running, with the aim to assess the safety and feasibility of per-oral antibiotic monotherapy compared with intravenous antibiotic therapy continued by per oral antibiotics in the treatment of uncomplicated AA. Early results of the APPAC II are expected to be published in 2020 [125].

The results of the RCT by Park et al. challenged the need for antibiotic therapy in uncomplicated AA and reported promising results regarding possible spontaneous resolution of uncomplicated AA with supportive care only. Analysis of the primary outcome measure indicated that treatment failure rates in patients presenting with CT-confirmed uncomplicated AA were similar among those receiving supportive care with either a non-antibiotic regimen or a 4-day course of antibiotics, with no difference in the rates of perforated AA between the two groups reported [126]. Whether recovery from uncomplicated AA is the result of antibiotic therapy or natural clinical remission, and so whether antibiotics are superior to simple supportive care remains to be established.

The APPAC III multicenter, double-blind, placebo-controlled, superiority RCT comparing antibiotic therapy with placebo in the treatment of CT scan-confirmed uncomplicated AA is now in its enrollment phase. This new RCT aims to evaluate the role of antibiotics in the resolution of CT-diagnosed uncomplicated AA by comparing antibiotic therapy with placebo to evaluate the role of antibiotic therapy in the resolution of the disease [127].

If future research demonstrates that antibiotics do not provide any advantage over observation alone in uncomplicated AA, this could have a major impact on reducing the use of antimicrobial agents, especially in this era of increasing antimicrobial resistance worldwide.

**Statement 2.3** Current evidence supports initial intravenous antibiotics with subsequent conversion to oral antibiotics until further evidence from ongoing RCT is available. **Recommendation 2.3** In the case of NOM, we recommend initial intravenous antibiotics with a subsequent switch to oral antibiotics based on patient’s clinical conditions [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 2.4** Uncomplicated acute appendicitis may safely resolve spontaneously with similar treatment failure rates and shorter length of stay and costs compared with antibiotics. However, there is still limited data for the panel to express in favor of or against the symptomatic treatment without antibiotics [QoE: Moderate; No recommendation].

**Topic 3: Timing of appendectomy and in-hospital delay**

Q.3.1: Does in-hospital delay increase the rate of complications or perforation for adult patients with uncomplicated acute appendicitis?

The theory hypothesizing that perforated AA might be a different disease entity from uncomplicated AA, rather than being the natural evolution of the disease, has some support in the recent meta-analysis by van Dijk et al., demonstrating that delaying appendectomy for up to 24 h after admission does not appear to be a risk factor for complicated AA, postoperative morbidity, or surgical-site infection. Pooled adjusted ORs revealed no significantly higher risk for complicated AA when appendectomy was delayed for 7–12 or 13–24 h, and meta-analysis of unadjusted data supported these findings by yielding no increased risk for complicated AA or postoperative complications with a delay of 24–48 h [22].

Data from the American College of Surgeons NSQIP demonstrated similar outcomes of appendectomy for AA when the operation was performed on hospital day 1 or 2. Conversely, appendectomies performed on hospital day 3 had significantly worse outcomes, as demonstrated by increased 30-day mortality (0.6%) and all major postoperative complications (8%) in comparison with operations taking place on hospital day 1 (0.1%; 3.4%) or 2 (0.1%; 3.6%). Patients with decreased baseline physical status assessed by the ASA Physical Status class had the worst outcomes (1.5% mortality; 14% major complications) when an operation was delayed to hospital day 3. However, logistic regression revealed higher ASA Physical Status class and open operations as the only predictors of major complications [128].

In the study by Elniel et al., a significant increase in the likelihood of perforated AA occurred after 72 h of symptoms, when compared to 60–72 h. The authors argued that it may be reasonable to prioritize patients approaching 72 h of symptoms for operative management [129].

In a large retrospective series of pregnant women with suspected AA (75.9% with uncomplicated AA, 6.5% with complicated AA, and 17.6% with normal appendix), initial US was diagnostic in 57.9% of patients, whereas...
55.8% of patients underwent a delayed repeat study. In this cohort, performing a delayed repeat US during a period of observation in those patients who remained otherwise equivocal increased the diagnostic yield of the US, whereas delaying surgery did not affect maternal or fetal safety. Such algorithm increased the diagnostic yield without increasing the proxies of maternal or fetal morbidity. There was no increased rate of perforated appendices in patients with delayed surgery. Still, the negative appendectomy rate was 17.7% [130].

**Statement 3.1** Short, in-hospital surgical delay up to 24 h is safe in uncomplicated acute appendicitis and does not increase complications and/or perforation rate in adults. Surgery for uncomplicated acute appendicitis can be planned for the next available list minimizing delay wherever possible (better patient comfort, etc.). Short, in-hospital delay with observation and repeated trans-abdominal US in pregnant patients with equivocal appendicitis is acceptable and does not seem to increase the risk of maternal and fetal adverse outcomes. **Recommendation 3.1** We recommend planning laparoscopic appendectomy for the next available operating list within 24 h in case of uncomplicated acute appendicitis, minimizing the delay wherever possible [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 3.2** Delaying appendectomy for uncomplicated acute appendicitis for up to 24 h after admission does not appear to be a risk factor for complicated appendicitis, postoperative surgical site infection, or morbidity. Conversely, appendectomies performed after 24 h from admission are related to increased risk of adverse outcomes. **Recommendation 3.2** We recommend against delaying appendectomy for acute appendicitis needing surgery beyond 24 h from the admission [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Q.3.2: Does in-hospital delay increase the rate of complications or perforation for pediatric patients with uncomplicated acute appendicitis?**

In children appendectomy performed within the first 24 h from presentation is not associated with an increased risk of perforation or adverse outcomes [131]. Similarly, in the multivariate logistic regression analysis by Almstrom et al., increased time to surgery was not associated with increased risk of histopathologic perforation, and there was no association between the timing of surgery and postoperative wound infection, intra-abdominal abscess, reoperation, or readmission [132].

Data from NSQIP-Pediatrics demonstrated that a 16-h delay from emergency department presentation or a 12-h delay from hospital admission to appendectomy was not associated with an increased risk of SSI. Compared with patients who did not develop an SSI, patients who developed an SSI had similar times between emergency department triage and appendectomy (11.5 h vs 9.7 h, \( P = 0.36 \)) and similar times from admission to appendectomy (5.5 h vs 4.3 h, \( P = 0.36 \)). Independent risk factors for SSI were complicated AA, longer symptom duration, and presence of sepsis/septic shock [133].

Gurien et al. retrospectively analyzed data from 484 children who underwent appendectomy at 6, 8, and 12 h from admission for AA and reported a mean elapsed time from admission to theatre of 394 min. SSIs, appendiceal perforations, and small bowel obstructions were similar between early and delayed groups, and no statistically significant differences were found for SSIs in the non-perforated delayed versus immediate groups. Time from admission to theatre did not predict perforation, whereas WBC count at the time of admission was a significant predictor of perforation (OR 1.08; \( P < 0.001 \)) [134].

Recently, the American Pediatric Surgical Association Outcomes and Evidence-Based Practice Committee developed recommendations regarding time to appendectomy for AA in children by a systematic review of the published articles between January 1, 1970, and November 3, 2016. The committee stated that appendectomy performed within the first 24 h from presentation is not associated with an increased risk of perforation or adverse outcomes [135].

Regarding complicated AA, some authors support initial antibiotics with delayed operation whereas others support immediate operation. Regarding complicated appendicitis, some authors support initial antibiotics with delayed operation whereas others support immediate operation. A population-level study with a 1-year follow-up period found that children undergoing late appendectomy were more likely to have a complication than those undergoing early appendectomy. These data support that early appendectomy is the best management in complicated AA [136].

**Statement 3.3** Appendectomy performed within the first 24 h from presentation in the case of uncomplicated appendicitis is not associated with an increased risk of perforation or adverse outcomes. Early appendectomy is the best management in complicated appendicitis. **Recommendation 3.3** We suggest against delaying appendectomy for pediatric patients with uncomplicated acute appendicitis needing surgery beyond 24 h from the admission [QoE: Low; Strength of Recommendation: Weak; 2C].

**Topic 4: Surgical treatment**

**Q.4.1: Does laparoscopic appendectomy confer superior outcomes compared with open appendectomy for adult patients with acute appendicitis?**

Several systematic reviews of RCTs comparing laparoscopic appendectomy (LA) versus open appendectomy...
(OA) have reported that the laparoscopic approach for AA is often associated with longer operative times and higher operative costs, but it leads to less postoperative pain, shorter length of stay, and earlier return to work and physical activity [137]. LA lowers overall hospital and social costs [138], improves cosmesis, and significantly decreases postoperative complications, in particular SSI.

The 2018 updated Cochrane review on LA versus OA showed that, except for a higher rate of IAA (intra-abdominal abscess) after LA in adults, laparoscopic demonstrates advantages over OA in pain intensity on day one, SSI, length of hospital stay, and time until return to normal activity [139].

In the meta-review by Jaschinski et al. including nine systematic reviews and meta-analyses (all moderate to high quality), the pooled duration of surgery was 7.6 to 18.3 min shorter with OA. Pain scores on the first post-operative day were lower after LA in two out of three reviews. The risk of IAA was higher for LA in half of six meta-analyses, whereas the occurrence of SSI pooled by all reviews was lower after LA. LA shortened hospital stay from 0.16 to 1.13 days in seven out of eight meta-analyses [14].

The evidence regarding treatment effectiveness of LA versus OA in terms of postoperative IAA, however, changed over the last decade. The cumulative meta-analysis by Ukai et al. demonstrated that, of the 51 trials addressing IAA, trials published up to and including 2001 showed statistical significance in favor of OA. The effect size in favor of OA began to disappear after 2001, leading to an insignificant result with an overall cumulative OR of 1.32 (95% CI 0.84–2.10) when LA was compared with OA [140].

LA appears to have significant benefits with improved morbidity compared to OA in complicated AA as well, as demonstrated in the meta-analysis by Athanasiou et al. In the pooled analysis, LA had significantly less SSI, with reduced time to oral intake, and length of hospitalization. There was no significant difference in IAA rates. Operative time was longer during LA but did not reach statistical significance in the RCT subgroup analysis [141].

Statement 4.1 Laparoscopic appendectomy offers significant advantages over open appendectomy in terms of less pain, lower incidence of surgical site infection, decreased length of hospital stay, earlier return to work, overall costs, and better quality of life scores. Recommendation 4.1 We recommend laparoscopic appendectomy as the preferred approach over open appendectomy for both uncomplicated and complicated acute appendicitis, where laparoscopic equipment and expertise are available [QoE: High; Strength of recommendation: Strong; 1A].

Q.4.2: Does laparoscopic appendectomy confer superior outcomes compared with open appendectomy for pediatric patients with acute appendicitis?

The laparoscopic approach to AA seems to be safe and effective in children.

Zhang et al. conducted a meta-analysis of nine studies to compare the influence of different surgical procedures on perforated AA in the pediatric population and found that LA was associated with lower incidence of SSI and bowel obstruction, but the rate of IAA was higher than in OA [142].

Yu et al. conducted a meta-analysis of two RCTs and 14 retrospective cohort studies, showing that LA for complicated AA reduces the rate of SSIs (OR 0.28; 95% CI 0.25–0.31) without increasing the rate of postoperative IAA (OR 0.79; 95% CI 0.45–1.34). The results showed that the operating time in the LA group was longer than that of the OA groups (WMD 13.78, 95% CI 8.99–18.57), whereas the length of hospital stay in the LA groups was significantly shorter (WMD = 2.47, 95% CI = 3.75 to = 1.19), and the time to oral intake was shorter in the LA group than in the OA group (WMD = 0.88, 95% CI = 1.20 to = 0.55) [15].

Statement 4.2 Laparoscopic appendectomy is associated with lower postoperative pain, lower incidence of SSI, and higher quality of life in children. Recommendation 4.2 We recommend laparoscopic appendectomy should be preferred over open appendectomy in children where laparoscopic equipment and expertise are available [QoE: Moderate; Strength of recommendation: Strong; 1B].

Q.4.3: Does laparoscopic single-incision surgery confer any advantage over the three-trocars technique in performing laparoscopic appendectomy for adult patients with acute appendicitis?

Recent studies provide level 1a evidence that single-incision laparoscopic appendectomy (SILA) is as feasible, effective, and safe as the conventional three-port LA. High-level meta-analyses conducted in adults, although demonstrating no significant difference in the safety of SILA versus that of three-port LA, have not supported the application of SILA because of its significantly longer operative times and the higher doses of analgesia required compared with those for three-port LA [143]. A total of 8 RCTs published between 2012 and 2014 with a total of 995 patients were included in the meta-analysis by Aly et al. No significant differences between SILA and conventional three-port laparoscopic appendectomy (CLA) was found in terms of complication rates, postoperative ileus, length of hospital stay, return to work, or postoperative pain. CLA was significantly superior to SILA with reduced operating time (mean difference 5.81 [2.01, 9.62], P = 0.003) and conversion rates (OR 4.14
Statement 4.3 Single-incision laparoscopic appendectomy is basically feasible, safe, and as effective as conventional three-port laparoscopic appendectomy, operative times are longer, requires higher doses of analgesia, and is associated with a higher incidence of wound infection. **Recommendation 4.3** We recommend conventional three-port laparoscopic appendectomy over single-incision laparoscopic appendectomy, as the conventional laparoscopic approach is associated with shorter operative times and more severe surgical trauma compared with the three-port technique, as measured by CRP and IL-6 levels [146]. In the large meta-analysis by Zhang et al., no significant differences were observed between SILA and CLA with respect to the incidence of total postoperative complications, IAA, ileus, wound hematoma, length of hospital stay, or the frequency of use of additional analgesics. However, SILA was associated with a higher incidence of SSI compared with three-port LA and required a longer operative time [147].

Karam et al. conducted a retrospective study with the aim to compare surgical outcomes of children with AA treated with the transumbilical laparoscopically assisted appendectomy (TULAA) versus the CLA and showed that TULAA had a shorter operative time (median, 40 vs 67 min; \( P < 0.001 \)), a shorter length of stay (median, 20 vs 23 h; \( P < 0.001 \)), and lower costs (median $6266 vs $8927; \( P < 0.001 \)), even if SSI rate was slightly higher in the TULAA group (6% vs 4%; \( P = 0.19 \)) [148].

Sekioka et al. reported that mean operative time was significantly shorter in TULAA than in CLA for both uncomplicated and complicated AA. In addition, complication rates in complicated AA were significantly lower in TULAA than in CLA. Moreover, the postoperative hospital stay was significantly shorter in TULAA than in CLA [149].

**Statement 4.4** In children with acute appendicitis, the single incision/transumbilical extracorporeal laparoscopic-assisted technique is as safe as the laparoscopic three-port technique. **Recommendation 4.4** In pediatric patients with acute appendicitis and favorable anatomy, we suggest performing single-incision/transumbilical extracorporeal laparoscopic assisted appendectomy or traditional three-port laparoscopic appendectomy based on local skills and expertise [QoE: Low; Strength of recommendation: Weak; 2C].

Q.4.5: Is outpatient laparoscopic appendectomy safe and feasible for patients with uncomplicated acute appendicitis? In the USA, outpatient LA protocols are currently applied at multiple institutions with the aim to reduce the length of stay and decrease overall health care costs for AA. Results from these experiences demonstrate that outpatient LA can be performed with a high rate of success, low morbidity, and low readmission rate in the case of non-perforated AA [150]. In the study by Frazee et al., 484 patients with uncomplicated AA were managed as outpatients. Only seven patients (1.2%) were re-admitted after outpatient management for transient fever, nausea/vomiting, migraine headache, urinary tract infection, partial small bowel obstruction, and deep venous thrombosis. There were no mortalities or reoperations. Including the readmissions, overall success with outpatient management was 85% [151]. The recent RCT by Trejo-Avila et al. stated that ERAS implementation for appendectomy is associated with a significantly shorter LOS, allowing for the ambulatory management of patients with uncomplicated AA. The authors concluded that ambulatory LA is safe and feasible with similar rates of morbidity and readmissions compared with conventional care [152].

**Statement 4.5** Outpatient laparoscopic appendectomy for uncomplicated acute appendicitis is feasible and safe without any difference in morbidity and readmission rates. It is associated with potential benefits of earlier recovery after surgery and lower hospital and social costs. **Recommendation 4.5** We suggest the adoption of outpatient laparoscopic appendectomy for uncomplicated appendicitis, provided that an ambulatory pathway with well-defined ERAS protocols and patient information/consent are locally established [QoE: Moderate; Strength of recommendation: Weak; 2B].
longer operative times and shorter hospital stay. Overall complications, graded according to the Clavien-Dindo classification, were slightly more frequent in patients after LA, whereas severe complications occurred more frequently in patients after OA [153]. For high-risk patients, LA has proven to be safe and feasible and was also associated with decreased rates of mortality, postoperative morbidity, and shorter hospitalization.

In the recent meta-analysis by Wang et al., 12 studies with 126,237 elderly patients in the LA group and 213,201 patients in the OA group were analyzed. Postoperative mortality, as well as postoperative complications and SSI were reduced following LA. IAA rate was similar between LA and OA. Duration of surgery was longer following LA, and the length of hospital stay was shorter following LA [154].

Results from the American College of Surgeons NSQIP (pediatric database) demonstrated that obesity was not found to be an independent risk factor for postoperative complications following LA. Although operative time was increased in obese children, obesity did not increase the likelihood of 30-day postoperative complications [155].

LA also appears to be a safer alternative approach to OA in obese adult patients. In the systematic review by Dasari et al. including seven retrospective cohort studies and one randomized controlled trial, LA in obese patients was associated with reduced mortality (RR 0.19), reduced overall morbidity (RR 0.49), reduced superficial SSI (RR 0.27), and shorter operating times and postoperative length of hospital stay, compared to OA [156].

Despite concerns about the safety of LA during pregnancy being highlighted over the last 10 years due to a possible increase in fetal loss rate, more recent large systematic reviews and meta-analyses of comparative studies concluded that it is not reasonable to state that LA in pregnant women might be associated with a greater risk of fetal loss. Twenty-two comparative cohort studies were included in the pooled analysis by Lee et al., which involved 4694 women of whom 905 underwent LA and 3789 underwent OA. Fetal loss was significantly higher among those who underwent LA compared with those who underwent OA, with a pooled OR of 1.72. However, the sensitivity analysis showed that the effect size was influenced by one of the studies because its removal resulted in there being no significant difference between LA and OA with respect to the risk of fetal loss (OR 1.16). A significant difference was not evident between LA and OA with respect to preterm delivery (OR 0.76), and patients who underwent LA had shorter hospital stays and a lower SSI risk compared with those who underwent OA [157].

Statement 4.6 Laparoscopic appendectomy seems to show relevant advantages compared to open appendectomy in obese adult patients, older patients, and patients with comorbidities. Laparoscopic appendectomy is associated with reduced mortality, reduced overall morbidity, reduced superficial wound infections, and shorter operating times and postoperative length of hospital stay in such patients. Recommendation 4.6 We suggest laparoscopic appendectomy in obese patients, older patients, and patients with high peri- and postoperative risk factors [QoE: Moderate; Strength of recommendation: Weak; 2B].

Statement 4.7 Laparoscopic appendectomy during pregnancy is safe in terms of risk of fetal loss and preterm delivery and it is preferable to open surgery as associated to shorter length of hospital stay and lower incidence of surgical site infection. Recommendation 4.7 We suggest laparoscopic appendectomy should be preferred to open appendectomy in pregnant patients when surgery is indicated. Laparoscopy is technically safe and feasible during pregnancy where expertise of laparoscopy is available [QoE: Moderate; Strength of recommendation: Weak; 2B].

Q.4.7: Does aspiration alone confer clinical advantages over lavage and aspiration for patients with complicated acute appendicitis?

The best available evidence suggests that peritoneal irrigation with normal saline during LA does not provide additional benefits compared with suction alone in terms of IAA, SSI, and length of stay, but it may prolong the operative time.

The recent meta-analysis by Siotos et al., including more than 2500 patients from five studies, has shown that the use of irrigation, despite adding 7 min to the duration of the operation, overall did not demonstrate a significant decrease in IAA. Both for the adult and pediatric subpopulations, the use of irrigation was associated with a non-significant lower odd of IAA [158].

In the same way, the large meta-analysis by Hajibande et al. (three RCTs and two retrospective observational studies included) demonstrated that there was no difference between peritoneal irrigation and suction alone in terms of IAA rate, SSI, and length of stay. These results remained consistent when RCTs, adult patients, and pediatric patients were analyzed separately [159]. However, the quality of the best available evidence on this point is moderate; therefore, high-quality, adequately powered randomized studies are required to provide a more robust basis for definite conclusions.

Statement 4.8 Peritoneal irrigation does not have any advantage over suction alone in complicated appendicitis in both adults and children. The performance of irrigation during laparoscopic appendectomy does not seem to prevent the development of IAA and wound infections in neither adults nor pediatric patients.
Recommendation 4.8 We recommend performing suction alone in complicated appendicitis patients with intra-abdominal collections undergoing laparoscopic appendectomy [QoE: Moderate; Strength of recommendation: Strong; 1B].

Q.4.8: Does the type of mesoappendix dissection technique (endoclip, endoloop, electrocoagulation, Harmonic Scalpel, or LigaSure) produce different clinical outcomes for patients with acute appendicitis undergoing appendectomy?

Simplified and cost-effective techniques for LA have been described. They use either two endoloops, securing the blood supply, or a small number of endoclips.

In the case of an inflamed and edematous mesoappendix, it has been suggested that the use of LigaSure™, especially in the presence of gangrenous tissue, may be advantageous [160, 161]. Despite the potential advantages, LigaSure™ represents a high-cost option and it may be logical using endoclips if the mesoappendix is not edematous. Diamantis et al. compared LigaSure™ and Harmonic Scalpel with monopolar electrocoagulation and bipolar coagulation: the first two caused more minimal thermal injury of the surrounding tissue than other techniques [162]. Recently, significantly higher thermal damage was found on the mesoappendix and appendiceal base in patients treated with LigaSure™ than in patients for whom Harmonic Scalpel was used during LA [163].

Monopolar electrocoagulation, being safe, quick, and related to very low rates of complications and conversion to OA, can be considered the most cost-effective method for mesoappendix dissection in LA [164]. A recent retrospective cohort study by Wright et al. has proposed that the use of a single stapler line for transection of the mesoappendix and appendix as a safe and efficient technique that results in reduced operative duration with excellent surgical outcomes [165].

Statement 4.9 There are no clinical differences in outcomes, length of hospital stay, and complication rates between the different techniques described for mesentery dissection (monopolar electrocoagulation, bipolar energy, metal clips, endoloops, LigaSure, Harmonic Scalpel, etc.).

Recommendation 4.9 We suggest the use of monopolar electrocoagulation and bipolar energy as they are the most cost-effective techniques, whereas other energy devices can be used depending on the intra-operative judgment of the surgeon and resources available [QoE: Moderate; Strength of recommendation: Weak; 2B].

Q.4.9: Does the type of stump closure technique (stapler or endoloop, ligation or invagination of the stump) produce different clinical outcomes for patients with acute appendicitis undergoing appendectomy?

The stump closure may vary widely in practice and the associated costs can be significant. While earlier studies initially reported advantages with routine use of endostaplers in terms of complication and operative times, more recent studies have repeatedly demonstrated no differences in intra- or postoperative complications between either endostapler or endoloops stump closure [166].

Recent evidence shows that the use of Hem-O-Lok (HOL) clips is safe and reduced the costs of the procedure in comparison to the use of endoloops. In the study by Al-Termini et al., HOL clip use was associated with lower overall complications rate compared with endoloops. The minimum endoloop cost per single appendectomy was $273.13, while HOL clip cost was $32.14 [167].

The multicenter prospective observational study by Van Rossem et al. has demonstrated that the infectious complication rate is not influenced by the type of appendicular stump closure when comparing endoloops or an endostapler. Median operating time was not different between endoloop and endostapler use (42.0 vs 44.0 min) and no significant effect of stump closure type was observed for any infectious complication or IAA. In multivariable analysis, complicated AA was identified as the only independent risk factor for IAA [168].

In the same way, the large systematic review and meta-analysis by Ceresoli et al. showed that in complicated AA, the stump closure technique did not affect outcomes. A total of 5934 patients from 14 studies were included in the analysis. Overall, endostapler use was associated with a similar IAA rate but a lower incidence of SSI, whereas the length of stay and readmission and re-operation rates were similar [169].

The most recent Cochrane review comparing mechanical appendix stump closure (stapler, clips, or electrothermal devices) versus ligation (endoloop, Roeder loop, or intracorporeal knot techniques) for uncomplicated AA included eight RCTs encompassing 850 participants. Five studies compared titanium clips versus ligature, two studies compared an endoscopic stapler device versus ligature, and one study compared an endoscopic stapler device, titanium clips, and ligature. No differences in total complications, intra-operative complications, or postoperative complications between ligature and all types of mechanical devices were found. However, the analyses of secondary outcomes revealed that the use of mechanical devices saved approximately 9 min of the total operating time when compared with the use of a ligature, even though this result did not translate into a clinically or statistically significant reduction in inpatient hospital stay [170].

Recently, 43 randomized controlled trials enrolling over 5,000 patients were analyzed in the network meta-analysis by Antoniou et al. The authors concluded that the use of suture ligation of the appendix in LA seems to be superior to other methods for the composite parameters of organ/space and superficial operative site infection [171].
Current evidence suggests that polymeric clips are an effective and cost-efficient method for stump closure in laparoscopic appendectomy (LA) for acute appendicitis (AA). In the recent meta-analysis by Knight et al., including over 700 patients, polymeric clips were found to be the cheapest method (€20.47 average per patient) and had the lowest rate of complications (2.7%) compared to other commonly used closure methods. Meanwhile, operative time and duration of in-patient stay were similar between groups [172].

Many studies compared the simple ligation and the stump inversion and no significant difference was found. Eleven RCTs (2634 patients) were included in the systematic review and meta-analysis by Qian et al. Postoperative pyrexia and infections were similar between simple ligation and stump inversion groups, respectively, but the former group had a shorter operative time, less incidence of postoperative ileus, and quicker postoperative recovery. The clinical results revealed that simple ligation was significantly superior to stump inversion [173].

**Statement 4.10** There are no clinical advantages in the use of endostaplers over endoloops for stump closure for both adults and children in either simple or complicated appendicitis, except for a lower incidence of wound infection when using endostaplers in children with uncomplicated appendicitis. Polymeric clips may be the cheapest and easiest method (with shorter operative times) for stump closure in uncomplicated appendicitis.

**Recommendation 4.10** We recommend the use of endoloops/suture ligation or polymeric clips for stump closure for both adults and children in either uncomplicated or complicated appendicitis, whereas endostaplers may be used when dealing with complicated cases depending on the intra-operative judgment of the surgeon and resources available [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 4.11** Simple ligation should be preferred to stump inversion, either in open or laparoscopic surgery, as the major morbidity and infectious complications are similar. Simple ligation is associated with shorter operative times, less postoperative ileus and quicker recovery.

**Recommendation 4.11** We recommend simple ligation over stump inversion either in open and laparoscopic appendectomy [QoE: High; Strength of recommendation: Strong; 1A].

**Q.4.10: Is the use of abdominal drains recommended after appendectomy for complicated acute appendicitis in adult patients?**

The updated 2019 Cochrane review on the issue included six RCTs (521 participants), comparing abdominal drainage and no drainage in patients undergoing emergency OA for complicated AA. The authors found that there was insufficient evidence to determine the effects of abdominal drainage and no drainage on intra-abdominal abscess or for SSI at 14 days. The increased risk of a 30-day overall complication rate in the drainage group was rated as very low-quality evidence, as well as the evidence that drainage increases hospital stay by 2.17 days compared to the no drainage group. Thus, there is no evidence for any clinical improvement by using abdominal drainage in patients undergoing OA for complicated AA [174].

Low-quality studies have reported that routine drainage has not proven its utility and seems to cause more complications, higher length of hospital stay, and transit recovery time [175]. In the large retrospective cohort study by Schlottmann et al. the placement of intra-abdominal drains in complicated AA did not present benefits in terms of reduced IAA and even lengthened hospital stay [176].

**Statement 4.12** In adult patients, the use of drains after appendectomy for perforated appendicitis and abscess/peritonitis should be discouraged. Drains are of no benefit in preventing intra-abdominal abscess and lead to longer length of hospitalization, and there is also low-quality evidence of increased 30-day morbidity and mortality rates in patients in the drain group.

**Recommendation 4.12** We recommend against the use of drains following appendectomy for complicated appendicitis in adult patients [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Q.4.11: Is the use of abdominal drains recommended after appendectomy for complicated acute appendicitis in pediatric patients?**

The prophylactic use of abdominal drainage after LA for perforated AA in children does not prevent postoperative complications and may be associated with negative outcomes.

Aneiros Castro et al. retrospectively analyzed 192 pediatric patients (mean age of 7.77 ± 3.4 years) undergoing early LA for perforated AA and reported that there were no statistically significant differences between the drain and no drain groups in the rate of IAA, SSI, and bowel obstruction. However, drains were statistically associated with an increased requirement for antibiotic and analgesic medication, fasting time, operative time, and length of hospital stay [177].

**Statement 4.13** The prophylactic use of abdominal drainage after laparoscopic appendectomy for perforated appendicitis in children does not prevent postoperative complications and may be associated with negative outcomes.

**Recommendation 4.13** We suggest against the prophylactic use of abdominal drainage after laparoscopic appendectomy for complicated appendicitis in children [QoE: Low; Strength of recommendation: Weak; 2C].
Q.4.12: What are the best methods to reduce the risk of SSI in open appendectomies with contaminated/dirty wounds? Wound edge protectors significantly reduce the rate of SSI in open abdominal surgery. The systematic review and meta-analysis by Mihaljevic et al. (16 randomized controlled trials including 3695 patients investigating wound edge protectors published between 1972 and 2014) showed that wound edge protectors significantly reduced the rate of SSI (RR 0.65). A similar effect size was found in the subgroup of patients undergoing colorectal surgery (RR 0.65). Of the two common types of wound protectors, double-ring devices were found to exhibit a greater protective effect (RR 0.29) than single-ring devices (RR 0.71) [178].

The use of ring retractors showed some evidence of SSI reduction (RR 0.44) in the meta-analysis by Ahmed et al., which included four RCTs with 939 patients. On subgroup analysis, ring retractor was more effective in more severe degrees of appendiceal inflammation (contaminated group) [179].

A recent RCT comparing primary and delayed primary wound closure in complicated AA showed that the superficial SSI rate was lower in patients who underwent primary wound closure than delayed primary wound closure (7.3% vs 10%), although the risk difference of −2.7% was not statistically significant. Postoperative pain, length of stay, recovery times, and quality of life were nonsignificantly different with corresponding risk differences of 0.3, −0.1, −0.2, and 0.02, respectively. However, costs for primary wound closure were lower than delayed primary wound closure [180].

In the RCT by Andrade et al. comparing skin closure with a unique absorbable intradermal stitch and traditional closure technique (non-absorbable separated stitches), OA skin closure with the former has shown to be safe, with a reduced seroma and abscess incidence and an equivalent dehiscence and superficial SSI incidence. Furthermore, the relative risk of complications with traditional skin closure was 2.91 higher, compared to this new technique [181].

Statement 4.14 The use of wound ring protectors shows some evidence of surgical site infection reduction in open appendectomy, especially in case of complicated appendicitis with contaminated/dirty wounds. Recommendation 4.14 We recommend wound ring protectors in open appendectomy to decrease the risk of SSI [QoE: Moderate; Strength of recommendation: Strong; 1B].

Statement 4.15 Delayed primary skin closure increases the length of hospital stay and overall costs in open appendectomies with contaminated/dirty wounds and does not reduce the risk of SSI. Subcuticular suture seems preferable in open appendectomy for acute appendicitis as it is associated with a lower risk of complications (surgical site infection/abscess and seroma) and lower costs. Recommendation 4.15 We recommend primary skin closure with a unique absorbable intradermal suture for open appendectomy wounds [QoE: Moderate; Strength of recommendation: Weak; 2B].

Topic 5: Intra-operative grading of acute appendicitis
Q.5.1: What is the value of scoring systems for intra-operative grading of acute appendicitis?
There is considerable variability in the intra-operative classification of AA. In the multicenter cohort study by Strong et al. involving 3,138 patients, the overall disagreement between the surgeon and the pathologist was reported in 12.5% of cases (moderate reliability, κ 0.571). Twenty-seven percent of appendices assessed as normal by the surgeon revealed inflammation at histopathological assessment, while 9.6% of macroscopically appearing inflamed AA revealed to be normal [182].

In 2018, a survey among Dutch surgeons demonstrated that a clear standard of care is missing both in patient selection and in determining the length of antibiotic treatment following appendectomy. However, the authors assessed the inter-observer variability in the classification of AA during laparoscopy and demonstrated that agreement was minimal for both the classification of AA (κ score 0.398) and the decision to prescribe postoperative antibiotic treatment (κ score 0.378) [183].

The definition of complicated AA varies among studies. Apart from the common component of perforation, it may or may not also include non-perforated gangrenous AA, the presence of a fecalith and/or AA in the presence of pus, or purulent peritonitis, or abscess. Although most surgeons agree that AA with perforation, intra-abdominal abscess, or purulent peritonitis can be defined as complicated AA, for which postoperative antibiotic therapy is indicated, there is still a considerable variation in the indications for prolonged antibiotic therapy after appendectomy, and the antibiotic regimen that should be used [184].

As the intra-operative classification of AA dictates the patient’s postoperative management, such variation in practice may influence clinical outcomes, and standardization may impact the appropriate use of antibiotics worldwide given the issue of rising antimicrobial resistance.

In order to evaluate the appendix during diagnostic laparoscopy, in 2013, Hamminga et al. proposed the LAPP (Laparoscopic APPendicitis) score (six criteria), with a single-center prospective pilot study (134 patients), reporting high positive and negative predictive values (99% and 100%, respectively) [185]. In 2015, Gomes et al. proposed a grading system for AA that incorporates clinical presentation, imaging, and laparoscopic findings. The system, encompassing four grades
(0 = normal looking appendix, 1 = inflamed appendix, 2 = necrosis, 3 = inflammatory tumor, 4 = diffuse peritonitis) provides a standardized classification to allow more uniform patient stratification for AA research and to aid in determining optimal management according to the grade of the disease [186].

In 2018, the WSES grading system was validated in a prospective multicenter observational study, performed in 116 worldwide surgical departments from 44 countries over a 6-month period, which showed that 3.8% of patients had grade 0, while 50.4% had grade 1, 16.8% grade 2a, 3.4% grade 2b, 8.8% grade 3a, 4.8% grade 3b, 1.9% grade 3c, and 10.0% grade 4. About half of the patients were grade 1 (inflamed appendix), and this is probably the most common situation for an emergency surgeon [186, 187].

In 2014, the AAST also proposed a system for grading the severity of emergency general surgery diseases based on several criteria encompassing clinical, imaging, endoscopic, operative, and pathologic findings, for eight commonly encountered gastrointestinal conditions, including AA, ranging from grade 1 (mild) to grade V (severe) [188]. In 2017, Hernandez et al. validated this system in a large cohort of patients with AA, showing that increased AAST grade was associated with open procedures, complications, and length of stay. AAST grade in emergency for AA determined by preoperative imaging strongly correlated with operative findings [189]. In 2018, the same researchers assessed whether the AAST grading system corresponded with AA outcomes in a US pediatric population. Results showed that increased AAST grade was associated with increased Clavien-Dindo severity of complications and length of hospital stay [190].

Moreover, increasing anatomic severity, as defined by AAST grade, has shown to be associated with increasing costs. Length of stay exhibited the strongest association with costs, followed by AAST grade, Clavien-Dindo Index, age-adjusted Charlson score, and surgical wound classification [191]. In 2019, a study by Mällinen et al. corroborated the known clinical association of an appendicitis [192]. In the same way, the AAST grading score or AAST EGS grading score) based on clinical, imaging and operative findings [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Statement 5.1** The incidence of unexpected findings in appendectomy specimens is low. The intra-operative diagnosis alone is insufficient for identifying unexpected disease. From the currently available evidence, routine histopathology is necessary. **Recommendation 5.1** We recommend routine histopathology after appendectomy [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 5.2** Operative findings and intra-operative grading seem to correlate better than histopathology with morbidity, overall outcomes and costs, both in adults and children. Intra-operative grading systems can help the identification of homogeneous groups of patients, determining optimal postoperative management according to the grade of the disease and ultimately improve utilization of resources. **Recommendation 5.2** We suggest the routine adoption of an intra-operative grading system for acute appendicitis (e.g., WSES 2015 grading score or AAST EGS grading score) based on clinical, imaging and operative findings [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Q.5.2: Should the macroscopically normal appendix be removed during laparoscopy for acute right iliac fossa pain when no other explanatory pathology is found?**

Laparoscopic management of normal appendix still represents a dilemma for the surgeon, as no high-level evidence-based recommendations are available to date.

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) 2010 guidelines stated that, if no other pathology is identified, the decision to remove the appendix should be considered, but based on the individual clinical scenario [194]. In the same way, the European Association of Endoscopic Surgery (EAES) 2016 guidelines recommended performing an appendectomy in the case of a normal appearing appendix during surgery for suspected AA [195].

Intra-operative macroscopic distinction between a normal appendix and AA during surgery can be challenging. Several studies have shown a 19% to 40% rate of
pathologically abnormal appendix in the setting of no visual abnormalities [182, 196]. Therefore, the risk of leaving a potentially abnormal appendix must be weighed against the risk of appendectomy in individual scenarios. Cases of postoperative symptoms requiring reoperation for appendectomy have been described in patients whose normal appendix was left in place at the time of the original procedure. The risks of leaving in situ an apparently normal appendix are related to later AA, subclinical or endo-appendicitis with persisting symptoms, and missed appendiceal malignancy.

According to the retrospective study by Grimes et al., including 203 appendectomies performed with normal histology, fecaliths may be the cause of right iliac fossa pain in the absence of obvious appendiceal inflammation. In this study, the policy of routine removal of a normal-looking appendix at laparoscopy in the absence of any other obvious pathology appeared to be an effective treatment for recurrent symptoms [197]. In the same way, Tartaglia et al. supported an appendectomy in patients undergoing laparoscopy for acute right lower quadrant abdominal pain even when the appendix appears normal on visual inspection, based on the results of a study in which 90% of the removed normal-looking appendices at laparoscopy for abdominal pain and no other intra-abdominal acute disease harbored inflammatory changes at the definitive pathology [198].

Recently, Sørensen et al. performed a retrospective cohort analysis of patients who underwent a diagnostic laparoscopy due to clinical suspicion of AA where no other pathology was found, and the appendix was not removed. Of the 271 patients included, 56 (20.7%) were readmitted with right iliac fossa pain after a median time of 10 months. Twenty-two patients (8.1%) underwent a new laparoscopic procedure, and the appendix was removed in 18 patients, of which only one showed histological signs of inflammation. Based on results from this study, the authors did not consider that it is necessary to remove a macroscopic normal appendix during laparoscopy for clinically suspected AA [199]. This year, Allaway et al. published the results of a single-centre retrospective case note review of patients undergoing LA for suspected AA. Patients were divided into positive and negative appendectomy groups based on histology results. The authors reported an overall negative appendectomy rate of 36.0% among 1413 patients who met inclusion criteria (904 in the positive group and 509 in the negative group). Morbidity rates (6.3% vs 6.9%; \(P = 0.48\)) and types of morbidity were the same for negative appendicectomy and uncomplicated AA, and there was no significant difference in complication severity or length of stay (2.3 vs 2.6 days; \(P = 0.06\)) between negative appendicectomy and uncomplicated AA groups [200].

The 2014 Cochrane review on the use of laparoscopy for the management of acute lower abdominal pain in women of childbearing age showed that laparoscopy was associated with an increased rate of specific diagnoses. A significant difference favoring the laparoscopic procedure in the rate of removal of normal appendix compared to open appendectomy was found [201].

**Statement 5.3** Surgeon’s macroscopic judgment of early grades of acute appendicitis is inaccurate and highly variable. The variability in the intra-operative classification of appendicitis influences the decision to prescribe postoperative antibiotics and should be therefore prevented/avoided. **Recommendation 5.3** We suggest appendix removal if the appendix appears “normal” during surgery and no other disease is found in symptomatic patients [QoE: Low; Strength of recommendation: Weak; 2C].

**Topic 6: Management of perforated appendicitis with phlegmon or abscess**

**Q.6.1: Is early appendectomy an appropriate treatment compared with delayed appendectomy for patients with perforated acute appendicitis with phlegmon or abscess?**

The optimal approach to complicated AA with phlegmon or abscess is a matter of debate.

In the past, immediate surgery has been associated with a higher morbidity if compared with conservative treatment, while the non-surgical treatment of appendicular abscess or phlegmon has been reported to succeed in over 90% of patients, with an overall risk of recurrence of 7.4% and only 19.7% of cases of abscess requiring percutaneous drainage [202].

The meta-analysis by Similis et al. (including 16 non-randomized retrospective studies and one non-randomized prospective study for a total of 1572 patients, of whom 847 treated with conservative treatment and 725 with appendectomy) revealed that conservative treatment was associated with significantly less overall complications (wound infections, abdominal/pelvic abscesses, ileus/bowel obstructions, and re-operations) if compared to immediate appendectomy [203].

In the large series from the National Inpatient Sample (NIS) by Horn et al., 25.4% of a total of 2,209 adult patients with appendiceal abscesses who received drains failed conservative management and underwent operative intervention [204].

Current evidence shows that surgical treatment of patients presenting with appendiceal phlegmon or abscess is preferable to NOM with antibiotic oriented treatment in the reduction of the length of hospital stay and need for readmissions when laparoscopic expertise is available.
In the retrospective study by Young et al., early appendectomy has shown superior outcomes compared with initial NOM. Of 95 patients presenting with complicated AA, 60 underwent early appendectomy, and 35 initially underwent NOM. All patients who experienced failed NOM (25.7%) had an open operation with most requiring bowel resection. Early appendectomy demonstrated a lower incidence of bowel resection (3.3% vs 17.1%, \( P = 0.048 \)) when compared to all patients initially undergoing NOM [206].

Recently, the cumulative meta-analysis by Gavriilidis et al. has shown a more widespread use of the laparoscopic approach for the management of complicated AA. Although overall complications, abdominal/pelvic abscesses, wound infections, and unplanned procedures were significantly lower in the conservative treatment cohort in the general analysis, on the contrary, the subgroup analysis of three RCTs revealed no significant difference in abdominal/pelvic abscesses (OR 0.46). High-quality RCTs demonstrated shorter hospital stay by 1 day for the LA cohort compared to conservative treatment [207].

According to the results of the Cochrane review published by Cheng et al. in 2017, it is unclear whether early appendectomy shows any benefit in terms of complications compared to delayed appendectomy for people with appendiceal phlegmon or abscess. The review included only two RCTs with a total of 80 participants. The comparison between early versus delayed open appendectomy for appendiceal phlegmon included 40 participants (pediatric and adults), randomized either to early appendectomy (appendectomy as soon as appendiceal mass resolved within the same admission, \( n = 20 \)) or to delayed appendectomy (initial conservative treatment followed by interval appendectomy 6 weeks later, \( n = 20 \)). There was insufficient evidence to determine the effect of using either early or delayed open appendectomy on overall morbidity (RR 13.00), the proportion of participants who developed wound infection (RR 9.00), or fecal fistula (RR 3.00). Even the quality of evidence for increased length of hospital stay and time away from normal activities in the early appendectomy group was of very low quality. The comparison between early versus delayed laparoscopic appendectomy for appendiceal abscess included 40 pediatric patients, randomized either to early appendectomy (emergent laparoscopic appendicectomy, \( n = 20 \)) or to delayed appendectomy (initial conservative treatment followed by interval laparoscopic appendicectomy 10 weeks later, \( n = 20 \)). Health-related quality of life score measured at 12 weeks after appendectomy was higher in the early appendectomy group than in the delayed appendectomy group, but the quality of evidence was very low [208].

The high-quality RCT by Mentula et al. (not included in the Cochrane review), conversely, demonstrated that LA in experienced hands is a safe and feasible first-line treatment for appendiceal abscess. In this study, early LA was associated with fewer readmissions and fewer additional interventions than conservative treatment, with a comparable hospital stay. Patients in the laparoscopy group had a 10% risk of bowel resection and 13% risk of incomplete appendectomy. There were significantly fewer patients with unplanned readmissions following LA (3% versus 27%, \( P = 0.026 \)). Additional interventions were required in 7% of patients in the laparoscopy group (percutaneous drainage) and 30% of patients in the conservative group (appendectomy). Conversion to open surgery was required in 10% of patients in the laparoscopy group and 13% of patients in the conservative group. The rate of uneventful recovery was 90% in the laparoscopy group versus 50% in the conservative group (\( P = 0.002 \)) [209].

Luo et al. analyzed the outcomes of 1,225 patients under 18 years of age who had non-surgical treatment for an appendiceal abscess between 2007 and 2012 in Taiwan. The authors compared outcomes of percutaneous drainage with antibiotics or antibiotics alone. Of 6, 190 children having an appendiceal abscess, 1,225 patients received non-operative treatment. Patients treated with percutaneous drainage and antibiotics had a significantly lower rate of recurrent AA, significantly smaller chance of receiving an interval appendectomy, and significantly fewer postoperative complications after the interval appendectomy than those without percutaneous drainage treatment. In addition, patients treated with percutaneous drainage were significantly less indicated to receive an interval appendectomy later [210].

Two recent meta-analyses addressed the role of early appendectomy in children with appendiceal phlegmon or abscess. The meta-analysis by Fugazzola et al. found that children with appendiceal abscess/phlegmon reported better results in terms of complication rate and readmission rate if treated with NOM [211]. Similarly, the meta-analysis by Vaos et al. reported that NOM was associated with lower rates of complications and wound infections, whereas the development of IAA and postoperative ileus was not affected by the treatment of choice [212]. In both the meta-analyses, early appendectomy was associated with reduced length of hospital stay.

**Statement 6.1** Non-operative management is a reasonable first-line treatment for appendicitis with phlegmon or abscess. Percutaneous drainage as an adjunct to antibiotics, if accessible, could be beneficial, although there is a lack of evidence for its use on a routine basis. Laparoscopic surgery in
experienced hands is a safe and feasible first-line treatment for appendiceal abscess, being associated with fewer readmissions and fewer additional interventions than conservative treatment, with a comparable hospital stay. **Recommendation 6.1** We suggest non-operative management with antibiotics and—if available—percutaneous drainage for complicated appendicitis with a periappendicular abscess, in settings where laparoscopic expertise is not available [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Statement 6.2** Operative management of acute appendicitis with phlegmon or abscess is a safe alternative to non-operative management in experienced hands and may be associated with shorter LOS, reduced need for readmissions, and fewer additional interventions than conservative treatment. **Recommendation 6.2** We suggest the laparoscopic approach as treatment of choice for patients with complicated appendicitis with phlegmon or abscess where advanced laparoscopic expertise is available, with a low threshold for conversion. [QoE: Moderate; Strength of recommendation: Weak; 2B].

**Q.6.2: Is interval appendectomy always indicated for patients with acute appendicitis following successful NOM?**

The reported rate of recurrence after non-surgical treatment for perforated AA and phlegmon is up to 12% [213]. In order to avoid this quite high chance of recurrence, some authors recommend routine elective interval appendectomy following initial conservative management. However, this procedure is associated with a non-negligible rate of morbidity of 12.4% [202]. The systematic review by Hall et al., including three retrospective studies for a total of 127 cases of non-surgical treatment of appendix mass in children, showed that after successful non-operative treatment the risk of recurrent AA was found to be 20.5%. Overall, the complications reported included SSI, prolonged postoperative ileus, hematoma formation, and small bowel obstruction, but the incidence of any individual complication was not determined [23].

In the recent systematic review by Darwazeh et al., interval appendectomy and repeated NOM in the case of recurrence of appendiceal phlegmon were associated with similar morbidity. However, elective interval appendectomy was related to additional operative costs to prevent recurrence in only one of eight patients, such as not to justify the routine performance of appendectomy [213].

In the same way, Rushing et al., who found a risk of recurrence of 24.3% in patients, managed with NOM for appendiceal abscess or phlegmon and recommended against routine interval appendectomy in otherwise asymptomatic patients [214]. The CHINA RCT recently compared the outcomes of active observation versus interval appendectomy after successful NOM of an appendix mass in children. Results showed that more than three-quarters of children could avoid appendectomy during early follow-up after successful NOM of an appendix mass. The proportion of children with histologically proven recurrent AA under active observation was 12%, and the proportion of children with severe complications related to interval appendicectomy was 6%.

Although the risk of complications after interval appendectomy was low, adoption of a wait-and-see approach, reserving appendectomy for patients who develop AA recurrence or recurrent symptoms, should be considered a most cost-effective management strategy compared with routine interval appendectomy [215].

In the study by Renteria et al., unexpected malignancy was 3% in the elderly (mean age 66 years) and 1.5% in the young (mean age 39 years) cohorts of patients who underwent appendectomy as primary treatment for AA [216]. Adult patients with complicated AA treated with interval appendectomy can be diagnosed with appendiceal neoplasm in up to 11% of cases, in contrast to 1.5% of the patients who have early appendectomy [217]. Recently, the RCT by Mällinen et al. comparing interval appendectomy and follow-up with MRI after initial successful nonoperative treatment of periappendicular abscess was prematurely terminated owing to ethical concerns following the unexpected finding at the interim analysis of a high rate of neoplasm (17%), with all neoplasms in patients older than 40 years [218]. If this significant rate of neoplasms after periappendicular abscess is validated by future studies, it would argue for routine interval appendectomy in this setting.

**Statement 6.3** The reported rate of recurrence after non-surgical treatment for perforated AA and phlegmon ranges from 12% to 24%. Interval appendectomy and repeated NOM in case of recurrence of appendiceal phlegmon are associated with similar morbidity. However, elective interval appendectomy is related to additional operative costs to prevent recurrence in only one of eight patients, such as not to justify the routine performance of appendectomy. **Recommendation 6.3** We recommend against routine interval appendectomy after NOM for complicated appendicitis in young adults (< 40 years old) and children. Interval appendectomy is recommended for those patients with recurrent symptoms [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 6.4** The incidence of appendicular neoplasms is high (3–17%) in adult patients ≥ 40 years old with complicated appendicitis. **Recommendation 6.4** We suggest both colonic screening with colonoscopy and interval full-dose contrast-enhanced CT scan for patients with appendicitis treated nonoperatively if ≥ 40 years old [QoE: Low; Strength of recommendation: Weak; 2C].
**Topic 7: Perioperative antibiotic therapy**

**Q.7.1: Is preoperative antibiotic therapy recommended for patients with acute appendicitis?**

In 2001, a Cochrane meta-analysis supported that broad-spectrum antibiotics given preoperatively are effective in decreasing SSI and abscesses. RCTs and non-randomized comparative studies in which any antibiotic regimen was compared to placebo in patients undergoing appendectomy were analyzed. Forty-four studies including 9,298 patients were included in this review. Antibiotics were superior to placebo for preventing wound infection and intra-abdominal abscess, with no apparent difference in the nature of the removed appendix [219]. The same final results have been obtained by the 2005 updated version of the review, including 45 studies with 9,576 patients [220]. The timing of pre-operative antibiotics does not affect the frequency of SSI after appendectomy for AA. Therefore, the optimal timing of preoperative antibiotic administration may be from 0 to 60 min before the surgical skin incision [221].

**Statement 7.1** A single dose of broad-spectrum antibiotics given preoperatively (from 0 to 60 min before the surgical skin incision) has been shown to be effective in decreasing wound infection and postoperative intra-abdominal abscess, with no apparent difference in the nature of the removed appendix. **Recommendation 7.1** We recommend a single preoperative dose of broad-spectrum antibiotics in patients with acute appendicitis undergoing appendectomy. We recommend against postoperative antibiotics for patients with uncomplicated appendicitis [QoE: High; Strength of recommendation: Strong; 1A].

**Q.7.2: Are postoperative antibiotics always indicated in adult patients following appendectomy?**

Prospective trials demonstrated that patients with perforated AA should receive postoperative antibiotic treatment, especially if complete source control has not been achieved. Cho et al. recently demonstrated in a large cohort of patients that the role of antibiotic treatment for preventing post-appendectomy IAA seems to be related with achieving intraperitoneal infectious source control. The authors found that the mean durations of postoperative antibiotic therapy were 3.1 days for the non-IAA group and 3.3 days for the IAA group, with no significant difference between the groups [222].

In the large observational study by McGillen et al., patients with complicated AA were significantly more likely to be started on antibiotics after surgery (83.9% versus 33.3%; \( P < 0.001 \)) compared with patients with simple AA. The development of a SSI was significantly associated with a clinical diagnosis of diabetes, the presence of free fluid, abscess, or perforation on preoperative imaging [223].

The optimal course of antibiotics remains to be identified, but current evidence suggests that longer postoperative courses do not prevent SSI compared with 2 days of antibiotics.

The meta-analysis by Van den Boom et al., including nine studies with more than 2,000 patients with complicated AA, revealed a statistically significant difference in IAA incidence between the antibiotic treatment of ≤ 5 vs > 5 days (OR 0.36), but not between ≤ 3 vs > 3 days (OR 0.81) [224].

A total of 80 patients were enrolled in a recent RCT comparing the outcomes of short (24 h) and the extended (> 24 h) postoperative antibiotic therapy in complicated AA. The overall rate of complications was 17.9% and 29.3% in the short and extended group, respectively (\( P = 0.23 \)). Mean complication index did not differ between the study groups (\( P = 0.29 \)), whereas hospital length of stay was significantly reduced in the short therapy group (61 ± 34 h vs 81 ± 40 h, \( P = 0.005 \)). Based on the results of this RCT, 24 h of antibiotic therapy following appendectomy does not result in worse primary outcomes in complicated AA, but results in a significant reduction in length of hospitalization, with a major cost-saving and antibacterial stewardship benefits [225].

Although discontinuation of antimicrobial treatment should be based on clinical and laboratory criteria, a period of 3–5 days for adult patients is generally sufficient following appendectomy for complicated AA. The 2015 "STOP-IT" RCT by Sawyer et al. on 518 patients with complicated intra-abdominal infection, including also complicated AA, undergoing adequate source control demonstrated that outcomes after fixed-duration antibiotic therapy (approximately 4 days) were similar to those after a longer course of antibiotics (approximately 8 days) that extended until after the resolution of physiological abnormalities [226].

**Statement 7.2** In patients with complicated acute appendicitis, postoperative broad-spectrum antibiotics are suggested, especially if complete source control has not been achieved. For adult patients deemed to require them, discontinuation of antibiotics after 24 h seems safe and is associated with shorter length of hospital stay and lower costs. In patients with intra-abdominal infections who had undergone an adequate source control, the outcomes after fixed-duration antibiotic therapy (approximately 3–5 days) are similar to those after a longer course of antibiotics. **Recommendation 7.2** We recommend against prolonging antibiotics longer than 3–5 days postoperatively in case of complicated appendicitis with adequate source control [QoE: High; Strength of recommendation: Strong; 1A].

**Q.7.3: Are postoperative antibiotics always indicated in pediatric patients following appendectomy?**

A retrospective review conducted by Litz et al. demonstrated that antibiotic administration within 1 h of...
appendectomy in pediatric patients with AA who receive antibiotics at diagnosis did not change the incidence of postoperative infectious complications [227].

Children with non-perforated AA should receive a single broad-spectrum antibiotic. Second- or third-generation cephalosporins, such as cefoxitin or cefotetan, may be used in uncomplicated cases.

In complicated AA, intravenous antibiotics that are effective against enteric gram-negative organisms and anaerobes including *E. coli* and *Bacteroides* spp. should be initiated as soon as the diagnosis is established. Broad-spectrum coverage is obtained with piperacillin-tazobactam, ampicillin-sulbactam, ticarcillin-clavulanate, or imipenem-cilastatin. For perforated AA, the most common combination is ampicillin, clindamycin (or metronidazole), and gentamicin. Alternatives include ceftriaxone-metronidazole or ticarcillin-clavulanate plus gentamicin, in accordance with the epidemiology of bacteria [228]. Metronidazole is not indicated when broad-spectrum antibiotics such as aminopenicillins with β-lactam inhibitors or carbapenems and select cephalosporins are used [229]. In a recent retrospective cohort study of 24,984 children aged 3 to 18 years, Kronman et al. compared the effectiveness of extended-spectrum versus narrower-spectrum antibiotics for children with AA. The exposure of interest was receipt of systemic extended-spectrum antibiotics (piperacillin ± tazobactam, ticarcillin ± clavulanate, ceftazidime, ceftiraxone, or a carbapenem) on the day of appendectomy or the day after. The primary outcome was 30-day readmission for SSI or repeat abdominal surgery. The authors reported that extended-spectrum antibiotics seem to offer no advantage over narrower-spectrum agents for children with surgically managed acute uncomplicated or complicated AA [230].

Broad-spectrum, single, or double agent therapy is equally efficacious as but more cost-effective than triple agent therapy. It was reported that dual therapy consisting of ceftriaxone and metronidazole only offers a more efficient and cost-effective antibiotic management compared with triple therapy, but prospective studies are required to determine whether

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![Practical WSES algorithm for diagnosis and treatment of adult patients with suspected acute appendicitis](image)

*Fig. 1* Practical WSES algorithm for diagnosis and treatment of adult patients with suspected acute appendicitis.
this policy is associated with higher rates of wound infections and change in antibiotic therapy [231].

Postoperative antibiotics can be administered orally if the patient is otherwise well enough to be discharged. Arnold et al. conducted a RCT of 82 pediatric patients to compare the effect of home intravenous versus oral antibiotic therapy on complication rates and resource utilization following appendectomy for perforated AA. Fosrt-y-four patients (54%) were randomized to the IV group and 38 (46%) to the oral group. The study showed no difference in length of stay (4.4 ± 1.5 versus 4.4 ± 2.0 days), postoperative abscess rate (11.6% vs 8.1%), or readmission rate (14.0% vs 16.2%), whereas hospital and outpatient charges were higher in the IV group [232].

Other retrospective cohort studies have confirmed that after appendectomy for perforated AA in children, oral antibiotics show equivalent outcomes compared with intravenous antibiotics, but with shorter length of hospitalizations and less medical encounters required [233].

Compared to pediatric patients who receive intravenous antibiotics, those who are treated with oral antibiotics have statistically lower rates of repeated US imaging (49.6% vs 35.1%) and PICC placement (98.3% vs 9.1%), whereas the rates of IAA are similar (20.9% vs 16.0%). Moreover, early transition to oral antibiotics allows shorter hospital times and decreased hospital charges, with similar total antibiotic days and readmission rate [234].

**Statement 7.3** Administering postoperative antibiotics orally in children with complicated appendicitis for periods shorter than 7 days postoperatively seems to be safe and it is not associated with increased risk of complications. Early transition to oral antibiotics is safe, effective, and cost-efficient in the treatment of complicated appendicitis in the child. **Recommendation 7.3** We recommend early switch (after 48 h) to oral administration of postoperative antibiotics in children with complicated appendicitis, with an overall length of therapy shorter than seven days [QoE: Moderate; Strength of recommendation: Strong; 1B].

**Statement 7.4** Postoperative antibiotics after appendectomy for uncomplicated acute appendicitis in children seems to have no role in reducing the rate of surgical site infection. **Recommendation 7.4** In pediatric patients operated for uncomplicated acute appendicitis, we suggest against using postoperative antibiotic therapy [QoE: Low; Strength of recommendation: Weak; 2C].

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**Fig. 2** Practical WSES algorithm for diagnosis and treatment of pediatric patients with suspected acute appendicitis.
Conclusions
The current evidence-based guidelines are the updated 2020 International Comprehensive Clinical Guidelines for the diagnosis and management of acute appendicitis. After reaching consensus on each of the above mentioned, the panel experts and the scientific committee members developed two WSES flow-chart algorithm for the diagnosis and management of acute appendicitis to be used for adults and pediatric patient population, reported respectively in Figs. 1 and 2.

Supplementary information
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Additional file 1. Search Syntaxes.
Additional file 2.
Additional file 3.
Additional file 4.
Additional file 5.
Additional file 6.

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Additional file 1.
Additional file 2.
Additional file 3.
Additional file 4.
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2020 update of the WSES guidelines for the management of acute colonic diverticulitis in the emergency setting


Abstract

Acute colonic diverticulitis is one of the most common clinical conditions encountered by surgeons in the acute setting. An international multidisciplinary panel of experts from the World Society of Emergency Surgery (WSES) updated its guidelines for management of acute left-sided colonic diverticulitis (ALCD) according to the most recent available literature. The update includes recent changes introduced in the management of ALCD. The new update has been further integrated with advances in acute right-sided colonic diverticulitis (ARCD) that is more common than ALCD in select regions of the world.

Keywords: Acute left-sided colonic diverticulitis, Acute right-sided colonic diverticulitis, Peritonitis, Abscess

Introduction

Acute left-sided colonic diverticulosis is common in Western countries with its prevalence increasing throughout the world, which is likely due to changes in lifestyle [1]. Although left-sided colonic diverticulosis remains more common among elderly patients, a dramatic rise of its incidence has been seen in younger age groups in recent years [2]. Recent evidence suggests that lifetime risk of developing acute left-sided colonic diverticulitis (ALCD) is about 4% among patients with diverticulosis [3], and data from Western populations suggest that up to one fifth of patients with acute diverticulitis are under 50 years of age [4–6].

ALCD is a common problem encountered by Western surgeons in the acute setting. The sigmoid colon is usually the most commonly involved part, while acute right-sided diverticulitis (ARCD) is rarer but much more common in non-Western populations.

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Methods
The World Society of Emergency Surgery (WSES) guidelines for management of ALCD were published in 2016 [7]. In 2020, the guidelines were revised and updated.

The present guidelines have been developed according to the GRADE methodology [8, 9]. The GRADE system is a hierarchical, evidence-based tool, which systematically evaluates the available literature and focuses on the level of evidence based upon the types of studies included. The quality of evidence can be marked as high, moderate, low, or very low. This could be either downgraded in case of significant bias or upgraded when multiple high-quality studies showed consistent results. The highest quality of evidence studies (systematic reviews with meta-analysis of randomized controlled trials) was assessed first. If the meta-analysis was of sufficient quality, it was used to answer the research question. If no meta-analysis of sufficient quality was found, randomized controlled trials (RCTs) and non-randomized cohort studies (n-RCS) were evaluated. The strength of the recommendation was based on the level of evidence and qualified as weak or strong.

A multidisciplinary panel of experts, coordinated by a central coordinator, was selected to serve as experts in this 2020 update of the WSES guidelines for the management of acute left-sided colonic diverticulitis (ALCD). The experts reviewed and updated the original list of key questions on the diagnosis and treatment of ALCD addressed in the previous version of the guidelines.

For each statement, a consensus among the panel of experts was reached using a Delphi approach. Statements were approved with an agreement of ≥ 80%.

After the approval of the statements, the expert panel met via email to prepare and revise the definitive guidelines. The manuscript was successively reviewed by all members and ultimately revised as the present manuscript.

Which classification should be used in patients with ALCD?
There are multiple classification systems for ALCD. None has been conclusively proven to be superior in predicting patient outcomes, and therefore, a specific recommendation cannot be provided.

ALCD ranges in severity from uncomplicated phlegmonous diverticulitis to complicated diverticulitis including abscesses and/or perforation.

For the past three decades, the Hinchey classification has been the most used classification in the international literature [10].

In patients with surgical findings of abscesses and peritonitis, Hinchey et al. classified the severity of acute diverticulitis into four levels:

1. Pericolic abscess
2. Pelvic, intra-abdominal, or retroperitoneal abscess
3. Generalized purulent peritonitis
4. Generalized fecal peritonitis

In recent years, the management of ALCD has changed dramatically.

Computer tomography (CT) imaging has become a primary diagnostic tool in the diagnosis and staging of patients with ALCD, and more detailed information provided by CT scans led to several modifications of the Hinchey classification [4, 11–15].

In 1989, Neff et al. presented a new classification of ALCD based on CT findings. It consisted of five stages, ranging from radiological diagnosis of uncomplicated (stage 0) to pneumoperitoneum with abundant free liquid (stage 4) [11]:

0 Uncomplicated diverticulitis; diverticula, thickening of the wall, increased density of the pericolic fat
1 Locally complicated with local abscess
2 Complicated with pelvic abscess
3 Complicated with distant abscess
4 Complicated with other distant complications

In 2002, Ambrosetti et al. [12] classified ALCD into severe or moderate disease. In this classification, the CT scan determined the grade of severity guiding the physician in the treatment of acute complications. Moderate diverticulitis was defined by wall thickening of ≥ 5 mm and signs of pericolic fat inflammation. Severe diverticulitis was defined by wall thickening accompanied by abscess, extraluminal gas, or extraluminal contrast:

1. Moderate diverticulitis
   (a) Localized sigmoid wall thickening (≥ 5 mm)
   (b) Pericolic fat stranding
2. Severe diverticulitis
   (a) Abscess
   (b) Extraluminal gas
   (c) Extraluminal contrast

In 2005, Kaiser et al. [13] modified the Hinchey classification according to specific CT findings:
Stage 0: mild clinical diverticulitis
Stage 1a: confined pericolic inflammation
Stage 1b: confined pericolic abscess
Stage 2: pelvic or distant intra-abdominal abscess
Stage 3: generalized purulent peritonitis
Stage 4: fecal peritonitis at presentation

In 2013, Mora Lopez et al. proposed [14] a modification of the previous Neff classification dividing Neff stage 1 into stage 1a (localized pneumoperitoneum in the form of gas bubbles) and 1b (abscess < 4 cm).
Uncomplicated diverticulitis. Diverticula, thickening of the wall, increased density of the pericolic fat
1Locally complicated diverticulitis
1aLocalized pneumoperitoneum in the form of gas bubbles
1bAbscess (≤ 4 cm)
2Complicated diverticulitis with pelvic abscess. Abscess > 4 cm in pelvis
3Complicated diverticulitis with distant abscess. Abscess in abdominal cavity (outside pelvis)
4Complicated diverticulitis with other distant complications. Abundant pneumoperitoneum and/or intra-abdominal free liquid

Recently, Sallinen et al. [15] published an interesting retrospective study of patients treated for ALCD, setting the stage for the treatment of acute diverticulitis based on clinical, radiologic, and physiologic parameters:
1Uncomplicated diverticulitis
2Complicated diverticulitis with small abscess (< 6 cm)
3Complicated diverticulitis with large abscess (≥ 6 cm)
or distant intraperitoneal or retroperitoneal gas
4Generalized peritonitis without organ dysfunction
5Generalized peritonitis with organ dysfunction

Finally, a proposal for a CT-guided classification of ALCD was published in 2015 by the WSES acute diverticulitis working group [7].

It is a simple classification system of ALCD based on CT scan findings. It may guide clinicians in the management of acute diverticulitis and may be universally accepted for day to day practice. The WSES classification divides acute diverticulitis into 2 groups: uncomplicated and complicated.

In the event of uncomplicated acute diverticulitis, the infection only involves the colon and does not extend to the peritoneum. In the event of complicated acute diverticulitis, the infectious process proceeds beyond the colon. Complicated acute diverticulitis is divided into 4 stages, based on the extension of the infectious process:

Uncomplicated
0Diverticula, thickening of the wall, increased density of the pericolic fat

Complicated
1APericolic air bubbles or small amount of pericolic fluid without abscess (within 5 cm from inflammed bowel segment)
1BAbscess ≤ 4 cm
2AAbcess > 4 cm
2BDistant gas (> 5 cm from inflammed bowel segment)
3DDiffuse fluid without distant free gas
4DDiffuse fluid with distant free gas

What is the best way to make a diagnosis of ALCD?
In patients with suspected ALCD, we suggest a complete assessment of the patients using clinical history, signs, laboratory inflammation markers, and radiological findings (weak recommendation based on very low-quality evidence, 2D).

In patients with suspected, ALCD we suggest against diagnosis based only on clinical examination (weak recommendation based on very low-quality evidence, 2D).

Clinical findings of patients having ALCD include acute pain or tenderness in the left lower quadrant that may be associated with increased inflammatory markers, including C-reactive protein (CRP) and white blood cell count (WBC). Clinical diagnosis of ALCD usually lacks accuracy. In a prospective analysis [16] conducted on 802 consecutive patients who presented with abdominal pain to the emergency department, positive and negative predictive values of clinical diagnosis were 0.65 and 0.98, respectively. Additional cross-sectional imaging had a positive and negative predictive value of 0.95 and 0.99, respectively. Additional radiology examinations improved the diagnostic accuracy in 37% of the patients, but changed the management in only 7%.

In 2010, using logistic regression analysis, Laméris et al. [17] developed a clinical decision rule for diagnosis of ALCD, based on 3 criteria: (1) direct tenderness only in the left lower quadrant, (2) CRP > 50 mg/l, and (3) absence of vomiting. Of 126 clinically suspected patients enrolled in this prospective study, 30 patients had all 3 features (24%), of whom 29 had a final diagnosis of acute diverticulitis (97%; 95% CI 83–99%). Of the 96 patients without all 3 features, 45 (47%) did not have diverticulitis. In a quarter of patients with suspected diverticulitis, the diagnosis could be made clinically based on the combination of the three criteria.

Andeweg et al. in 2011 [18], using retrospective data from 287 patients, developed a clinical scoring system for the diagnosis of ALCD with diagnostic accuracy of 86%. It was based on independent predictors of ALCD including age, a clinical history of one or more previous episodes, localization of symptoms in the lower left abdomen, aggravation of pain on movement, the absence of vomiting, localization of abdominal tenderness on examination in the lower left abdomen, and C-reactive protein of 50 mg/l or higher.

CRP has been identified as a useful biomarker of inflammation, and it may be useful in the prediction of the clinical severity of acute diverticulitis as demonstrated by several recent studies [19–21]. To investigate the value of CRP and of other laboratory parameters of the patients in the prediction of the clinical severity of acute diverticulitis, a retrospective study was published in 2014 [19]. A CRP cutoff value of 170 mg/l significantly discriminated severe from mild diverticulitis (87.5% sensitivity, 91.1% specificity, area under the curve 0.942, p < 0.00001). The authors concluded that CRP is a useful tool in the prediction of the clinical severity of acute diverticulitis. A mild episode is very likely in patients with
CRP less than 170 mg/l. Those with higher CRP values have a greater probability of undergoing surgery or percutaneous drainage.

In another study, the diagnostic value of serological infection markers and body temperature, in discriminating complicated from uncomplicated diverticulitis, was assessed [20]. A total of 426 patients were included in this study of which 364 (85%) presented with uncomplicated and 62 (15%) with complicated diverticulitis. Only CRP was of sufficient diagnostic value (area under the curve 0.715). The median CRP in patients with complicated diverticulitis was significantly higher than in patients with uncomplicated disease (224 mg/l, range 99–284, vs. 87 mg/l, range 48–151, respectively). Patients with a CRP of 25 mg/l had a 15% chance of having complicated diverticulitis. This increased from 23% at a CRP value of 100 mg/l to 47% for 250 mg/l or higher. The optimal threshold was reached at 175 mg/l with a positive predictive value of 36%, negative predictive value of 92%, sensitivity of 61%, and specificity of 82%.

Mäkelä et al. [21] published a study comparing the CRP values of 350 patients who presented for the first time with symptoms of acute diverticulitis with the CT findings and clinical parameters by means of both univariate and multivariate analyses. CRP cutoff value of 149.5 mg/l significantly discriminated acute uncomplicated diverticulitis from complicated diverticulitis (specificity 65%, sensitivity 85%, area under the curve 0.811, \( p = 0.0001 \)). In multivariate analysis, a CRP value over 150 mg/l and old age were independent risk factors for acute complicated diverticulitis. The mean CRP value was significantly higher in the patients who died (mean CRP of 207 mg/l) than in those who survived (mean CRP of 139 mg/l). In addition, a CRP value over 150 mg/l and free abdominal fluid in CT were independent variables predicting postoperative mortality. The study confirmed that CRP is useful for predicting the severity of acute diverticulitis on admission. The authors concluded that patients with a CRP value higher than 150 mg/l have an increased risk of complicated diverticulitis and should always undergo a CT examination.

In 2018, a prospective study of patients with ALCD was published [22]. All patients underwent CT. Index parameters obtained at the initial evaluation in the emergency unit were analyzed to assess the association with the outcome. Ninety-nine patients were analyzed. Eighty-eight had mild radiological grading (Hinchey Ia/Ib), and 11 had severe radiological grading (Hinchey > Ib) (median index CRP 80 mg/l vs. 236 mg/l, \( p < 0.0001 \)). The median CRP level for Hinchey III/IV was 258.5 mg/l (201–297 mg/l). WBC, neutrophils/lymphocytes, serum creatinine, serum glucose, generalized peritonitis, generalized abdominal tenderness, urinary symptoms, and index CRP were related to severe disease. Index CRP was the only independent predictor for Hinchey > Ib (\( p = 0.038 \)). The optimal cutoff value calculated by receiver operating characteristic curve analysis was found to be 173 mg/l (sensitivity 90.9%, specificity 90.9%, \( p < 0.001 \)). All patients who underwent radiologic-guided percutaneous or surgery had an index CRP > 173 mg/l and Hinchey > Ib. However, the authors concluded that CRP should not be used as a predictor of severity if there are concomitant conditions that may affect its baseline levels.

The expert panel states that in very acutely onset disease, CRP values might not have risen yet, since there is a delay of 6–8 h from the onset of the disease, reaching peak at 48 h. Therefore, caution should be used in using low CRP as excluding acute diverticulitis [23].

What is the best imaging technique in patients with suspected ALCD? What is the role of ultrasound (US) in patients with ALCD?

In patients with suspected ALCD, we suggest contrast-enhanced CT scan of the abdomen as the imaging technique of first choice (weak recommendation based on moderate-quality evidence, 2B).

We suggest to use US in the initial evaluation of patients with suspected ALCD where it is performed by an expert operator. It has wide availability and easy accessibility. A step-up approach with CT performed after an inconclusive or negative US may be a safe approach for patients suspected of acute diverticulitis (weak recommendation based on moderate-quality evidence, 2B).

Radiological imaging techniques that are used for diagnosing ALCD in the emergency setting are US and CT. Currently, CT is the established method of choice when compared to US and most guidelines cite the high accuracy and other advantages of CT. This approach is the gold standard for both the diagnosis and the staging of patients with ALCD due to its excellent sensitivity and specificity [24–26]. CT scan can also rule out other diagnoses such as ovarian pathology, or leaking aortic or iliac aneurysm.

CT findings in patients with ALCD may include diverticulosis with associated colon wall thickening, fat stranding, phlegmon, extraluminal gas, abscess formation, or intra-abdominal free fluid. CT imaging can go beyond accurate diagnosis of ALCD. CT criteria may also be used to determine the grade of severity and may drive treatment planning of patients [27]. US is a real-time dynamic examination with wide availability and easy accessibility [28]. Its limitations include operator dependency, poor assessment in obese patients, and difficulty in the detection of free gas and deeply located abscesses [29].

A systematic review and meta-analysis of studies [30] that reported diagnostic accuracy of the clinical diagnosis and diagnostic modalities in patients with suspected
diverticulitis was published in 2014. Summary sensitivity estimates for US were 90% (95% CI 76–98%) versus 95% (95% CI 91–97%) for CT (p = 0.86). Summary specificity estimates for US were 90% (95% CI 86–94%) versus 96% (95% CI 90–100%) for CT (p = 0.04).

Although CT is the most sensitive imaging investigation for patients with suspected acute diverticulitis, a step-up approach with CT performed after an inconclusive or negative US has been proposed as safe and alternative approach for patients with suspected acute diverticulitis [30, 31].

Magnetic resonance imaging, which is not constrained by the operator dependency limitation of compared to US [32, 33], until now is currently difficult to perform at the in the emergency department.

**Are immunocompromised patients with ALCD at risk for failure of standard, non-operative treatment?**

We suggest that immunocompromised patients with ALCD be considered at high risk for failure of standard, non-operative treatment (weak recommendation based on very low-quality evidence, 2D).

Immunocompromised patients are at increased risk for complicated ALCD [34–37]. Immunocompromised patients may fail standard, non-operative treatment. As such, most of these patients require urgent surgical intervention, and this is associated with a significantly higher mortality rate [38].

A recent study by Biondo et al. [39] analyzed the relationship between the different causes of immunosuppression (IMS) and ALCD. Immunocompromised patients were divided in 5 groups according to the causes of IMS: group I, chronic corticosteroid therapy; group II, transplant patients; group III, malignant neoplasm disease; group IV, chronic renal failure; and group V, other immunosuppressant treatments. The rate of emergency surgery was high (39.3%), and it was needed more frequently in group I (chronic corticosteroid therapy). In this study, postoperative mortality was of 31.6% and recurrence rate after successful non-operative management occurred in 30 patients (27.8%).

**Should antibiotics be recommended in immunocompetent patients with uncomplicated acute diverticulitis?**

In immunocompetent patients with uncomplicated diverticulitis without signs of systemic inflammation, we recommend not to prescribe antibiotic therapy (strong recommendation based on high-quality evidence, 1A).

In patients requiring antibiotic therapy, we recommend oral administration whenever possible, primarily, because an early switch from intravenous to oral therapy may facilitate a shorter inpatient length of stay (strong recommendation based on moderate-quality evidence, 1B).

The definition of uncomplicated acute diverticulitis is often vague and poorly defined. Uncomplicated acute diverticulitis is defined as localized diverticular inflammation without any abscess or perforation. A universally accepted classification divides intra-abdominal infections (IAIs) into complicated and uncomplicated [40]. In uncomplicated IAIs, the infection only involves a single organ and does not extend to the peritoneum, while in complicated IAIs, the infectious process extends beyond the organ, causing either localized or diffuse peritonitis [40]. For a better definition of acute diverticulitis in these guidelines, we use the term complicated and uncomplicated according to the classification of IAIs.

Uncomplicated acute diverticulitis is an anatomic favorably inflammatory process. CT findings include diverticula, thickening of the wall, and increased density of the pericolic fat. Patients with uncomplicated diverticulitis usually have an indolent course with a low incidence of subsequent complications.

The utility of antibiotics in acute uncomplicated acute diverticulitis has been a point of controversy. In recent years, several studies demonstrated that antimicrobial treatment was not superior to withholding antibiotic therapy, in terms of clinical resolution, in patients with mild unperforated diverticulitis [41]. The current consensus is that uncomplicated acute diverticulitis may be a self-limiting condition in which local host defenses can manage the inflammation without antibiotics in immunocompetent patients. In this context, antibiotics are not necessary in the treatment of uncomplicated disease.

A multicenter randomized trial was published in 2012 by Chabok et al. involving ten surgical departments in Sweden and one in Iceland recruiting 623 patients with computed tomography-confirmed acute uncomplicated left-sided diverticulitis [42]. Patients were randomized to treatment with (314 patients) or without (309 patients) antibiotics. Antibiotic treatment for acute uncomplicated diverticulitis neither accelerated recovery nor prevented complications or recurrence. Therefore, antibiotics should be reserved for the treatment of complicated diverticulitis.

A prospective, single-arm, study overviewed [43] the safety and efficacy of symptomatic (non-antibiotic) treatment for CT-proven uncomplicated acute diverticulitis during a 30-day follow-up period. Overall, 161 patients were included in the study, and 153 (95%) completed the 30-day follow-up. A total of 14 (9%) patients had pericolic gas. Altogether, 140 (87%) patients were treated as outpatients, and 4 (3%) of them were admitted to the hospital during the follow-up. The primary outcome measure of the study was to find the incidence of complicated diverticulitis. None of the patients developed complicated diverticulitis or required surgery, but 2 days
(median) after inclusion, antibiotics were given to 14 (9%, 6 orally, 8 intravenously) patients. A recent Dutch randomized controlled trial of observational versus systemic antibiotic treatment (DIABOLO trial) [43] for a first episode of CT-proven ALCD Hinchey stages 1a and 1b confirmed that observational treatment without antibiotics did not prolong recovery and could be considered appropriate in these patients.

This study included 22 clinical sites involving 528 patients; Hinchey modified stages 1a (confined pericolic inflammation or phlegmon) to 1b (pericolic or mesocolic abscess) and Ambrosetti’s “mild/moderate” diverticulitis stage confirmed within 24 h by CT were included. Patients with previous diverticulitis, higher Hinchey stages, or “severe” diverticulitis on Ambrosetti’s classification were excluded. The antibiotic treatment was a 10-day course of IV amoxicillin-clavulanic acid, 1200 mg four times daily for at least 48 h. After 48 h, the administration route could be switched to per os, 625 mg three times daily. For observational treatment, patients had to meet the criteria of tolerating a normal diet, temperature less than 100.4 °F, a pain score below 4 on a visual analogue scale (using only acetaminophen for pain control), and the ability to support self at the same level as before illness. If the patient deteriorated, CT was repeated and antibiotic treatment was started if the temperature rose above 102.2 °F, blood cultures were positive, or the patient was septic.

No significant differences between the observation and antibiotic treatment groups were found for secondary endpoints: complicated diverticulitis (3.8% vs. 2.6%, respectively; p = 0.377), ongoing diverticulitis (7.3% vs. 4.1%, respectively; p = 0.183), recurrent diverticulitis (3.4% vs. 3.0%, respectively; p = 0.494), sigmoid resection (3.8% vs. 2.3%, respectively; p = 0.323), readmission (17.6% vs. 12.0%, respectively; p = 0.148), adverse events (48.5% vs. 54.5%, respectively; p = 0.221), and mortality (1.1% vs. 0.4%, respectively; p = 0.432). Hospital stay was significantly shorter in the observation group (2 vs. 3 days; p = 0.006). However, even if no significant differences between Hinchey stages 1a and 1b diverticulitis were found, the vast majority of patients included had a diagnosis of Hinchey stage 1a ALCD (90.1% in the observational and 94% in the antibiotic-treated group) with only a small percentage of patients with Hinchey stage 1 stage 1b diverticulitis. Based on these results, the authors concluded that antibiotics can be safely omitted in patients with a first episode of uncomplicated (Hinchey 1a) ALCD. Similar results were found for Hinchey 1b diverticulitis. However, since the trial lacked power to detect smaller subgroup effects and there are no other reports in literature, the authors concluded that observational treatment should be limited to Hinchey 1a cases [44].

More recently, the long-term effects of omitting antibiotics in uncomplicated ALCD were assessed after 24 months’ follow-up of the DIABOLO trial [44]. Complete case analyses showed no difference in rates of recurrent diverticulitis (15.4% in the observational group vs. 14.9% in the antibiotic group; p = 0.885), complicated diverticulitis (4.8% vs. 3.3%; p = 0.403), and sigmoid resection (9.0% vs. 5.0%; p = 0.085). Young patients (< 50 years) and patients with a pain score at presentation of 8 or higher on a visual analogue pain scale were at risk for complicated or recurrent diverticulitis. In this multivariable analysis, treatment type (with or without antibiotics) was not an independent predictor for complicated or recurrent diverticulitis [45].

Although the above studies have shown there is limited evidence that antibiotics should be routinely administered to patients with uncomplicated diverticulitis, it is understood that disease severity varies in uncomplicated diverticulitis and that further studies are needed to better risk-stratify these patients in order to determine the appropriate treatment course.

The high mortality associated with sepsis requires clinicians to maintain a high index of clinical suspicion, in the conditions that predispose to sepsis in high-risk patients [46]. The expert panel suggests antibiotic therapy covering Gram-negative bacilli and anaerobes in patients with radiological documented uncomplicated acute diverticulitis associated with systemic manifestations of infection or in high-risk patients such as immunocompromised patients, elderly patients, and those with comorbidities.

If antibiotic therapy is necessary, oral administration of antibiotics may be equally as effective as intravenous administration. An expeditious switch from intravenous to oral may allow a rapid patient discharge.

A randomized controlled trial (RCT) of oral versus intravenous therapy for clinically diagnosed acute uncomplicated diverticulitis was published in 2009 [47]. Oral and intravenous regimens utilizing ciprofloxacin and metronidazole were compared. There were 41 patients in the oral arm and 38 in the IV arm (n = 79). No patients had to be converted to intravenous antibiotics from the oral group. There was a complete resolution of symptoms in both groups. No studies have examined the value of dietary restriction or bed rest [48].

Could patients with uncomplicated ALCD be treated as outpatient?

We suggest management in an outpatient setting for patients with uncomplicated ALCD and no comorbidities. We suggest re-evaluation within 7 days. If the clinical condition deteriorates, re-evaluation should be carried out earlier (weak recommendation based on moderate-quality evidence, 2B).
Patients with uncomplicated acute diverticulitis symptoms without significant comorbidities, who are able to take fluids orally and manage themselves at home, can be treated as outpatients. They should be re-evaluated within 7 days from the time of the diagnosis. However, if the clinical condition deteriorates, re-evaluation should be carried out earlier. Patients with significant comorbidities and unable to take fluids orally should be treated in hospital with intravenous fluids.

Etzioni et al. [49] in 2010 published a retrospective analysis, demonstrating that outpatient treatment was effective for the vast majority (94%) of patients suffering from acute diverticulitis. A systematic review on outpatient management of acute uncomplicated acute diverticulitis was recently published [50]. Jackson et al. concluded that current evidence suggested that a more progressive, ambulatory-based approach to the majority of cases of acute uncomplicated acute diverticulitis was justified. Rodríguez-Cerrillo et al. [51] have recently shown that also elderly patients with comorbidities can be safely treated at home avoiding hospital admission.

The DIVER trial [52] has demonstrated that outpatient treatment may be safe and effective in selected patients with uncomplicated acute diverticulitis and can reduce the costs without negatively influencing the quality of life of these patients. This multicenter, RCT included patients older than 18 years with acute uncomplicated diverticulitis. All the patients underwent abdominal CT. The first dose of antibiotic was given intravenously to all patients in the emergency department, and then, patients were either admitted to hospital or discharged. Among a total of 132 patients, four patients in those admitted to hospital and three patients in those discharged to home management developed treatment failure (there were no differences between the groups \( p = 0.62 \)). The overall health care cost per episode was 3 times less in the outpatient treated group, with significant costs savings of €1124.70 per patient. No differences were observed between the groups in terms of quality of life.

A systematic review including 21 studies (11 prospective, 9 retrospective, and only 1 randomized trial) with 1781 patients who had outpatient management of ALCD was recently published [53]. The meta-analysis concluded that outpatient management is safe, and the overall failure rate in an outpatient setting was 4.3% (95% CI 2.6–6.3%). Location of diverticulitis is not a selection criterion for an outpatient strategy \( p = 0.512 \). The other subgroup analyses did not report any factors that influence the rate of failure: previous episodes of acute diverticulitis \( p = 0.163 \), comorbidities \( p = 0.187 \), pericolic gas \( p = 0.653 \), intra-abdominal abscess \( p = 0.326 \), treatment according to a registered protocol \( p = 0.078 \), type of follow-up \( p = 0.700 \), type of antibiotic treatment \( p = 0.647 \), or diabetes \( p = 0.610 \). In patients who failed outpatient treatment, the majority had prolonged antibiotic therapy and only few had percutaneous drainage for an abscess (0.13%) or surgical intervention for perforation (0.06%). However, these results should be interpreted with some caution because of the low quality of available data. The data reported suggested that outpatient management is safe if associated with an accurate selection of patients (40%); no subgroup analysis demonstrated significant differences between groups (including comorbidities, previous episode and diabetes). The main limitations of the findings of the present review concern their applicability in common clinical practice as it was impossible to identify strict criteria of failure.

Another review about outpatient management of ALCD was published in 2017 [54]. The search yielded 192 publications. Of these, 10 studies met the inclusion criteria including 1 RCT, 6 clinical controlled trials, and 3 case series. There was no difference in failure rates of medical treatment (6.5 vs. 4.6%, \( p = 0.32 \)) or in recurrence rates (13.0 vs. 12.1%, \( p = 0.81 \)) between those receiving ambulatory care and inpatient care for uncomplicated diverticulitis. Ambulatory treatment was associated with an estimated daily cost savings of between €600 and €1,900 per patient treated. Meta-analysis of data was not possible due to heterogeneity in study designs and inclusion criteria.

**What is the best treatment for patients with acute diverticulitis with CT findings of pericolic extraluminal gas?**

*In patients with CT findings of pericolic extraluminal gas, we suggest a trial of non-operative treatment with antibiotic therapy (weak recommendation based on low-quality evidence, 2C).*

High mortality associated with sepsis requires maintaining a high index of clinical suspicion for deterioration and more aggressive management. WSES expert panel recommends antibiotic therapy in patients with pericolic extraluminal gas [27]. A sub-analysis of the DIA-BOLO trial was recently published [55]. All patients with Hinchey 1a diverticulitis and with isolated pericolic gas on CT were identified. Pericolic gas was defined as gas located < 5 cm from the affected segment of colon. The primary outcome of the study was failure of non-operative management that was defined as need for percutaneous abscess drainage or emergency surgery within 30 days after presentation. A multivariate logistic regression analysis of clinical, radiological, and laboratory parameters with respect to treatment failure was performed. A total of 109 patients were included. Fifty-two (48%) patients were treated with antibiotics. Nine (8%) patients failed non-operative management, seven (13%) in the antibiotic treatment group and two (4%) in the non-antibiotic group \( p = 0.083 \). Only increased CRP level at presentation was an
independent predictor for treatment failure. The authors concluded that non-operative treatment in diverticulitis patients with isolated pericolic gas is a suitable treatment strategy. However, due to the low event rate, it remains uncertain whether antibiotic treatment is necessary in patients with isolated pericolic gas.

What is the best treatment for patients with a small diverticular abscess (< 4–5 cm)? What is the best treatment for patients with large diverticular abscesses?

For patients with a small (< 4–5 cm) diverticular abscess, we suggest an initial trial of non-operative treatment with antibiotics alone (weak recommendation based on low-quality evidence, 2C).

We suggest to treat patients with large abscesses with percutaneous drainage combined with antibiotic treatment; whenever percutaneous drainage of the abscess is not feasible or not available, we suggest to initially treat patients with large abscesses with antibiotic therapy alone, clinical conditions permitting. Alternatively, an operative intervention is required (weak recommendation based on low-quality evidence, 2C).

Approximately 15–20% of patients admitted with acute diverticulitis have an abscess on CT scan [56]. The treatment of abscess always requires antibiotic therapy. If the abscess is limited in size, systemic antibiotic therapy alone is considered safe and effective in removing the abscess and solving acute inflammation with a pooled failure rate of 20% and a mortality rate of 0.6% [57].

When abscess diameter is larger, antibiotics could fail to reach the adequate concentration inside the abscess leading to an increased failure rate.

The size of 4–5 cm may be a reasonable limit between antibiotic treatment alone, versus percutaneous drainage combined with antibiotic treatment in the management of diverticular abscesses [58–62]. When the patient’s clinical conditions allow it and percutaneous drainage is not feasible, antibiotic therapy alone can be considered. However, careful clinical monitoring is mandatory. A high suspicion for surgical control of the septic source should be maintained and a surgical treatment should be performed if the patient shows a worsening of inflammatory signs or the abscess does not reduce with medical therapy.

There are currently no randomized studies available on the best treatment of intra-abdominal abscess from acute diverticulitis, and current recommendations are based only on observational studies. A retrospective study comparing outcomes of selected patients treated with initial antibiotics alone versus percutaneous drainage was published in 2015 by Elagili et al. [63]. All patients with diverticular abscess ≥ 3 cm in diameter treated in a single institution in 1994–2012 with percutaneous drainage or antibiotics alone followed by surgery were identified from an institutional diverticular disease database. Groups were compared based on patient and disease characteristics, treatment failures, and postoperative outcomes. Thirty-two patients were treated with antibiotics alone because of either technically impossible percutaneous drainage or surgeon preference, while 114 underwent percutaneous drainage. Urgent surgery was required in 8 patients with persistent symptoms during treatment with antibiotics alone (25%) and in 21 patients (18%) after initial percutaneous drainage (p = 0.21). Patients treated with antibiotics had a significantly smaller abscess diameter (5.9 vs. 7.1 cm, p = 0.001) and shorter interval from initial treatment to sigmoidectomy (mean 50 vs. 80 days, p = 0.02). Postoperative complications following antibiotics alone were significantly less severe than after percutaneous drainage based on the Clavien-Dindo classification (p = 0.04).

In patients displaying an appropriate clinical improvement, the drainage catheter can be removed when the output has ceased or decreased substantially. In doubtful cases, a CT scan can be performed with water-soluble contrast via the percutaneous drainage catheter prior to drain removal. If no identifiable cavity remains, the catheter should be removed. If resolution of the abscess is not reached and the patient has no clinical improvement, further drainage or catheter repositioning might be indicated and may eventually necessitate surgery.

Should an early colonic evaluation be planned in patients treated non-operatively for a diverticular abscess? Should an early colonic evaluation be recommended for patients with a CT-proved uncomplicated acute diverticulitis treated non-operatively?

In patients with diverticular abscesses treated non-operatively, we suggest an early colonic evaluation (4–6 weeks) (weak recommendation based on low-quality evidence, 2C).

In patients with CT-proven uncomplicated diverticulitis treated non-operatively, we do not recommend routine colonic evaluation (weak recommendation based on moderate-quality evidence, 2B).

Colonic localized abscess is an uncommon, but possible, presentation of an occult colon malignancy, and it may mimic complicated diverticular disease [64, 65]. It has been demonstrated that the risk of malignancy after a CT-proven uncomplicated diverticulitis is low and, in the absence of other indications, routine colonoscopy may not be necessary. A systematic review investigating the rate of colorectal cancer (CRC) found by colonoscopy after an episode of uncomplicated diverticulitis was published in 2014 [66]. Nine studies met the inclusion criteria and included a total number of 2490 patients...
with uncomplicated diverticulitis. Subsequent colonoscopy after an episode of uncomplicated diverticulitis was performed in 1468 patients (59%). Seventeen patients were diagnosed with CRC, having a prevalence of 1.1% (95% confidence interval 0.72–1.9% for CRC). Hyperplastic polyps were seen in 156 patients (10.6%), low-grade adenoma in 90 patients (6.1%), and advanced adenoma in 32 patients (2.2%). The results of this review demonstrate that unless colonoscopy is regarded for screening in individuals aged 50 years and older, routine colonoscopy in the absence of other clinical signs of CRC is not required in patients following an episode of acute uncomplicated diverticulitis.

Another systematic review and meta-analysis on the role of routine colonic evaluation after radiologically confirmed acute diverticulitis was published in 2014 [67]. Eleven studies from 7 countries were included in the analysis. Among 1970 patients, cancer was only found in 22 (0.01%) cases. The risk of malignancy after a radiologically proven episode of acute uncomplicated diverticulitis was low. Patients with complicated diverticulitis had a significant risk of CRC at subsequent colonic evaluation.

A retrospective study of 633 patients with acute diverticulitis diagnosed by CT was published in 2014 [68]. Of the 663 patients, 97 patients underwent emergency resection, while 536 patients were treated non-operatively, 394 of whom subsequently underwent colonoscopy. The findings showed 17 cancers (2.7%) in patients with an initial diagnosis of acute diverticulitis. As shown by CT, 16 cancer patients (94%) had an abscess, while one patient had pericolic extraluminal gas but no abscess. Of the patients with an abscess, 11.4% had cancer mimicking acute diverticulitis. No cancer was found in the patients with uncomplicated diverticulitis.

What is the role of non-operative treatment in patients with CT findings of distant gas without diffuse intra-abdominal fluid?

In patients with CT findings of distant free gas without diffuse intra-abdominal fluid, we suggest a non-operative treatment in selected patients only if a close follow-up can be performed (weak recommendation based on very low-quality evidence, 2D).

Although most patients hospitalized for acute diverticulitis can be managed by non-operative treatment, up to 25% may require urgent operative intervention [69]. Patients with diffuse peritonitis are typically critically ill patients and require prompt fluid resuscitation, antibiotic administration, and surgery. While the absolute prevalence of perforated diverticulitis complicated by generalized peritonitis is low, it is associated with significant postoperative mortality, regardless of selected surgical strategy.

Despite CT findings of distant free gas (a known predictor of failure of non-operative treatment [27]), Dharmarajan et al. [70] described a high success rate for non-operative management in patients with acute diverticulitis and a pneumoperitoneum, excluding those with hemodynamic instability. Sallinen et al. [71] reported results of non-operative management in patients with CT verified extraluminal gas. The study showed that non-operative treatment was feasible therapy only for hemodynamically stable patients with pericolic extraluminal gas or with small amount of distant intraperitoneal gas in the absence of clinical diffuse peritonitis or fluid in the fossa Douglas. Occurrence of large amount of distant intraperitoneal gas or distant retroperitoneal gas even in the absence of clinical generalized peritonitis was associated with high failure rate (57–60%) of non-operative management. Moreover, nearly 60% patients with distant intraperitoneal gas were primarily treated by surgery.

Highly selected group of patients at this stage may be treated by conservative treatment. However, it may be associated with a significant failure rate and a careful clinical and CT monitoring is mandatory [20]. Suggested intervention for patients at this stage should be surgical resection and anastomosis with or without stoma in stable patients without comorbidities, and Hartmann’s procedure (HP) in unstable patients or in patients with multiple comorbidities [27].

Should laparoscopic lavage and drainage be recommended in patients with diffuse peritonitis due to diverticular perforation?

We suggest performing laparoscopic peritoneal lavage and drainage only in very selected patients with generalized peritonitis. It is not considered as the first line treatment in patients with peritonitis from acute colonic diverticulitis (weak recommendation based on high-quality evidence, 2A).

A minimally invasive approach using laparoscopic peritoneal lavage and drainage has been debated in recent years as an alternative to colonic resection [72]. It can potentially avoid a stoma in patients with diffuse peritonitis. It consists of the laparoscopic aspiration of pus followed by abdominal lavage and the placement of abdominal drains, which remain for many days after the procedure. In 2013, a Dutch retrospective analysis of 38 patients [73] treated by laparoscopic lavage was published highlighting some doubts about this procedure to treat critically ill patients. In seven patients, this approach did not control abdominal sepsis, two patients died of multiple organ failure and five ones required further surgical interventions (three Hartmann resection, one diverting stoma, and one perforation closure). One of these died from aspiration, and the remaining four
experience prolonged and complicated hospital stay. Multiple comorbidities, IMS, a high CRP level, and/or a high Mannheim Peritonitis Index were also predictors of a high risk of failure. The authors concluded that patient selection was of utmost importance and identification of an overt sigmoid perforation is of critical importance. Great debate is still open on this topic, mainly due to the discrepancy and sometime disappointing results of the latest prospective trials such as SCANDIV, Ladies, and DILALA trials [74–76].

In 2014, the first results from the RCT DILALA were published [74]. Initial diagnostic laparoscopy showing Hinchey III disease was followed by randomization between laparoscopic lavage and colon resection and stoma. Morbidity and mortality after laparoscopic lavage did not differ when compared with the Hartmann procedure. Laparoscopic lavage resulted in shorter operating time, shorter time in the recovery unit, and shorter hospital stay with the avoidance of a stoma. In this trial, laparoscopic lavage as treatment for patients with perforated diverticulitis Hinchey III disease was feasible and safe in the short-term. In 2015, the results of SCANDIV study were published [75]. Among patients with likely perforated diverticulitis and undergoing emergency surgery, the use of laparoscopic lavage vs. primary resection did not reduce severe postoperative complications and led to worse outcomes in secondary endpoints. These findings do not support laparoscopic lavage for treatment of perforated diverticulitis. In the same year, the result of LADIES study was published. This showed that laparoscopic lavage was not superior to sigmoidectomy for the treatment of purulent perforated diverticulitis [76].

After their publication, the results of the three studies were summarized in six different meta-analyses, with similar findings [77–82]. When compared with emergency surgery with resection, laparoscopic lavage in Hinchey III acute diverticulitis shows a comparable mortality but is associated with a failure rate with a significantly augmented need for reoperation due to the failure of the treatment and to intra-abdominal abscess formation. Long-term results were similar, with no difference in morbidity and mortality.

Several controversies remain about laparoscopic lavage and drainage. It may be an acceptable alternative in selected patients [83]; however, it cannot be considered the first line treatment in patients with diverticular peritonitis.

**Should primary anastomosis with or without protecting stoma be preferred instead of Hartmann’s procedure in patients with diffuse peritonitis from diverticular perforation?**

We recommend Hartmann’s procedure (HP) for managing diffuse peritonitis in critically ill patients and in selected patients with multiple comorbidities (strong recommendation based on low-quality evidence, 2B).

In clinically stable patients with no comorbidities, we suggest primary resection with anastomosis with or without a diverting stoma (weak recommendation based on low-quality evidence, 2B).

HP has been considered the procedure of choice in patients with generalized peritonitis and remains a safe technique for emergency colectomy in diverticular peritonitis, and is especially useful in critically ill patients and in patients with multiple comorbidities. However, restoration of bowel continuity after a HP is associated with significant morbidity and resource utilization [84]. As a result, many of these patients do not undergo reversal surgery and remain with a permanent stoma [85].

Common use of the HP in treating diverticular peritonitis worldwide is confirmed by a recent Australian study analyzing administrative data of patients with acute diverticulitis admitted, from 2009 to 2013, in eight tertiary referral centers with specialist colorectal services [86]. The HP was the most commonly performed emergency operation, accounting for 72% of resections.

Another population-based retrospective cohort study using administrative discharge data, conducted in Ontario, Canada, was published in 2014 [87]. Among 18,543 patients hospitalized with a first episode of diverticulitis, from 2002 to 2012, 3873 underwent emergency surgery. The use of laparoscopy increased (9 to 18%, p < 0.001), whereas the use of the HP remained unchanged (64%), and like in the Australian study, was the most frequently used operative approach in patients with complicated acute diverticulitis.

In recent years, some authors have reported the role of primary resection and anastomosis with or without a diverting stoma, in the treatment of acute diverticulitis, even in the presence of diffuse peritonitis [88]. The decision regarding the surgical choice in patients with diffuse peritonitis is generally left to the judgment of the surgeon, who takes into account the clinical condition and the comorbidities of the patient. Studies comparing mortality and morbidity of the HP versus primary anastomosis did not show any significant differences. However, most studies had relevant selection biases, as demonstrated by four systematic reviews [89–91].

A study evaluating all patients with acute diverticulitis undergoing emergent primary anastomosis with diverting loop ileostomy and HP was recently published using the ACS-NSQIP Colectomy Procedure Targeted Database from 2012 to 2016 [92]. Out of 130,963 patients, 2729 patients were included. The median age was 64 years, and 48.5% were male; the majority of patients underwent a HP, and only 208 (7.6%) underwent primary anastomosis with diverting loop ileostomy. Patients undergoing a HP had more comorbidities [e.g., COPD (9.8% vs. 4.8%, p = 0.017)], were more functionally dependent [6.3% vs. 2.4%, p = 0.025], and were more...
unwell [e.g., septic shock (11.1% vs. 5.3%, \( p = 0.015 \)] compared to primary anastomosis with diverting loop ileostomy patients. The mortality rates for the patients undergoing a HP versus primary anastomosis with diverting loop ileostomy were 7.6% and 2.9%, respectively (\( p = 0.011 \)). The morbidity rates were 55.4% and 48.6%, respectively (\( p = 0.056 \)). In multivariable analyses, compared to the HP, primary anastomosis with diverting loop ileostomy did not result in increased rates of mortality (OR = 0.21, 95% CI 0.03–1.58, \( p = 0.129 \)) or morbidity (OR = 0.96, 95% CI 0.63–1.45, \( p = 0.834 \)). The authors concluded that primary anastomosis with diverting loop ileostomy appears to be at least a safe alternative to the HP for select patient populations needing emergent surgical management of acute diverticulitis.

A comparison of primary resection and anastomosis with or without defunctioning stoma to the HP as the optimal operative strategy for patients presenting with Hinchey stage III–IV was published by Constantinides et al. [93]. A total of 135 primary resection and anastomosis, 126 primary anastomosis with defunctioning stoma, and 6619 HPs were considered in the study. Morbidity and mortality were 55% and 30% for primary resection and anastomosis, 40% and 25% for primary anastomosis with defunctioning stoma, and 35% and 20% for the HP. Stomas remained permanent in 27% of HPs and in 8% of primary anastomoses with defunctioning stoma. The authors concluded that primary anastomosis with defunctioning stoma may be the optimal strategy for selected patients with diverticular peritonitis and may represent a good compromise between postoperative adverse events, long-term quality of life, and risk of permanent stoma.

A small randomized trial of primary anastomosis with ileostomy versus a HP in patients with diffuse diverticular peritonitis was published by Oberkofler et al. in 2012 [94]. Sixty-two patients with acute left-sided colonic perforation (Hinchey III and IV) from 4 centers were randomized to Hartmann procedure (\( n = 30 \)) and to primary anastomoses with diverting ileostomy (\( n = 32 \)). A planned stoma reversal operation was performed after 3 months in both groups. The study reported no difference in initial mortality and morbidity (mortality 13% vs. 9% and morbidity 67% vs. 75% in the HP vs. primary anastomosis), but a reduction in length of stay, lower costs, fewer serious complications, and greater stoma reversal rates in the primary anastomosis group.

A multicenter RCT conducted between June 2008 and May 2012, the DIVERTI (Primary vs. Secondary Anastomosis for Hinchey Stage III-IV Diverticulitis) trial [95], was published in 2017. All 102 patients enrolled were comparable for age (\( p = 0.4453 \)), sex (\( p = 0.2347 \)), Hinchey stage III vs. IV (\( p = 0.2347 \)), and Mannheim Peritonitis Index (\( p = 0.0606 \)). Overall mortality did not differ significantly between the HP (7.7%) and primary anastomosis (4%) (\( p = 0.4233 \)) groups. Morbidity for both resection and stoma reversal operations was comparable (39% in the HP arm vs. 44% in the primary anastomosis arm; \( p = 0.4233 \)). At 18 months, 96% of primary anastomosis patients and 65% of the HP patients had a stoma reversal (\( p = 0.0001 \)). Although mortality was similar in both arms, the rate of stoma reversal was significantly higher in the primary anastomosis arm. This trial provides additional evidence in favor of primary anastomosis with diverting ileostomy over the HP in patients with diverticular peritonitis.

In 2019, the results of the LADIES study [96] demonstrated that in hemodynamically stable, immunocompetent patients younger than 85 years, primary anastomosis is preferable to the HP as a treatment for perforated diverticulitis (Hinchey III or Hinchey IV disease). Patients aged between 18 and 85 years who presented with clinical signs of general peritonitis and suspected perforated diverticulitis were eligible for inclusion if plain abdominal radiography or CT scan showed diffuse free gas or fluid. Patients with Hinchey I or II diverticulitis were not eligible for inclusion. Patients were allocated (1:1) to the HP or sigmoidectomy with primary anastomosis, with or without defunctioning ileostomy. The 12-month stoma-free survival was significantly better for patients undergoing primary anastomosis compared with the HP (94.6% [95% CI 88.7–100%] vs. 71.7% [95% CI 60.1–83.3%], hazard ratio 2.79 [95% CI 1.86–4.18]; log-rank \( p < 0.0001 \)). There were no significant differences in short-term morbidity and mortality after the index procedure for the HP compared with primary anastomosis (morbidity, 29 [44%] of 66 patients vs. 25 [39%] of 64, \( p = 0.60 \); mortality, two [3%] vs. four [6%], \( p = 0.44 \)).

Recently, a systematic review of the existing literature about surgical management of Hinchey III and IV diverticulitis was published [97]. A total of 25 studies involving 3546 patients were included in this study. The overall mortality in patients undergoing a HP was 10.8% across the observational studies and 9.4% in the RCTs. The mortality rate in patients undergoing a primary anastomosis was lower than that in the HP group, at 8.2% in the observational studies and 4.3% in the RCTs. A comparison of primary anastomosis with the HP demonstrated a 40% lower mortality rate in the primary anastomosis group than in the HP group (OR 0.60, 95% CI 0.38–0.95, \( p = 0.03 \)), when analyzing the observational studies. However, meta-analysis of the RCTs did not demonstrate any difference in mortality. Wound infection rates between the two groups were comparable.

**Should laparoscopic resection be preferred to open resection in patients with diffuse peritonitis due to perforated diverticulitis?**

In patients with diffuse peritonitis due to perforated diverticulitis, we suggest to perform an emergency...
laparoscopic sigmoidectomy only if technical skills and equipment are available (weak recommendation based on low-quality evidence, 2C).

Laparoscopic sigmoidectomy for diverticulitis had initially been confined to the elective setting. However, in physiologically stable patients, laparoscopic sigmoidectomy may be feasible in the setting of purulent and fecal diverticular peritonitis. In 2015, a systematic review on laparoscopic sigmoidectomy for diverticulitis in the emergency setting was published [98].

The review included 4 case series and one cohort study (total of 104 patients) out of 1706 references. A HP was performed in 84 patients, and primary anastomosis was fashioned in 20 patients. The mean operating time varied between 115 and 200 min. The conversion to open surgery rate varied between 0 and 19%. The mean length of hospital stay ranged between 6 and 16 days. Surgical re-intervention was necessary in 2 patients. In 20 patients operated upon without defunctioning ileostomy, no anastomotic leakage was reported. Three patients died during the postoperative period. Stoma reversal after HP was performed in 60 out of 79 evaluable patients (76%).

These guidelines are limited by the low-quality evidence that showed that emergency laparoscopic sigmoidectomy for the treatment of perforated diverticulitis with generalized peritonitis is feasible. These studies occurred in selected patients and in experienced units and are not generalizable to all centers. High-quality prospective or randomized studies are needed to demonstrate benefits of emergency laparoscopic sigmoidectomy compared to open sigmoidectomy for perforated diverticulitis.

**Should damage control surgery with staged laparotomies be recommended in patients with acute peritonitis due to diverticular perforation?**

We suggest damage control surgery (DCS) with staged laparotomies in selected unstable patients with diffuse peritonitis due to diverticular perforation (weak recommendation based on low-quality evidence, 2C).

A damage control surgical strategy may be useful for patients in physiological extremis from abdominal sepsis [99]. The initial surgery focuses on control of the sepsis, and a subsequent operation deals with the anatomical restoration of the gastrointestinal tract, after a period of physiological resuscitation. This strategy facilitates both the control of the severe sepsis control as well as potentially improving the rate of primary anastomosis [100].

Generalized diverticular peritonitis is a life-threatening condition requiring prompt emergency operation. To improve outcomes and reduce the rate of colostomy formation, a new algorithm for damage control operation, lavage, limited resection or closure of perforation, and second look surgery to restore intestinal continuity was developed in recent years [101, 102]. Some patients may be physiologically deranged. These patients, who are hemodynamically unstable, are not optimal candidates for immediate complex operative interventions. After initial surgery, which should be limited to source control, e.g., primary closure of the perforation/local resection of the diseased bowel, the patient is taken to the intensive care unit (ICU) for physiologic optimization. However, this strategy will also delay bowel anastomosis to a period of physiological stability [103] potentially changing the intraoperative physiological milieu, potentially favoring a primary anastomosis, and avoiding the formation of a stoma altogether. In the setting of acute diverticulitis, several reports (with low level of evidence) were published. In 2010, a prospective observational study was published by Kafka-Ritsch et al. [101]. A total of 51 patients (28 females 55%) with a median age of 69 (range 28–87) years, with perforated diverticulitis Hinchey III (n = 40, 78%) or Hinchey IV (n = 11, 22%), were prospectively enrolled in the study. Patients were initially managed with limited resection, lavage, and temporary abdominal closure followed by second, reconstructive operation 24–48 h later, which are supervised by a colorectal surgeon. Bowel continuity was restored in 38 (84%) patients, of which four were protected by a loop ileostomy. Five anastomotic leaks (13%) were encountered requiring loop ileostomy in two patients and a HP in remaining three patients. The overall mortality rate was 9.8%, and 35 of 46 surviving patients (76%) left the hospital with reconstructed colon continuity. Fascial closure was achieved in all patients.

Sohn et al. performed a case-control study comparing traditional strategy versus damage control: there were no differences in morbidity and mortality, but there was a significant reduction of stoma creation in the damage control group [104].

Despite promising experiences, little robust or large-scale data are available, and the open abdomen and damage control strategy are not without risk: for example, such procedures are associated with the formation of entero-atmospheric fistula and high costs, among other issues. Guidelines recommend this strategy only in critically ill patients who cannot withstand major surgery. Although there is now a biologic rationale for such an intervention as well as non-standardized and erratic clinical utilization, this remains a novel therapy with potential side effects and clinical equipoise. The WSES recommends to use an open abdomen approach in selected significantly physiologically deranged patients with ongoing sepsis [105]. The Closed Or Open after Laparotomy (COOL) study constitutes a prospective RCT that will randomly allocate eligible surgical patients intraoperatively to either formal closure of the fascia or use of...
the open abdomen with application of with active negative peritoneal pressure therapy. This trial will be powered to demonstrate a mortality difference in this highly lethal and morbid condition to ensure critically ill patients are receiving the best care possible and not being harmed by inappropriate therapies based on opinion only [106].

**What factors should be considered in planning elective resection in cases of acute diverticulitis treated non-operatively?**

We suggest evaluating patient-related factors and not number of previous episodes of diverticulitis in planning elective sigmoid resection (weak recommendation based on very low-quality evidence, 2D).

After an episode of ALCD treated conservatively, we suggest planning of an elective sigmoid resection in high-risk patients, such as immunocompromised patients (weak recommendation based on very low-quality evidence, 2D).

Recurrence of acute diverticulitis is lower than previously thought. Historically, it has been reported that about one third of all patients with acute diverticulitis will have a recurrent attack, often within 1 year [107, 108]. However, the recurrence after an uncomplicated episode of diverticulitis appears much lower: with a recent prospective study reported a recurrence of only 1.7% over 5 years of follow-up [109, 110]. After a follow-up of 4 years, El Sayed et al. [111], in an English study of over 65,000 patients managed non-operatively for their first episode of diverticulitis, found the recurrence rate to be around 11.2%. Emergency and elective colectomy rates were 0.9 and 0.75%, respectively. Female gender, young age, smoking, obesity, and complicated initial disease were risk factors for readmission and emergency surgery. The study also pointed out that some factors associated with recurrence are modifiable; weight reduction and smoking cessation can be championed.

In 2014, a systematic review of studies reviewing the diagnosis and management of chronic and recurrent diverticulitis (from studies published between January 2000 to March 2013) was published [112]. The 68 studies included were almost exclusively observational and had limited certainty of treatment effect. The authors found that complicated recurrence after recovery from an uncomplicated episode of diverticulitis was rare (< 5%) and that age at onset younger than 50 years and 2 or more recurrences did not increase the risk of complications.

The authors concluded that the indication for elective colectomy following 2 episodes of diverticulitis is no longer accepted. Indication to colectomy should be made based on consideration of the risks of recurrent diverticulitis, the morbidity of surgery, ongoing symptoms, the complexity of disease, and operative risk.

A recent open-label randomized multicenter trial (DIRECT trial) randomized 109 patients from 24 teaching and two academic hospitals in the Netherlands presenting with recurrent and persisting abdominal complaints after an episode of diverticulitis to receive surgical treatment or non-operative management [113]. After a brief follow-up of 6 months, elective sigmoidectomy resulted in a better quality of life (assessed by many specific questionnaires) compared to non-operative management. However, the results of the study may be affected by the heterogeneity of patients enrolled (patients with both recurrent diverticulitis and patients with persistent abdominal complaints).

Currently, the decision to perform an elective resection after one or more episodes of AD should be undertaken on a case-by-case basis, taking into account risk factors, complications, age, and severity of episodes as well as the patient’s personal circumstances and comorbidities (e.g., immunosuppressed patients) [114].

**What is the optimal antibiotic therapy for patients with diffuse peritonitis due to diverticular perforation?**

What is the optimal duration of antibiotic therapy after surgical source control in diffuse peritonitis due to diverticular perforation?

We suggest to choose the empirically designed antibiotic regimen on the basis of the underlying clinical condition of the patient, the pathogens presumed to be involved, and the risk factors for major antimicrobial resistance patterns (strong recommendation based on moderate-quality evidence, 1B).

We suggest a 4-day period of postoperative antibiotic therapy in complicated ALCD if source control has been adequate (weak recommendation based on moderate-quality evidence, 2B).

Antibiotic therapy plays an important role in the management of complicated acute diverticulitis. Typically, it is an empiric antibiotic treatment. The regimen should depend on the severity of infection, the pathogens presumed to be involved, and the risk factors indicative of major resistance patterns [39]. Several recommendations have been recently published in literature [39]. However, consideration of local epidemiological data and resistance profiles is essential for antibiotic selection.

Considering intestinal microbiota of large bowel acute diverticulitis requires antibiotic coverage for Gram-positive and Gram-negative bacteria, as well as for anaerobes. Most of the complicated acute diverticulitis is mainly a community-acquired infection. The main resistance threat in IAIIs is posed by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, which are becoming increasingly common in community-acquired infections worldwide [33]. The most significant risk factors for ESBL-producing pathogens include prior exposure to antibiotics and comorbidities requiring concurrent antibiotic therapy [39]. Anti-ESBL-producer coverage should be warranted...
for patients with these risk factors. Discontinuation of antibiotic treatment should be at 4 days from source control as this has been demonstrated as non-inferior to longer therapy based on the STOP IT trial [115].

The recent prospective trial by Sawyer et al. demonstrated that in patients with complicated IAIs undergoing an adequate source-control procedure, the outcomes after approximately 4 days fixed-duration antibiotic therapy were similar to those after a longer course of antibiotics that extended until after the resolution of physiological abnormalities [115]. Patients who have signs of sepsis beyond 5 to 7 days of adequate antibiotic treatment warrant aggressive diagnostic investigation in search of a reservoir of infection.

Which are the principles of the treatment of acute right-sided colonic diverticulitis?

Although studies have shown that the percentage of complications requiring surgery is higher in patients with ALCD than in patients with ARCD, the principles of diagnosis and treatment of patients with ARCD are similar to those with ALCD. We suggest that all the statements for ALCD also apply to ARCD.

Acute colonic diverticulitis is a common condition affecting the adult population. Traditionally, the sigmoid colon is considered the most commonly involved part, and ARCD is much rarer [116]. However, in some regions of the world, ARCD outnumber ALCD [116]. The ARCD differs from the ALCD in some aspects. The former is usually solitary [29, 117], and has a low rate of complicated diverticulitis [118].

ARCD generally occurs in middle-aged men, and its incidence does not increase with age. Especially the ARCD located in the cecum, it is difficult to distinguish ARCD from acute appendicitis because of their similar symptoms and signs.

CT scanning appears to be the best overall imaging modality in the diagnosis of possible ARCD [119, 120]. However, US is more economic than CT and poses no radiation, which may be particularly important since the patients having right-sided diverticulitis are relatively younger.

US features, including diverticular wall thickening, surrounding echogenic fat, and intra-diverticular echogenic material, can provide clear information for making correct preoperative diagnosis. However, US is operator dependent. Ambiguous US studies may be complemented with a contrast-enhanced CT [121].

Currently, the management of ARCD is not well defined, and no unique guidelines have been proposed.

Although previous studies have shown that the percentage of complications requiring surgery is higher in patients with ALCD than in patients with ARCD [122], the principles of diagnosis and treatment of ARCD are very similar to those of ALCD. As a treatment option, non-operative methods should be preferred, in cases without diffuse peritonitis although differentiating benign and malignant cases pre-operatively is often difficult [123]. Surgical treatment is usually used in the treatment of complicated cases [116, 124, 125]. Resection of the inflamed colon with primary anastomosis can be performed by laparoscopy in experienced centers [126].

Conclusions

ALCD is a common problem encountered by Western surgeons in the acute setting. The sigmoid is usually the most commonly involved colonic segment, while ARCD is much rarer.

An international multidisciplinary panel of experts from the World Society of Emergency Surgery (WSES) updated its guidelines on the management of acute left-sided colonic (ALCD) diverticulitis according to the most recent available literature. The update includes recent changes introduced in the management of ALCD. The new update contains a section on ARCD, which is more prevalent than ALCD in some regions of the world.

Abbreviations

ALCD: Acute left-sided colonic diverticulitis; ARCD: Acute right-sided colonic diverticulitis; CRC: Colorectal cancer; CRP: C-reactive protein; CT: Computed tomography; DCS: Damage control surgery; ESBL: Extended-spectrum beta-lactamase; HP: Hartmann’s procedure; IAIs: Intra-abdominal infections; ICU: Intensive care unit; IMS: Immunosuppression; RCT: Randomized controlled trial; US: Ultrasound; WBC: White blood cell; WSES: World Society of Emergency Surgery.

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Consent for publication

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2017 WSES guidelines for the management of iatrogenic colonoscopy perforation

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Abstract

Iatrogenic colonoscopy perforation (ICP) is a severe complication that can occur during both diagnostic and therapeutic procedures. Although 45–60% of ICPs are diagnosed by the endoscopist while performing the colonoscopy, many ICPs are not immediately recognized but are instead suspected on the basis of clinical signs and symptoms that occur after the endoscopic procedure. There are three main therapeutic options for ICPs: endoscopic repair, conservative therapy, and surgery. The therapeutic approach must vary based on the setting of the diagnosis (intra- or post-colonoscopy), the type of ICP, the characteristics and general status of the patient, the operator’s level of experience, and surgical device availability.

Although ICPs have been the focus of numerous publications, no guidelines have been created to standardize the management of ICPs. The aim of this article is to present the World Society of Emergency Surgery (WSES) guidelines for the management of ICP, which are intended to be used as a tool to promote global standards of care in case of ICP. These guidelines are not meant to substitute providers’ clinical judgment for individual patients, and they may need to be modified based on the medical team’s level of experience and the availability of local resources.

Keywords: Iatrogenic colonoscopy perforation, Colonoscopy, Gastrointestinal endoscopy, Emergency surgery, Laparoscopy, Antibiotic therapy, Intra-abdominal infection, Open abdomen

Background

Iatrogenic colonic perforations (ICPs) are an infrequent but severe complication of colonoscopy. Globally, the incidence is estimated to be 0.016–0.8% for diagnostic colonoscopies and 0.02–8% for therapeutic colonoscopies [1–10], but considering the increasing numbers of screening, diagnostic, and therapeutic colonoscopies being performed every year, the frequency of ICP is not insignificant [11, 12].

Approximately 45–60% of ICPs are detected by the endoscopist while performing the colonoscopy, although a considerable number of ICPs are not recognized immediately, but rather are suspected on the basis of clinical signs and symptoms occurring after the endoscopic procedure. In this latter case, colonic perforations may lead to the development of secondary peritonitis, which is associated with significant morbidity and...
mortality [5, 13–18]. Depending on the delay in the management of the ICP and the pre-existing pathologies, ICP-related mortality is as high as 5–25% [5, 14–16, 18–22].

One of the most important issues in the management of ICPs is the time period between the diagnosis and the treatment. There are different treatment alternatives for ICP, including conservative, endoscopic, and surgical approaches. The therapeutic strategy varies based on the setting in which the ICP is diagnosed (i.e., intra- or post-colonoscopy), the specific characteristics of the perforation (e.g., size, location, and etiology), the patient’s general status, and the skill level of the operator [8, 23, 24]. Although ICPs have been the subject of numerous publications, no randomized clinical trials have been conducted to evaluate the best treatment option and no guidelines have been defined to standardize its management. For this reason, the World Society of Emergency Surgery (WSES) convened a consensus conference to review the available literature, discuss the current controversies, and create guidelines for the management of ICP. The present article is the summary of the WSES consensus conference, including (1) the incidence of and risk factors for ICP, (2) the diagnosis of ICP, (3) the conservative and endoscopic treatments for ICP, (4) the surgical treatments for ICP, and (5) the follow-up after ICP treatment. Based upon the evidence emerging from the consensus conference, a decision-making algorithm was developed to guide clinicians and surgeons through the different medical, endoscopic, and surgical treatments for ICP.

Materials and methods: expert panel and consensus conference organization

On September 2016, the President of the WSES (Luca Ansaloni) appointed five WSES members (Nicola de’Angelis, Fausto Catena, Federico Coccolini, Salvatore Di Saverio, Massimo Sartelli) to establish the project committee and determine the organization of an international multidisciplinary expert panel deputed to develop the WSES Guidelines for the management of ICP. The project committee agreed to develop practice guidelines by formal consensus, which consists of formalizing the degree of agreement among experts by identifying and selecting, through ratings and feedback, the points on which the experts agree and the points on which they disagree or are undecided. Additionally, it involves drafting a small number of concise and unambiguous recommendations that address the questions asked.

Briefly, the development of the WSES guidelines was structured upon two phases: the synthesis of the literature and the consensus conference. For phase 1, the project committee identified 17 key questions regarding ICP risk, diagnosis, and treatments that would guide the literature search (Table 1). Then, an expert panel composed of surgeons, endoscopists, gastroenterologists, and anesthesiologists from five continents was invited to participate and answer the selected questions. The experts who agreed to participate (n = 50) were divided into 17 groups of at least 3 experts each who were asked to answer one of the selected key questions regarding ICP. For each group, a group leader was nominated; the group leader was

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Key questions used to develop the Consensus Conference on iatrogenic colonoscopy perforation (ICP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of ICP</td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>What are the general recommendations to minimize the risk of ICP during screening and therapeutic colonoscopies?</td>
</tr>
<tr>
<td>Q2</td>
<td>What is the maximum incidence of ICP considered acceptable for centers where diagnostic or therapeutic colonoscopies are performed?</td>
</tr>
<tr>
<td>Diagnosis of ICP</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>What is the minimum information the endoscopist must report after diagnosing an ICP during a colonoscopy procedure?</td>
</tr>
<tr>
<td>Q4</td>
<td>What are the minimum biochemical and imaging investigations that should be requested in the case of suspected ICP?</td>
</tr>
<tr>
<td>Conservative and endoscopic treatments of ICP</td>
<td></td>
</tr>
<tr>
<td>Q5</td>
<td>What are the indications for a conservative treatment or an immediate surgical intervention after an ICP diagnosis?</td>
</tr>
<tr>
<td>Q6</td>
<td>What is the minimum duration of the hospital observation period for patients who have undergone successful endoscopic closure or conservative management of ICP?</td>
</tr>
<tr>
<td>Q7</td>
<td>What investigations (clinical, biochemical, and imaging) should be performed during the observation period in patients who have undergone successful endoscopic closure or conservative management of ICP?</td>
</tr>
<tr>
<td>Q8</td>
<td>What is the recommended type and duration of antibiotic therapy in patients who have undergone successful endoscopic closure or conservative management of ICP?</td>
</tr>
<tr>
<td>Q9</td>
<td>What is the recommended type and duration of antithrombotic prophylaxis in patients who have undergone successful endoscopic closure or conservative management of ICP?</td>
</tr>
<tr>
<td>Q10</td>
<td>How long is the fasting time in patients who have undergone successful endoscopic closure or conservative treatments for ICP?</td>
</tr>
<tr>
<td>Surgical treatment of ICP</td>
<td></td>
</tr>
<tr>
<td>Q11</td>
<td>Is explorative laparoscopy indicated in all patients with ICP?</td>
</tr>
<tr>
<td>Q12</td>
<td>What are the indications for conversion from laparoscopy to open surgery in patients with surgical ICP?</td>
</tr>
<tr>
<td>Q13</td>
<td>What are the key factors when choosing the best surgical approach for ICP?</td>
</tr>
<tr>
<td>Q14</td>
<td>What are the indications for performing a diverting or terminal stoma in patients with ICP?</td>
</tr>
<tr>
<td>Q15</td>
<td>What are the indications for drainages in patients with ICP?</td>
</tr>
<tr>
<td>Q16</td>
<td>What are the indications for the use of damage control surgery in patients with ICP?</td>
</tr>
<tr>
<td>Follow-up of ICP</td>
<td></td>
</tr>
<tr>
<td>Q17</td>
<td>Is there any recommendation to perform a surveillance endoscopy after a successful ICP treatment? If so, what is the recommended timing for it?</td>
</tr>
</tbody>
</table>
responsible for coordinating the work of the experts in his/her group, providing a summary document that aligned the group’s agreement upon answers to the specific question assigned, and meeting the assigned deadline. Experts were solicited to search the literature using a systematic approach within different databases (e.g., PubMed, EMBASE, and Scopus) and assess the level of evidence and the grade of the recommendation based on the recommendations of Guyatt et al. [25] (Table 2). For the literature search, the following keywords and MeSH terms were used: management of colonic/colon perforations, repair of iatrogenic large bowel perforations, abdominal imaging in colonic perforations, evolution of imaging, colonic perforation complications/outcomes, endoscopic treatment of colonic perforations, and peritonitis after colonoscopy.

Within each group, a scientific discussion ensued via email, and modifications were implemented when necessary based on feedback, consistent evidence from the literature, and, whenever pertinent, clinical experience (empirical evidence). The answers provided for each question constituted the provisional statements about the management of ICP that were submitted for review to all participants at the consensus conference (phase II). The Consensus Conference on ICP management was held in Campinas, Brazil, on May 20, 2017, during the 4th WSES World Congress. During the first part of the consensus conference, the group leaders presented the results of their group discussion with the answer to the key question assigned, the provisional statements along with the supporting literature, the level of evidence, and the grade of the recommendation. Each statement was then discussed and voted on by the audience. The percentage of agreement was recorded immediately; in cases of disagreement greater than 30%, the statement was modified after discussion. Furthermore, relevant comments about each statement were collected and used during the revision process. During the final portion of the consensus conference, a comprehensive algorithm for the management of ICP was developed based on the results of the literature review and the plenary discussion among the experts.

The revised statements, their level of evidence, and the recommendation grade are presented below. Please note that the WSES guidelines must be considered an adjunctive tool in the decision-making process regarding the management of ICP; they are not intended to substitute a provider’s clinical judgment for an individual patient, and they may need to be modified based on the medical team’s experience and the available local resources.

### Table 2: Grading of recommendations (from Guyatt et al.)

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Description</th>
<th>Benefits vs. risks</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risks and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
<td>Strong recommendation based on limited evidence; recommendations may change when higher quality or more extensive evidence becomes available</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burdens</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation; best action may differ depending on circumstances, expertise of clinician, the patient in question, or other social issues</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burdens</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation; best action may differ depending on circumstances, expertise of clinician, the patient in question, or other social issues</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, low-quality or very low quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burdens; benefits, risks, and burdens may be closely balanced</td>
<td>Observational studies or case series</td>
<td>Very weak recommendation; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>
Results

Incidence of and risk factors for ICP

What are the general recommendations for minimizing the risk of ICP during screening and therapeutic colonoscopies? There are a number of risk factors that have been related to ICP in the literature (Table 3). Older patients are more vulnerable to ICP, and the ages of 65, 75, and 80 years have been shown to be independent risk factors for ICPs [23, 26, 27]. Female gender [28, 29], low BMI [28, 30], low albumin level, the presence of comorbidities, diverticulosis, Crohn's disease, and admission to an ICU are also acknowledged to be risk factors in several studies [20, 23, 26, 28]. The endoscopist's level of experience may also be considered a risk indicator, as higher incidences of ICP have been reported for non-gastroenterologist endoscopists and low-volume endoscopy centers [31–33]. Finally, anesthesia during colonoscopy has been associated with an increased risk of ICP, in relation to the worsening of patient's comorbidities and the increasing technical complexity of these procedures [34, 35].

In a recent study of 56,882 colonoscopies, full-thickness large bowel perforation occurred in forty patients, corresponding to an incidence rate of 0.07% (0.05% in diagnostic/screening procedures and 0.17% in therapeutic colonoscopies) [18]. A greater risk of ICP was associated with low-volume practices, female gender (due to greater colonic length and a more mobile transverse colon), advanced age (reduced wall strength), history of diverticular disease, previous abdominal surgery (especially pelvic), and colonic obstruction (risk of over-insufflation).

| Table 3 Principal risk factors for iatrogenic colonoscopy perforations (ICP) |
|--------------------------|-----------------|
| Risk factors             | References      |
| Increasing age (> 65 years) | [18, 23, 26, 27, 36] |
| Female gender            | [18, 28, 29, 36] |
| Low BMI                  | [28, 29]        |
| Low albumin level         | [20, 23, 26, 28] |
| Presence of comorbidities | [18, 36]        |
| Crohn's disease and diverticulosis | [16, 18, 20, 23, 26, 28] |
| Admission in ICU          | [20, 23, 26, 28] |
| Endoscopist's experience  | [18, 29, 31–33] |
| Non-gastroenterologist endoscopists | [31, 33] |
| Low volume centers        | [31, 33]        |
| Previous abdominal surgery | [16, 36]      |
| Colonic obstruction       | [16, 18]        |
| Bevacizumab therapy       | [44, 46, 47]    |
| Therapeutic vs. diagnostic procedure | [5, 10, 37–42, 44, 49] |
| Colonoscopy vs. sigmoidoscopy | [5, 29, 36]   |
| General anesthesia        | [34, 35]        |

In a Spanish study of 16,285 colonoscopies, ICPs were reported in 0.09% of cases [16]. Colonic obstruction, prior abdominal surgery, and sigmoid diverticular disease were indicated as potential risk factors.

A review from the Netherlands including 30,366 endoscopic procedures found that ICP occurred in 35 patients (0.12%) [5]. The authors described a 4-fold higher risk of ICP in colonoscopies compared with sigmoidoscopies and a 5-fold greater risk of ICP in therapeutic compared with diagnostic procedures.

A review of 10,486 colonoscopies performed in a single institution included 20 ICPs over a period of 10 years (corresponding to an incidence rate of 0.19%) [29]. During the same time interval, 46,501 flexible sigmoidoscopies were performed and only two ICPs occurred (0.004%). Female patients had significantly more ICPs compared with males and, although not statistically significant, the risk of ICP was numerically higher for endoscopists in training than experienced endoscopists [29].

In a review of studies published between 2001 and 2009 analyzing 969,913 colonoscopies [36], the incidence of ICP ranged from 0.032 to 0.14%. The risk factors for ICP included age over 75 years (4- to 6-fold increase), colonoscopy instead of sigmoidoscopy (2–4 times greater), female gender, diverticular disease, previous abdominal surgery, and multiple comorbidities, including diabetes mellitus, chronic pulmonary disease, congestive heart failure, myocardial infarction, cerebrovascular disease, peripheral vascular disease, renal insufficiency, liver disease, and dementia.

Therapeutic colonoscopies generally involved a higher risk for ICP, particularly the following procedures: polypectomy for large polyps, multiple polypectomies, pneumatic dilatation for Crohn's stricture [37], the use of argon plasma coagulation, and endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for colorectal neoplasia [38]. For endoscopic polypectomies, the related perforation risk has been related to the size of the polyp (larger than 10 mm in the right colon or 20 mm in the left colon) and a sessile morphology [38], and it is considered to be less than 1%, even when more challenging polypectomy techniques such as EMR are performed [39]. Complex procedures such as EMR and ESD are associated with a higher perforation incidence and should be considered to have a high risk of ICP. In 2014, a meta-analysis by Wang et al. comparing procedure-related complications in EMR and ESD for colorectal tumors (including 4 retrospective case-control studies) reported ESD-related perforations in 31/347 cases and EMR-related perforations in 33/566 cases [40]. The current literature demonstrates that the perforation risk for ESD is decreasing in higher volume centers to less than 5% [41, 42].

Perforation in colorectal stenting is the main early adverse event [43]. Use of a self-expandable metal stent
(SEMS) has been associated with an overall perforation rate of 7–8% [10, 44]. In cases of acute malignant colonic obstruction, retrospective studies have shown an SEMS-related perforation risk of 5–9% [45]. Stenting of either benign or neoplastic strictures has been associated with a 7.4% incidence of ICP in a recent meta-analysis [43]; the type of stent, benign etiology, bevacizumab therapy, and the need for re-dilation have been identified as risk factors for ICP [44, 46, 47].

Endoscopic balloon dilation may entail perforation rates up to 11%, even though the rate of iatrogenic perforation for Crohn’s disease stricture treatment is less than 5% in the majority of retrospective studies [37, 45, 48]. Balloon dilation of rectal anastomotic strictures has been associated with a 1.1% rate of ICP [49].

The most common site of perforation is the sigmoid colon (53–65%), followed by the cecum, the ascending colon, the transverse colon, the descending colon, and the rectum [6, 13, 15, 29, 50] (Fig. 1). ICPs are generally intra-peritoneal perforations; extra-peritoneal perforations may manifest as pneumoretroperitoneum, pneumomediastinum, or subcutaneous emphysema. Combined intra- and extra-peritoneal perforations have been reported anecdotally [51].

There is only one randomized study concerning the risk factors and preventive measures for ICP, whereas several reviews of large clinical series and meta-analyses to define the incidence and risk factors for ICP have been published [52, 53]. Recommendations for preventive measures derive from these studies and expert opinions [54].

Statement 1

1.1. During diagnostic endoscopy training, a low threshold at which the senior endoscopist should assume manual control or abort the procedure should be established. Unusual difficulty in traversing the sigmoid colon, a difficult examination in a female or elderly patient, or the presence of diverticular disease or colonic obstruction should be considered alarming conditions (Recommendation Grade 1C).

1.2. During diagnostic or screening colonoscopies, endoscope progression should be gently performed and loop formation avoided. Alternative maneuvers (e.g., compression, decubitus changes) should be used in case of pain, but when difficulties in the progression are observed, it is recommended to abort the procedure (Recommendation Grade 1C).

1.3. Air should be insufflated judiciously to avoid barotrauma, especially if bowel obstruction is suspected. The use of CO₂ further minimizes bowel distension, abdominal discomfort, and the risk of perforation (Recommendation Grade 1B).

1.4. During en bloc endoscopic polypectomy, the maximum size of the tissue sample safely included in the SNARE should be 2 cm (especially if the lesion is proximal to the splenic flexure). Pre-polypectomy submucosal injection reduces the risk of electro-coagulative damage to the muscularis propria. Blended current mode limits the depth of tissue damage, and cold techniques are preferred for small polyps (<5 mm) (Recommendation Grade 1C).

1.5. Endoscopic submucosal dissection (ESD) should be limited to selected cases because of the high rate of associated complications (Recommendation Grade 1C).

1.6. Stenting of a malignant disease should be discouraged in patients receiving bevacizumab. In the case of Crohn’s disease, dilatation of a long stenotic area in the presence of active disease or a suspected fistula before or after stent placement is not advisable (Recommendation Grade 1C).

1.7. Whenever risky endoscopic procedures must be performed, the availability of and close collaboration with a hospital-based multidisciplinary team can improve patient outcomes (Recommendation Grade 1C).

What is the maximum incidence of ICP considered acceptable for centers where diagnostic or therapeutic colonoscopies are performed?

Colonoscopy has been demonstrated to be the most cost-effective method for colorectal cancer screening. As the number of procedures performed worldwide is increasing, gastrointestinal professional societies have adopted strict safety standards for endoscopic practice, including the monitoring and auditing of complications to detect performance gaps and continuously improve the safety of colonoscopy [55]. The American Society for Gastrointestinal Endoscopy (ASGE)/American College of Gastroenterology (ACG) Task Force on Quality in Endoscopy recommends that post-colonoscopy perforation rates should be maintained at ≤1 per 500 colonoscopies (≤1/1000 in screening
healthy subjects) [56]. For screening colonoscopies, the European Society of Gastrointestinal Endoscopy (ESGE) proposes that perforation should require surgery in ≤ 1/1000 [57]. In an audit of post-colonoscopy complications before starting national colorectal cancer screening, the British Society of Gastroenterology (BSG) reported post-colonoscopy perforation rates of 1/769 over a total of 9223 colonoscopies [58].

Statement 2
2.1. The maximum acceptable incidence of ICP for diagnostic colonoscopies should not exceed 0.1% (Recommendation Grade 1A).
2.2. During therapeutic colonoscopy, the maximum acceptable incidence of ICP should be ≤ 1% for complex polypectomy (Recommendation 1A) and less than 7% for SEMS placement (Recommendation Grade 1C).

Diagnosis of ICP
What is the minimum information the endoscopist must report after diagnosing an ICP during a colonoscopy procedure?
Perforation during diagnostic or screening endoscopic procedures may occur from one of these two main pathways: (a) direct mechanical damage to the colonic wall by the tip or the side of the endoscope as it is pushed forward or (b) a pneumatic distension due to barotrauma (Table 4). Direct mechanical trauma is the most frequent etiology of ICP, and perforations originating from mechanical trauma are commonly large and located in the sigmoid region. The injury is usually produced by direct trauma due to an inaccurate instrumental insertion, colonoscope movements toward the mucosal surface, retro-flexion maneuvers, or excessive torsion. Indirect injuries can also occur as the consequence of bowing or stretching the distal part of the colon. The presence of redundant colon diverticula or adhesions from previous surgeries can increase the risk of mechanical trauma during colonoscopy [16]. Baro-trauma is instead produced by the excessive distension of the bowel due to over-insufflation, which produces linear lacerations at the colonic wall that may evolve into full-thickness defects. This type of perforation is more frequently located at the cecal region, where the thinner muscular layer and the larger lumen diameter make this region more vulnerable to pressure-related injuries [6, 16, 59, 60]. For interventional endoscopies, the mechanism of perforation can be the same as those occurring during diagnostic endoscopy, or they may be due to thermal/electrical injury of the colonic wall, manifesting as a wall ischemia. In this latter case, the perforation can occur with a delay of 24–72 h [18, 54]. Wall damage can be incomplete and the perforation concealed as it is confined by the surrounding tissues. During the following days or weeks, an abscess may develop that may delay the diagnosis.

Up to 60% of ICPs are detected by the endoscopist while performing the procedure [14, 16, 18, 60–62]. In a retrospective evaluation of a single institution, 68% of ICPs were identified on the day of endoscopy, 23% on day 1 or 2 after the endoscopy, and 9% were identified at least 2 weeks after the procedure [29]. The results of a survey of 30,336 colonoscopies showed a mean delay of 0.36 days for the diagnosis of ICP after diagnostic endoscopies and 1.5 days after therapeutic procedures [5].

Table 4 Main etiologies of iatrogenic colonoscopy perforation (ICP)

<table>
<thead>
<tr>
<th>Type of injury</th>
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</thead>
<tbody>
<tr>
<td>• Direct mechanical trauma</td>
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<tr>
<td>• Barotrauma</td>
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<tr>
<td>• Thermal/electrical injury</td>
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Endoscopic therapeutic procedures at risk for ICP
• Colorectal stenting
• Polypectomy
• Colonic dilation
• Argon plasma coagulation (APC)
• Endoscopic mucosal resection (EMR)
• Endoscopic submucosal dissection (ESD)

Statement 3
3.1. If the ICP is detected during the procedure by the endoscopist, a detailed description should be provided including the following information:
• Colonoscopy indication (i.e., diagnostic or therapeutic)
• Associated colonic pathology (e.g., strictures, polyps, tumors)
• Administration of sedation, analgesia, or anesthesia for the colonoscopy
• Patient’s general status and presence of comorbidities
• Gas type used for insufflation
• Quality of the colonic preparation
• Time of the ICP occurrence
• Most likely reason for ICP (e.g., thermal injury, mechanical injury)
• Injury localization and size
• Whether an endoscopic resolution was intended, attempted, or completed
• How the endoscopic repair was performed
• Presence of abdominal distention increasing the probability of abdominal compartment syndrome

This recommendation was obtained by consensus after discussion with the panel experts (Recommendation Grade 2C).
Which are the minimum biochemical and imaging investigations that should be requested in the case of a suspected ICP?

A delay in the diagnosis of ICP is a critical issue for therapeutic outcomes; when the diagnosis is delayed more than 24 h, the chance increases that more invasive treatments (e.g., surgery) will be required [2, 63]. Physicians should therefore search for this potentially life-threatening complication and run clinical and biochemical tests if an ICP is suspected.

An ICP can be appreciated by direct visualization of the parietal defect or the view of intra-abdominal tissues through the colonic wall during the endoscopy [15]. Otherwise, the diagnosis of ICP is based on clinical, laboratory, and radiologic findings [64]. The clinical presentation of an ICP can vary widely, depending on the size of the perforation, the type of etiologic agent, the affected colonic location, the degree of intra-peritoneal contamination, and the patient’s general status. In the majority of patients (91–92%), symptoms develop within the first 48 h following the completion of the endoscopy [14, 29]. The most common symptom is abdominal pain associated with distension, although painless cases of ICP or cases with severe cramp-like pain have been described [13, 16, 18]. In two large clinical series, the most consistent symptoms were abdominal pain (from 74 to 95%), guarding/rebound tenderness (82.5%) with diffuse peritonitis, tachycardia (62.5%), leukocytosis (40%), fever (38%), rectal bleeding (15%), and isolated abdominal distension (6.6%) [16, 18]. Only a small number of patients with ICP (5%) remained asymptomatic [52, 59]. An unusual clinical sign (1/55 patients with ICPs) was a delayed subcutaneous emphysema and an ongoing necrotizing infection of the abdominal wall [16, 18]. It is a common belief that patients with diffuse peritonitis can be diagnosed and treated for perforation on a clinical basis, but peritonitis-like clinical scenarios can also occur in the absence of perforation. For instance, a transmural thermal injury after polypectomy with serosal irritation without any obvious perforation produces localized peritonitis that is amenable to non-operative management. Thus, biochemical and imaging studies are always indicated when an ICP is suspected.

Laboratory tests should be run for inflammatory markers that can reveal severe bacterial infections associated with the perforation [65], such as white blood cell count (WBC) and C-reactive protein (CRP) [66, 67]. In case of delayed presentation (> 12 h), the pro-calcitonin level (PCT) can be useful for ICP diagnosis.

Perforations of intra-peritoneal segments of the colon (e.g., the cecum, transverse colon, or sigmoid colon) more often lead to free intra-peritoneal fluid and air (large amounts in cases of barotrauma from insufflation), whereas perforations of the ascending and descending colon and rectum or wall injuries contained in the supplying mesentery result mainly in extraperitoneal air. Mixed situations are possible if the perforation is in the middle between an intra- and extra-peritoneal portion [68]. Upright or decubitus abdominal radiographs can detect small amounts of free peritoneal air, but they are insensitive to the presence of fluid. Plain thoracic and abdominal radiographs have a positive predictive value (PPV) of 92% for ICPs [13]. Of note, the PPV has been shown to be higher for ICPs occurring during diagnostic procedures (PPV 100%) than for ICPs occurring during therapeutic procedures (PPV 45%) [2]. Alternatively, an ultrasound may be useful in cases in which the radiation burden should be limited, notably in children and pregnant women. However, this method should not be considered definitive in excluding a pneumoperitoneum [69].

If the clinical suspicion of ICP persists after a normal plain radiograph, a computed tomography (CT) scan with contrast enhancement should be requested, as this imaging tool can easily detect small amounts of both free intra-peritoneal air and fluids, in some cases with the foci of the gas congregating near the perforation site [68]. Air trapped in the mesenteric folds is found in perforation of the colon. A pneumoretroperitoneum is caused by extraperitoneal perforations such as perforations of the descending colon and rectum. Gas in the right anterior pararenal space indicates ascending colon perforation, whereas gas in the left pararenal space indicates descending or sigmoid colon perforations. Generally, rectal perforation causes bilateral pneumoretroperitoneum [70]. For extra-peritoneal perforations, the CT scan can show air tracking along the mesenteric and fascial planes, even in the mediastinum and abdominal, and chest and neck walls. Of note, the retro-peritoneal air dissecting the mediastinum and the retropharyngeal tissues can cause a change in the tone of the larynx, resulting in voice change [71].

Colonoscopy may also dissect within the wall of the colon with pneumatosis. Moreover, mucosal injury and intraluminal pressure may dissect air inside the mesenteric and portal venous system. For all these reasons, CT is much more effective in the diagnosis of extraluminal air compared to conventional radiography [15]. Double contrast CT (intravenous and rectal) is increasingly used in patients with clinical suspicion of ICP and without diffuse peritonitis. This diagnostic tool may be useful for detecting concealed or sealed perforations that are eligible for non-operative management [72]. Multi-detector CT (MDCT) is superior to single helical or conventional CT because it can provide rapid, high-volume coverage, and diagnostic images, even in patients who are unable to perform prolonged breath holds. One study showed that MDCT was 86% accurate in predicting the site of perforation [69].
The following recommendations were developed using a large clinical series and expert opinions, since randomized studies on this topic are lacking.

**Statement 4**

1. After diagnostic or therapeutic colonoscopies, all patients who present with abdominal pain, and/or tenderness, and/or abdominal distention, and/or fever, and/or rectal bleeding should be investigated for ICP by laboratory tests and imaging exams (Recommendation Grade 1B).

2. The minimum biochemical markers that should be requested in the case of suspected ICP are white blood cell count and C-reactive protein (Recommendation Grade 1C).

3. ICP should be confirmed with the demonstration of free intra-peritoneal or extra-peritoneal air (Recommendation 1B). CT scan is more sensitive than standard abdominal radiographs to detect free air (Recommendation Grade 1C).

4. In the case of localized peritoneal signs, double contrast enhanced CT scan can be a useful adjunctive tool to confirm the feasibility of non-operative management of ICP (Recommendation Grade 1C).

**Conservative and endoscopic treatments for ICP**

**Which are the indications for conservative treatment or an immediate surgical intervention after an ICP diagnosis?**

Once the diagnosis of perforation is confirmed by clinical and radiological examinations, the decision between surgical and non-operative treatments will depend on the type of injury, the quality of the bowel preparation, the underlying colonic pathology, and the clinical stability of the patient [6]. However, a surgical consultation should be obtained in all cases of perforation [73].

Whenever the risk of a large perforation is present and the patient presents with signs and symptoms of peritonitis, the emergency surgery approach is reasonable and safe [6]. Surgical management is also recommended in patients with concomitant colonic diseases requiring surgery, transplanted patients, and immunosuppressed patients [36, 74]. In selected patients with localized pain, free air without diffuse free fluids in radiographs, hemodynamic stability, and an absence of fever, non-operative management (conservative) may be appropriate [61, 68, 75–78] and is associated with low morbidity, low mortality, and short hospital stays. Conservative management is usually suitable for small, sealed-off perforations that occurred during a therapeutic colonoscopy in patients with an optimal bowel preparation [8, 23, 24].

Conservative treatment consists of serial clinical and imaging monitoring (every 3–6 h) with absolute bowel rest, intravenous fluids for hydration, intravenous administration of broad-spectrum antibiotics, and a close multidisciplinary team follow-up to promptly detect the development of sepsis and peritoneal signs [6, 78, 79]. Drainage of the peritoneal air through a Veress needle puncture may be useful in relieving abdominal pain, improving respiratory function, and facilitating the closure of the perforation site [80]. The overall success rate of conservative treatments for colonic perforation varies from 33 to 90% [36].

An early success with non-surgical treatment does not rule out the potential need for surgery [52]. If the conservative treatment is successful, clinical improvement will gradually occur within 24 h, but a continuous and strict clinical and biochemical follow-up is recommended. In cases of clinical deterioration or progression to a septic condition or peritonitis, surgical treatment should not be delayed. The sole presence of subdiaphragmatic free air does not constitute an indication for urgent surgery. Of note, complication rates and lengths of hospital stay are significantly higher in patients who have undergone surgery after conservative management than in patients who were initially treated with surgery [81]. Indeed, when surgical treatment is delayed, the peritonitis and colonic wall inflammation could worsen, requiring a more invasive surgery that is associated with a poorer prognosis [13, 82]. Ideally, the decision to pursue surgery should be made as early as possible after the endoscopy [2].

Endoscopic treatment is possible when the perforation site is recognized intra-procedurally or within 4 h following the procedure and the bowel preparation is still adequate [45]. Urgent endoscopic therapy with clip placement and the use of CO₂ may limit the volume of extraluminal insufflation and subsequently the need for surgery [83–85]. Endoscopic clip closure of ICP was first reported in the literature in 1997 [86]. Today, it should be considered a valuable non-invasive method for ICP that is recognized during a colonoscopy. It has been shown to be effective in sealing and healing the perforation and avoiding surgery in most cases [2]. The decision to perform the endoscopic closure of colonic perforation depends on the size and the cause of the iatrogenic damage as well as the endoscopist’s experience and the availability of appropriate endoscopic devices [45]. Clipping closure of ICP is recommended for small perforations (less than 1 cm) originating from either diagnostic or therapeutic colonoscopies [2, 24, 87], with a success rate of 59–100% [2, 4, 88, 89]. In larger or difficult perforations, a combination of endoclips and endoloops might be used. There are also few reports in the literature about closure with conventional clips for perforations larger than 1 cm [90–92]. A limitation of the endoscopic closure is the difficulty of evaluating the completeness of the colonic closure after the clip application. This might result in delayed complications such as intra-
abdominal abscesses, which can occur due to the persistence of intestinal fluids in the peritoneal cavity or an intermittent leakage [2].

Over the last several years, new devices have been introduced to widen the spectrum of possibilities of performing an endoscopic closure of a gastrointestinal perforation. Through-the-scope (TTS) clips and over-the-scope clips (OTSC) are both effective for the early closure of defects smaller than 2 cm, with overall technical and clinical success rates of 93 and 89%, respectively [88, 93–95]. TTS clips are more suitable for closure of small therapeutic perforations (less than 1 cm), whereas OTSC may be used for larger defects. The OTSC is a nitinol clip shaped to mimic a trap that allows for the inclusion of more tissue and consequently closure of larger perforations than the conventional clips [96]. Recent studies focusing on the outcomes after OTSC placement revealed a rate of procedural success of 80–100% and clinical success rates of 57–100% [96–98].

The overstitch endoscopic suturing device (Apollo Endosurgery, Austin, TX, USA) was recently developed and might play a role in the future ICP closures [99]. Partially or totally covered stenting could potentially allow closing the perforation, but data supporting its clinical application are still lacking. A clear indication for surgery in the setting of endoscopic treatment of an ICP consists of a complicated procedure or a failed endoscopic closure with an ongoing leak that is causing fecal peritonitis [45].

Statement 5

5.1. Non-operative (conservative) management of ICPs may be appropriate in selected patients, including patients who are hemodynamically stable, without sepsis, experiencing localized pain, and with no free fluid in radiographs (Recommendation Grade 1C).

5.2. Endoscopic treatment can be considered as an initial approach if it is feasible within 4 h following the procedure depending on the size and cause of the iatrogenic injury and the operator’s level of experience (Recommendation Grade 2C).

5.3. Emergency surgery is recommended when the patient develops signs and symptoms of peritonitis, in cases of clinical deterioration, suspected large perforation, failure of conservative management, poor bowel preparation, or in the presence of an underlying colonic disease requiring surgery (Recommendation Grade 1A).

Statement 7

7.1. During the observation period, the patient treated for ICP should be monitored clinically, by laboratory tests (including WBC, PCT, CRP) and imaging (CT scan) (Recommendation Grade 2C).

What is the minimum duration of the hospital observation period for patients who have undergone successful endoscopic closure or conservative management of ICP?

After a successful endoscopic closure, it is advisable that a multidisciplinary team, including abdominal surgeons, endoscopists, gastroenterologists, and anesthesiologists, are involved in the patient’s follow-up [52]. Fasting, broad-spectrum antibiotic therapy and intravenous hydration are the basis of treatment [3, 88, 100]. Close observation for signs of peritoneal irritation and monitoring of biochemical inflammatory parameters are crucial. When pain disappears and the inflammatory parameters and bowel function return to normal, oral intake can be resumed [100]. The duration of observation is subjective but obviously related to the patient’s status and the response to the conservative (non-operative) or endoscopic treatment. The mean duration of hospital stay after non-surgical ICP management ranges from 9 to 13 days [88].

Statement 6

6.1. After conservative or endoscopic treatment of ICP, monitoring and follow-up should be assured by a multidisciplinary team, including surgeons. There is no optimal duration of the observation period, but it depends on the patient’s clinical status and response to treatment (Recommendation Grade 1C).

Which investigations (clinical, biochemical, and imaging) should be performed during the observation period in patients who have undergone successful endoscopic closure or conservative management of ICP?

There are no studies in the literature focusing specifically on the clinical and biochemical follow-up of patients who have undergone endoscopic closure or conservative management of ICP.

The available evidence is mainly supported by retrospective series. During the observation period, the patient treated for ICP should be monitored clinically as well as through laboratory values and imaging. Clinically, peritoneal signs such as tenderness, rebound tenderness, and muscle guarding, as well as signs of infection, such as fever, nausea, vomiting, abdominal distension, and diarrhea, should be recorded [36, 69]. Frequent assessment of the physical status and vital signs should be completed by laboratory tests for WBC, CRP, Hb, blood urea nitrogen, PCT, and electrolytes [66]. As an imaging technique, the CT scan remains the most accurate tool to be performed in case of clinical deterioration, especially when the need for surgery is in question and before discharge for non-operative treatments.
What is the recommended type and duration of antibiotic therapy in patients who have undergone successful endoscopic closure or conservative management of ICP?

In patients who have undergone endoscopic repair of ICP, infection control is usually attained with a short-term course of antibiotic therapy (3–5 days). Antibiotics should be stopped if there are no signs of systemic inflammation and/or peritonitis after the short-term treatment. Considering the composition of the intestinal microbiota in the large bowel, patients with ICP require antimicrobial coverage for Gram-negative bacteria as well as for anaerobes. The potential infecting organisms in colorectal procedures are derived from enteric bacteria as well as for anaerobes. The potential infecting organisms in colorectal procedures are derived from Enterobacteriaceae such as Escherichia coli are the most common bacteria [101].

If there is any sign of an ongoing infectious process, antibiotics should be continued. An abdominal CT is recommended after 5–7 days to exclude residual signs of peritonitis or abscess formation and to exclude the possible need for a surgical intervention.

The duration of antimicrobial therapy in patients with complicated intra-abdominal infections has been debated. Antibiotic therapy should be shortened in those patients demonstrating a positive response to treatment. A prospective trial published recently by Sawyer et al. demonstrated that, in patients with complicated intra-abdominal infections undergoing an adequate source-control procedure, the outcomes after approximately 4 days of fixed-dose antibiotic therapy were similar to those after a longer course of antibiotics that extended until after the resolution of physiological abnormalities [102].

Statement 8

8.1. In patients who have undergone conservative management of ICP, even if there is no sign of diffuse peritonitis, antibiotic therapy covering Gram-negative bacteria and anaerobes is recommended (Recommendation Grade 1C).

8.2. In patients with perforation repaired by endoscopic closure, a short-term course of antibiotic therapy (3–5 days) covering Gram-negative bacteria and anaerobes is recommended. Antibiotics should be stopped if there are no signs of systemic inflammation and/or peritonitis after the short-term treatment. Abdominal CT is suggested to help rule out peritonitis or early abscess formation (Recommendation Grade 1C).

8.3. In patients who have undergone a surgical procedure with an adequate source-control procedure, postoperative therapy should be shortened as much as possible after the resolution of physiological abnormalities (Recommendation Grade 1C).

Which is the recommended type and duration of antithrombotic prophylaxis in patients who have undergone successful endoscopic closure or conservative management of ICP?

Sepsis is associated with activation of blood coagulation (hypercoagulability) contributing to venous thromboembolism (VTE) [103–105]. Patients with abdominal sepsis may be at increased risk of VTE due to their premorbid conditions, surgical intervention, admitting diagnosis of sepsis, and events and exposures such as central venous catheterization, invasive tests and procedures, and drugs that potentiate immobility. A prospective cohort study using the National Surgical Quality Improvement Program database of the American College of Surgeons (ACS-NSQIP) was designed to evaluate the impact of preoperative sepsis on the risk of postoperative arterial and venous thrombosis. The study included 2,305,380 adults who underwent a range of surgical procedures [106]. The systemic inflammatory response syndrome was defined by the presence of two or more of the following: temperature > 38 or < 36 °C; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or a PaCO2 < 32 mmHg (< 4.3 kPa); white blood cell count > 12,000 cells/mm3, < 4000 cells/mm3, or > 10% immature band forms; or anion gap acidosis (> 12 mEq/L). Among all surgical procedures, patients with preoperative systemic inflammatory response syndrome or any sepsis had three times the odds of having an arterial or venous postoperative thrombosis. The risk of thrombosis increased with the severity of the inflammatory response and was higher in both emergent and elective surgical procedures. Thus, patients with ICP should be considered at risk, and thromboprophylaxis should be recommended.

Statement 9

9.1. In patients with ICP undergoing a surgical procedure, thromboprophylaxis is generally recommended during hospitalization and thereafter according to the underlying disease and comorbidities (Recommendation Grade 1B).

How long is it recommended that patients fast following successful endoscopic closure or conservative treatments for ICP?

There are no prospective clinical trials assessing the necessary duration of fasting following non-operative management or endoscopic repair of ICP. In the setting of conservative treatment, the general recommendations called for “bowel rest,” but the duration is unclear. Retrospective studies reported fasting durations of between 2 and 6 days. In one of the largest series, 24 patients with ICP were managed with conservative treatment, which failed in 3 patients; 31 patients were initially clipped, of which 22 procedures were successful. Poor outcomes were
Surgical procedures for the management of ICP include technique to apply according to the different scenarios. Related to surgery for ICP, morbidity and mortality associated with colorectal perforation [108].

Preoperative blood pressure, can have higher risks of patients, such as older patients and patients with low – such as unresected polyps with high suspicion of being a carcinoma [6, 60, 78].

The duration of fasting was significantly shorter in the non-surgery group than in the surgery group (3.8 vs. 5.6 days). The mean fasting time was also 1 day shorter for patients treated by endoscopic repair versus surgery in the study by Kim et al. [4]. Moreover, the fasting duration was not related to ICP treatment failure.

It has been suggested that a clear liquid diet can begin immediately after the endoscopic repair of ICP; the evidence is not strong, but there are no data to indicate that this practice is not feasible or unsafe [36]. Following open or laparoscopic repair of ICP, there is no restriction on oral intake, as supported by numerous studies that provided enteral nutrition in the early period after colorectal surgery [107].

Statement 10

10.1A liquid diet may begin within 1 to 2 days after the initiation of conservative management of ICP according to the patient’s clinical status (Recommendation Grade 1C)

10.2A liquid diet may begin immediately after endoscopic repair of ICP according to the patient’s clinical status (Recommendation Grade 1C)

Surgical treatment of ICP

Is explorative laparoscopy indicated in all patients with ICP?

Surgery is indicated as the first treatment in patients with ongoing sepsis, signs of diffuse peritonitis, large perforations, and failure of conservative management and in the presence of certain concomitant pathologies, such as unresected polyps with high suspicion of being a carcinoma [6, 60, 78].

The peri-operative morbidity and mortality related to surgery for ICP are considerable, with rates of 21–44% and 7–25%, respectively [5, 13–18]. Particularly frail patients, such as older patients and patients with low preoperative blood pressure, can have higher risks of mortality associated with colorectal perforation [108]. Thus, appropriate patient selection and surgical procedures are crucial in limiting the morbidity and mortality related to surgery for ICP.

In general, intraoperative findings determine the best technique to apply according to the different scenarios. Surgical procedures for the management of ICP include colorrhaphy, wedge resection, colostomy by exteriorization of the perforation, and colonic resection with or without primary anastomosis or stoma. The decision regarding the type of surgical procedure depends on (a) the size, location, and etiology of the ICP; (b) the viability of the surrounding colon and mesocolon; (c) the degree of and time from the development of peritonitis; (d) the patient's general status and the presence of comorbidities; (e) the quality of the colonic preparation; and (f) the presence of residual lesions not resected during the colonoscopy procedure [2, 8, 24, 60, 82, 109, 110].

The decision of which procedure to perform, therefore, depends on many variables, and it must be made after a careful inspection of the whole colon and peritoneal cavity. Explorative laparoscopy should be considered a minimally invasive technique useful for performing both diagnostic and potentially therapeutic procedures. A timely application of explorative laparoscopy may prevent ongoing inflammation and injury that would necessitate more invasive measures, such as open laparotomy and/or colonic diversion [82]. The use of laparoscopy allows for visualizing the parietal defect and its size and specific location, as well as for identifying the potential cause of the perforation (e.g., perforation caused by the shaft of the endoscope, cautery, presence of mesenteric hematomas, emphysema, or effusions), which, as previously stated, are the main factors influencing the choice of treatment option. Early diagnosis is mandatory, and when timely management is ensured, laparoscopy can be the best option, offering reduced morbidity and length of stay and faster postoperative recovery. If no underlying lesion requiring surgical resection is seen during the endoscopy, the size of the tear is small, and the colon is healthy and well perfused, then a laparoscopic primary repair can be safely performed [52, 111].

Moreover, laparoscopic exploration allows the presence of potential signs of peritonitis to be evaluated and eventually allows aspiration, culture, and irrigation of the peritoneal cavity to be performed. Indeed, peritoneal washout and drainage have gained acceptance in the treatment of more advanced cases of colonic infection, such as Hinchey grade 2–3 diverticulitis [112]. Accordingly, the treatment of less advanced inflammatory processes, such as ICP, seems reasonable and indicated.

To summarize, explorative laparoscopy is indicated:

- For both diagnostic and therapeutic purposes [5, 9, 13, 17, 52, 100, 109, 113–119], and depending on the surgeon's skills, the potential exists for definitive surgical procedures, including suturing the defect, wedge resection, and segmental resection with or without anastomosis and/or stoma
- In questionable situations to rule out the need for further treatments, including laparotomy [82, 118, 120]
- In the case of failure of endoscopic treatment or an inability to perform endoscopic clip application after visualization of the ICP intra-procedurally
In the case of development of peritonitis after a defined period of observation following perforation

Explorative laparoscopy has a significantly lower morbidity and mortality compared with explorative laparotomy in the emergency setting [121]: specifically, the reported postoperative complication rate is 18.2% for laparoscopy vs. 53.5% for laparotomy. The postoperative mortality rate is 1.11% for laparoscopy vs. 4.22% for laparotomy; and the need for further procedures is significantly lower for laparoscopy (1.11%) than for laparotomy (8.45%).

Explorative laparoscopy may not be indicated when there is:

- A potential risk for anesthesia-related complications, particularly in elderly or frail patients [122, 123], or any contraindications to surgery in general (e.g., hemodynamic instability, coagulopathy, or associated co-morbidities) [9, 122, 123]
- Recent laparotomy or previous abdominal surgery (more than 4 laparotomies) with extensive adhesions and a high risk of iatrogenic injury (relative contraindication)
- The presence of massive bowel dilatation (relative contraindication)
- Aorto-iliac aneurysmal disease (relative contraindication)

The potential diagnostic/therapeutic value of explorative laparoscopy should also be compared with the role of a CT scan in the evaluation of ICP. There is no study in the literature focusing on whether explorative laparoscopy should be performed instead of CT scans in patients with highly suspected ICP. However, when comparing these two modalities for penetrating abdominal trauma, CT scans have a sensitivity/specificity rate of 95%/95%, whereas explorative laparoscopy can achieve a 67–100% sensitivity and 50–100% specificity [121]. Thus, a CT scan should be performed in all cases before contemplating explorative laparoscopy, with the only obvious impediment being hemodynamic instability.

**Statement 11**

11.1 Explorative laparoscopy is safe and can be considered as the preferred first-line surgical approach for the management of ICP (Recommendation Grade 1C).

11.2 Explorative laparoscopy should be performed according to the surgeon’s experience and skills, as well as the availability of adequate technology and surgical devices (Recommendation Grade 1C).

**Statement 12**

12.1 Conversion from laparoscopy to laparotomy should be considered whenever necessary with regard to the ability of the operator to proceed laparoscopically, the tissue viability, and the patient’s status (Recommendation Grade 1C).

**What are the indications for conversion from laparoscopy to open surgery in patients with surgical ICP?**

Thanks to the improvements in minimally invasive surgery, the laparoscopic approach has been increasingly used in recent years, and it should currently be considered a safe and feasible technique for the management of ICP [9, 24, 82, 113, 124–126]. Current literature comparing outcomes of laparoscopy versus laparotomy for the treatment of ICP is scarce and consists mainly of small retrospective studies. The first relevant study was published in 2008 [110] and compared the perioperative outcomes between laparoscopic and open procedures for ICP by including only primary colonic closures without diversion. The authors found fewer complications and a shorter length of hospital stay for the patients in the laparoscopic group [110]. Other studies by Rothold et al. [125] and Schloricke et al. [127] also observed fewer postoperative complications and significantly shorter hospital stays when utilizing the laparoscopic approach. Similar studies with similar results were published by Coimbra et al. [124] and Kim et al. [128], although in these studies, delayed surgeries (> 24 h) and ostomy formation rates were more frequently observed in the open groups, with higher primary repair rates in the laparoscopic groups.

Due to its favorable short-term outcomes, laparoscopy should be considered the preferred approach for both exploration and repair of ICPs that are not manageable with medical treatments. However, the surgeon’s experience and skills are the key factors limiting the applicability and feasibility of laparoscopic ICP management. Conversion from laparoscopy to laparotomy should be considered whenever necessary. The most frequent reasons for conversion are the inability of the surgeon to complete the procedure laparoscopically, the large size of the ICP defect, the extensive peritoneal contamination, the highly inflammatory or neoplastic conditions of the colon, and the patient’s hemodynamic instability.
excessive narrowing of the colonic lumen (e.g., cecum) [108]. Whenever the perforation is too large, the edges appear devitalized, or an avulsion of the adjacent mesocolon is seen, colonic resection might constitute the best option. Generally, patients who undergo surgery within 24 h are more appropriate candidates for less invasive techniques, such as primary suturing of the defect or linear wedge resection. In cases of delayed surgery (> 24 h from the colonoscopy), extensive peritoneal contamination, important comorbidities, or a deterioration of the general status of the patient (i.e., sepsis), a staged repair or colostomy by exteriorization of the perforation (e.g., double-barreled colostomy) must be considered [36, 52].

Currently, there are no prospective or retrospective studies in the English literature comparing the different types of repair (primary suture or wedge resection vs. segmental resection). Therefore, the choice of the surgical technique appears to be mainly empirical, and it is left to the surgeon’s discretion according to the intraoperative findings. Independent of the surgical approach, the main goal of the therapy is the rapid diagnosis, repair, and prevention of abdominal sepsis. If an ICP is to be repaired laparoscopically, the operating surgeon and the surgical team should be comfortable with the laparoscopic techniques, such as mobilization of the colon and intracorporeal suturing. A clinical algorithm mainly based on the size of the perforation and the necrotic area was proposed in 1999 to assist in choosing which type of repair to perform [8]. The maximal size for sutured repair was set at 1 cm. Between 1 and 2.5 cm, a transverse tangential stapled resection was recommended, whereas above 2.5 cm, a segmental resection was indicated [8, 129]. The condition of the bowel to be repaired and the level of contamination and inflammation are the most important factors in determining whether the laparoscopic approach is safe [109]. Both sutured and stapled repair techniques seem to be safe and feasible to repair defects of up to 4 cm [82].

In case of perforated colon cancer, surgery must follow the oncologic principles of cancer resection.

**Statement 13**

13.1. The best surgical technique for the management of ICP should be decided after a careful inspection of the abdominal cavity and considering the underlying colonic pathology (Recommendation Grade 2C).

13.2. Primary repair can be used if the colonic tissues appear healthy and well vascularized, and an approximation of perforation edges could be done without tension (Recommendation Grade 2C).

13.3. Wedge resection would be feasible if it does not imply an excessive narrowing of the colonic lumen (e.g., perforation of the cecum or sigmoid colon) (Recommendation Grade 2C).

13.4. Colonic resection may be indicated if the perforation is too large, the edges appear devitalized, or an avulsion of the adjacent mesocolon is seen (Recommendation Grade 2C).

13.5. Staged repair or colostomy may be necessary in cases of delayed surgery (> 24 h from the colonoscopy), extensive peritoneal contamination, important comorbidities or a deterioration of the patient’s general status (i.e., hemodynamically unstable or sepsis) (Recommendation Grade 2C).

**What are the indications for performing a diverting or terminal stoma in patients with ICP?**

The formation of a stoma is often included in the overall surgical strategy for the management of ICP. However, no randomized controlled trials or other high-level evidence trials exist to guide this operative decision in this specific indication. Case series of ICP report variable rates of stoma formation (up to 59.7%) [59, 114, 116, 126, 130]. As such, the formation of a stoma forms an adjunct to the overall treatment strategy for these patients.

The precise clinical or operative reasons for stoma formation are incompletely reported in the case series on ICP. Furthermore, these reports are generally limited by their largely retrospective study designs and low event numbers, complicating subgroup analyses. Notwithstanding these limitations, some authors have established increased stoma formation rates in patients with delayed diagnoses, significant peritonitis, and patients with left-sided perforations [114, 126]. Apart from these observations, the limited publications in this area infer that surgical judgment remains essential in the decision-making surrounding the formation of a stoma. Finally, no data exist to specifically address the type of stoma formation in ICP.

**Statement 14**

14.1. Stoma formation is an accepted and practiced adjunct in the surgical management of ICP (Recommendation Grade 1C).

14.2. Surgical judgment is crucial in the decision regarding stoma need: patient, disease, and situational/environmental factors need to be considered in the individual clinical circumstance (Recommendation Grade 1C).

**What are the indications for drainage in patients with ICP?**

The placement of an intra-abdominal drainage after surgical management of an ICP can be justified by either the presence of peritoneal contamination or the early diagnosis of a potential bleeding or leakage of the repair used for the perforation (i.e., colorraphy, wedge resection, colonic resection) [131–133]. There are no studies...
available in the literature focusing on the indications of abdominal drainage after successful surgical treatment of ICP. The decision is left to the discretion of the surgeon according to the ICP setting, the intraoperative findings, the type of surgical procedure performed, the adequateness of infection source control, and the patient's general status [5, 14, 108].

Statement 15

15.1. In the case of early surgery (< 24 h from colonoscopy) in a patient with good bowel preparation, minimal peritoneal contamination, and adequate infection source control, intra-abdominal drainage placement should be avoided (Recommendation Grade 2C).

15.2. In the case of delayed surgery (> 24 h from colonoscopy) in a patient with poor bowel preparation or extensive peritoneal contamination, drainage placement may be recommended (Recommendation Grade 2C).

What are the indications for the use of damage control surgery in patients with ICP?

At present, no study concerning ICP and damage control surgery (DCS) is available in the literature. However, once colonic perforation has occurred, the course of sepsis will develop independent of the underlying disease. Thus, to evaluate the use of DCS in cases of ICP, we could analyze the experience in similar settings, such as in perforated diverticulitis (PD), equating ICP to PD [134, 135].

Damage control is a surgical technique originally used in trauma surgery consisting of three stages: (1) an abbreviated initial laparotomy with the aim of controlling hemorrhage and contamination with temporary abdominal closure (TAC); (2) resuscitation until normal physiology is improved; and (3) return to the operating room after 24–72 h for definitive injury repair and abdominal wall closure [136–138].

Untreated or misdiagnosed ICP can progress to peritonitis and sepsis, resulting in serious morbidity and a very poor prognosis. Notably, morbidity rates as high as 43% and mortality rates as high as 25% have been reported [17, 20, 36, 50, 60, 139]. Nearly one quarter of patients will receive a delayed diagnosis, with a 45% incidence of fecal peritonitis [140]. The resultant inflammatory process associated with peritonitis clearly limits the operative options, precluding a single-stage procedure and resulting in fecal diversion in 38% of patients with fecal peritonitis. Several studies reported that age > 67 years, ASA score, blunt injuries, poor bowel preparation, and steroids are risk factors for increased postoperative morbidity (Table 5) [20, 123, 141, 142].

Over the last decade, DCS has become a valuable technique in unstable patients with fecal peritonitis [36, 136, 143]. The potential progression of ICP in fecal peritonitis is as probable as it is in perforated diverticulitis. In accordance with the WSES guidelines for the management of acute left-sided colonic diverticulitis, DCS may be suggested for clinically unstable patients (severe sepsis/septic shock) [135]. Critically ill patients with severe sepsis, hemodynamically unstable patients with hypotension, and patients with myocardial depression combined with coagulopathy are not candidates for endoscopic treatment or immediate complex operative interventions. In such patients, DCS allows rapid source control, enhances physiologic optimization, improves primary anastomosis rates, and decreases the need for stoma formation [144]. Therefore, in patients with abdominal sepsis, the application of DCS is individualized but not routinely used, as suggested by current clinical guidelines [145], stressing the importance of a careful assessment by the surgeons. Clearly, an individual approach tailored to each patient's clinical status might be the most appropriate. In cases of ICP, DCS should be performed in combination with the resection of the perforated colonic segment to bridge the patient to the definitive injury and colonic continuity repair. DCS can represent a very resource-heavy procedure for institutions, however, because of the requirements for access to facilities (operating rooms and intensive care units) and committed staff.

Statement 16

16.1. DCS following ICP may be indicated in hemodynamically unstable patients, patients receiving a delayed diagnosis of ICP, and patients

<table>
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<tr>
<th>Table 5 Risk factors to evaluate when considering damage control strategy for iatrogenic colonoscopy perforations (ICP)</th>
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<td>Age</td>
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<td>Delayed diagnosis</td>
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<td>“Blunt” ICP</td>
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<td>Severe sepsis</td>
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Follow-up of ICP
Is there any recommendation to perform a surveillance endoscopy after successful ICP treatment? If any, what is the recommended timing for it?

At present, there are no studies in the literature focusing on the indications and timing for surveillance endoscopy after successful ICP treatment. However, based on the available evidence and clinical experience, a surveillance colonoscopy may be performed based on the initial indication (e.g., benign or malignant pathology) and type (e.g., screening or interventional) of the primary colonoscopy (during which the ICP occurred) and considering the risk-benefit ratio of performing an endoscopic exam.

Colonoscopy is specifically contraindicated in cases of known or suspected perforation. Consequently, any endoscopy after ICP treatment should be performed once the colonic wall has completely healed. Assuming that the healing time after ICP treatment is comparable to that after surgical sutures or anastomosis, a surveillance endoscopy may be indicated after approximately 3 months from the successful ICP treatment, depending on the size of the perforation and the type of repair.

In general, prior to any surveillance colonoscopy, it is necessary to carefully re-evaluate the presence of specific conditions favoring perforation, including increasing age, female gender, low BMI, intensive care unit stay, inpatient setting, diverticular disease, Crohn's disease, obstruction as an indication for the primary colonoscopy, and invasive interventional colonoscopy. Indeed, colonoscopy is contraindicated whenever the risks for the patient's health or life are judged to outweigh the most favorable benefits of the procedure.

Statement 17

17.1 In cases of perforation occurring during a diagnostic colonoscopy for screening or surveillance of colorectal cancer, a repeat endoscopy is indicated within 3 to 6 months postoperatively if the screening or clearing colonoscopy was incomplete due to malignant obstruction or inadequate preparation (Recommendation Grade 1C).

17.2 In cases of perforation occurring during a colonoscopy for gastrointestinal bleeding, a surveillance endoscopy is indicated for diagnostic and therapeutic purposes; in cases of acute lower gastrointestinal bleeding, it is necessary to ascertain the resolution of the perforation (Recommendation Grade 1C).

Conclusions

Iatrogenic perforation is a potentially severe complication of colonoscopy that requires a prompt and specific treatment to avoid further morbidity and mortality. In general, a multidisciplinary management, involving gastroenterologists, endoscopists, surgeons, and anesthesiologists, is recommended. The treatment strategy must be chosen based on the clinical setting and the patient's characteristics, but it should also be adapted to the medical team's experience and local resources. The comprehensive algorithm presented in Fig. 2 summarizes the management strategies in cases of ICP.

The risk of ICP should be carefully evaluated before a procedure; whenever a risky endoscopy must be performed, the availability of a hospital-based multidisciplinary team can improve patient outcomes. Continuous monitoring and auditing of endoscopic standards and related complications is recommended in each endoscopic center to detect possible performance gaps and improve the safety of colonoscopy. Close collaboration between endoscopists and surgeons is advisable; whenever an ICP occurs, the endoscopist is expected to provide a detailed description of the perforation, procedure, and patient to determine the best treatment option.

Endoscopic repair should be attempted whenever the perforation is detected during the procedure, though outcomes depend on the size and cause of the iatrogenic injury, as well as on the operator's level of experience.

When the ICP is not immediately detected, it should be suspected and investigated in all patients who present with abdominal pain, tenderness, abdominal distension, fever, and/or rectal bleeding after a diagnostic or therapeutic colonoscopy. CT scan is the most accurate imaging tool to diagnose ICP. Non-operative (conservative) management may be appropriate in selected patients who remain hemodynamically stable in the absence of signs of sepsis. Conservative management consists of complete bowel rest, short-course broad-
spectrum antibiotics and intravenous hydration together with close clinical observation.

It must be stressed that early improvement with conservative treatment does not rule out the potential need for surgery. Close monitoring of the patient will allow detection of clinical deterioration, which may signal the need for emergency surgery. Where surgical intervention is required, timely decisions for proceeding with the operation are important. Ideally, these surgeries should occur early and within 24 h of the perforation, as further delays are related to a worse prognosis.

Colonic closure, wedge resection, ostomy, and colonic resection are the main surgical options for ICP management. No RCTs have assessed the superiority of one method over the others. Thus, the therapeutic decision remains essentially empirical, based on the perforation characteristics (e.g., size, time of evolution, and degree of peritoneal contamination), the patient’s general status (e.g., comorbidities), and the availability of adequate technology and surgical devices. Explorative laparoscopy is safe and should be considered the first line approach to assess the perforation-related damages. In patients with good bowel preparation, minimal peritoneal contamination, and adequate infection source control, the perforation repair can possibly be performed by laparoscopy and without drainage placement. Alternatively, staged repair or, in extreme cases, damage control surgery may be required.

The present WSES guidelines contribute to clarifying the complex decision-making process for the management of ICP. Despite the large number of publications, evidence is often derived from observational and moderate to low quality studies. However, it is scarcely feasible to design RCTs for an infrequent complication often requiring emergency treatment. Prospective registries would be highly advantageous to defining the validity of the present recommendations and proposed guidelines.

**Abbreviations**
ASA: American Society of Anesthesiologist score; BMI: Body mass index; CRP: C-reactive protein; CT: Computed tomography; DCS: Damage control surgery; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; ICP: Iatrogenic colonoscopy perforation; MDCT: Multidetector computed tomography; OTSC: Over-the-scope clips; PCT: Pro-calcitonin; PD: Perforated diverticulitis; PPV: Positive predictive value; RCT: Randomized controlled trial.
controlled trial; TAC: Temporary abdominal closure; TTS: Through-the-scope clips; VTE: Venous thromboembolism; WBC: White blood cell

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References
The role of open abdomen in non-trauma patient: WSES Consensus Paper


Abstract

The open abdomen (OA) is defined as intentional decision to leave the fascial edges of the abdomen un-approximated after laparotomy (laparostomy). The abdominal contents are potentially exposed and therefore must be protected with a temporary coverage, which is referred to as temporal abdominal closure (TAC). OA use remains widely debated with many specific details deserving detailed assessment and clarification. To date, in patients with intra-abdominal emergencies, the OA has not been formally endorsed for routine utilization; although, utilization is seemingly increasing. Therefore, the World Society of Emergency Surgery (WSES), Abdominal Compartment Society (WSACS) and the Donegal Research Academy united a worldwide group of experts in an international consensus conference to review and thereafter propose the basis for evidence-directed utilization of OA management in non-trauma emergency surgery and critically ill patients. In addition to utilization recommendations, questions with insufficient evidence urgently requiring future study were identified.

Keywords: Open abdomen, Laparostomy, Non-trauma, Peritonitis, Pancreatitis, Vascular emergencies, Fistula, Nutrition, Re-exploration, Re-intervention, Closure, Biological, Synthetic, Mesh, Technique, Timing

Background

The decision by a surgeon to utilize the open abdomen (OA) technique is a dramatically non-anatomic situation that dramatically increases resource utilization and has potential severe side effects. It is, however, often dramatically effective at countering the drastically impaired physiology of critical illness when no other perceived options exist. There are both mandatory and relative indications for OA use, which are heavily influenced by the primary pathophysiologic insults and responses to intra-abdominal sepsis and inflammation, both inherent to the patient and induced through medical treatments.

The abdominal compartment is dramatically affected in both its contents and the characteristics of the abdominal wall. Several factors as systemic inflammatory response syndrome, increased vascular permeability, and aggressive crystalloid resuscitation predispose to fluid sequestration leading to peritoneal fluid formation. Patients with severe sepsis and septic shock commonly receive large amounts of resuscitation fluids and may develop excessive gut edema and diminished contractility and motility. These changes in combination with sequestration of second and third space fluids and forced closure of an abdominal wall with altered compliance may result in increased intra-abdominal pressure (IAP) ultimately leading to intra-abdominal hypertension (IAH) or even abdominal compartment syndrome (ACS) [1, 2].
The pathophysiologic implications of elevated IAP have been restarted to be studied in deep during the last 20 years [2–4]. In 2013, The Abdominal Compartment Society (WSACS) updated the previously published definition and guidelines for the management of intra-abdominal hypertension [5]. Elevated IAP constitutes IAH and was classified into four grades: (1) grade I IAP 12–15 mmHg, (2) grade II IAP 16–20 mmHg, (3) grade III IAP 21–25 mmHg, and (4) grade IV IAP >25 mmHg. Elevated IAP commonly causes marked deficits in loco-regional and whole body perfusion that may result in organ failure [5]. An uncontrolled IAH, with an IAP exceeding 20 mmHg and new onset organ failure, is defined as an abdominal compartment syndrome (ACS) [2, 5]. ACS is a syndrome and not a disease, as such, it can have many causes and it can occur in many disease processes, it is an all or nothing phenomenon, while IAH is a more graded continuum. ACS in turn has further effects on intra-abdominal organs, as well as indirect effects on the other organ(s) and system(s). The ACS is a potentially and frequently lethal complication characterized by effects on splanchnic, cardiovascular, pulmonary, renal, and central nervous systems [2, 5]. While medical therapies should be attempted, the ACS is rapidly lethal and opening of the abdominal cavity conducted promptly if medical interventions do not quickly alleviate or temporize the situation. If surgery has been undertaken for the index disease, leaving the abdomen temporarily open is often required to prevent inducing ACS in a critically ill pro-inflammatory patient with visceral edema and ongoing resuscitation. Whether leaving the abdomen open will primarily influence the septic response is also intriguing but unproven at the present time.

The OA procedure is defined as intentionally leaving the fascial edges of the abdomen un-approximated (laparostomy). The abdominal contents are exposed and thus must be protected with a temporary coverage, which is itself termed a temporary abdominal coverage (TAC) [2, 6]. The OA technique, when used appropriately, may be useful in the management of surgical patients with compromised general conditions due to any critical illness/injury but most frequently cases of intra-abdominal sepsis and severe pancreatitis are seen recently [7]. Despite many serious potential complications, the OA is perceived to be a life-saving intervention in catastrophically injured patients [2]. Compared to trauma patients, however, patients undergoing OA management for intra-abdominal non-trauma emergencies have greater risks subsequent to OA utilization, including entero-atmospheric fistula (EAF) and a “frozen abdomen”, intra-abdominal abscesses, and lower rates of definitive fascial closure [8, 9] with resultant large ventral hernia defects. This discrepancy in risks and benefits, along with economic considerations [10], was the primary reason the WSACS suggested not routinely using the OA for septic cases versus traumatic cases [5]. Thus, every effort should be exerted to attempt abdominal closure as soon as the patient can physiologically tolerate it.

Methods
The recommendations are formulated and graded according to the modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) hierarchy of evidence from the GRADE Group, summarized in the Table 1 [11].

The WSES and Abdominal Compartment Society together with the Donegal Research Academy united a group of subject-matter experts coordinated by a central coordinator to review and summarize the evidence and thereafter to express their evidence-based opinion on important issues concerning OA utilization in non-trauma patients:

- Which non-trauma patients can benefit from OA techniques and for which specific critical conditions is indicated (example, peritonitis, vascular emergencies, and severe pancreatitis)?
- What is the optimum TAC technique for use in non-trauma patients?
- Is there a role for fluid instillation?
- What is the optimum timing of re-exploration before definitive closure in non-trauma patients?
- What is the optimum timing to definitively close an OA in non-trauma patients?
- What are the optimum adjunctive techniques to definitively close an OA in non-trauma patients considering both non-mesh-mediated techniques and mesh-mediated techniques?
- What is the optimum treatment to treat frozen abdomen and enteral fistulas?
- What nutritional support is indicated in OA?

A central project coordinator compiled the answers and statements derived from the first round of presentations and discussions. The statements were discussed during the Consensus Conference held in Dublin (Ireland) in July 2016. Once an agreement was reached within the experts groups, a final round of discussion among a larger group of experts led to the final version of recommendations reflecting the final expert-consensus document (Table 2).

Open abdomen in peritonitis
The open abdomen is an option for emergency surgery patients with severe peritonitis and septic shock under the following circumstances: abbreviated laparotomy due to the severe physiological derangement, or the need for a deferred intestinal anastomosis or a planned second look.
for intestinal ischemia, or persistent source of peritonitis (failure of source control), or extensive visceral edema with the concern for development of abdominal compartment syndrome (grade 2C).

In severe secondary peritonitis, some patients may experience a disease progression to severe sepsis and septic shock experiencing progressive organ dysfunction, hypotension, myocardial depression, and coagulopathy and a staged approach may be required [12]. These are often hemodynamically unstable and unfit for immediate complex surgical interventions [12]. If the patient is not in a condition to be undergone to a definitive repair and/or abdominal wall closure, the intervention should be abbreviated due to suboptimal local conditions for healing and global susceptibility to spiraling organ failure. For instance, intestinal continuity restoration can be deferred to a subsequent surgical intervention, which is particularly important in hypotensive patients who are receiving inotropes [13]. In facing the impossibility to completely obtain a source control of the contamination in a single operation or if extensive visceral edema and decreased abdominal wall compliance increases the risk of ACS development, primary fascial closure should not be attempted and the abdomen should be left open [14]. The rationale for using the OA is to leave the abdomen open and to treat the infected peritoneal cavity like an “open abscess” with subsequent re-operations involving generous irrigations and potentially active TAC techniques [15] to definitively control the contamination while also preventing IAH progression to ACS. No definitive data exist about the management of severe peritonitis with the open abdomen. Robledo et al. compared open versus closed abdomen procedures in 40 patients with severe secondary peritonitis; no significant differences in mortality rates were found (55% open vs. 30% closed). The study was interrupted at the first interim analysis for high relative risk and odds ratios for death in the open group (1.83 and 2.85, respectively) [16]. However, the TAC technique that was selected as the “intervention” would be relatively contraindicated in current OA management. Some other

<table>
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<th>Grade of recommendation</th>
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<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses or imprecise conclusions) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, Low-quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
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Table 2 Statement Grid

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<th>Statements</th>
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<tr>
<td>➢ Peritonitis</td>
<td>The open abdomen is an option for emergency surgery patients with severe peritonitis and septic shock under the following circumstances: abbreviated laparotomy due to the severe physiological derangement, or the need for a deferred intestinal anastomosis or a planned second look for intestinal ischemia, or persistent source of peritonitis (failure of source control), or extensive visceral edema with the concern for development of abdominal compartment syndrome (Grade 2C).</td>
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<td>➢ Vascular Emergencies</td>
<td>The open abdomen should be strongly considered following management of hemorrhagic vascular catastrophes such as ruptured abdominal aortic aneurysm (Grade 1C). The open abdomen should be considered following surgical management of acute mesenteric ischemic insults (Grade 2C).</td>
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<td>➢ Pancreatitis</td>
<td>In patients with severe acute pancreatitis unresponsive to step-up conservative management surgical decompression and leaving the abdomen open is effective in treating abdominal compartment syndrome (Grade 2C). Leaving the abdomen open after surgical necrosectomy for infected pancreatic necrosis is not recommended excepted in those situation at high risk of abdominal compartment syndrome (Grade 1C).</td>
</tr>
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</table>

Optimal technique for temporary abdominal closure

Negative pressure wound therapy with continuous fascial traction is suggested as the preferred technique for temporary abdominal closure (Grade 1B). Temporary Abdominal Closure without Negative pressure wound therapy (e.g., mesh alone, Bogota bag) whenever possible should NOT be applied for the purpose of temporary abdominal closure, because of low delayed fascial closure rate and being accompanied by a significant intestinal fistula rate (Grade 1B).

Is there a role for NPWT with Fluid Instillation?

There is inadequate evidence to make a recommendation regarding use of negative pressure wound therapy in combination with fluid instillation in patients with temporary abdominal closure (NOT GRADED).

Planning re-exploration before definitive closure

- In critically ill non-trauma patients with open abdomen, once any requirements for on-going resuscitation have ameliorated, early re-operation with the intention of closing the abdomen should be given a high priority (Grade 1C).
- In critically ill patients with open abdomen, re-laparotomy with concern for ongoing ischemia or contamination reoperation should be conducted no later than 24–48 h after the index operation, with the duration from the index operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (Grade 1C).

Best timing to definitively close an open abdomen

- Fascia should be closed as soon as possible (Grade 1C).
- Acidosis (pH < 7.25), hypothermia (temperature < 34 °C) and coagulopathy (TEG, INR) are not predictive of the need for maintaining the open abdomen in non-trauma patients (Grade 2A).
- The abdomen should be maintained open in non-trauma patients if the source of contamination persists, if a condition of haemodynamic instability persists meaning in presence of on-going fluid resuscitation or vasopressor support necessity, if a deferred intestinal anastomosis is needed, if there is the necessity for a planned second look for ischemic intestine and lastly if there are concerns about abdominal compartment syndrome development (Grade 2C).
- Early fascia closure (within 7 days) should be the strategy for management of the open abdomen once the source control has been reached, the severe sepsis has been controlled meaning that the patient is haemodynamically stable and the hypoperfusion has been definitively corrected, no further surgical re-exploration is needed and there are no concerns for abdominal compartment syndrome (Grade 2C).

Best solution to definitively close an open abdomen

➢ Non-mesh mediated techniques

- Primary fascia closure is the ideal solution to restore the abdominal closure (2A).
- Component separation is an effective technique; however, it's early use is NOT recommended in fascial temporary closure. It should be considered only for definitive closure or reconstructive interventions (Grade 2C).
- Planned ventral hernia (skin graft or skin closure only) remains an option for complicated open abdomen (i.e. in the presence of entero-atmospheric fistula or in cases with a protracted open abdomen due to underlying diseases) or in those low resource setting where no other facilities are present (Grade 2C).

➢ Mesh mediated techniques

- A fascial bridge using prosthetic mesh (polypropylene, polytetrafluoroethylene (PTFE) and polyester products) should NOT be recommended to achieve definitive fascial closure in patients with open abdomen and should be placed only in patients without other alternatives (Grade 1B).
- Biologic meshes are reliable for definitive abdominal wall reconstruction in the presence of a large wall defect, bacterial contamination, comorbidities and difficult wound healing. NPWT can be used combined with biologic mesh to facilitate granulation and skin closure (Grade 2B).
- Non–cross-linked biologic mesh seems to be preferred in sublay position when the linea alba can be reconstructed. Non–cross-linked biologic mesh is easily integrated, with reduced fibrotic reaction and lesser infection and removal rate (Grade 2B).
cohort studies showed the effectiveness of OA technique in treating severe peritonitis. At present, however, no definitive data from randomized trials exist.

**Open abdomen in vascular emergencies**

The open abdomen should be strongly considered following management of hemorrhagic vascular catastrophes such as ruptured abdominal aortic aneurysm (grade 1C).

The open abdomen should be considered following surgical management of acute mesenteric ischemic insults (grade 2C).

The ACS has been well described in the setting of ruptured abdominal aortic aneurysm (rAAA) [17]. Rupture of aortic as well as iliac or visceral aneurysm often results in life-threatening hemorrhagic shock. The combination of severe shock and massive resuscitation contributes to retroperitoneal, mesenteric, and bowel wall edema and production of ascites that can increase abdominal pressure and lead to ACS. Intra-abdominal hypertension occurs in up to 50% of patients following AAA repair, and ACS occurs in 8–20%. Mortality after rAAA is as high as 30–50%; of note, mortality is generally twice as high among patients who develop ACS compared with those who do not [18].

Consequently, prevention of ACS, if possible, would be of tremendous benefit to the patient.

In prospective non-randomized studies, the incidence of ACS is reduced when prophylactic OA is employed [19]. Unfortunately, selection criteria for employing OA are not well defined; the surgeon might consider inability to close the fascia without tension; use of aortic balloon occlusion catheter; and preoperative blood loss >5 L [19, 20]. Such criteria should prompt the surgeon to consider temporary OA utilization. When the abdominal is closed primarily, postoperative monitoring of IAP is recommended, with vigilance for ACS as reflected by elevated airway pressures, reduced cardiac output, or oliguria. Concerns for infection of aortic grafts with OA are allayed by existing data, indicating a relatively low rate [21]. Patients are often selected for endovascular repair (EVAR) of rAAA if they have less hemodynamic compromise. Although it is less common, ACS still occurs after EVAR [17]. The major risk factor appears to be massive resuscitation. These patients should have vigilant monitoring for elevated IAP and the onset of ACS.

Mesenteric ischemia may result from arterial (thrombotic, embolic, or low perfusion) or venous (venous thrombosis) insults. Fundamental principles of management include making the diagnosis, restoration of intestinal perfusion, and assessment of bowel viability with resection as necessary. The bowel ischemia leads to bowel wall and mesenteric edema, as well as ascites.

### Table 2 Statement Grid (Continued)

| Best treatment for open abdomen and entero-atmospheric fistulas | - Several clinical circumstances may contribute to the development of entero-atmospheric fistula and few risk factors may predict its development. Awareness of this complication and avoidance of contributing conditions for its development are mandatory; moreover preemptive measures are imperative (Grade 1C). | - The management of entero-atmospheric fistula should be personalized according to standard classification and grading system. Current different classification schemes echo the problematic and challenging issues related to their management (Grade 1C). |
| - The ACS has been well described in the setting of ruptured abdominal aortic aneurysm (grade 1C). | - The caloric intake and protein demands of patients with entero-atmospheric fistula increase; the Nitrogen balance should be corrected and protein supplemented. Nutrition should be started immediately upon recognition of entero-atmospheric fistula (Grade 1C). | - Entero-atmospheric fistula effluent isolation is essential for proper wound healing. Separating the wound into different compartments in order to facilitate the collection of fistula output is of paramount importance (Grade 2A). |
| - The open abdomen should be considered following surgical management of acute mesenteric ischemic insults (grade 2C). | - Many methods for wound care exist; however in the presence of entero-atmospheric fistula in open abdomen, negative pressure wound therapy makes effluent isolation feasible and wound healing conceivable (Grade 2A). | - Definitive management of entero-atmospheric fistula should be delayed to after the patient has recovered and the wound completely healed (Grade 1C). |
| Nutritional support | - Open abdomen patients are in a hyper-metabolic condition; an immediate and adequate nutritional support is mandatory (Grade 1C). | - Open abdomen techniques result in a significant nitrogen loss that must be replaced with a balanced nutrition regimen (Grade 1C). |
| | - Early enteral nutrition should be started as soon as possible if the gastrointestinal tract allows (Grade 1C). | - Enteral nutrition should be delayed in patients with high output fistula with no possibility to obtain feeding access distal to the fistula (Grade 2C). |
| | - Oral feeding is not contraindicated; whenever it is possible it could be started as soon as the patient is able to eat (Grade 2C). | - Oral feeding is not contraindicated; whenever it is possible it could be started as soon as the patient is able to eat (Grade 2C). |
| Patient Mobilization | - To date, no recommendations can be made about early mobilization of patients with open abdomen. | - The management of entero-atmospheric fistula should be personalized according to standard classification and grading system. Current different classification schemes echo the problematic and challenging issues related to their management (Grade 1C). |

...
production; reperfusion of the bowel can exacerbate bowel edema and ascites and thus increase risk of ACS. For this reason, OA use should be considered following restoration of perfusion in a patient with acute mesenteric ischemia. As there are no reliable independent predictors of ACS in this setting, the surgeon should assess bowel swelling and the patient’s physiology to make this decision [22, 23]. Another reason to consider temporary OA following mesenteric ischemia is to facilitate second-look laparotomy to assess bowel viability and perform bowel anastomosis as needed [24]. Bowel resection is much less common in the setting of venous thrombosis than arterial occlusion, so the patients with mesenteric venous thrombosis probably do not require OA as often as those with acute arterial occlusion [25]; although, IAP should be followed.

Open abdomen in pancreatitis

In patients with severe acute pancreatitis unresponsive to step-up conservative management, surgical decompression and leaving the abdomen open is effective in treating abdominal compartment syndrome (grade 2C).

Leaving the abdomen open after surgical necrosectomy for infected pancreatic necrosis is not recommended except in those situations at high risk of abdominal compartment syndrome (grade 1C).

Acute pancreatitis (AP) is a mild self-limiting disease in the majority of cases, even though the 15% of patients with AP progress to severe disease identified by development of persistent organ failure [26]. Multiple organ failure (MOF) is the factor mainly associated to mortality in AP, as a counterpart in absence of organ dysfunction or if it transient the risk of dying is very low [27–29]. However, in those with severe AP, MOF develops generally early, with over half of the patients exhibiting organ dysfunction’s signs at hospital admission and in any case, most part of them develops within the first 4 days after admission [28, 30]. More than half of the deaths happen within the first week from onset of AP and generally within a week after MOF first symptoms [31]. Principal treatments of MOF are support therapies: vasopressors, fluid replacement, and renal replacement therapy and mechanical ventilation if indicated. During AP, IAH/ACS may aggravate MOF, and therefore, constant IAP measurements are crucial to identify patients with high risk of developing ACS [32]. ACS should be prevented and treated, whenever possible, with non-operative management. Surgical decompression is the last but the most effective tool to decrease the IAP, and it should not be postponed if the patient presents ACS manifestation [5, 33].

In the event of AP, the risk to develop subsequent infections (i.e., bacteremia, pneumonia and infection of pancreatic or peripancreatic necrosis) is increased. The first week of illness is crucial for the extra-pancreatic infection occurrence, whereas pancreatic necrosis usually becomes infected later [34]. Some factors are associated to an increased risk of infected necrosis: the presence of organ failure, early bacteremia, and the extent of pancreatic necrosis [34]. Surgical necrosectomy is the last resort if more conservative management including percutaneous drainage failure [35]. Patients with persistent organ failure complicated with infected pancreatic necrosis face a very high mortality risk [36].

Optimal technique for temporary abdominal closure

Negative pressure wound therapy with continuous fascial traction is suggested as the preferred technique for temporary abdominal closure (grade 1B).

Temporary abdominal closure without negative pressure wound therapy (e.g., mesh alone, Bogota bag) whenever possible should NOT be applied for the purpose of temporary abdominal closure, because of low delayed fascial closure rate and being accompanied by a significant intestinal fistula rate (grade 1B).

There is inadequate evidence to make a recommendation regarding use of negative pressure wound therapy in combination with fluid instillation in patients with temporary abdominal closure (NOT GRADED).

The perceived indications and subsequent treatment choices in managing OA differ among surgeons. The existing techniques result in different risk of enterocutaneous fistula (EAF) and the different rate of delayed fascial closure. Overall, 74 relevant studies exist for a total of 4358 patients: 3461 (79%) with peritonitis. The described OA indications are considerably different. Thirty-eight out of 78 series described negative pressure wound therapy (NPWT) TAC systems. NPWT with a dynamic component (mesh-mediated fascial traction or dynamic sutures) gives the best results in terms of delayed fascial closure, but dynamic sutures result more often in fistula. NPWT without a dynamic component (Barker’s VAC or commercial products) for the use of temporary fascial closure has a moderate delayed fascial closure rate and a fistula rate similar to mesh closure without NPWT.

Several TAC techniques exist that could be used alone or combined together. Six-eight series reported about one TAC technique. Ten series described patients managed with combined TAC systems. NPWT was used alone in 32 studies [37–68], and in 6 studies, NWPT is combined with fascial traction (mesh or sutures) [69–74] and eight series described the use of meshes (non-absorbable and/or absorbable) [75–81]. Six series reported about the Bogota-bag use [75, 82–86]; five, about Zipper [87–91]; and other five, about dynamic retention sutures [92–96]. Two more series described loose packing [97, 98]. Lastly, the Wittmann patch was used in one series [99]. The remnant three series applied
differing TAC systems [82, 100, 101]. The delayed fascial closure rate ranged from 3.2 to 100%. Twenty-two series were prospective, and ten out of them described NPWT (608 patients) showing a weighted fascial closure rate of 53.9% and an EAF rate of 9.8%. The four prospective series on NPWT with fascial traction (411 patients) showed a weighted fascial closure rate of 77.8% and an EAF rate of 4.3%. Including retrospective studies data per closure type are in line with the aforementioned results. With the highest weighted fascial closure rate for NPWT with fascial traction (73.1%) and dynamic retention sutures (73.6%). TAC using a mesh or zipper showed the lowest delayed closure rates (34.2 and 34.0% respectively). Nine series were not exhaustive in describing eventual fascial closure attempts [16, 45, 75, 81, 87, 89, 98, 102, 103].

Is there a role for NPWT with fluid instillation?

There are no series published on the use of NPWT with instillation in situations of TAC in non-trauma patients or in trauma patients. Recently, a systematic review performed by an expert consensus group has been published underlining the need of more evidence to support the fluid instillation and giving no recommendation of its use in abdominal wound [104].

Planning re-exploration before definitive closure

In critically ill non-trauma patients with open abdomen, once any requirements for on-going resuscitation have ameliorated, early re-operation with the intention of closing the abdomen should be given a high priority (grade 1C).

In critically ill patients with open abdomen, re-laparotomy with concern for ongoing ischemia/contamination re-operation should be conducted no later than 24–48 h after the index operation, with the duration from the index operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (grade 1C).

A related question for clinicians is when to re-operate (if ever) for the sole purpose of “revise” when there is recognition that closing an abdomen will not be possible. This question may be further conceptually complicated in an attempt to distinguish indications to re-operate because the patient is not improving or deteriorating and there is fear that contamination or ischemia is ongoing and those cases of non-improvement or only modest improvement in whom there is operation intention to “wash” the peritoneal cavity and to “change” the TAC dressing or device. No RCTs or meta-analyses examining the timing of re-operation in OA patients exist. Guidelines and review papers did not generally discuss timing of re-operation [8, 105]. In the position paper of the WSES, it is recommended that as a general principle, patients should be taken back to the operating room at 24–48 h after the initial surgery [2]. Other expert opinions come from the survey of Trauma Association of Canada in 2006, and the majority of responders indicated the best timing included between 24 and 72 h [106, 107]. Pommerening et al. utilized the American Association for the Surgery of Trauma (AAST) Open Abdomen Registry to evaluate time to the first re-operation on trauma OA patients as a predictor of primary fascial closure using a hierarchical multivariate logistic regression analysis [108]. Adjusting for other factors, including resuscitation volumes, increasing delay to the first re-operation was associated with a decreased likelihood of primary fascial closure (PFC), with a 1.1% decrease in PFC rates for every hour after 24 h from the index operation [108]. Further, there was a trend (95% CI 1.0–3.25 OR) of increased complications in patients having the first re-operation after 48 h [108].

It should be clearly understood however that extrapolation of these findings regarding the timing of re-operation in trauma patients might not be directly applicable to non-trauma patients with OA. It is becoming apparent that infected and non-infected patients with auto-activation of the immune responses leading to multi-organ dysfunction syndrome (MODS) and MOF have more fundamental differences than previously appreciated [109]. Fundamental evidences from basic science are emerging justifying the OA in critically ill/injured patients in order to manipulate the systemic immune response and ameliorate the bio mediator burdens of catastrophic illness [110–113]. There are also newly described populations of fully mature indwelling peritoneal macrophages that migrate locally within the peritoneal cavity within an hour of injury [114]. Whether mechanically removing such cell populations through scheduled “wash-outs” is beneficial or harmful is a completely unstudied question. Thus, the timing of re-operation is more complex in non-trauma patients and urgently requires further study. Lastly, in critically ill patients with an OA, re-laparotomy with the intention of cleaning or “washing-out” the abdomen has an unknown priority and should be subjected to future randomized study.

Best timing to definitively close an open abdomen

Fascia should be closed as soon as possible (grade 1C).

Acidosis (pH <7.25), hypothermia (temperature <34 °C), and coagulopathy (TEG, INR) are not predictive of the need for maintaining the open abdomen in non-trauma patients (grade 2A).

The abdomen should be maintained open in non-trauma patients if the source of contamination persists, if a condition of hemodynamic instability persists meaning in the presence of an on-going fluid resuscitation or vaso-pressor support necessity, if a deferred intestinal anastomosis is needed, if there is the necessity for a planned second look for ischemic intestine, and lastly if there are
concerns about abdominal compartment syndrome development (grade 2C).

Early fascia closure (within 7 days) should be the strategy for management of the open abdomen once the source control has been reached, the severe sepsis has been controlled meaning that the patient is hemodynamically stable and the hypoperfusion has been definitively corrected, no further surgical re-exploration is needed, and there are no concerns for abdominal compartment syndrome (grade 2C).

The early definitive abdominal closure is the first goal to achieve in order to reduce the OA complications rate [115], (i.e., EAF, fascial retraction with loss of abdominal wall domain, and incisional hernias) [115, 116]. The primary closure rates have a bimodal distribution, with early closure depending on postoperative intensive care management and delayed closure depending on the choice of the TAC technique [117]. Mortality, complications, and length of stay were compared between early and delayed fascial closure in a meta-analysis [118]. 3125 patients were included and 1942 (62%) successfully achieved early fascial closure. Early fascial closure is a factor significantly associated with a reduced mortality (12.3 versus 24.8%, RR 0.53, P < 0.0001) and complication rate (RR, 0.68, P < 0.0001). Early fascial closure is commonly performed within 4–7 days of the initial laparostomy [13]. No major technical difficulties are described to obtain primary fascial closure within few days from the index operation. Patients having abdominal sepsis are less likely to achieve an early fascial closure [119] and therefore should have closure attempts performed as soon as possible after severe abdominal sepsis is controlled [120].

Best solution to definitively close an open abdomen

Often the OA, particularly if prolonged, results in fascia retraction and consequently in large abdominal wall defects that require complex abdominal wall reconstruction. Moreover, the situation is often complicated by a contaminated field [121] with high risk of infections and wound complications, such as wound infections, seromas, fistula formation, recurrence of the defect, and mortality [122–124].

Non-mesh-mediated techniques

Primary fascia closure is the ideal solution to restore the abdominal closure (grade 2A).

Component separation is an effective technique; however, its early use is NOT recommended in fascial temporary closure. It should be considered only for definitive closure or reconstructive interventions (grade 2C).

Planned ventral hernia (skin graft or skin closure only) remains an option for complicated open abdomen (i.e., in the presence of entero-atmospheric fistula or in cases with a protracted open abdomen due to underlying diseases) or in those low-resource setting where no other facilities are present (grade 2C).

Abdominal component separation is most commonly considered an elective procedure for ventral hernia repair [118]. One important technique described for the reconstruction of the abdominal wall is the component separation. The technique of anterior component separation consists in a relaxing incision made in the aponeurosis of the external oblique muscle, a separation of the external and internal oblique muscle and the incision of the rectus fascia to achieve the advancement of the abdominal wall to cover the defect. This technique has been well studied and described in elective giant ventral hernia repair, and it provides an effective technique with a recurrence rate of 16% [125, 126] but a very relevant complication rate of 50%. Other surgical techniques that have been described include the posterior component separation: the rectus sheath is opened and the posterior rectus fascia and rectus muscle are separated. At the lateral margin of the rectus muscle, the aponeurosis of the transverse abdominis muscle is incised with the separation of the internal oblique muscle from the transverse abdominis muscle.

However, the use of abdominal component separation technique was recently described in acute fascia closure after open abdomen in a small case series by Rasilainen et al. [127] with 75% of primary fascia closure. At present, there is not enough evidence to support component separation in the acute setting due to the related high morbidity and the fact that these techniques can only be performed on a patient once, so that if ill timed, future options are not available. Therefore, a valuable alternative option for closure of the open abdomen remains the planned ventral hernia: its main goal is to cover abdominal viscera to prevent complications such as EAF. The abdominal wall defect could be closed only with skin suture and or a skin graft put on the underlying granulating tissue creating a planned laxity. After physiologic recovery and a significant period of scar and adhesion maturation, the complete restoration of the patient’s abdominal wall through reconstructive techniques can be undertaken as an elective procedure.

Mesh-mediated techniques

A fascial bridge using prosthetic mesh (polypropylene, polytetrafluoroethylene (PTFE) and polyester products) should not be recommended to achieve definitive fascial closure in patients with open abdomen and should be placed only in patients without other alternatives (grade 1B).

Biologic meshes are reliable for definitive abdominal wall reconstruction in the presence of a large wall defect, bacterial contamination, comorbidities, and difficult wound healing. NPWT can be used combined with
biologic mesh to facilitate granulation and skin closure (grade 2B).

Non-cross-linked biologic meshes seem to be preferred in sublay position when the linea alba can be reconstructed. Non-cross-linked biologic mesh is easily integrated, with reduced fibrotic reaction and lesser infection and removal rate (grade 2B).

The long-term outcome of a bridging non-cross-linked biologic mesh is laxity of the abdominal wall and a high rate of recurrent ventral hernia. In the bridge position (no linea alba closure), cross-linked biologic meshes maybe associated with less ventral hernia recurrence (grade 2B).

Two meta-analyses exist on BP in abdominal wall defect. The first, by Sharrock et al. investigated the management and closure of OA in trauma patients [128]. Among the included studies, the point estimate recurrence rate of ventral hernia after 1 year of BP positioning was 51%. However, the authors highlighted the small number of included studies and their poor quality; moreover, as above mentioned, great differences exist between trauma and septic patients and great caution should be addressed in interpretation of this result.

A systematic review and meta-analysis by Atema et al. [129] investigated the utilization of BP in abdominal wall reconstruction. They clearly stated that the poor quantity and quality of available data strongly limits taking a clear message from the results. Biological material in infected fields had a recurrence rate of 30% compared with 7% of synthetic material, but data were derived from a single study and does not justify the use of synthetic materials, especially as a bridge position after OA.

The “bridging” technique refers to using some mesh (either prosthetic or biologic) to physically interpose between native abdominal wall fascia that either cannot or should not be primarily opposed. Thus, such fascial defects can be closed with a mesh in a bridging position. In general, non-absorbable synthetic materials (i.e., polypropylene mesh) reinforce any fascial repair through a combination of mechanical tension and intense inflammatory reaction, resulting in the entrapment of the mesh into scar tissue. However, in a bridging position, there is no native tissue to protect viscera from the mesh and thus, the persistent inflammatory response combined with the contaminated field may induce local side effects such as adhesions, erosions, and fistula formation [130–135]. International guidelines on emergency repair of abdominal wall hernia therefore do not recommend the use of synthetic meshes in contaminated fields [136].

Biological prosthesis (BP) has been designed to perform as permanent surgical prosthesis in the abdominal wall repair, minimizing mesh-related complications [137]. The rationale of their usage in OA is based on the premise that the implantation of a biologic material triggers a cascade of events leading to new healthy tissue deposition and prosthesis remodeling. The presence of vital tissue therefore allows for perfusion and a native immune response preventing mesh infection and abscess formations. The ideal BP will also maintain mechanical characteristics of a synthetic mesh with a sufficient mechanical strength to withstand the physiological and anatomic stresses of the human abdominal wall. Such an ideal BP should also tolerate adjunctive NPWT to facilitate wound healing, granulation, and skin closure [100, 138].

Discordant data have been published about the use of BP to bridge a wide defect of the abdominal wall. The evidence is limited with few studies, all non-randomized, and with an overall small number of cases. Further among heterogeneous patients reported, recurrence rates have ranged between 0 and 100% [139–152]. When used as a bridge to close the fascia defect, the reported recurrence rate in a large retrospective series was >80% [153]. Another study by Booth and colleagues compared primary fascia closure with mesh reinforcement with the use of the mesh as a bridge and demonstrated a higher recurrence rate in the mesh in a bridge position (8 vs. 56%, p < 0.001) [154].

Several studies investigated the best anatomical position in terms of BP function, but were not specifically focused on OA reconstruction. Nonetheless, evidence, including that from randomized trials, suggest that implanting the BP in the sublay position results in a lower recurrence and complication rate [155–157]. However, it should be stressed that the data included was not specific for the OA situation and the heterogeneity among patients and indications was very high, resulting in a poor level of evidence.

Two meta-analyses exist on BP in abdominal wall defect. The first, by Sharrock et al. investigated the management and closure of OA in trauma patients [128]. Among the included studies, the point estimate recurrence rate of ventral hernia after 1 year of BP positioning was 51%. However, the authors highlighted the small number of included studies and their poor quality; moreover, as above mentioned, great differences exist between trauma and septic patients and great caution should be addressed in interpretation of this result.

A systematic review and meta-analysis by Atema et al. [129] investigated the utilization of BP in abdominal wall reconstruction; the poor quantity and quality of available data strongly limits the results. Biological material in infected fields had a recurrence rate of 30% compared with 7% of synthetic material, but data were derived from a single study and does not justify the use of synthetic materials, especially as a bridge position after OA.

In conclusion, no definitive evidence-based conclusions could be obtained currently from the literature. The
available evidence is really weak: most of the cited meta-
analysis included rather poor quality retrospective case
series. There is also great heterogeneity among the indica-
tions for mesh implantation, the anatomic positioning of
the mesh, and the type of mesh. This further weakens the
quality of the evidences. Thus, well-performed random-
ized trials comparing different type of meshes and the
techniques of mesh positioning are urgently required.

**Best treatment for open abdomen and enter-
atmospheric fistulas**

Several clinical circumstances may contribute to the
development of entero-atmospheric fistula and few risk
factors may predict its development. Awareness of this
complication and avoidance of contributing conditions
for its development are mandatory; moreover, preemptive
measures are imperative (grade 1C).

The management of entero-atmospheric fistula should
be personalized according to standard classification and
grading system. Current different classification schemes
echo the problematic and challenging issues related to
their management (grade 1C).

The caloric intake and protein demands of patients
with entero-atmospheric fistula increase; the nitrogen
balance should be corrected and protein supplemented.
Nutrition should be started immediately upon recogni-
tion of entero-atmospheric fistula (grade 1C).

Entero-atmospheric fistula effluent isolation is essential
for proper wound healing. Separating the wound into dif-
ferent compartments in order to facilitate the collection
of fistula output is of paramount importance (grade 2A).

Many methods for wound care exist; however, in the
presence of entero-atmospheric fistula in an open abdo-
men, negative pressure wound therapy makes effluent iso-
lation feasible and wound healing conceivable (grade 2A).

Definitive management of entero-atmospheric fistula
should be delayed to after the patient has recovered and
the wound completely healed (grade 1C).

Enteric fistula is a severe complication following ab-
dominal surgery. The opening of a fistula onto dehisced
wound therefore exposing and communicating the bowel
and its effluent to the atmosphere is defined as EAF.
The incidence of EAF varies from 4.5 to 25% in the
trauma setting [158] and from 5.7 and 17.2% in non-
trauma patients [105]. The presence of this complication
dramatically increases considerably mortality, length of
stays, and costs [159].

Many factors may contribute to the development of
EAF. All linked as a “vicious cycle”: the lack of overlying
soft tissue, with its blood supply, precludes spontaneous
healing and the exposed viscera predispose to additional
disruptions in the gastrointestinal tract. EAFs may result
from various etiologies: anastomotic dehiscence or dis-
ruption, iatrogenic injury during dissection or inappro-
priate handling, and presence of synthetic prosthetic
material (i.e., mesh) and from the prolonged exposure of
bowel [160–163]. ACS and severe IAH may result in re-
duced bowel blood supply and therefore contribute to
EAF development [68]. A prospective analysis of 517
trauma emergency laparotomies showed that large bowel
resections, large volume fluid resuscitation (>5 L/24 h),
and increased number of re-explorations were signifi-
cantly associated with an increased incidence of EAF.
Few studies suggest that octreotide may reduce fistula output by diminishing GI secretions [177] while others argue their benefit due to this agents’ reduction in splanchnic blood flow and reduction in immune function [178, 179].

The main goal in the management of EAF should be the closure of the fistula. Differently from common GI fistulas, the EAF is not a true fistula since a fistula tract does not exist. The lack of surrounding tissues prevents the spontaneous closure. The goal of the treatment should be focused on trying to isolate the fistula effluent and enhancing the formation of granulation tissues surrounding it. Several different techniques were described and proposed in the literature to control and treat EAF, and some attempts to standardize its management exist [169, 170]. A patient diagnosed with EAF in the setup of OA should be treated by medical personnel familiar with this complication and its consequences.

Accurate fistula definition and anatomy should be made. Sepsis control and management is important. Diversion of the fistula output in order to maintain clean the peritoneal cavity is mandatory. Fistula effluent should be measured in order to facilitate fluid balance and to ensure skin protection from its digestive nature on the skin. This will enhance and allow better patient care and mobility.

Several different dressing and techniques were described for the management of EAF, each one with relatively small case series and discordant results with a consequent poor level of evidence [162, 170, 180–183]. Proposed treatments vary from primary suture and fibrin glue for small exposed distal fistula to a fistula suspension fixing the fistula edges to the skin. Several variants of NPWT with devices for fistula isolation and diversion were described with promising outcomes.

The several techniques are described in detail elsewhere and are not in the scope of the current position paper [170]. The described method to manage NPWT in patients with EAF in the setup of OA should be applied depending on surgeon preference, skills, and expertise and according to hospital facilities and material availability. Generally, negative pressure wound therapy, with specifically described variants, is the most accepted technique. EAF isolation and proper wound management will enable skin grafting and converting EAF to a more controllable one with ease of applying effluent collection bag. The definitive treatment, i.e., closure of the fistula and repairing the abdominal wall defect should be postponed at least 6 months and only after the patient and the wound healed completely.

**Nutritional support**

*Open abdomen patients are in a hyper-metabolic condition; an immediate and adequate nutritional support is mandatory (grade 1C).*
Open abdomen techniques result in a significant nitrogen loss that must be replaced with a balanced nutrition regimen (grade 1C). Early enteral nutrition should be started as soon as possible if the gastrointestinal tract allows (grade 1C). Enteral nutrition should be delayed in patients with high output fistula with no possibility to obtain feeding access distal to the fistula (grade 2C). Oral feeding is not contraindicated; whenever its possible, it could be started as soon as the patient is able to eat (grade 2C).

The hyper-catabolic state of critically ill patients is associated with muscle proteolysis, acute protein malnutrition, immune function impairment, and subclinical development of MOF. Several studies clearly demonstrated malnutrition as a fundamental risk factor associated to poor outcomes during hospital stay [184]. Furthermore, in a critically ill patient, OA leads to significant nitrogen loss estimated to be 2 g per liter of abdominal fluid output. This issue requires adequate consideration and an adjusted integration [185]. For this reason, the measurement of the abdominal fluid loss is mandatory [185]. This loss in nitrogen and protein is further greatly increased in the presence of EAF. A particular attention must be given to this critical aspect because patients with OA are the sickest, most inflamed, and subsequently most hypermetabolic among surgical patients. During the OA patient management, once the resuscitation is almost completed and the GI tract allows it, EN should be started as soon as possible. Thus, it will bring beneficial effects for the patient as faster fascia closure and lower pneumonia and fistula rate [173, 186, 187]. If malnutrition occurs, mucosal atrophy and malabsorption are among the earliest consequences. Gut-associated lymphoid tissue seems to be diminished, and as a consequence, it can increase the risk for disseminated infection due to bacterial translocation through the intestinal wall [188]. EN helps in maintaining gut mucosal barrier in good shape and function; as a consequence, it has been demonstrated to enhance immunity and IgA secretion, to prevent muscle atrophy, and lastly to decrease systemic inflammation and oxidative injury [188, 189]. Early EN within the first 24–48 h is demonstrated to improve wound healing, decrease catabolism, preserve GI tract integrity, and finally, it reduces complications, length of hospital stay, and costs. Compared to TPN early EN decreases septic complications especially in abdominal trauma and traumatic brain injuries. A retrospective, single-institution study comparing DCS interventions with open abdomen performed to treat ACS, 43 patients underwent early (<4 days) and 35 late (>4 days) EN. Early EN significantly increased primary closure (74% vs. 49%), reduced the fistula rate (9% vs. 26%) with no difference in infections and but with a significant reductions in hospitalization costs [186].

Patient mobilization
To date, no recommendations can be made about early mobilization of patients with open abdomen.

Patients with an open abdomen generally should not be mobilized out of bed until their abdomens are definitively closed, for risk of evisceration [190]. This statement was extrapolated from trauma literature [191]. However, prolonged bed rest is associated with significant increase in complication rate. More recent attention has been focused on intensive care unit (ICU)-acquired weakness and the long-term adverse functional sequelae for ICU survivors, particularly in the physical domain and this has led to an increased interest in early mobilization in the ICU as a potential means of prevention [192–196]. The optimal timing for initiation of mobilization of patients with OA has yet to be defined. Early mobilization is currently defined as occurring within the first 2 to 5 days of ICU admission [197].

Patients with open abdomen managed with NPWT however, may be mobilized by active or passive transfer. Further research must occur to provide the rationale to early mobilization prior to definitive abdominal closure.

Conclusions
Management of the open abdomen remains a very controversial domain, in which many techniques are still debated. Many important issues remain to be addressed through carefully designed and rigorously conducted studies. Until better data is available, the use of the OA should be carefully tailored to each single patient taking care to not overuse this effective tool. Every effort should be exerted to attempt abdominal closure as soon as the patient can physiologically tolerate it. Finally, all the precautions should be considered to minimize the complication rate.

Abbreviations

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**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Competing interest**

Manu LNG Malbrain is Founding President and current Treasurer of the Abdominal Compartment Society (WSACS, www.wsacs.org). He is also a member of the executive committee of the International Fluid Academy (IFA). The IFA is integrated within the not-for-profit charitable organization member of the executive committee of the International Fluid Academy Abdominal Compartment Society (WSACS, www.wsacs.org). He is also a Manu LNG Malbrain is Founding President and current Treasurer of the

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2016 WSES guidelines on acute calculous cholecystitis


Abstract

Acute calculus cholecystitis is a very common disease with several area of uncertainty. The World Society of Emergency Surgery developed extensive guidelines in order to cover grey areas. The diagnostic criteria, the antimicrobial therapy, the evaluation of associated common bile duct stones, the identification of “high risk” patients, the surgical timing, the type of surgery, and the alternatives to surgery are discussed. Moreover the algorithm is proposed: as soon as diagnosis is made and after the evaluation of cholecodocholithiasis risk, laparoscopic cholecystectomy should be offered to all patients exception of those with high risk of morbidity or mortality. These Guidelines must be considered as an adjunctive tool for decision but they are not substitute of the clinical judgement for the individual patient.

Keywords: Acute calculous cholecystitis, Diagnosis, Cholecystectomy, Biliary tree stones, Surgical risk, Gallbladder percutaneous drainage, Endoscopic ultrasound, Magnetic resonance, Antibiotic, Abdominal infections

Background

Gallstones are common and present as acute calculus cholecystitis (ACC) in 20 % of patients with symptomatic disease, with wide variation in severity. In developed countries, 10–15 % of the adult population is affected by gallstones. According to the third National Health and Nutrition Examination Survey, 6.3 million men and 14.2 million women aged 20 to 74 in the United States had gallbladder disease [1–5]. In Europe, the Multicenter Italian Study on Cholelithiasis (MICOL) examined nearly 33,000 subjects aged 30 to 69 years in 18 cohorts of 10 Italian regions. The overall incidence of gallstone disease was 18.8 % in women and 9.5 % in men [6]. However, the prevalence of gallstone disease varies significantly between ethnicities. Biliary colic occurs in 1 to 4 % annually [1, 7–9]. ACC occurs in 10 to 20 % of untreated patients [9]. In patients discharged home without operation after ACC, the probability of gallstone related events is 14, 19, and 29 % at 6-weeks, 12 weeks, and at 1 year, respectively. Recurrent symptoms involve biliary colic in 70 % while biliary tract obstruction occurs in 24 % and pancreatitis in 6 % [10]. Despite the relevant frequency of ACC, significant controversies remain regarding the diagnosis and management of ACC. The 2007 and 2013 Tokyo guidelines (TG) attempted to establish objective parameters for the diagnosis of ACC [11, 12]. However debates continue in the diagnostic value of single ultrasound (US) signs, as well as of laboratory tests. With regard to the treatment of ACC, historically, the main controversies were around the timing of surgery. The need for surgery as compared to conservative management has been less investigated, particularly in high surgical risk patients. The other major disagreements include: method and need to diagnose potential associated biliary tree stones during ACC, treatment options, type of surgery, definition and management of high surgical risk patients (with clarification of the role for cholecystostomy).

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While the TG have certainly improved the understanding of ACC, some criticisms have followed [13, 14]. Indeed, the references in the TG are outdated for some recommendations; the ACC scoring system has not been validated and it does not distinguish between suspected gallbladder inflammation and systemic signs of ACC. Finally, the conclusions are not clear because all the different therapeutic options are available for the same “cholecystitis severity grade”. For these reasons the World Society of Emergency Surgery (WSES) decided to convene a consensus conference (CC) to investigate these controversies and define its guidelines regarding diagnosis and treatment of ACC.

Material and methods: consensus conference organizational model

On August 2013 the Scientific Board of the 2nd World Congress of the World Society of Emergency Surgery (WSES), endorsed its president, to organize the CC on ACC in order to develop the WSES Guidelines on this topic. The WSES President appointed four members to a Scientific Secretariat, eight members to an Organization Committee and eight members to a Scientific Committee, choosing them from the expert affiliates of WSES. Eight relevant key questions regarding diagnosis and treatment of ACC (reported in Table 1) were developed to thoroughly analyse and fully cover the topic. Under the supervision of the Scientific Secretariat, a bibliographic search related to these questions was performed by an expert library documentarist (medical library of Papa Giovanni XXIII Hospital of Bergamo, Italy), who provided the results of the electronic search of PubMed and EMBASE through May 2015 without time or language restriction. The key words used for the electronic search are listed in Table 1. An additional manual bibliography search was performed by each of the members of the working groups involved in the analysis of the above mentioned eight questions. Before the CC, a number of statements were developed for each of the main questions, along with the Level of Evidence (LoE) and the Grade of Recommendation (GoR) for each statement. The 2011 Oxford Classification was used to grade the LoE and GoR (available at http://www.cebm.net/explanation-2011-oecmb-levels-evidence/) Provisional statements and their supporting evidence were then submitted for review to all the participating members of the CC and to the WSES board members by email before the CC. Modifications were performed when necessary based on feedback.

The CC on ACC was held in Jerusalem, Israel, on July 6th, 2015 during the 3rd World Congress of the WSES. During the first part of the CC, a member of each group presented each of the statements along with LoE, GoR, and the literature supporting each statement. Each statement was then voted upon by the audience in terms of “agree” or “not agree” using an electronic voting system. The percentage of agreement was recorded immediately; in case of disagreement greater than 30%, the statement was modified after discussion. Furthermore, comments for each statement were collected; the results of vote are available in Appendix 1. Before the second part of the CC, the president and representatives from the Organization Committee, Scientific Committee and Scientific Secretariat modified the statements according to the findings of the first session of the CC. The revised statements were then presented again to the audience. During the CC, a comprehensive algorithm for the treatment of ACC was developed based on the results of the first session of the CC and voted upon for definitive approval (Fig. 1). Simple

Table 1 Key questions and key words used to develop the Consensus Conference on Acute Calculous Cholecystitis (ACC)

<table>
<thead>
<tr>
<th>Key questions</th>
<th>Key words</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Diagnosis of ACC: investigations.</td>
<td>Acute calculous cholecystitis Diagnosis, Ultrasound, Gallstones disease diagnosis.</td>
</tr>
<tr>
<td>3) Antibiotic therapy for ACC.</td>
<td>Antibiotics,Acute calculous cholecystitis, Gallstone disease, Management Gallstones.</td>
</tr>
<tr>
<td>4) Patient selection for surgery: risk stratification i.e. definition of high risk patients</td>
<td>Acute calculous cholecystitis, Gallstone disease, Surgical risk score, High risk patient, old patient, PPOSsum score, Apache score.</td>
</tr>
<tr>
<td>5) Timing for surgery for ACC</td>
<td>Acute calculous cholecystitis, acute cholecystitis</td>
</tr>
<tr>
<td>6) Type of surgery for ACC</td>
<td>Acute calculous cholecystitis, Surgery, Laparoscopy, Laparatomy, Cholecystectomy, Partial cholecystectomy, Subtotal cholecystectomy, Cirrhosis, Pregnancy</td>
</tr>
<tr>
<td>7) Associated common bile duct stone: suspicion and diagnosis at the presentation</td>
<td>common bile duct stone; choledocholithiasis; endoscopic ultrasound, MRCP, ERCP.</td>
</tr>
<tr>
<td>8) Alternative treatments for high risk patients</td>
<td>Acute calculous cholecystitis, Surgery, Gallbladder Drainage, Percutaneous gallbladder drainage, Cholecystostomy, High Risk Patient</td>
</tr>
</tbody>
</table>
statements along with their LoE and GoR are available in Appendix 2. Meanwhile all statements are reported in the following Results section, subdivided by each of the eight questions, with the relative discussion and supportive evidence.

These Guidelines must be considered as an adjunctive tool for decision but they are not substitute of the clinical judgement for the individual patient.

Results

Diagnosis: investigations

Although ACC is a common disease encountered in the Emergency Department, its diagnosis remains a major challenge. Different diagnostic criteria have been reported in the literature as indicated in the development of the TG [12]. Evidence of an inflamed gallbladder containing stones is the cornerstone for an appropriate diagnosis. The diagnosis of ACC is based on clinical findings, laboratory data, and imaging studies.

Statement 1.1 There is no single clinical or laboratory finding with sufficient diagnostic accuracy to establish or exclude acute cholecystitis (LoE 2 GoR B). Combination of detailed history, complete clinical examination, and laboratory tests may strongly support the diagnosis of ACC (LoE 4 GoR C)

A systematic review and meta-analysis of the role of different clinical signs and bedside tests in the diagnosis of ACC included 17 studies in which quantitative assessment of diagnostic values of clinical tests were reported [15]. Twelve variables related to history and clinical examination, 5 variables related to basic laboratory tests, and one variable which was a combination of a clinical sign and a laboratory test were tested in a cohort of patients with abdominal pain or suspected acute cholecystitis. Results showed that with the exception of Murphy’s sign, none of the summary positive likelihood ratios (LR) of the clinical test was higher than 1.6 and none of the summary negative LR was less than 0.4. Murphy’s sign had a positive LR of 2.8 (CI 95 % 0.8 to 8.6) and a negative LR of 0.5 (CI 95 % 0.2 to 1) but the 95 % CI included the value 1. Although the study was classified as one of high quality according to the Oxford classification, it presents some limitations. The study did not report the proportion of patients with abdominal pain and the proportion of patients with suspected acute cholecystitis. Although LR is robust to assess the prevalence, the inclusion of patients with abdominal pain together with patients having suspicion of acute cholecystitis, may be a source of heterogeneity since different pre-test probabilities may be associated with each, modifying the LRs values as a result. Furthermore, reference standards for the definitive diagnosis of acute cholecystitis varied in different studies; this might introduce further bias in the results due to inadequate reference standards. Finally, both ACC and acute acalculous cholecystitis had been included as target condition in this review; the results may have been different if ACC alone had been included as the target condition. In a different prospective diagnostic study, findings from history, clinical examination, and
laboratory tests were evaluated in a large cohort of patients complaining abdominal pain [16]. The diagnostic accuracy of a total of 22 variables from the history, clinical symptoms, 15 signs from clinical examinations, and two laboratory tests were evaluated with a reported positive LR of 25.7 and a negative LR of 0.24. The diagnosis was based on the combination of clinical tests without providing details on how such clinical tests had been combined. The study may have a lower strength of evidence, but it refers to a large prospective study including more than 1300 patients.

Statement 1.2 Abdominal ultrasound (AUS) is the preferred initial imaging technique for patients who are clinically suspected to have ACC because of its lower cost, better availability, lack of invasiveness, and high accuracy for gallbladder stones (LoE 2 GoR B)

Widespread availability, lack of invasiveness, lack of exposure to ionizing radiation, and a short period of examination are the characteristics that make AUS the first choice imaging investigation for the diagnosis of ACC [17]. To reach the diagnosis of ACC, two conditions must be satisfied: the presence of gallbladder stones and presence of inflammatory changes in the gallbladder wall. There is no doubt that AUS is the best available investigation for the first condition. A meta-analysis by Shea strongly supports this statement. Pooled sensitivity and specificity of AUS in the diagnosis of gallstones were 84 % (95 % CI: 84–92 %) and 99 % (95 % CI: 99–100 %) respectively based on diagnostic accuracy data reported in three studies [18].

Statement 1.3 AUS exploration is a fairly reliable investigation method but its sensitivity and specificity for diagnosing ACC is relatively low according to the adopted AUS criteria (LoE 3 GoR C)

Diagnostic performance of AUS in the diagnosis of inflammation of the gallbladder is not as good as its performance in the diagnosis of gallstones, as indicated in a recent meta-analysis [17]. The meta-analysis was based on the results of 26 studies including a total of 2847 patients. The sensitivity in individual studies ranged from 50 to 100 % and specificity from 33 to 100 %; indicating some heterogeneity in the diagnostic performance of AUS. Summary sensitivity was 81 % (95 % CI: 75 to 87 %) and summary specificity was 83 % (95 % CI: 74 to 89 %). However strong heterogeneity was indicated by the inconsistency index, which was reported to be 80 % for sensitivity and 89 % for specificity. The review authors have also highlighted that 14 different definitions of positive AUS had been reported in 26 studies; the heterogeneity exploration was however reported to be inconclusive. The quality of studies was not reported to allow a firm conclusion. Two cross-sectional diagnostic accuracy studies of high quality according to the Oxford classification have been published [19, 20]. The criteria for patient selection, diagnostic criteria, reference method, and timing from diagnosis to reference method were sound and well described similarly in both studies. In the study by Hwang et al. [19] which included 107 patients, a sensitivity of 54 % (95 % CI: not reported) and a specificity of 81 % (95 % CI: not reported) were reported by using the combination of sonographic Murphy sign, gallbladder wall thickening greater than 3 mm, peri-cholecystic fluid collection as major criteria and hepatic biliary dilation and gallbladder hydrops as minor criteria. In the study by Borzellino et al [20] which included 186 patients, diagnostic criteria were assessed using a multivariate analysis. Following the multivariate analysis, distension of the gallbladder, wall oedema, and peri-cholecystic fluid collection were adopted as the criteria for the presence of ACC. The presence of at least one of these three criteria on AUS resulted in a sensitivity of 83.7 % (95 % CI: 75.1 to 89.7 %) and specificity of 47.7 % (95 % CI: 37.6 to 58 %). It appears therefore that AUS may be of limited utility to diagnose or exclude the diagnosis of acute cholecystitis according to the used ultrasound criteria.

Statement 1.4 Evidence on the diagnostic accuracy of computed tomography (CT) is scarce. While diagnostic accuracy of magnetic resonance imaging (MRI) might be comparable to that of AUS, insufficient data are available to support it. Hepatobiliary iminodiacetic acid scan (HIDA scan) has the highest sensitivity and specificity for acute cholecystitis, although its scarce availability, long time required to perform the test, and exposure to ionizing radiation limit its use (LoE 2 GoR B)

Because of the poor diagnostic performance of AUS in the diagnosis of ACC, diagnostic accuracy of other imaging modalities must be assessed. A meta-analysis by Kiewiet et al included studies on CT, MRI, and HIDA in addition to those on AUS [17]. Data on diagnostic accuracy of CT is limited. Kiewiet et al identified only one study including 49 patients. CT findings of acute cholecystitis included gallbladder distension (41 %), gallbladder wall thickening (59 %), peri-cholecystic fat density (52 %), peri-cholecystic fluid collection (31 %), sub-serosal oedema (31 %) and high gallbladder bile attenuation (24 %) [21]. Thus, there is no single CT feature which is useful in the diagnosis of ACC. Furthermore, the ionizing radiation to which patients are exposed is an issue. CT is therefore usually indicated when sonography is non-diagnostic or patients have confusing signs and symptoms [22]. Kiewiet et al included three studies on MRI including a total of 131 patients [17]. Summary sensitivity was 85 % (95 % CI: 66 to 95 %) and specificity was 81 % (95 % CI: 69 to 90 %). There was substantial heterogeneity for sensitivity (I^2 = 65 %) and no heterogeneity for specificity (I^2 = 0 %). In a head-to-head comparison, diagnostic accuracy of MRI was comparable
with that of AUS. The comparison was however based on two studies including only 59 patients; therefore, the strength of evidence is low. Kieiwiet et al included 40 studies with a total of 4090 patients undergoing HIDA scan. Summary sensitivity was 96 % (95 % CI: 94 to 97 %) and specificity 90 % (95 % CI: 86 to 93 %) with no statistically significant heterogeneity for sensitivity ($I^2 = 18 \%$) but a significant heterogeneity for specificity ($I^2 = 76 \%$). In a head-to-head comparison of HIDA with AUS based on 11 studies including a total of 1199 patients, HIDA proved to have better diagnostic accuracy than AUS. The summary sensitivity of HIDA versus AUS was 94 % (95 % CI: 90 to 97 %) and 80 % (95 % CI: 71 to 87 %) respectively with a $P$ value $< 0.001$. The summary specificity of HIDA versus AUS was 89 % (95 % CI: 84 to 92 %) and 75 % (95 % CI: 67 to 82 %) respectively with $P$ value $< 0.001$. As reported in the literature [23] and highlighted by Kieiwiet et al [17], limitation of the information about the biliary tract, the lack of availability of HIDA, and an examination time of several hours strongly shrink the use of HIDA in clinical practice.

Statement 1.5 Combining clinical, laboratory and imaging investigations is recommended, although the best combination is not yet known (LoE 4 GoR C)

Combining clinical and AUS findings may improve the diagnostic accuracy; however, studies that report results related to some clinical and imaging combination are few. Hwang et al. [19] reported a 74 % sensitivity and 62 % specificity by combining positive Murphy sign, elevated neutrophil count, and positive AUS. It is interesting to note that within this study, the sensitivity of elevated neutrophil count alone was 79 %; therefore higher than the 74 % sensitivity of combined clinical, laboratory test, and AUS signs. Furthermore, specificity of AUS alone was 81 % which was higher than 62 % reported when combined clinical, laboratory, and AUS findings were analysed.

Another study reported 97 % sensitivity and 76 % specificity by combining C-reactive protein (CRP) and AUS. However, based on the inclusion criteria, generalisability of findings may be an issue in applying the findings to routine clinical practice [24].

The study of Yokoe et al evaluated the Tokyo guidelines criteria and found a sensitivity of 91.2 % and a specificity of 96.9 % of these guidelines in the diagnosis of ACC [12]. Different clinical, laboratory, and imaging findings are combined in the Tokyo guidelines, giving a larger probability to reach the diagnosis. However, the different combinations were not defined in this report. As previously stated, generalisability of these findings to routine clinical practice may be problematic because of the inclusion criteria used in this study.

A full clinical examination should be performed and recorded. This should be combined with laboratory tests for inflammation and AUS. In case of uncertainty in AUS imaging but with a clinical suspicion of ACC, there is no definitive evidence on whether to perform a high cost although highly accurate investigation or to treat the patient empirically as if he or she had ACC.

Treatment: best options

Statement 2.1 There is no role for gallstones dissolution, drugs or extra-corporal shock wave lithotripsy (ESWL) or a combination in the setting of ACC (LoE 2 GoR B)

The opportunity to dissolve gallstones by medication or break them by ESWL, or combination of both, instead of mechanical removal, has never been tested in the setting of ACC. Strict selection is required to obtain satisfactory results from these therapeutic options: less than 5 mm stone, single stone, cholesterol gallstones, functional gallbladder, and integrity of gallbladder wall when applying external wave to the gallbladder [25]. The rate of recurrence after ESWL is 30 to 50 % at 5 years [26]. Ursodeoxycholic acid was ineffective in a large randomized, double-blind, placebo-controlled trial in patients waiting for elective cholecystectomy in the setting of biliary colic [27]. After gallstone disappearance, the persistence of the same pathogenic factors that induced gallstone formation is primarily responsible for their recurrence after nonsurgical treatments of gallstones [28].

Statement 2.2 Since there are no reports on surgical gallstone removal in the setting of ACC, surgery in the form of cholecystectomy remains the main option (LoE 4 GoR C)

The opportunity to remove the gallstones in a different way than cholecystectomy has never been tested in the acute setting and the report of this technique are very few. In 2013 Yong et al published the results of 316 consecutive laparoscopic gallbladder-preserving cholecystectomy. The simultaneous use of a choledochoscope to assess the gallbladder clearance appears to drastically reduce the rate of recurrence to 15 % compared to 70 % in the early reports of the 1980’s. The required main patient selection criteria is the functioning gallbladder; this condition is not present in ACC [29].

Statement 2.3 Surgery is superior to observation of ACC in the clinical outcome and shows some cost-effectiveness advantages due to the gallstone-related complications and to the high rate of readmission and surgery in the observation group (LoE 3 GoR C)

We found only one prospective randomized study comparing observation to surgery after ACC, published in 2011 by Schmidt [30]. The population size was 33 patients assigned to observation versus 31 assigned to surgery. After an average follow up period of 14 years, 33 % (11 patients) in the observation experienced relapse of gallstones disease (8/11: ACC) and all required surgery.
After five years the relapse of symptoms was described as negligible. Despite the value of a long follow-up, the study is underpowered as recognized by the authors themselves. Furthermore, of the eligible patients, 41.3 % were excluded for unknown reasons and the randomization methods were not reported either. Clinical Evidence in 2014 rated this study as moderate/low quality [31]. On the basis of the Shmidt study on ACC and a RCT on symptomatic but uncomplicated gallstone disease [32], Brazzelli et al. produced a clinical and cost-effectiveness analysis, comparing surgery to observation, using an UK based economic model. They found that patients randomized to observation experienced a higher rate of cholelithiasis complications (14 % versus 2 %) when compared to surgical group; this happened more frequently in patients with ACC than in those with biliary colic only. From the economic point of view, the frequency of surgery in the observational group (with the need for re-admission) slightly favoured surgery. The authors concluded with words of caution because the number of patients was small. In addition, not all aspects were analysed (e.g. abdominal pain in the long term follow up in patients underwent surgery, pain medications cost in the observational group patients, number of visit to the General Practitioner in both groups for biliary related symptoms, etc.) [33, 34].

Statement 2.4 Antibiotics should be suggested as supportive care; they are effective in treating the first episode of ACC but a high rate of relapse can be expected. Surgery is more effective than antibiotics alone in the treatment of ACC. (LoE 2 GoR C)

Although ACC is an inflammatory process at the beginning, a secondary infection can occur in the case of continuous bile stasis due to cystic duct occlusion by calculus and oedema, which can lead to sepsis. While many clinicians advocate routine administration of antibiotics in all patients diagnosed with acute cholecystitis, others restrict the antibiotics to patients likely to develop sepsis on the basis of clinical, laboratory, and imaging findings [35]. As a consequence, antibiotics constitute the primary therapy in patients undergoing delayed surgery or observation. In a meta-analysis including 9 RCT on early or delayed cholecystectomy, Papi et al. reported that of 503 patients in the delayed group, 9.3 % experienced a primary failure of antibiotics and supportive therapy and almost 15 % who initially responded suffered recurrences. The rate of unplanned surgery was 26.5 % and a total of 23 % had a failure of conservative treatment [36]. Similar results were reported later in the Cochrane review including only laparoscopic cholecystectomy by Gurusamy in 2013. Approximately, 18.3 % of patients had relapse of symptoms during the waiting period when treated by antibiotics and delayed laparoscopic cholecystectomy for ACC [37]. In 2012 de Mestral et al. published a Ontario-Canada population-based analysis between 2004 and 2011. They collected 25,397 patients with ACC. About 41 % of these patients were not operated at the index admission. Gallstone-related events were measured at 6 weeks, 12 weeks and at 1 year. The respective rates were 14, 19 and 29 %. Pancreatitis and common biliary tract obstruction accounted for 30 % of these events. Gallstone-related events were more frequent in patients aged between 18 and 34 years old [10].

Statement 2.5 Cholecystectomy is the gold standard for treatment of ACC (LoE 3 GoR C)

Statement 2.6 If surgery is not available, medications such as antibiotics and analgesic should be prescribed and the patients should be referred to a surgical center (depending upon the general condition) due to the high rate of gallstone-related events (LoE 5 GoR D)

Non-surgical options (such as gallbladder drainage) can be considered in surgical high risk patients. The role of non-surgical options will be analysed in a different section.

Antibiotic therapy

Therapy with appropriate antimicrobial agents is an important component in the management of patients with ACC [38, 39]. Antibiotics are always recommended in complicated cholecystitis and in delayed management of uncomplicated cholecystitis.

Statement 3.1 Patients with uncomplicated cholecystitis can be treated without post-operative antibiotics when the focus of infection is controlled by cholecystectomy (LoE 1 GoR B)

In a recently published prospective randomised controlled trial [40], a total of 414 patients treated at 17 medical French centres for grade I or II ACC and who received 2 g of amoxicillin plus clavulanic acid three times a day and once at the time of surgery were randomized after surgery to an open-label, non-inferiority, randomized clinical trial between May 2010 and August 2012. Patients were randomized to either no antibiotics after surgery or continuation with the preoperative antibiotic regimen three times daily for 5 days. An imputed intention-to-treat analysis of the 414 patients showed that the postoperative infection rates were 17 % (35/207) in the non-treatment group and 15 % (31/207) in the antibiotic group (absolute difference, 1.93 %; 95 % CI, -8.98 to 5.12 %). In the per-protocol analysis, which involved 338 patients, the corresponding rates were both 13 % (absolute difference, 0.3 %; 95 % CI, -5.0 to 6.3 %). Among patients with mild or ACC who received preoperative and intra-operative antibiotics, lack of postoperative treatment with amoxicillin plus clavulanic acid did not result in a greater incidence of postoperative infections.
The choice of the antimicrobial regimen may be problematic in the management of critically ill patients with ACC. In patients with severe sepsis or septic shock of abdominal origin, early correct empirical antimicrobial therapy has a significant impact on the outcome [47]. In a prospective observational study involving 180 consecutive patients with secondary generalized peritonitis, Riché et al. [48] demonstrated a significantly higher mortality rate in septic shock than in those without septic shock (35 versus 8%).

Recent international guidelines for the management of severe sepsis and septic shock (Surviving Sepsis Campaign) [49] recommend broad-spectrum intravenous antibiotics with good penetration into the presumed site of infection within the first hour. In the event of biliary sepsis, drug pharmacokinetics may be altered significantly in patients with severe sepsis and septic shock. Dosage of antibiotics should be reassessed daily, based on both the pathophysiological status of the patient and the pharmacokinetic properties of the employed antibiotics [50].

**Statement 3.3 The results of microbiological analysis are helpful in designing targeted therapeutic strategies for individual patients to customize antibiotic treatment and ensure adequate antimicrobial coverage in patients with complicated cholecystitis and at high risk for antimicrobial resistance. (LoE 3 GoR C)**

Identifying the causative organism(s) is an essential step in the management of ACC, especially in patients at high risk for antimicrobial resistance such as healthcare-associated infections. It has been reported that positive rates of either bile or gallbladder cultures range from 29 to 54% for acute cholecystitis [51–58]. In Table 3 are reported the antimicrobial regimens suggested for ACC.

**Patient selection for surgery: risk stratification (i.e. definition of high risk patients)**

ACC is a heterogeneous condition. The severity of inflammation and its life-threatening potential is strongly determined by the general status of the patient. It could be argued that alternative treatment to early cholecystectomy could be of benefit for patients with reduced functional reserve. Our search reviewed the available literature to identify the parameters to stratify the risk of surgery in this population and verify if there is any available method to select the best course of action in selected high-risk groups.

**Statement 4.1 Patient’s age above 80 in ACC is a risk factor for worse clinical behaviour, morbidity and mortality. (LoE 3 GoR B)**

Several studies identify old age as a perioperative risk factor for cholecystectomy. However, it is not clear if early laparoscopic cholecystectomy is the best treatment...
option for elderly patients with ACC. In the retrospective cohort study by Kirshtein et al, the age groups above and below 75 showed a significant difference in mortality (4.8 % versus 0.5 %), morbidity (31 % versus 15 %), and average hospital stay (3.9 versus 2.8) [59]. A recent study by Nielsen et al reported that the odds ratio for mortality in ACC patients older than 80 years with low anaesthetic risk (American Score of Anaesthesiologist I-II (ASA) was significantly higher than in the age groups of 65 to 79 and 50 to 64 (30.9 % vs 5.5 % vs 1 %) [60]. According to Girgin et al, patients’ age, Mannheim peri-tornitis index ≥29, and co-morbidities are significantly related to morbidity, while increased age and low WBC count are significantly related to mortality in gangrenous cholecystitis [61]. In the case series by Lupinacci et al, mortality of patients older than 80 years was 34.2 % in urgent cholecystectomy versus 0 % in both the elective and semi-elective groups. Statistically significant differences were also demonstrated in morbidity and length of hospital stay. However, the study showed a significantly higher incidence of patients with ASA score of III and IV in the urgent cholecystectomy group (76 % versus 25.6 % versus 28.6 %), and a notably lower number (20 % versus 81.3 % versus 82.8 %) of laparoscopic cholecystectomies [62].

Few retrospective cohort studies compare the outcome of early versus delayed cholecystectomy in aged ACC patients. They fail to demonstrate a significant difference in mortality and postoperative complications [63–66]. A study by Cull et al showed that recurrent episodes of pancreatitis, cholecystitis, and cholangitis were significantly less likely after early than delayed cholecystectomy, irrespective of whether delayed cholecystectomy was preceded by percutaneous cholecystostomy [65]. These findings confirmed the results of a recent population-based analysis on a sample of the Medicare Claims Data System. In this analysis, a lack of a definitive surgical treatment at the index admission in an aged population is associated with 38 % gallstone-related readmission rate in two years versus 4.4 % in similar patients who had early cholecystectomy [67].

### Table 3 Antimicrobial regimens suggested for acute calculous cholecystitis

<table>
<thead>
<tr>
<th>Community acquired</th>
<th>Health-care associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Beta-lactam/beta-lactamase inhibitor combinations based regimens AMOXICILLIN/CLAVULANATE (in stable patients) TICARCELLIN/CLAVULANATE (in stable patients) PIPERACILLIN/TAZOBACTAM (in unstable patients)</td>
<td>TIGECYCLINE + PIPERACILLIN/TAZOBACTAM (in stable patients) IMIPENEM/CLISTATIN +/- TEICOPLANIN (only in unstable patients) MEROPENEM +/- TEICOPLANIN (only in unstable patients)</td>
</tr>
<tr>
<td>2) Cephalosporins based regimens CEFTRIAZONE + METRANIDAZOLE (in stable patients) CEFEPIME + METRANIDAZOLE (in stable patients) CEFTAZIDIME + METRANIDAZOLE (in stable patients)</td>
<td>DORIPENEM +/- TEICOPLANIN (only in unstable patients)</td>
</tr>
<tr>
<td>3) Carbapenem based regimens ERTAPENEM (in stable patients) IMIPENEM/CLISTATIN (only in unstable patients) MEROPENEM (only in unstable patients) DORIPENEM (only in unstable patients)</td>
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<td>4) Fluoroquinolone based regimens (In case of allergy to beta-lactams) CIPROFLOXACIN + METRONIDAZOLE (only in stable patients) LEVOFLOXACIN + METRONIDAZOLE (only in stable patients) MOXIFLOXACIN (only in stable patients)</td>
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<tr>
<td>5) Glycylcycline based regimen TIGECYCLINE (in stable patients if risk factors for ESBLs)</td>
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Statement 4.2 The co-existence of diabetes mellitus does not contraindicate urgent surgery but must be re-considered as a part of the overall patient comorbidity (LoE 3 GoR C)

In 1995, Shpitz et al showed a greater incidence of cardiovascular disease and associated bacterobilia in diabetics who underwent urgent cholecystectomy for ACC; however, they did not report a significant difference in the postoperative outcome [68]. A recent analysis of a large ACC cholecystectomy series from the American College of Surgeons National Surgical Quality Improvement Program database demonstrated that diabetes increased the risk of mortality (4.4 % versus 1.4 %, adjusted odds ratio (OR) 1.79 (95 % CI: 1.09 to 2.94), adjusted P value = 0.022), cardiovascular events (2.3 versus 0.5 %; OR 2.50 (95 % CI: 1.25 to 4.99); adjusted P value = 0.010), and renal failure (2.5 versus 0.3 %; OR 3.91 (95 % CI: 1.82 to 8.40); adjusted P value = 0.001) [69]. A second study on the same series showed that delay in surgery in diabetic patients was associated with significantly higher odds of developing surgical site infections and a longer hospital stay. The same findings were not found in the non-diabetic
patients of the same series [70], suggesting that a prompt course of action is appropriate in diabetics.

Statement 4.3 Currently, there is no evidence of any scores in identifying patient’s risk in surgery for ACC. ASA, POSSUM and APACHE II are correlated to surgical risk in patients with gallbladder perforation, higher accuracy being for APACHE II. However, APACHE II is built to predict morbidity and mortality in the patients admitted to ICU: its use as a preoperative score should be considered as an extension usage from the original concept. (LoE 4 GoR C).

Therefore, prospective and multicentre studies to compare different risk factors and scores are necessary

None of the available clinical scores for the evaluation of surgical risk for acute conditions has been validated for ACC. Recently, the Tokyo guidelines attempted to address the heterogeneity of the ACC population with a therapeutic algorithm that includes some elements of risk stratification. They suggest a staging system based upon severity assessment criteria such as degree of local inflammation and patient conditions, without including any of the most commonly adopted risk stratification scores [71]. However, their classification lacks a clinical validation and has not been validated by studies showing an improved outcome after its introduction. In fact, a retrospective series failed to find any significant benefit [13]. In 2006, Yi et al stratified the risk in relation to the ASA score. The study shows a significant difference in morbidity (20% versus 9.1%) in patients in ASA III vs ASA I, with no significant difference in the conversion rate, recovery time or hospital postoperative stay [72]

The only available comparison of risk assessment scores (ASA, APACHE II and POSSUM) is limited to series of perforated ACC. The study highlights a significant association of the three scores with morbidity and mortality. Both POSSUM and APACHE II were superior to ASA in risk prediction [73]. Finally, we would like to point out that the usefulness of any score is to add but not to trump surgical judgement: in other words not all patient variables (e.g. recent coronary stent or recent pulmonary embolism, etc.) will be included in any score.

Timing for surgery: what is early cholecystectomy?

Several randomised controlled trials have investigated early laparoscopic cholecystectomy versus delayed laparoscopic cholecystectomy [74–82].

Early and delayed laparoscopic cholecystectomy have been defined differently in different trials. In general, early laparoscopic cholecystectomy has been defined variably as that performed in patients with acute cholecystitis with symptoms less than 72 h or symptoms less than 7 days but within 4 to 6 days of diagnosis. This roughly translates to 10 days from onset of symptoms. The delayed laparoscopic cholecystectomy is defined variably as that performed between 7 days to 45 days and that performed at least 6 weeks after initial diagnosis.

Statement 5.1 Early laparoscopic cholecystectomy is preferable to delayed laparoscopic cholecystectomy in patients with ACC as long as it is completed within 10 days of onset of symptoms (LoE 1 GoR A)

Different patients were included in the trial and the definitions of early laparoscopic cholecystectomy used by these trials comparing early laparoscopic cholecystectomy versus delayed laparoscopic cholecystectomy performed within 6 weeks after initial diagnosis were different in various studies. Six trials provided clinical results. Overall, the systematic review and meta-analysis of randomised controlled trials which included clinical data from five of these six trials demonstrated no significant difference in the complication rate or conversion to open cholecystectomy between early and delayed laparoscopic cholecystectomy and a hospital stay which was statistically shorter by 4 days in the early laparoscopic cholecystectomy group compared to the delayed laparoscopic cholecystectomy group [37]. One trial which was not included in the systematic review also showed similar results as the systematic review (i.e. there was no significant difference in the complication rate between early and delayed laparoscopic cholecystectomy and the hospital stay was shorter by 4 days in the early laparoscopic cholecystectomy group compared to the delayed laparoscopic cholecystectomy group) despite including participants with symptoms > 72 h [81].

Statement 5.2 Laparoscopic cholecystectomy should not be offered for patients beyond 10 days from the onset of symptoms unless symptoms suggestive of worsening peritonitis or sepsis warrant an emergency surgical intervention. In people with more than 10 days of symptoms, delaying cholecystectomy for 45 days is better than immediate surgery (LoE 2 GoR B)

One trial compared early laparoscopic cholecystectomy versus delayed laparoscopic cholecystectomy performed between 7 days and 45 days after initial diagnosis [83]. In this trial, the duration of symptoms in the participants was not reported. Early laparoscopic cholecystectomy was performed within 24 h of admission while delayed laparoscopic cholecystectomy was performed between 7 days and 45 days. This trial demonstrated that the morbidity was higher in the delayed laparoscopic cholecystectomy compared to early laparoscopic cholecystectomy group and the length of hospital stay was 5 days longer in the delayed laparoscopic cholecystectomy group compared to early laparoscopic cholecystectomy group [83]. There was no significant difference in the conversion to open cholecystectomy between the two groups [83].
Statement 5.3 Early laparoscopic cholecystectomy should be performed as soon as possible but can be performed up to 10 days of onset of symptoms. (Level 1 Evidence; Grade A recommendation). However, it should be noted that earlier surgery is associated with shorter hospital stay and fewer complications (LoE 2 GoR B)

One randomised controlled trial compared early laparoscopic cholecystectomy as soon as surgical schedule allows with early laparoscopic cholecystectomy after resolution of symptoms but within 5 days of admission [74] in patients with ACC. The duration of symptoms prior to admission was not reported in this trial. There was no statistically difference in the complication rate or conversion to open cholecystectomy between patients who underwent surgery as soon as the scheduling allowed compared to those who underwent surgery after resolution of symptoms but within 5 days of admission [74]. However, the length of hospital stay was shorter in patients who underwent surgery as soon as the scheduling allowed compared to those who underwent surgery after resolution of symptoms but within 5 days of admission within 2 days of admission had fewer complications than those who underwent surgery between 2 and 5 days of admission, and those who had surgery between 6 days and 10 days of presentation. There was no significant difference in the groups between conversion to open surgery [84]. Finally, several studies suggest that cholecystectomy performed as soon as possible, especially in the scenario of an Acute Care Surgery Service, is cost-effective [83, 85, 86].

Type of surgery

Statement 6.1 In ACC, a laparoscopic approach should initially be attempted except in case of absolute anaesthesiology contraindications or septic shock (LoE 2 GoR B)

According to Tokyo Guidelines 2013 (TG13), laparoscopic cholecystectomy is now accepted as a safe surgical technique when it is performed by expert surgeons even in the setting of ACC. TG13 described the surgical treatment of ACC according to the degree of severity of the disease. Early laparoscopic cholecystectomy is indicated for patients with Grade I (Mild) ACC. Early laparoscopic cholecystectomy is indicated also for patients with Grade II (Moderate) ACC in experienced centers, but in the case of severe signs of local inflammation (WBC >18.000; a palpable tender mass in the right upper quadrant and >72 h from the onset) should be indicated a conservative treatment with gallbladder drainage followed by a delayed cholecystectomy. For patients with severe local complications such as biliary peritonitis, emphysematous cholecystitis, gangrenous cholecystitis and purulent cholecystitis, emergency surgery is conducted (open or laparoscopic) along with the usual supportive measures. For Grade III (Severe) ACC, TG13 suggest gallbladder drainage and delayed cholecystectomy after improvement of general clinical conditions [71]. Some Scientific Societies also support, more strongly than TG13, laparoscopic cholecystectomy in ACC as the first line approach [87–89].

Statement 6.2 Laparoscopic cholecystectomy for ACC is safe, feasible, with a low complication rate and associated with shortened hospital stay (LoE 1 GoR A)

Although Borzellino et al. in their meta-analysis suggested that laparoscopy is not indicated for all cases of ACC due to the difficulty of cholecystectomy in patients with severe inflammation [90], several recent case control, randomized clinical trials have compared laparoscopic cholecystectomy to open cholecystectomy in ACC [91–100]. A recently published meta-analysis demonstrated that laparoscopic cholecystectomy in ACC is the preferable approach with lower mortality and morbidity, significantly shorter post-operative hospital stay and reduced rate of pneumonia and wound infections, compared to the open technique. Conversion rate ranged from 8 to 35% [101].

Statement 6.3 Among high-risk patients, in those with Child A and B cirrhosis, advanced age >80, or pregnant women, laparoscopic cholecystectomy for ACC is feasible and safe (LoE 3 GoR C)

Some studies suggested that laparoscopic cholecystectomy should be the first line approach in specific categories of patients such as the elderly or pregnant women [102, 103]. According to meta-analysis published by de Goede et al., elective laparoscopic cholecystectomy in patients with Child A or B cirrhosis is associated with significantly less postoperative complications, shorter duration of hospitalization and shorter time to resume normal diet compared to open technique [104]. According to Lucidi et al. laparoscopic cholecystectomy should be recommended as the first choice approach in cirrhotic patients; however recommendation for laparoscopic cholecystectomy in patients with Child C cirrhosis is not clear [105]. Cirrhosis is a major risk factor for surgery. Laparoscopic cholecystectomy in cirrhotic patients is associated with significantly prolonged duration of surgery, increased operative blood loss, conversion rate, hospital stay and overall morbidity and mortality when compared with non-cirrhotic patients [106]. Laparoscopic cholecystectomy-related morbidity in cirrhotic patients is directly related to the Child Pugh score [107, 108]. In patients with advanced cirrhosis and severe portal hypertension, specific technical difficulties may be encountered, due to the presence of a portal cavernoma, the difficulty in exposure of Calot’s triangle and dissection of the gallbladder hilum, the presence.
of adhesions and neovascularization or the difficulty in controlling bleeding from the liver bed. Subtotal cholecystectomy can avoid many of these difficulties [109]. In conclusion, laparoscopic approach should be the first choice for the cholecystectomy in Child A and B patients. The approach to patients with Child Pugh C no-compensated cirrhosis remains a matter of debate. As a first recommendation, cholecystectomy should be avoided in these patients, unless clearly indicated, such as in ACC not responding to antibiotics [105].

**Statement 6.4 Laparoscopic or open subtotal cholecystectomy is a valid option for advanced inflammation, gangrenous gallbladder, or any setting of the “difficult gallbladder” where anatomy is difficult to recognize and main bile duct injuries are more likely (LoE 2 GoR A)**

A recent systematic review with meta-analysis by Elshaer et al. reported that subtotal cholecystectomy was performed using the laparoscopic (72.9 %), open (19.0 %) and laparoscopic converted to open (8.0 %) techniques. The most common indications were severe cholecystitis (72.1 %), followed by cholelithiasis in liver cirrhosis and portal hypertension (18.2 %) and empyema or perforated gallbladder (6.1 %). They concluded that subtotal cholecystectomy is an important tool in the difficult cholecystectomy and achieves morbidity rates comparable to those reported for total cholecystectomy in simple cases [110]. Alternative surgical strategy is the fundus first approach to reach progressively the infundibulum, cystic duct and artery: also by using this technique the risk of lesions must be always kept in mind [111, 112].

**Statement 6.5 In case of local severe inflammation, adhesions, bleeding in Calot’s triangle or suspected bile duct injury, conversion to open surgery should be strongly considered. (LoE 3 GoR B)**

Tang et al. in their systematic review, identified the principal risk factors for conversion during laparoscopic cholecystectomy. Single factors that appear to be important include male gender, extreme old age, morbid obesity, cirrhosis, previous upper abdominal surgery, severe acute and chronic cholecystitis, and emergency laparoscopic cholecystectomy. The combination of patient and disease related risk factors increases the conversion rate [113]. According to Giger et al., extensive inflammation, adhesions and consequent increased oozing can make laparoscopic dissection of Calot’s triangle and recognition of the biliary anatomy hazardous and difficult. Therefore, conversion to open surgery is strongly recommended to secure patient safety in such difficult conditions [114]. An elevated WBC count (>18 × 10⁹/L) and fever > 38 °C are predictive for the development of complications and conversion [115]. Sugrue et al. recently published the proposal of a new scoring system to evaluate the intraoperative difficulty of the cholecystectomy in order to provide objective suggestion for conversion to open technique [116] and results may clarify and standardize the definition of “difficult surgery”. According to Eldar et al. the complication rate in ACC tended to be associated with duration of complaints >48 h, gangrenous cholecystitis, male sex, age >60 years, other associated diseases, larger bile stones and elevated serum bilirubin levels. Generally, laparoscopic cholecystectomy is safe in all forms of ACC, with acceptably low conversion and complication rates, [117] excluding gangrenous cholecystitis where a conversion rate range between 4 to 40 % [87, 117]. In conclusion gangrenous gallbladder, obscure anatomy, bleeding, bile duct injuries, adhesions and previous upper abdominal surgery represent clinical conditions for which conversion to open cholecystectomy should be strongly considered [118].

**Associated common bile duct stone: suspicion and diagnosis at the presentation**

Cholelithiasis, i.e. the presence of common bile duct stones (CBDS), is reported to occur in 10% to 20 % in case series of cholelithiasis, with lower incidence during ACC ranging from 5 to 15 % of the patients [119–122]. Investigation for CBDS require time and can delay the surgical intervention. Due to the relatively low incidence of CBDS during ACC, the issue is to select patients with a high likelihood of CBDS who would benefit from further diagnostic tests and eventually the removal of the stones. An uncommon condition that mimics CBDS is the Mirizzi syndrome which occurs in 1 % of patients with cholelithiasis: preoperative investigation may help in the diagnosis although the vast majority are identified at surgery [123, 124].

**Statement 7.1 Elevation of liver biochemical enzymes and/or bilirubin levels are not sufficient to identify ACC patients with choledocholithiasis and further diagnostic tests are needed. (LoE 2 GoR B)**

Liver biochemical tests historically have a great utility in determining the presence of CBDS. However, the majority of published studies are not in patients with ACC and also include asymptomatic cholelithiasis. Normal liver biochemical tests have a negative predictive value of 97 %, whereas the positive predictive value of any abnormal liver biochemical test result is only 15 % [125]. Positive predictive value of liver function studies is a poor tool for prediction of CBDS, even in non-ACC, with results ranging from 25 to 50 % [119, 126, 127]. In fact, in ACC, liver biochemical tests may be altered due to the acute inflammatory process of the gallbladder and the biliary tree. 15 to 50 % of patients with ACC show elevation in liver enzymes without choledocholithiasis. Song et al demonstrated that 424 of 1178 patients with ACC had increased...
liver tests (alanine transaminase (ALT), aspartate transaminase (AST) greater than twice normal levels). Of these only 246 (58 %) had choledocholithiasis [128]. Chang et al showed that 51 and 41 % of ACC patients without choledocholithiasis had elevated ALT and AST, respectively. However, increased bilirubin levels with leukocytosis may predict gangrenous cholecystitis [129]. Padda et al demonstrated that approximately 30 % of patients with ACC without choledocholithiasis had abnormal alkaline phosphatase (ALP) and/or bilirubin and 50 % had abnormal ALT. Among patients with ACC and choledocholithiasis, 77 % had abnormal ALP, 60 % abnormal bilirubin and 90 % elevated ALT. By multivariate analysis increased common bile duct size and elevated ALT and ALP were predictors of choledocholithiasis [130]. The diagnostic accuracy increases for cholestasis tests such serum bilirubin with the duration and the severity of obstruction. Specificity of serum bilirubin level for CBDS was 60 % with a cut-off level of 1.7 mg/dL and 75 % with a cut-off level of 4 mg/dL [126]; however, mean level of bilirubin in patients with CBDS is generally lower (1.5 to 1.9 mg/dL) [119, 127]. In a prospective study, Silvestein reported the diagnostic accuracy of serum bilirubin and serum ALP at two cut-offs for each test. Serum bilirubin at a cut-off of greater than 22.23 μmol/L had a sensitivity of 0.84 (95 % CI 0.65 to 0.94) and a specificity of 0.91 (0.86 to 0.94). Bilirubin at a cut-off of greater than twice the normal limit, had a sensitivity of 0.42 (95 % CI 0.22 to 0.63) and a specificity of 0.97 (95 % CI 0.95 to 0.99). For ALP at a cut-off of greater than 125 IU/L, sensitivity was 0.92 (95 % CI 0.74 to 0.99) and specificity was 0.79 (95 % CI 0.74 to 0.84). For ALP at a cut-off of greater than twice the normal limit, sensitivity was 0.38 (95 % CI 0.19 to 0.59) and specificity was 0.97 (95 % CI 0.95 to 0.99) [131, 132].

**Statement 7.2 At AUS, the visualization of CBDS is a very strong predictor of choledocholithiasis. (LoE 5 GoR D).**

Indirect signs of stone presence such as increased diameter of common bile duct are not sufficient to identify ACC patients with choledocholithiasis and further diagnostic tests are needed. (LoE 1 GoR A)

AUS is the preferred imaging technique to diagnose ACC. Simultaneously, the common bile duct can be visualized and investigated. A recently published meta-analysis investigated the diagnostic potential of ultrasound [131]: sensitivity ranged from 0.32 to 1.00 with a summary sensitivity of 0.73 (95 % CI 0.44 to 0.90), and specificity ranged from 0.77 to 0.97 with a summary specific of 0.91 (95 % CI 0.84 to 0.95). In a retrospective analysis, Boys et al [133] demonstrated that AUS mean common bile duct diameter in ACC patients without and with CBDS was 5.8 and 7.1 mm, respectively (P value = 0.004). Diameter ≥10 mm was associated with 39 % incidence of CBDS, while diameter <9.9 mm was associated with common bile duct stones in 14 %. The authors’ conclusion was that AUS common bile duct diameter is not sufficient to identify patients at significant risk for CBDS.

**Statement 7.3 Liver biochemical tests, including ALT, AST bilirubin, ALP, gamma glutamyl transferase (GGT), AUS should be performed in all patients with ACC to assess the risk for CBDS. (LoE 2 GoR B)**

Several predictive scores of CBDS have been proposed and validated but none are specific for ACC. The implementation of these predictive scores in clinical practice is poor [126, 134–138]. All combine the same clinical variables differently. Hugrier et al combined diameter of common bile duct > 12 mm, gallstones < 10 mm, advanced age and symptomatic disease; Barkun et al combined age > 55, elevated serum bilirubin, dilated common bile duct and evidence of CBDS; Menezes combined age > 55, male sex, ascending cholangitis, dilated common bile duct, CBDS, and abnormal liver tests; Soltan et al included history of symptomatic disease, abnormal liver tests, dilated common bile duct and presence of CBDS; Sun et al included male sex, abnormal liver test and dilated common bile duct; Sarli et al combined positive AUS and abnormal liver tests. The American Society of Gastrointestinal Endoscopy and the Society of American of Gastrointestinal Endoscopic Surgeons combined the various published validated clinical scores and proposed a risk stratification of CBDS in three different classes: low risk (<10 %), moderate (10 to 50 %) and high risk (>50 %), based on the presence of predictive factors for having CBDS in its guidelines [139]. This proposed classification has clear clinical implications. Patients with a low risk of CBDS should be operated upon without further investigation. Patients with moderate risk should be interrogated with a second level examination: preoperatively by endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) or intraoperatively by laparoscopic ultrasound or laparoscopic cholangiography, to select patients who need stone removal prior, during or after surgery. Patients with high risk of CBDS should undergo directly preoperative diagnostic and therapeutic ERCP.

**Statement 7.4 common bile duct stone risk should be stratified according to the proposed classification, modified from the American Society of Gastrointestinal Endoscopy and the Society of American Gastrointestinal Endoscopic Surgeon Guidelines (LoE 5 GoR D)**

ASGE guidelines seem to be the best tool available for the diagnosis and the management of CBDS during ACC [139]. However, according to this classification high risk patients have a probability of having CBDS > 50 %; this means that up to 49 % of patients that undergo ERCP may have no CBDS and, given the potential complications of ERCP, this is not acceptable. For this reason we prefer a
more cautious approach: only patients with evidence of CBDS at AUS should be considered at high risk of CBDS and should undergo directly diagnostic and therapeutic ERCP; patients with total serum bilirubin > 4 mg/dL, or enlarged common bile duct diameter at AUS plus bilirubin level 1.8 to 4 mg/dL should be considered as moderate risk and should undergo second level investigation such as EUS/MRCP, or intraoperative Laparoscopic ultrasound/cholangiography to avoid the ERCP complications. See Table 4 for the modified risk stratification.

Statement 7.5 Patients with moderate risk for choledocholithiasis should undergo preoperative MRCP, EUS, intraoperative cholangiography, or Laparoscopic ultrasound depending on the local expertise and availability. (LoE 1 GoR A)

Two preoperative imaging techniques are available for the detection of CBDS, MRCP and EUS. These diagnostic tools, according to the ASGE guidelines [139] should be reserved for patients with moderate risk for choledocholithiasis and have been shown to delay definitive ACC treatment [133]. On the other hand, these tests could exclude the presence of CBDS with high diagnostic accuracy, thereby avoiding further invasive procedures such as ERCP or intraoperative cholangiography and their complications. In fact, the implementation of these techniques resulted in a reduction of ERCP ranging from 30 to 75% in non-selected patients. [140–142]. A Cochrane meta-analysis compared these two different techniques [143]: both had good diagnostic accuracy and did not differ significantly with a summary sensitivity of 95% for EUS and 93% for MRCP and a summary specificity of 97 and 96% respectively. As noted by some authors interpreting similar results, considerations other than diagnostic efficacy (local availability, costs, expertise, delay of surgery) might be important when deciding which imaging method to use [144].

Statement 7.6 Patients with high risk for choledocholithiasis should undergo preoperative ERCP, intraoperative cholangiography, Laparoscopic ultrasound, depending on the local expertise and the availability of the technique. (LoE 1 GoR A)

ERCP has both a diagnostic and therapeutic role in the management of choledocholithiasis but is an invasive procedure with potential severe complications. The literature emphasizes that diagnostic ERCP has risks. Morbidity associated with diagnostic ERCP includes pancreatitis, cholangitis, haemorrhage, duodenal perforation, or allergy to contrast. These occur in 1 to 2% and increase to 10% when associated with sphincterotomy [145–148]. On the other hand intraoperative cholangiography significantly increases the length of surgery [149] and requires dedicated staff in the operating room. This is not always available, especially in the acute setting with non-planned operation as in ACC. Positive findings on intraoperative cholangiography lead to intraoperative management of CBDS with additional operative time. A recently published meta-analysis compared the two techniques [131]: for ERCP, the summary sensitivity was 0.83 (95% confidence interval 0.72 to 0.90) and specificity was 0.99 (95% CI 0.94 to 1.00). For intraoperative cholangiography, the summary sensitivity was 0.99 (95% CI 0.83 to 1.00) and specificity was 0.99 (95% CI 0.95 to 1.00). Sensitivities showed a weak statistical difference (p = 0.05) but due to the quality and the methodology of the included studies, the two diagnostic techniques should be considered equivalent. Recently, Laparoscopic ultrasound has been introduced for the detection of CBDS. A recent meta-analysis has shown that intraoperative cholangiography and Laparoscopic ultrasound have the same pooled sensitivity and similar pooled specificity for the detection of CBDS [150]. As in the case of intraoperative cholangiography, intraoperative evidence of CBDS leads to intraoperative management of common bile duct with additional operating time.

Statement 7.7 CBDS could be removed preoperatively, intraoperatively, or postoperatively according to the local expertise and the availability of the technique. (LoE 1 GoR A)

CBDS could be removed with varying techniques in different timings: preoperative ERCP with sphincterotomy, intraoperative ERCP with sphincterotomy, laparoscopic or open common bile duct exploration, or post-operative ERCP with sphincterotomy. A systematic review assessed the difference between these

### Table 4 Predictive factors and risk classes for choledocholithiasis

<table>
<thead>
<tr>
<th>Predictive factor for choledocholithiasis</th>
<th>Very strong</th>
<th>Strong</th>
<th>Moderate</th>
<th>Low</th>
<th>Intermediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of common bile duct stone at abdominal ultrasound</td>
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<tr>
<td>Common Bile duct diameter &gt; 6 mm (with gallbladder in situ)</td>
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<tr>
<td>Total Serum Bilirubin &gt; 4 mg/dL</td>
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<td>Bilirubin level 1.8 to 4 mg/dL</td>
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<tr>
<td>Abnormal liver biochemical test other than bilirubin</td>
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<td>Age older than 55 years</td>
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<tr>
<td>Clinical gallstone pancreatitis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk class for choledocholithiasis</th>
<th>High</th>
<th>Low</th>
<th>Intermediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of any VERY STRONG</td>
<td></td>
<td>No predictors present</td>
<td></td>
</tr>
<tr>
<td>All other patients</td>
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</tbody>
</table>

Modified from [139]
different techniques [151]. No differences in terms of morbidity, mortality and success rate were reported comparing these methods. Therefore, these techniques should be considered suitable options. Another meta-analysis investigated two different techniques for ERCP plus sphincterotomy: preoperative or intraoperative with the rendezvous technique [152]. These two techniques were equal in safety and efficacy; intraoperative technique reduced the risk for post-ERCP pancreatitis, but obviously requires dedicated staff in the theatre and prolongs the length of surgery.

Alternative treatments for high risk patients

**Statement 8.1** Gallbladder drainage, together with antibiotics, converts a septic cholecystitis into a non-septic condition; however the level of evidence is poor (LoE 4, GoR C)

As already stated, the definitive treatment of ACC is early laparoscopic cholecystectomy. However some patients may not be suitable candidates for surgery, due to co-morbidities. Cholecystectomy for ACC in the elderly and in high risk patients has always been considered a high-risk procedure with a reported mortality up to 19 % [153]. Recently published articles show that emergency cholecystectomy for ACC could be considered a feasible and safe procedure [89, 153–157].

Gallbladder drainage, also known as percutaneous cholecystostomy (PC) is a potential alternative to cholecystectomy in high-risk patients, but its role is difficult to determine because different definitions are used to identify “high-risk” patients. Gallbladder drainage decompresses the infected bile or pus in the gallbladder, removing the infected collection without removing the gallbladder. The removal of the infected material, in addition to antimicrobial therapy, can result in a reduced inflammation with an improvement of the clinical condition. Several case series, retrospective and observational studies exist on cholecystostomy. A systematic review of the literature included 53 studies with 1918 patients outlining a high success rate of the procedure (85.6 %) with a low procedure related mortality (0.36 %); however, the 30-day mortality was 15.4 % [153]. A major limitation of the study was the inclusion of patients with both acute acalculus cholecystitis and ACC. After the aforementioned review, about 27 further observational studies have been published, confirming that the groups considered in the studies, their inclusion criteria, the results and even the conclusions reached by different authors are largely non-homogeneous [158]. With these limitations in mind, the reported in-hospital mortality for cholecystostomy varies between 4 and 50 % and morbidity ranges between 8.2 and 62 %.

**Statement 8.2** Among standardized gallbladder drainage techniques percutaneous transhepatic gallbladder drainage (PTGBD) is generally recognized as the preferred technique due to the ease and the reduced costs. (LoE 4, GoR C)

Cholecystostomy can be performed with several different techniques as summarized well by the TG [159]. These include PTGBD, percutaneous transhepatic gallbladder aspiration (PTGBA), endoscopic naso-biliary gallbladder drainage, endoscopic gallbladder stenting, and EUS-guided gallbladder drainage via the antrum of the stomach and the duodenum. A controlled trial by Ito et al. [160] compared PTGBD with PTGBA. All patients with ACC were treated conservatively and patients who showed no improvements after 24 h were randomized to receive either PTGBD or PTGDA. PTGBD was superior to gallbladder aspiration in terms of clinical effectiveness with the same complication rate as gallbladder aspiration. However this trial included high risk and low risk patients. No other good quality evidence exists on which is the best gallbladder drainage technique.

Finally, in case of evidence of cystic duct obstruction, PTGBD should be, even more, the preferred technique for gallbladder drainage.

**Statement 8.3** PC could be considered as a possible alternative to surgery after the failure of conservative treatment in a small subset of patients unfit for emergency surgery due to their severe co-morbidities (LoE 2 GoR B)

TG on ACC [11] consider the gallbladder drainage as mandatory in the severe grade (according to the Tokyo classification [12]) acute cholecystitis and also suggest its use in the moderate grade if conservative treatment fails. The panel of the Tokyo Guidelines states that it is known to be an effective option in critically ill patients, especially in elderly patients and patients with complications; however, there is a lack of good quality evidence to support the statement. Hatzidakis et al. published in 2002 a randomized trial comparing PC with conservative treatment in patients with acute acalculus cholecystitis or ACC [161]: there were no significant differences in mortality and morbidity. Akyurek et al published in 2005 a trial where patients with ACC were randomized to receive PC followed by early laparoscopic cholecystectomy or conservative treatment followed by delayed laparoscopic cholecystectomy [162]. There were no differences in term of mortality and morbidity; PC plus early laparoscopic cholecystectomy resulted in a reduction of the length of stay and of costs. Melloul et al. in 2011 published a retrospective case control study in critically ill patients with biliary sepsis treated by early laparoscopic cholecystectomy or PC [163]: mortality was not different between the two treatments but early laparoscopic cholecystectomy was associated with significantly higher complication rate. A Spanish retrospective study [164] compared critically ill
patients with ACC who underwent PC or early laparoscopic cholecystectomy. They found a significantly higher mortality rate in the PC group; however this study is of poor quality and has several limitations such as the retrospective study design and the selection bias. A Cochrane systematic review by Gurusamy et al. investigated the role of cholecystostomy: authors included the only two randomized trials, both at high risk of bias, concluding that “we are unable to determine the role of percutaneous cholecystostomy in the clinical management of high-risk surgical patients with acute cholecystitis” [165]. Currently, the CHOCOLATE trial is ongoing [161]: it is a randomized controlled trial comparing PC with early laparoscopic cholecystectomy in critically ill patients (APACHE score 7–14) with ACC; results may clarify the real role of the percutaneous drainage. Gallbladder drainage has been even described as a procedure reserved for those patients who failed the conservative treatment after a variable time of 24 to 48 h. A prospective study by Barak et al. [166] reported age above 70 years, diabetes, tachycardia, and a distended gallbladder at admission as predictors for the failure of conservative treatment at 24 h follow-up, while WBC > 15,000 cell/mm³, elevated temperature, and age above 70 years were predictors for the failure of conservative treatment at 48 h follow-up. There is no specific antibiotic regimen to be prescribed alongside PC. None of the examined studies reported the specific drug agent. No evidence exists supporting the need for a peculiar antibiotic regimen. For the antimicrobial therapy, please see the dedicated section. At the present time, PC seems to be a safe and effective procedure in critically ill patients with ACC. However, no evidence supports its superiority toward the conservative treatment or early laparoscopic cholecystectomy.

Statement 8.4 delayed laparoscopic cholecystectomy could be offered to patients after reduction of operative and anesthesiology-related risks to reduce further hospitalization (LoE 5 GoR D)

De Mestral et al. published a large retrospective epidemiological analysis in 2012 showing that only 40 % of patient underwent delayed laparoscopic cholecystectomy after PC; the 1 year readmission rate for patients who did not undergo delayed laparoscopic cholecystectomy after PC was 49 % with an in-hospital mortality of 1 % [10]. No randomized trial comparing the need for delayed laparoscopic cholecystectomy exists currently.

Conclusion: grey areas and opportunities for future research

After achieving the consensus for all the statements, the participants to the Consensus Conference voted for the WSES algorithm on ACC which is reported in Fig. 1.

Based on the evidence included in the present guidelines, it can be stated that early laparoscopic cholecystectomy is the best therapeutic approach for ACC and that postoperative antibiotics are not necessary in cases of uncomplicated cholecystitis. Moreover, studies providing a high level of evidence on the management of associated CBDS have also been published. Visualisation of CBDS by AUS is a good predictor; patients with a high risk of CBDS should have a pre-operative ERC; patients with a moderate risk should have non-invasive pre-operative investigation. However in both cases intra-operative exploration according to the local expertise has been reported as a recommended option with a high level of evidence. Furthermore we observed lack of studies investigating the cost savings of trans-cystic duct common bile duct removal of small stones.

The recommendations on the surgical treatment of ACC are however limited to patients who may be good candidates for urgent surgery. Grey areas still remain in the cases of patients not fit for urgent surgery or for laparoscopic surgery secondary to general conditions.

Diagnosis may be assessed by clinical, laboratory data and AUS but with such a diagnostic approach results appear controversial and supported by a limited number of high quality studies. A radiological investigation such as HIDA may be required to reach a diagnostic certainty. Since symptomatic gallbladder stones are, in any case, an indication for laparoscopic cholecystectomy, the former diagnostic uncertainty may not be relevant in healthy patients and the latter invasive radiological investigation should therefore be applied only in high-risk patients.

There is however no consensus on the evaluation of the operative risk. These WSES guidelines define the patient condition in lieu of the cholecystitis severity score as underlined in the TG13. This approach could favour a tailored therapy on patient’s condition. Although the role of percutaneous cholecystostomy after failed conservative treatment in those patients not fit for surgery secondary to severe co-morbidities has been reported, the present guidelines have failed to find valuable criteria for the definition of such high-risk patients. Data on criteria for a definition of a high-risk patient other than that of septic shock, are scarce and of poor level of evidence. This is an area for research to improve the management of patients with ACC.

According to some high quality studies, subtotal cholecystectomy and low threshold for conversion should be recommended in cases of severe acute inflammation of the gallbladder at operation. Although the threshold for conversion strongly depends on the experience and skills of the surgeon, we support the development of an intraoperative score to help the surgeon in the decision to complete the operation by partial cholecystectomy and/or by open approach when “the critical view of safety” cannot be reached without adding risk.
Appendix 1

Fig. 2 Vote results of statements
### Table 5 WSES Guidelines statements

<table>
<thead>
<tr>
<th>Topic</th>
<th>#</th>
<th>LoE</th>
<th>GoR</th>
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<tr>
<td><strong>Diagnosis</strong></td>
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<td><strong>Treatment</strong></td>
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<td><strong>High risk patients</strong></td>
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<tr>
<td>4.2</td>
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<tr>
<td><strong>Timing</strong></td>
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<td>5.1</td>
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<td>A</td>
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<td>5.2</td>
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<td>B</td>
<td></td>
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<tr>
<td>5.3</td>
<td>1</td>
<td>A</td>
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</tbody>
</table>
**Table 5** WSES Guidelines statements (Continued)

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1 2 B</td>
<td>In ACC, a laparoscopic approach should initially be attempted except in case of absolute anaesthesiology contraindications or septic shock.</td>
</tr>
<tr>
<td>6.2 1 A</td>
<td>LC for ACC is safe, feasible, with a low complication rate and associated with shortened hospital stay.</td>
</tr>
<tr>
<td>6.3 3 C</td>
<td>Among high-risk patients, in those with Child A and B cirrhosis, advanced age &gt; 80, or pregnant women, laparoscopic cholecystectomy for ACC is feasible and safe.</td>
</tr>
<tr>
<td>6.4 3 A</td>
<td>Laparoscopic or open subtotal cholecystectomy is a valid option for advanced inflammation, gangrenous gallbladder, or any setting of the “difficult gallbladder” where anatomy is difficult to recognize and main bile duct injuries are more likely.</td>
</tr>
<tr>
<td>6.5 3 B</td>
<td>In case of local severe inflammation, adhesions, bleeding in Calot’s triangle or suspected bile duct injury, conversion to open surgery should be strongly considered.</td>
</tr>
</tbody>
</table>

**Alternative treatments**

<table>
<thead>
<tr>
<th>Associated common bile duct stones</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1 2 B</td>
<td>Elevation of liver biochemical enzymes and/or bilirubin levels are not sufficient to identify ACC patients with choledocholithiasis and further diagnostic tests are needed.</td>
</tr>
<tr>
<td>7.2 1 A</td>
<td>At AUS, the visualization of CBDS is a very strong predictor of choledocholithiasis. Indirect signs of stone presence such as increased diameter of CBD are not sufficient to identify ACC patients with choledocholithiasis and further diagnostic tests are needed.</td>
</tr>
<tr>
<td>7.3 2 B</td>
<td>Liver biochemical tests, including ALT, AST bilirubin, ALP, gamma glutamyl transferase (GGT), AUS should be performed in all patients with ACC to assess the risk for CBS.</td>
</tr>
<tr>
<td>7.4 5 D</td>
<td>CBD stone risk should be stratified according to the proposed classification, modified from the American Society of Gastrointestinal Endoscopy and the Society American of Gastrointestinal Endoscopic Surgeon Guidelines.</td>
</tr>
<tr>
<td>7.5 1 A</td>
<td>Patients with moderate risk for choledocholithiasis should undergo preoperative MRCP, EUS, intraoperative cholangiography (IOC), or LUS depending on the local expertise and availability.</td>
</tr>
<tr>
<td>7.6 1 A</td>
<td>with high risk for choledocholithiasis should undergo preoperative ERCP, IOC, LUS, depending on the local expertise and the availability of the technique.</td>
</tr>
<tr>
<td>7.7 1 A</td>
<td>CBDS could be removed preoperatively, intraoperatively, or postoperatively according to the local expertise and the availability of the technique.</td>
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</table>

<table>
<thead>
<tr>
<th>Availability of data and supporting materials</th>
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<tr>
<td>There are no individual author data that reach the criteria for availability.</td>
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</table>

**Abbreviations**

ACC, acute calculous cholecystitis; APACHE II, acute physiology and chronic health evaluation II; ASA, American Society of Anaesthesiology; AUS, abdominal ultrasound 37; CBD, common bile duct; CBDS, common bile duct stones 37; DLC, delayed laparoscopic cholecystectomy; ELC, early laparoscopic cholecystectomy; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; GoR, grade of recommendation; IOC, intraoperative cholangiography; LC, laparoscopic cholecystectomy; LoE, level of evidence; LUS, laparoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; OC, Organization Committee; PoSSum, portsmouth physiological and operative severity score for the enUmeration of mortality and morbidity; SC, Scientific Committee; SS, Scientific Secretariat; TG, Tokyo guidelines; WSES, World Society of Emergency Surgery

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**Authors’ contributions**

The WSES president was supported by the Scientific Secretariat in establishing the timetable of the CC and choosing the eight plus eight experts who were asked to participate respectively to Organization Committee and Scientific Committee: the Organization Committee had the task to support the Scientific Secretariat in building the framework for the Consensus and to support the Scientific Committee for the strict scientific part; the Scientific Committee had the assignment to select the literature and to elaborate, in co-working to Scientific Secretariat and Organization Committee, the statements. The Scientific Secretariat supported the WSES President, establishing the agenda, choosing the working tools and finally collaborating with Organization Committee and Scientific Secretariat. Consequently each question was assigned to one team consisting of one member of Organization Committee, one member of Scientific Committee and one member of Scientific Secretariat (each member of Scientific Secretariat covered two questions). Each team reviewed, selected and analyzed the literature, wrote and proposed the statement’s drafts for one of the eight questions, WSES board reviewed the draft and made critical appraisals. All the statements were discussed and approved during the 3rd WSES World Congress, held in Jerusalem on 6th July 2015. The manuscript was further reviewed by Scientific...
Secretariat, Organization Committee and Scientific Committee according to congress comments and was then approved by the WSES board. FA, AA, LA, GB, FCC, FCA, MC, OC, FCCo, SDS, KG, JK, MDK, RI, ABP, DP, MP, BS, MSA, MSu, PLY: conception, design and coordination of the study; data acquisition, analysis and interpretation; draft the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

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2017 WSES and SICG guidelines on acute calcolous cholecystitis in elderly population

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Abstract

Background: Gallstone disease is very common afflicting 20 million people in the USA. In Europe, the overall incidence of gallstone disease is 18.8% in women and 9.5% in men. The frequency of gallstones related disease increases by age. The elderly population is increasing worldwide.

Aim: The present guidelines aims to report the results of the World Society of Emergency Surgery (WSES) and Italian Surgical Society for Elderly (SICG) consensus conference on acute calcolous cholecystitis (ACC) focused on elderly population.

Material and methods: The 2016 WSES guidelines on ACC were used as baseline; six questions have been used to investigate the particularities in elderly population; the answers have been developed in terms of differences compared to the general population and to statements of the 2016 WSES Guidelines. The Consensus Conference discusses, voted, and modified the statements. International experts contributed in the elaboration of final statements and evaluation of the level of scientific evidences.

Results: The quality of the studies available decreases when we approach ACC in elderly. Same admission laparoscopic cholecystectomy should be suggested for elderly people with ACC; frailty scores as well as clinical and surgical risk scores could be adopted but no general consensus exist. The role of cholecystostomy is uncertain.

Discussion and conclusions: The evaluation of pro and cons for surgery or for alternative treatments in elderly suffering of ACC is more complex than in young people; also, the oldest old age is not a contraindication for surgery; however, a larger use of frailty and surgical risk scores could contribute to reach the best clinical judgment by the surgeon. The present guidelines offer the opportunity to share with the scientific community a baseline for future researches and discussion.

Keywords: Acute calcolous cholecystitis, Elderly, Frailty, High-risk patients, Diagnosis, Surgery, Antibiotics

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Background and introduction

Gallstone disease is very common afflicting 20 million people in the USA [1, 2]. In Europe, the Multicenter Italian Study on Cholelithiasis (MICOL) published in 2008 reported the examination of nearly 33,000 subjects aged 30 to 69 years in 18 cohorts of 10 Italian regions. The overall incidence of gallstone disease was 18.8% in women and 9.5% in men [3].

Biliary colic is the most common acute presentation of gallstone disease occurring from 1 to 4% annually [4–7]. Untreated gallstones may lead to acute calculus cholecystitis (ACC) in 10% to 20% of people [7].

Other complications of gallstones include common bile duct stones and acute pancreatitis. In patients in whom cholecystectomy was not performed at the initial admission for ACC, the probabilities of gallstone-related complications are 14%, 19%, and 29% at 6 weeks, 12 weeks, and at 1 year, respectively [8].

The MICOL study showed that age is a strong risk factor in both sexes. The prevalence of gallstones at 70 years of age was 15% and 24% and at 90 years of age was 24% and 35% for males and females respectively. Moreover, the prevalence increases to 80% in institutionalized people aged 90 years or above [3]. According to the 2017 United Nations report, the population aged more than 60 years is predicted to increase in the near future: in Europe, this is predicted to increase from 25% currently to 35% in 2050; in Latin American and Caribbean countries and Asia from 12.5% currently to 25% in 2050; in North America from 22% currently to 28% in 2050; finally, the African population will also become older moving from 5 to 9% by year 2050 [9].

Because ACC is the most common complication of biliary gallstone disease and the population will become older, ACC in elderly is expected to increase. There are no guidelines for the management of ACC in elderly. The 2016 WSES guidelines on ACC touched upon the relationship between old age and surgery in ACC briefly, in one statement (statement 4.1): however, the level of evidence was low [10].

The aim of the Consensus conference and of the present guidelines is to investigate age-related factors that could influence a different approach, compared to general population, in terms of diagnosis and management of people over 65 years with suspicion of ACC.

The choice of 65 years as cut-off in terms of age is quite arbitrary; however, it should be underlined that the definition of old age is a composite of various factors including chronological age, social factors, economic factors (such as active economic work or pension system), cultural factors, and functional status. The relative weight of these parameters is different in developed and developing countries [9].

Material and methods

The 2016 WSES Guidelines on ACC were used as the main reference [10]; six questions were developed by Organizational Committee in order to investigate the topic (Table 1).

Each question was assigned to one researcher of the SIGC and to one researcher of the WSES. The external supervision was obtained, since the beginning of the project, by KG, who was a member of the panel for the 2016 WSES Guidelines on ACC.

According to the key words in Table 1, the electronic bibliography search was developed by the medical librarian of Papa Giovanni XXIII Hospital. Researchers supplemented the electronic searches by manual search.

Each working group developed few statements for the question assigned to them, and the level of evidence and the grade of recommendation was proposed according to the 2011 Oxford classification (available at https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf). The level of evidence and grade of recommendation were decreased when there was no evidence from studies on the elderly, as per guidance of the Oxford classification.

The statements were presented at the 30° Annual Meeting of the SIGC and each statement was voted by the audience. The vast majority of statements reached at least 70% initial agreement and most of them were comparable to the 2016 WSES Guidelines on ACC; after complete discussion about the different points of view, consensus (at least 70% of respondents agreed with the statement) was reached for all the proposed statements. As agreed in the meeting, the level of evidence and grade of recommendation were reviewed and revised (Appendix).

Results

Question 1: diagnosis: which test for elderly

Diagnosis algorithms of acute cholecystitis are based on clinical picture, laboratory data, and imaging finding [10, 11]. Despite recent advances in non-invasive imaging in the last decades, there is still uncertainty in the diagnosis of acute cholecystitis in patients of all ages. Moreover, age-related changes involving pain perception [12, 13], biliary tract physiology [14], and stress response to tissue injury [15] may modify the clinical
picture of ACC occurring in an elderly patient, making diagnosis even more complicated. Literature search identified approximately 70 publications on Embase and 140 on Medline.

Statement 1.1: There is no single investigation with sufficient diagnostic power to establish or exclude acute cholecystitis without further testing even in elderly people (LoE 2 GoR B). Combination of symptoms, signs, and laboratory tests results may have better diagnostic accuracy in confirming the diagnosis of ACC. (LoE 4 GoR D)

The most typical symptom of ACC is abdominal pain with a proportion of patients with right hypochondrial pain and epigastric pain of 72–93% in patients of all ages. Same range of 73–98% typical right hypochondrial and epigastric pain has been reported in studies focused on the elderly patients [16–18]. Atypical pain or no pain at all has been associated with an acute cholecystitis in 12% and 5% of elderly people respectively [18]. Vomiting has been reported in 38–48% of elderly patients in two studies [16, 18]. Abdominal tenderness or guarding was reported in 64.7% of patients over 65 years old in one study [17, 19], while signs of peritonitis have been reported in 5.3–14.5% of elderly patients [17, 19].

In one study, the rate of positive Murphy’s sign in elderly people has been reported to be 43.3% [17]. Another study reported a sensitivity of 0.48, specificity of 0.79, and a positive predictive value of 0.58 for Murphy’s sign in the diagnosis of acute cholecystitis in the elderly [20]. Fever has been reported in 36–74% of patients with ACC (8–10), but only 6.4% to 10% of patients with ACC had a temperature > 38 °C [18, 19]. Clinical features including pain, fever, abdominal defense, and vomiting have been compared in different age decades within elderly patients without finding any difference in old and very old patients [17, 18]. No study comparing the role of pain or other clinical features in young versus old patient has been found.

Some 41–59% of patients with ACC have leucocytosis [18, 21]. Two comparative studies have explored the role of leucocytosis in the diagnosis of acute cholecystitis in young and elderly patients [21, 22]. One study [21] reported that the elderly patients with ACC had a higher rate of leucocytosis (26.4%) than younger patients with ACC rates of (41.2% \( p = 0.005 \)); the other study reported a higher mean value of white blood count (WBC) in the elderly (19.5 ± 7.9) compared to the younger patients (17.4 ± 6.0) \( p = 0.02 \). These studies also compared C-reactive protein (CRP) in the elderly and younger patients. In one study, the proportion of patients with high CRP was more in the elderly patients (64.1%) compared to younger patients (35.1%) \( p < 0.01 \). In the other study [22], the mean value of CRP was higher in the elderly patients (26.4 ± 12) compared to the younger patients (22.4 ± 20.0); \( p = 0.04 \).

Statement 1.2: Abdominal ultrasound is the preferred initial imaging technique for elderly patients who are clinically suspected of having acute cholecystitis, in terms of lower costs, better availability, lack of invasiveness, and good accuracy for stones (LoE 3 GoR C).

Studies reporting quantitative data on the role of the imaging in the diagnosis of acute cholecystitis in the elderly patient are limited to abdominal ultrasound. A study has reported that only half of patients with acute cholecystitis had conventional ultrasound (US) signs of acute cholecystitis including gallbladder distension, wall thickening, double-layer shadow, echo in gallbladder fluid, and perigallbladder effusion [23]. This indicates the poor sensitivity of the ultrasound. In one study [21], there was no difference in the proportion of ACC patients with thickened gallbladder wall between elderly (72.5%) and non-elderly patients (65.5%) \( p = 0.176 \).

Statement 1.3: Even in elderly patients, evidence on the diagnostic accuracy of CT are scarce and remain elusive while diagnostic accuracy of MRI might be comparable to that of abdominal ultrasound, but no sufficient data are provided to support this hypothesis. HIDA-scan has the highest sensitivity and specificity for acute cholecystitis than other imaging modalities although its scarce availability, long time of execution and exposure to ionizing radiations limit its use (LoE 3 GoR C).
There is no specific data available on elderly on this topic.

Statement 1.4: Even in elderly patients, combining clinical, laboratory, and imaging investigations should be recommended, although the best combination is not yet known (LoE 5 GoR D)

There is no specific available data on elderly on this topic.

Statement 1.5: No high-quality studies on specific diagnostic findings of acute cholecystitis in the elderly have been found; therefore, the stated recommendations of the WSES guidelines previously reported remain unchanged (LoE 4 GoR D)

All the reported published studies on the elderly should be classified as level 4 according to the Oxford Classification since they report no or use poor reference standard for the diagnosis of acute cholecystitis. Because of the poor quality of the studies, caution should be paid to the results. Some findings seem contradictory to the theory of a lower responsiveness of elderly patients: one would have expected lower levels of WBC and CRP in the elderly compared to the younger age group [21, 22]. On the contrary, a statistically significant (but not clinically significant) increase in WBC and CRP was found in the elderly [21, 22]. The apparent contradiction could be explained by the occurrence of more severe forms of acute cholecystitis such as gangrenous cholecystitis (GC) in the elderly. In the study of Ambe et al. [22], a higher rate of severe cholecystitis (according to the Tokyo Guidelines 2013 criteria) has been reported in the elderly patient group. Furthermore, aging as risk factor for gangrenous cholecystitis has been well showed in the literature [24]. It has also been reported that gangrenous cholecystitis has overt clinical manifestations allowing an easier diagnosis in patients of all ages [25–27], although a clinically significant cholecystitis may present with few abdominal complaints in the elderly [28]. The fewer abdominal symptoms in the elderly, the lesser responsiveness of WBC and CRP levels with aging, and the higher rate of severe and or gangrenous acute cholecystitis in the elderly should be explored further.

Further studies are also necessary to assess whether the diagnostic approach may be influenced by the different natural history of cholecystitis in the elderly compared to the younger age group, for example, whether an extensive use of computed tomography (CT) scan in the elderly should be advocated due to its diagnostic value in detecting gangrenous cholecystitis [29–31].

The age is a useful and very common parameter that we use in describing the patient. Increased age is associated with increased comorbidities and decreased life expectancy: this has implications on the ability of the patients to recover from the treatments and thus to the natural history of the ACC.

In the last few decades, the concept of frailty is becoming more common in surgery. Definition of frailty is difficult because one person could be frail when exposed to some stress-inducing factors and not to others. Frailty scores usually consider the age among measurable parameters; interestingly, Locar et al. published a validation study for an emergency-general surgery-specific frailty index in 2016: among 15 variables included in the multivariate analysis, age was not an independent factor for predicting postoperative complications [32]. Moreover, more than 50% of frail people are aged >70 years [33].

A simple way to consider age in predicting postoperative complications was reported in a small cohort retrospective study of elderly patients above 80 years of age with ACC, by Novello et al.: mortality and postoperative morbidity were primarily not associated with surgery during the working hours; however, in surgery during the afternoon and night-time, patients with age greater than 90 years were at higher risk of postoperative mortality compared to patient with 80 to 89 years of age (50% vs. 17%; p < 0.0001) [34].

The age of patients, obviously, increases the considerations required in offering surgery for ACC. However, a large retrospective cohort study including 29,918 ACC patients demonstrated that the mortality rate of elderly patients (mean age 77.7 years) is significantly lower in those undergoing surgery during the same admission compared to those discharged home without receiving surgery at the index admission; the 30-day, 1-year, and 2-year cumulative mortality rates were 2%, 9%, and 15.2% for surgical group while they were 5%, 19.4%, and 29.3% in the non-surgical group (p < 0.0001) [1]. These results were similar when adjusted for comorbidities. The 30-day, 90-day, 1-year, and 2-year gallstone-related readmission rates were 2.4%, 2.7%, 3.7%, and 4.4% in the surgical group compared to 21%, 29%, 35%, and 38% (p < 0.0001). However, it should be noted that it is not possible to make any strong recommendations in the absence of evidence from randomized controlled trials.

Statement 2.2: Cholecystectomy is the preferred treatment for ACC even in elderly patients. (LoE 3 GoR C)

Surgery for elderly patients is increasing due to different reasons: the life expectancy and health of elderly is improving, possibly because of better medical and surgical healthcare [35]. Zenilman described the evolution of geriatric surgery: in 1907, elderly were people over 50 years old and surgery was an exception; less than
80 years later, Katlic reported the first series of surgery in centenarians [36]. The scientific evidence coming from the literature already reported in the consensus statement for ACC published in 2016 allows us to consider cholecystectomy during the index admission as the preferred treatment for elderly population with ACC also [1, 10, 32, 33]. To achieve this, elderly patients require a more detailed and rapid evaluation compared to the general population to take the higher susceptibility of elderly patients into account.

Statement 2.3: The evaluation of the risk for elderly patient with ACC should include:

- Mortality rate for conservative and surgical therapeutic options
- Rate of gallstone-related disease relapse and the time to relapse
- Age-related life expectancy
- Consider patient frailty evaluation by the use of frailty scores
- Consider estimation of specific risk (patient/type of surgery) by the use of surgical clinical scores (LoE 3 GoR C)

The evidence coming from the literature is of low quality: most of the evidence is not specific to the elderly population and there is some indirectness in extrapolating the results from overall ACC patients to elderly patients specifically. As mentioned above, a large retrospective study showed lower mortality in elderly ACC patients who received cholecystectomy in the same admission compared to those managed conservatively [1]. In 2016, Loozen et al. supported the conservative treatment for mild ACC in the general population because of mortality of 0.5%, recurrence of 20% (at 2 years), and initial success rate of 86%; however, limitations are, in part, underlined by the same authors: the definition of recurrence is not well defined among studies, the recurrence could be influenced from the wide period of follow-up ranging from 1 to 14 years, the definition of conservative treatment was variable and not always specified, the treatment at the time of recurrence and the outcome at the recurrence is not specified, the vast majority of the studies are retrospective, and, when randomized, the criteria of randomization are not always specified [37]. The same group conducted a systematic review of retrospective studies in 2017, focusing their attention on the safety of early cholecystectomy in 592 elderly patients (mean age 81 years) with a surgical risk evaluated by the American Society of Anesthesiologist (ASA) ≥ 3 in 44% of these patients: the authors concluded that early cholecystectomy is feasible because the overall mortality was 3% and the morbidity was 23%, which was similar that in the younger population (1% and 15% respectively) [38].

In order to avoid surgery for elderly and high-risk patients (often these two groups are mixed together), alternative treatments have been developed such as percutaneous drainage of the gall bladder (cholecystostomy) or the less common drainage of the gallbladder by retrograde endoscopic procedure: unfortunately, the results are not conclusive and we should wait for the prospective CHOCOLATE study [39, 40] to throw some light on this issue.

Another aspect that we should consider in order to develop the most appropriate statement/suggestion is the relationship between time to relapse of ACC patients with primary non-surgical successful treatment and life expectancy. In elderly patients with ACC, the relapse of biliary symptoms is significantly higher in patients who did not undergo surgery compared to those who underwent surgery: 2.4% vs. 21% after 30 days follow-up, 2.9% vs. 29% at 90 days follow-up, 3.7% vs. 35% at 1 year follow-up, and 4.4% vs. 38% at 2 years follow-up (p value < 0.0001 for all follow-up points). Furthermore, 63% of those who did not undergo surgery required surgery during readmission [37].

In the setting of ACC and old age, a single rule that fits “all patients” cannot be applied and research is necessary to stratify the surgical risk. ASA, P-POSSUM, and APACHE II showed the best correlation with surgical risk, but there is no validated way of stratifying risk in elderly patients, even though age is one of the factors considered for calculation of P-POSSUM and APACHE II scores. Frailty scoring systems may help in stratifying the risk. There are different frailty scores: some evaluate specific aspects such as cognition, ability of self routinely cure, and movement impairments, while other comprehensive scores require a large number of items to be considered, which can be difficult to apply in the emergency surgery setting.

Frail patients are at increased risk of morbidity or mortality (from 1.8- to 2.3-fold) from minor external stresses. Despite the frailty is not a condition affecting only elderly patients [33], overall 25% of patients aged more than 65 years old are frail [41]. A recent retrospective analysis of the NSQIP of approximately 230,000 patients who underwent surgery from 2012 to 2015 evaluated the relationship between age, frailty, and type of surgery: this study found an increased risk of mortality and morbidity among frail patients who underwent surgery (including “minor surgery”) [41]. Frailty scores in ACC surgical setting are currently under development after which external validation will be performed [32, 42, 43].

Question 3: which is the most appropriate timing and the most appropriate surgical technique for elderly?

In the general population, the standard of care for ACC is early laparoscopic cholecystectomy.
Laparoscopic approach is safer than open approach for ACC: the morbidity and mortality, in the case of laparoscopic procedure are 10% and 1%, respectively, compared to 25% and 2% for open procedure [1]. Elderly patients are at increased risk of conversion from laparoscopy to open procedure, with consequent worsening of final outcome. The reasons for the conversion can be attributable to a longer history of gallbladder inflammation episodes, delayed hospital presentation in case of acute attack [44–47]. As a consequence, we fully reviewed the literature supporting or refuting the statements published in the 2016 WSES guidelines for ACC. None of these statements were based on specific observations on elderly patients [10].

Statement 3.1: In elderly patients with acute cholecystitis, laparoscopic approach should always be attempted at first except in the case of absolute anesthetic contraindications and septic shock. (LoE 2 GoR B)

Coccolini and colleagues in 2015 published a systematic review and meta-analysis with the focus of comparing open and laparoscopic cholecystectomy for ACC: the analysis of morbidity and mortality favors the use of laparoscopic procedure but the analysis was not focused on elderly patients [48].

Statement 3.2: In elderly patients, laparoscopic cholecystectomy for acute cholecystitis is safe, feasible, with a low complication rate and associated with shortened hospital stay. (LoE 2 GoR B)

Coccolini et al. also found advantages for laparoscopic approach in terms of reduced hospital stay, with expected reduction in risk for nosocomial pulmonary infection, for cognitive and movement impairment, but not specifically in elderly patients [48].

Statement 3.3: In elderly patients, laparoscopic or open subtotal cholecystectomy is a valid option for advanced inflammation, gangrenous gallbladder, and "difficult gallbladder" where anatomy is difficult to be recognized and main bile duct injuries are highly probable. (LoE 3 GoR C)

An increased rate of conversion to open surgery is reported for elderly: this is probably due to greater difficulties in the dissection for previous attacks and late presentation. Instead of a formal laparoscopic cholecystectomy, alternative surgical strategies such as subtotal cholecystectomies should be kept in the armamentarium of the acute care surgeon [49, 50].

Statement 3.4: In elderly patients, conversion to open surgery may be predicted by fever, leucocytosis, elevated serum bilirubin, and extensive upper abdominal surgery. In case of local severe inflammation, adhesions, bleeding in the Calot's triangle, and suspect bile duct injury, conversion to open surgery should be considered. (LoE 3 GoR C)

Although primary laparoscopic approach should be attempted, the conversion from laparoscopy to open surgery is not a failure [51, 52]. Preoperative scores predicting the risk of conversion from laparoscopy to open are not reliable when applied in the context of ACC, due to the fact that a large number of variables are very often present at the ACC presentation [53, 54]. Sugrue and colleagues are developing an intraoperative scoring system that could assess the probability of conversion at the beginning of laparoscopy, reducing the time and unnecessary maneuvers before the decision to convert, thus potentially reducing the associated risk of morbidity and mortality [55].

Statement 3.5: Even in elderly patients, early laparoscopic cholecystectomy should be performed as soon as possible but can be performed up to 10 days of onset of symptoms. However, it should be noted that earlier surgery is associated with shorter hospital stay and fewer complications. (LoE 2 GoR B)

Although the historical rule of 72 h to perform cholecystectomy for ACC is no longer mandatory, surgery performed as soon as possible is associated with a better outcome [56–61]. Moreover, the expected reduction in reserve capacity in old patients should prompt the best treatment at the earliest. There are no specific studies evaluating early versus delayed laparoscopic cholecystectomy for elderly patients. Therefore, early laparoscopic cholecystectomy should be considered taking other factors mentioned in statement 2.3 into account.

Question 4: alternative treatments in case of reduced benefit from surgery in elderly: is there a role for percutaneous cholecystostomy?

Statement 4.1: Percutaneous cholecystostomy can be considered in the treatment of ACC patients (older than 65, with ASA III/IV, performance status 3 to 4, or septic shock) who are deemed unfit for surgery. (LoE 2 GoR B)

ACC is frequently encountered in emergency surgical setting. Although laparoscopic cholecystectomy is considered the gold standard therapy in healthy and young subjects, there are some concerns in elderly frail patients affected by several comorbidities [10]. Particularly, the mortality rate of laparoscopic cholecystectomy in the general population is 0–0.8%, but it increases dramatically up to 14–30% in elderly or critically ill patients with comorbid diseases [62].

Percutaneous cholecystostomy has been introduced with therapeutic purposes since the late 70s. Several guidelines recommend percutaneous cholecystostomy for moderate (grade II) or severe (grade III) acute cholecystitis, or as alternative, effective life-saving method to manage acute calculous cholecystitis in older or in frail patients, who are deemed unfit for surgery due to their severe comorbidities [56, 62, 63].

In a retrospective study on 325 patients suffering from acute cholecystitis, Kim et al. performed a multivariate analysis, and identified the following as
independent factors that correlate with percutaneous cholecystostomy: advanced age over 65 years ($p < 0.001$), a history of abdominal surgery ($p = 0.023$), a higher ASA score ($p = 0.015$), white blood cell (WBC) count ($p = 0.023$), and C-reactive protein levels ($p = 0.013$) [64].

In a retrospective evaluation of 27 consecutive ASA III-ASA IV old patients (median age of 71.4 years) undergoing percutaneous cholecystostomy, Bakkaloglu and coworkers demonstrated a percutaneous cholecystostomy morbidity rate of 25.9%. Percutaneous cholecystostomy was effective in reducing leukocytosis, C-reactive protein, and fever. No further treatment after percutaneous cholecystostomy was necessary in 72% of patients [62].

Nasim et al. reviewed 62 patients who underwent percutaneous cholecystostomy for acute cholecystitis. Seventy-six percent of them were either ASA III or IV and 61% were older than 60 years. Clinical resolution of toxemia was observed within 24–48 h in 92% of patients. Thirty-five percent of patients did not undergo any further treatment for cholecystitis after percutaneous cholecystostomy [65].

In considering these evidences, percutaneous cholecystostomy seems a reasonable option for the emergency setting management of elderly high-risk patients having ACC.

A systematic review of the role of percutaneous cholecystostomy in high-risk surgical patients with ACC concluded that the current role of percutaneous cholecystostomy in ACC is not clear [39]. The ongoing CHOCOLATE trial may provide information on the role of percutaneous cholecystostomy in the management of ACC [40].

Statement 4.2: If medical therapy failed, percutaneous cholecystostomy should be considered as a bridge to cholecystectomy in acutely ill (high-risk) elderly patients deemed unfit for surgery, in order to convert them in a moderate risk patient, more suitable for surgery (LoE 3 GoR C)

Percutaneous cholecystostomy is one of the alternative methods to manage acute calculous cholecystitis. The maneuver can be used to provide drainage of the gallbladder favoring the resolution of inflammatory status. Subsequently, interval cholecystectomy can be performed when there are better conditions. Tolan et al. in a retrospective evaluation of 40 ASA III-IV patients undergone percutaneous cholecystostomy recorded a 100% success rate of the procedure in reducing the inflammatory status and in controlling the infection condition. After removal of percutaneous cholecystostomy drainage, 40% of patient underwent subsequent surgery. Particularly, laparoscopic cholecystectomy was performed in 81.2% of cases. None of the patients who did not have operation experienced recurrence of acute cholecystitis or biliary symptoms [66].

Kim et al., in comparing clinical outcomes between those patients who underwent percutaneous cholecystostomy for both the mild and moderate acute cholecystitis and those who did not, demonstrated that preoperative and overall hospital stay were significantly longer in patients who underwent percutaneous cholecystostomy. This longer preoperative stay in the percutaneous cholecystostomy group may have been due to the time required to perform percutaneous cholecystostomy as well as improvement in the patient’s condition before surgery. Furthermore, mean operative time was significantly longer in percutaneous cholecystostomy group, probably because of the presence of adhesions, gallbladder wall thickness, the tendency for bleeding at the site of operation, and the difficulty in identifying anatomical structures during surgery [64]. For these reasons, percutaneous cholecystostomy should be adopted only in a subset of high-risk patients to convert them into moderate risk patients, more suitable for surgery.

Statement 4.3: As in the general population, even in elderly patients, percutaneous transhepatic cholecystostomy is the preferred method to perform percutaneous cholecystostomy. (LoE 4 GoR D)

Percutaneous cholecystostomy can be easily performed under local anesthesia. Two approaches are available for percutaneous cholecystostomy: transhepatic and transperitoneal. The former is to be preferred because it reduces the risk of biliary leak, allows the drain to be left in place for longer periods, and leads to quicker maturation of a drainage tract [67].

The percutaneous cholecystostomy-related complications account for about 3.4%, and include bile duct leak and biliary peritonitis, portal or parenchymal vessel injury and bleeding, catheter dislodgement, colon injury, and vagal reaction [67]. The transhepatic approach decreases the risk of bile leak, portal vessel injury, hollow viscus injuries, but it carries the risk of pneumothorax and bleeding from liver parenchyma. Notwithstanding these potential complications, this route seems to be the best approach for percutaneous cholecystostomy except in the presence of severe liver disease and coagulopathy [62].

Gallbladder drainage can be performed either under sonography guidance and computed tomography guidance. The procedure may be performed by “Seldinger technique” which uses a fine needle to reduce the potential risk of involuntary hollow viscous perforation, but has the disadvantages of multiplicity of maneuvers, or by the “trocar technique” which allows the direct insertion of an 8 French pig-tail. In the latter case, the trocar and the drain have the same diameter, which increases the risk of bleeding in the transhepatic approach is adopted.

In the literature, technical success, defined as satisfactory placement of the drain within the gallbladder, reaches 90%, being the causes of failure represented by small gallbladder lumen, a thin gallbladder wall, and porcelain gallbladder [67, 68]. However, it should be noted
that none of these studies are specific to the elderly population.

Statement 4.4: As in the general population, even in elderly patients, percutaneous cholecystostomy catheter should be removed between 4 and 6 weeks after placement, if a cholangiogram performed 2–3 weeks after percutaneous cholecystostomy demonstrated biliary tree patency (LoE 3 GoR C)

After percutaneous cholecystostomy, the duration of drainage ranges from 3 to 6 weeks, 1 month in average [67]. This represents the mean interval necessary for the maturation of the tract. Over this period, catheter removal is expected to become safer with respect to potential bile leak [65]. In case of associated diabetes, ascites, long-term steroid therapy, and malnutrition, the drain should be left in place for a longer period, because these conditions may hinder tract maturation.

The patients can be discharged home with the drain in place. A cholangiography via the drain is recommended before drain withdrawal. This procedure can ensure the absence of leak or obstructed cystic duct (a non obstructed cystic duct increases the chance of a leak after the removal of the drain lowering the risk of potential symptoms recurrence) [65–67].

In a series of 27 consecutive transhepatic percutaneous cholecystostomy, Bakkaloglu et al. performed cholecystocholangiography prior to the removal of the catheter in 88.8% cases: this demonstrated the cystic duct patency in 66.7% of subjects. Bleeding from the liver parenchyma was detected unexpectedly in only one patient following the removal of the catheter, while no bile leakage was detected in any patient [62].

However, it should be noted that none of these studies are specific to the elderly population and evidence for the use of a cholecystocholangiography is low.

**Question 5: Associated biliary tree stones: when to suspect, how to investigate when there is a high index of suspicion, when to treat, and which treatment?**

Common bile duct stones occur in about 5–10% of patients with ACC [69–72]. The strategy of non-selective preoperative endoscopic ultrasound or magnetic resonance cholangiopancreatography, or the routine use of intraoperative cholangiography may not be appropriate options to manage these patients.

Extensive research for specific suggestion for associated biliary tree stone in case of ACC in elderly patients has been done. There is no evidence for any difference in the likelihood or diagnostic accuracy of different investigations in elderly patients compared to general population, to warrant a change in the recommendations for elderly patients.

**Statement 5.1**: Even in elderly patients, elevation of liver biochemical enzymes and/or bilirubin levels is not sufficient to identify ACC patients with choledocholithiasis and further diagnostic tests are needed. (LoE 3 GoR C)

As reported in the 2016 WSES guidelines for ACC, the normal liver biochemical tests have a negative predictive value of 97%, whereas the positive predictive value of any abnormal liver biochemical test result is only 15% [56]. Positive predictive value of liver function studies is a poor tool for prediction of common bile duct stones, even in non-ACC, with results ranging from 25 to 50% [69, 73, 74].

The routine use of biochemical test should be used for the suspicion of common bile duct stones with the abovementioned limitations.

**Statement 5.2**: Even in elderly patients, the visualization of common bile duct stones on abdominal ultrasound is a very strong predictor of choledocholithiasis (LoE 5 GoR D). Even in elderly patients, indirect signs of stone presence such as increased diameter of common bile duct are not sufficient to identify ACC patients with choledocholithiasis and further diagnostic tests are needed. (LoE 2 GoR B)

The abdominal ultrasound can provide direct or indirect information on potential common bile duct stones. However, the common bile duct diameter on its own cannot be used to predict the risk of common bile duct stones: Boys et al., in a retrospective analysis, showed that a diameter > 10 mm was associated with 39% incidence of common bile duct stones, while diameter < 9.9 mm was associated with common bile duct stones in 14%. In elderly patients, the potential loss of musculature tone of the biliary duct may increase the diameter even in patients with common bile duct stones [75].

Further evidence arises from a recent meta-analysis that analyzed the predictive values of biochemical tests and abdominal ultrasound: the quality of studies considered was poor, many patients may have common bile duct stones despite having a negative ultrasound or liver function test and no studies tested the combination of liver function test and abdominal ultrasound [76]. As a consequence, a low threshold for further test could be suggested at the moment.

The direct visualization at the abdominal ultrasound of bile duct stone very strongly contributes to increases in the level of common bile duct stones suspicion in ACC patients.

**Statement 5.3** Liver biochemical tests, including ALT, AST, bilirubin, ALP, GGT, and abdominal ultrasound should be performed in all patients with ACC to assess the risk for common bile duct stones. (LoE 3 GoR C). Even in elderly patients, common bile duct stone risk should be stratified according to the proposed classification, modified from the American Society of Gastrointestinal Endoscopy and the Society of American...
Gastrointestinal Endoscopic Surgeon Guidelines (LoE 5 GoR D)

Many authors tried to design clinical scores for the suspicion and management of CBDS in case of gallbladder stone and ACC. Due to the inconclusiveness of such scores and the previously mentioned limitations of biochemical test and AUS, the WSES in 2016 adopted a modified score provided by the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) [77]: the bilirubin level greater than 4 mg/dl was changed from a “very strong predictor” to “strong predictor.”

Very strong predictor allowed SAGE and SAGES criteria to define a risk greater than 50% to have common bile duct stones and suggest endoscopic retrograde cholangio-pancreatography (ERCP) for these patients: on the other hand, a significant proportion of patients may receive potentially dangerous unnecessary ERCP (please see Table 2 for modified SAGE-AGES Classification) [56].

No specific data are available for elderly patients; however, we should stress the need to reduce the unnecessary stresses in elderly patients.

Statement 5.4: Even in elderly patients with moderate risk for choledocholithiasis preoperative magnetic resonance cholangio-pancreatography (MRCP), endoscopic US, intraoperative cholangiography, or laparoscopic ultrasound should be performed depending on the local expertise and availability. (LoE 2 GoR B)

In case of moderate risk of common bile duct stones (Table 2), the patient needs a more detailed test to confirm or not the suspicion. Preoperatively MRCP and endoscopic ultrasound (EUS) are the two methodologies available: because the accuracy is very high for both (sensitivity of 93% for MRCP and 95% for EUS and a summary specificity of 96% and 97% respectively), the choice should be influenced by local resources [78].

Depending on the local expertise available, the moderate risk can also be evaluated intraoperatively by means of laparoscopic ultrasound or intraoperative cholangiography: a recent meta-analysis showed that intraoperative cholangiography had a pooled sensitivity of 0.87 (95% CI 0.77–0.93) and a pooled specificity of 0.99 (95% CI 0.98–0.99) with no significant heterogeneity, while laparoscopic US had a pooled sensitivity of 0.87 (95% CI 0.80–0.92) and a specificity of 1.00 (95% CI 0.99–1.00). The only difference was a significant heterogeneity for specificity results among laparoscopic-US studies [79].

Statement 5.5: Elderly patients with high risk for choledocholithiasis should undergo preoperative ERCP, intraoperative cholangiography, or laparoscopic ultrasound, depending on the local expertise and the availability of the technique. (LoE 2 GoR B)

The WSES on 2016 suggested direct ERCP only in patients with confirmed common bile duct stones on abdominal ultrasound to allow immediate clearance of the duct. ERCP leads to complications (pancreatitis, cholangitis, duodenal perforations, hemorrhage, contrast media allergy) in 1% to 2% of patients which increases to 10% in case of sphincterotomy [80–83]. Therefore, additional tests such as MRCP should be performed to confirm the presence of common bile duct stones prior to ERCP.

Regarding the accuracy, ERCP and intraoperative cholangiography have showed excellent and comparable results: sensitivity from 0.83 to 0.99 respectively and specificity of 0.99 for both procedure [84].

Statement 5.6 Even in elderly patients, common bile duct stones could be removed preoperatively, intraoperatively, or postoperatively according to the local expertise and the availability of the technique. (LoE 2 GoR B)

In the general population, the three options carry the similar level of success, morbidity, and mortality; therefore, the choice can be based just on local issues such as expertise and service organization [84, 85].

In the absence of specific literature related to elderly patients, we should take the same considerations into account as in normal population.

**Question 6: antibiotic: which schedule for treatment?**

Therapy with appropriate antimicrobial agents is an important component in the management of geriatric patients with acute cholecystitis. Management of antibiotics in the elderly patient is often a major challenge. Advancing age is accompanied by changes in the pharmacokinetics and pharmacodynamics of antibiotics that often can be exacerbated by renal effects of coexisting diseases. Diabetes mellitus, congestive heart failure, and hypertension can predispose elderly patients to the risk of antibiotic-induced

### Table 2 2016 WSES predictive factor for CBDS and risk class (modified from SAGE-AGES)

<table>
<thead>
<tr>
<th>Predictive factor for choledocholithiasis</th>
<th>Very strong</th>
<th>Strong</th>
<th>Moderate</th>
<th>Risk class for choledocholithiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of CBD stone at abdominal ultrasound</td>
<td>Total serum bilirubin &gt; 4 mg/dL</td>
<td>Common bile duct diameter &gt; 6 mm (with gallbladder in situ)</td>
<td>Bilirubin level 1.8 to 4 mg/dL</td>
<td>Presence of any very strong</td>
</tr>
<tr>
<td>Age older than 55 years</td>
<td>Clinical gallstone pancreatitis</td>
<td></td>
<td></td>
<td>No predictors present</td>
</tr>
<tr>
<td>Risk class for choledocholithiasis</td>
<td>Intermediate</td>
<td>All other patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(please see Table 2 for modified SAGE-AGES Classification) [56].
toxicity, especially drugs with a narrow therapeutic index, such as aminoglycosides. Elderly patients often take multiple drugs that may adversely interact with antibiotics and contribute to a significant increase in the incidence of toxic reactions.

Moreover, elderly patients in institutions, such as nursing homes or geriatric hospitals, pose a particular challenge. Frailty combined with suboptimal hygiene (e.g., due to a high proportion of patients with dementia) can promote rapid dissemination of multidrug-resistant organisms (MDROs).

Therapy with appropriate antimicrobial agents is an important component in the management of patients with acute cholecystitis [86–88].

Statement 6.1: Elderly patients with uncomplicated cholecystitis can be treated without postoperative antibiotics with the focus of infection is controlled by cholecystectomy (LoE 2 GoR C).

Independent of age, patients with uncomplicated cholecystitis can be treated without postoperative antibiotic therapy.

A prospective trial on antibiotics in patients with uncomplicated cholecystitis was published in 2014 [89]. A total of 414 patients treated at 17 medical French centers for grade I or II acute calculus cholecystitis and who received 2 g of amoxicillin plus clavulanic acid three times a day and once at the time of surgery were randomized after surgery to antibiotic continuation versus non-antibiotic treatment group an open-label, non-randomized after surgery to antibiotic continuation versus non-antibiotic treatment group an open-label, non-randomized clinical trial between May 2010 and August 2012. An intention-to-treat analysis of the 414 patients showed that the postoperative infection rates were 17% (35/207) in the non-treatment group and 15% (31/207) in the antibiotic group (absolute difference, 1.93%; 95% CI, −8.98% to 5.12%). Loozen et al. published comparable results of a randomized trial shortly thereafter [90]. Therefore, postoperative antibiotics do not decrease postoperative infection rates.

Statement 6.2: In elderly patients with complicated acute cholecystitis, antibiotic regimens with broad spectrum are recommended as adequate empiric therapy should be guided by most frequently isolated bacteria taking into consideration antibiotic resistance and the clinical condition of the patient (LoE 2 GoR B).

In patients with complicated acute cholecystitis, initial empiric antibiotic therapy is necessary because the patient microbiological data (culture and susceptibility results) usually take at least 48 to 72 h to become fully available.

The decision for the empiric antimicrobial management of intra-abdominal biliary infections depends mainly on the presumed pathogens involved and risk factors for major resistance patterns and disease severity.

The empiric antibiotic treatment should be based on the most frequently isolated germs, always taking into consideration the local trend of antibiotic resistance. Organisms most often isolated in biliary infections are the gram-negative aerobes, Escherichia coli and Klebsiella pneumonia and anaerobes, especially Bacteroides fragilis [91, 92]. Health care-related infections are commonly caused by more resistant strains. For these infections, given that adequate empiric therapy appears to be a crucial factor affecting postoperative complications and mortality rates, complex regimens with broader spectra are recommended [93].

Many elderly patients come from institutions, such as nursing homes or geriatric hospitals and can be colonized by multidrug-related organisms: this poses a particular challenge. In these patients, intraoperative cultures should be always performed to reassess the antibiotic regimen.

The choice of the empirical antimicrobial regimen poses serious problems for the management of critically ill patients with intra-abdominal infections. Elderly patients are often frail, and infections can precipitate organ failure. In patients with sepsis, an early correct empirical antimicrobial therapy has a significant impact on the outcome [94]. Recent international guidelines for the management of severe sepsis and septic shock (Surviving Sepsis Campaign) recommend intravenous antibiotics within the first hour after severe sepsis and septic shock are recognized, use of broad-spectrum agents with good penetration into the presumed site of infection, and reassessment of the antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs [95]. In the event of biliary sepsis, clinicians should be aware that drug pharmacokinetics may be altered significantly in critically ill patients and antibiotics dosage should be reassessed daily on the basis of the pathophysiological status of the patient as well as the pharmacokinetic properties of the employed antibiotics [96].

In Table 3(a, b), the antimicrobial regimens suggested for acute cholecystitis are illustrated.

Statement 6.3: The results of microbiological analysis are helpful in designing targeted therapeutic strategies for individual patients with healthcare infections to customize antibiotic treatments and ensure adequate antimicrobial coverage (LoE 5 GoR D).

Identifying the causative organism(s) is an essential step in the management of acute cholecystitis. It has been reported that positive rates of either bile or gallbladder cultures range from 29 to 54% for acute cholecystitis [91]. Antibiotic therapy for 3–5 days is generally recommended for patients with complicated cholecystitis [91].

In patients who can tolerate oral feeding, to optimize antimicrobial therapy and minimize hospital stay, antibiotic therapy started initially intravenously may be
switched to oral therapy as soon as clinical conditions improve.

**Discussion**

Evidence-based guidelines were developed in the management of elderly patients with acute calculous cholecystitis. However, there were several challenges in developing these evidence-based guidelines. The first challenge was to define elderly population. There is no consensus in the definition of "elderly population." We used a pragmatic definition of an age of 65 years or above to define elderly population according to the job retirement and life expectancy in Italy; this may be different in other countries.

However, the present work has great value to offer the first dedicated guidelines to elderly, a framework that can be adopted in other populations with modifications to suit local requirements.

Despite an increasing emphasis on frailty measures, age still remains a key issue in the prognosis of patients and weighing the relative benefits of cholecystectomy versus conservative management, especially in the acute scenario. Surgical frailty scores are still under development and validation, and cannot be used easily: therefore, we are unable to recommend a uniform frailty score to be adopted in all hospitals and subjective clinical judgment on the prognosis of patients remains the main determinant factor in offering cholecystectomy to patients.

**Conclusions**

The main message of the present guidelines is that laparoscopic cholecystectomy should be considered for all; the age, on its own, is not a contraindication for surgery; only elderly patients with high surgical risk should be considered for non-surgical treatment. The role of cholecystostomy, as a bridging therapy until cholecystectomy, or as a definitive treatment in elderly patients, is uncertain.

Future research should focus on developing and validating a reliable prognostic score in assessing frailty that can guide the management on acute calculous cholecystitis. Majority of the randomized controlled trials exclude elderly patients; therefore, the evidence has to be extrapolated from that in younger patients. This indirectness causes significant uncertainty in developing guidelines for management of elderly population with acute cholecystitis. Future research on management of acute cholecystitis should include elderly patients whenever ethical and possible; the researchers should also present a subgroup analysis of the results in elderly patients, which can help in decreasing the uncertainty in many issues.

---

**Table 3** Antibiotic regimens

<table>
<thead>
<tr>
<th>Choice</th>
<th>Antibiotic class</th>
<th>Antimicrobial therapy for community-acquired cholecystitis</th>
<th>Antibiotic choice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Best choice from 1 to 5)</td>
<td>1. Beta-lactam/beta-lactamase inhibitor combinations based regimens</td>
<td>Amoxicillin/Clavulanate (in stable patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ticarcillin/Clavulanate (in stable patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Piperacillin/Tazobactam (in unstable patients)</td>
</tr>
<tr>
<td>2</td>
<td>Cephalosporins-based regimens</td>
<td>Ceftriazone + Metronidazole (in stable patients)</td>
<td>Cefepime + Metranidazole (in unstable patients)</td>
</tr>
<tr>
<td>3</td>
<td>Carbapenem-based regimens</td>
<td>Ertapenem (in stable patients if risk factors for ESBLs)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fluoroquinolone-based regimens (in case of allergy to beta-lactams)</td>
<td>Ciprofloxacin + Metronidazole (only in stable patients)</td>
<td>Levofloxacin + Metronidazole (only in stable patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moxifloxacin (only in stable patients)</td>
</tr>
<tr>
<td>5</td>
<td>Glycylcycline-based regimen</td>
<td>Tigecycline (in stable patients if risk factors for ESBLs)</td>
<td></td>
</tr>
</tbody>
</table>

b. Antimicrobial therapy for health care-associated

<table>
<thead>
<tr>
<th>Clinical patient’s condition</th>
<th>Antibiotic choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable</td>
<td>Tigecycline + Piperacillin/Tazobactam</td>
</tr>
<tr>
<td>Unstable</td>
<td>Imipenem/Cilastatin ± Teicoplanin</td>
</tr>
<tr>
<td></td>
<td>Meropenem ± Teicoplanin</td>
</tr>
<tr>
<td></td>
<td>Doripenem ± Teicoplanin</td>
</tr>
</tbody>
</table>
Appendix

Table 4 Statements

<table>
<thead>
<tr>
<th>Topic</th>
<th>#</th>
<th>LoE</th>
<th>GoR</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>1.1</td>
<td>2</td>
<td>B</td>
<td>There is no single investigation with sufficient diagnostic power to establish or exclude acute cholecystitis without further testing (LoE 2 GoR B). Combination of symptoms, signs, and laboratory tests results may have better diagnostic accuracy in confirming the diagnosis of ACC. (LoE 4 GoR D)</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>3</td>
<td>C</td>
<td>Abdominal ultrasound is the preferred initial imaging technique for elderly patients who are clinically suspected of having acute cholecystitis, in terms of lower costs, better availability, lack of invasiveness and good accuracy for stones.</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>3</td>
<td>C</td>
<td>Even in elderly patients, evidence on the diagnostic accuracy of CT are scarce and remain elusive while diagnostic accuracy of MRI might be comparable to that of abdominal ultrasound, but no sufficient data are provided to support this hypothesis. HIDA scan has the highest sensitivity and specificity for acute cholecystitis than other imaging modalities although its scarce availability, long time of execution, and exposure to ionizing radiations limit its use.</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>5</td>
<td>D</td>
<td>Even in elderly patients, combining clinical, laboratory, and imaging investigations should be recommended although the best combination is not yet known</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>4</td>
<td>D</td>
<td>No high-quality studies on specific diagnostic findings of acute cholecystitis in the elderly have been found; therefore, the stated recommendations of the WSES guidelines previously reported remain unchanged.</td>
</tr>
<tr>
<td>Surgical risk assessment and treatment</td>
<td>2.1</td>
<td>3</td>
<td>B</td>
<td>Old age (&gt; 65 years), by itself, does not represent a contraindication to cholecystectomy for ACC. Cholecystectomy is the preferred treatment for ACC even in elderly patients.</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>3</td>
<td>C</td>
<td>The evaluation of the risk for elderly patient with ACC should include: • Mortality rate for conservative and surgical therapeutic options • Rate of gallstone-related disease relapse and the time to relapse • Age-related life expectancy • Consider patient frailty evaluation by the use of frailty scores Consider estimation of specific risk (patient/type of surgery) by the use of surgical clinical scores</td>
</tr>
<tr>
<td>Timing and surgical technique</td>
<td>3.1</td>
<td>2</td>
<td>B</td>
<td>In elderly patients with acute cholecystitis, laparoscopic approach should always be attempted at first except in case of absolute anesthetic contraindications and septic shock.</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>2</td>
<td>B</td>
<td>In elderly patients, laparoscopic cholecystectomy for acute cholecystitis is safe, feasible, with a low complication rate, and associated with shortened hospital stay.</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>3</td>
<td>C</td>
<td>In elderly patients, laparoscopic or open subtotal cholecystectomy is a valid option for advanced inflammation, gangrenous gallbladder, and more in general in “difficult gallbladder” where anatomy is difficult to be recognized and main bile duct injuries are highly probable.</td>
</tr>
<tr>
<td></td>
<td>3.4</td>
<td>3</td>
<td>C</td>
<td>In elderly patients, conversion to open surgery may be predicted by fever, leucocytosis, elevated serum bilirubin, and extensive upper abdominal surgery. In case of local severe inflammation, adhesions, bleeding in the Calot’s triangle, and suspect bile duct injury, conversion to open surgery should be considered.</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>2</td>
<td>B</td>
<td>Even in elderly patients, early laparoscopic cholecystectomy should be performed as soon as possible but can be performed up to 10 days of onset of symptoms. However, it should be noted that earlier surgery is associated with shorter hospital stay and fewer complications.</td>
</tr>
<tr>
<td>Alternative treatments</td>
<td>4.1</td>
<td>2</td>
<td>B</td>
<td>Percutaneous cholecystostomy can be considered in the treatment of ACC patients (older than 65, with ASA II/IV, performance status 3 to 4, or septic shock) who are deemed unfit for surgery.</td>
</tr>
<tr>
<td></td>
<td>4.2</td>
<td>3</td>
<td>C</td>
<td>If medical therapy failed, percutaneous cholecystostomy should be considered as a bridge to cholecystectomy in acutely ill (high-risk) elderly patients deemed unfit for surgery, in order to convert them in a moderate risk patient, more suitable for surgery.</td>
</tr>
<tr>
<td></td>
<td>4.3</td>
<td>4</td>
<td>D</td>
<td>As in the general population, even in elderly patients, percutaneous transhepatic cholecystostomy is the preferred method to perform percutaneous cholecystostomy.</td>
</tr>
<tr>
<td></td>
<td>4.4</td>
<td>3</td>
<td>C</td>
<td>As in the general population, even in elderly patients, percutaneous cholecystostomy catheter should be removed between 4 and 6 weeks after placement, if a cholangiogram performed 2–3 weeks after percutaneous cholecystostomy demonstrated biliary tree patency.</td>
</tr>
<tr>
<td>Associated common bile duct stones</td>
<td>5.1</td>
<td>3</td>
<td>C</td>
<td>Even in elderly patients, elevation of liver biochemical enzymes and/or bilirubin levels is not sufficient to identify ACC patients with cholecdocholithiasis and further diagnostic tests are needed.</td>
</tr>
<tr>
<td></td>
<td>5.2</td>
<td>2</td>
<td>B</td>
<td>Even in elderly patients the visualization of common bile duct stones on abdominal ultrasound is a very strong predictor of cholecdocholithiasis (LoE 5 GoR D). Even in elderly patients, indirect signs of stone presence such as increased diameter of common bile duct are not sufficient to identify ACC patients with cholecdocholithiasis and further diagnostic tests are needed.</td>
</tr>
</tbody>
</table>
|                                                 | 5.3 | 3   | C   | Liver biochemical tests, including ALT, AST, bilirubin, ALP, GGT, and abdominal ultrasound should be performed in all patients with ACC to assess the risk for common bile duct stones. (LoE 5 GoR C) Even in elderly patients, common bile duct stone risk should be stratified according to the proposed...
Table 4 Statements (Continued)

<table>
<thead>
<tr>
<th>Topic</th>
<th>#</th>
<th>LoE</th>
<th>GoR</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4</td>
<td>2</td>
<td>B</td>
<td></td>
<td>Even in elderly patients with moderate risk for choledocholithiasis preoperative MRCP, endoscopic US, intraoperative cholangiography, or laparoscopic ultrasound should be performed depending on the local expertise and availability.</td>
</tr>
<tr>
<td>5.5</td>
<td>2</td>
<td>B</td>
<td></td>
<td>Elderly patients with high risk for choledocholithiasis should undergo preoperative ERCP, intraoperative cholangiography, or laparoscopic ultrasound, depending on the local expertise and the availability of the technique.</td>
</tr>
<tr>
<td>5.6</td>
<td>2</td>
<td>B</td>
<td></td>
<td>Even on elderly patients, common bile duct stones could be removed preoperatively, intraoperatively, or postoperatively according to the local expertise and the availability of the technique.</td>
</tr>
<tr>
<td><strong>Antibiotic therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1</td>
<td>2</td>
<td>C</td>
<td></td>
<td>Elderly patients with uncomplicated cholecystitis can be treated without postoperative antibiotics when the focus of infection is controlled by cholecystectomy.</td>
</tr>
<tr>
<td>6.2</td>
<td>2</td>
<td>B</td>
<td></td>
<td>In elderly patients with complicated acute cholecystitis antibiotic regimens with broad spectrum are recommended as adequate empiric therapy significantly affects outcomes in critical elderly patients. The principles of empiric antibiotic therapy should be guided by most frequently isolated bacteria taking into consideration antibiotic resistance and the clinical condition of the patient.</td>
</tr>
<tr>
<td>6.3</td>
<td>5</td>
<td>D</td>
<td></td>
<td>The results of microbiological analysis are helpful in designing targeted therapeutic strategies for individual patients with healthcare infections to customize antibiotic treatments and ensure adequate antimicrobial coverage.</td>
</tr>
</tbody>
</table>

**Abbreviations**


**Acknowledgements**

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**Availability of data and materials**

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**Authors’ contributions**

MP coordinated the working group, developed the design for the Consensus Conference, developed the section “Question 2” at the Consensus Conference and draft the paper section, draft the manuscript. LA created the project; chief coordinator, contributed to the final version of the paper, and final approval was obtained. FC was co-creator of the project; chief coordinator, development of section “Question 3” at the Consensus Conference, contributed to the final version of the paper, and final approval was obtained. MC developed the design for the Consensus Conference; co-coordination of the working groups; review of the manuscript; table development; references section assessment, contributed to the final version of the paper, and final approval was obtained. SC and MF developed the section “Question 4” at the Consensus Conference and draft the paper section, contributed to the final version of the paper, and final approval was obtained. KG supervised the Consensus Conference, reviewed all the statements for right graduation, reviewed the manuscript; contributed to the final version of the paper, and final approval was obtained. FC contributed to design of the Consensus Conference; developed the section “Question 3” at the Consensus Conference and for the paper, contributed to the final version of the paper, and final approval was obtained. GB and GC developed the section “Question 1” at the Consensus Conference and draft the paper section, and final approval was obtained. MS and BA developed the section “Question 6” at the Consensus Conference, draft the paper section, and final approval was obtained. DB reviewed the paper section “Question 4,” reviewed the entire manuscript, contributed for the final version of the paper, and final approval of the paper was obtained. NA, OC, and EP contributed to the coordination of the working group, contributed for the final version of the paper, and final approval of the paper was obtained. FCC, AC, and SDS developed the section “Question 5” at the Consensus Conference; they contributed for the final version of the paper and final approval of the paper was obtained. AC, FG, and YK contributed for the Consensus Conference, contributed for the final version of the paper, and final approval of the paper was obtained. AP, LC, PC, AG, SM, and CM they contributed for the final version of the paper and final approval of the paper was obtained. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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2019 WSES guidelines for the management of severe acute pancreatitis

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Abstract

Although most patients with acute pancreatitis have the mild form of the disease, about 20–30% develops a severe form, often associated with single or multiple organ dysfunction requiring intensive care. Identifying the severe form early is one of the major challenges in managing severe acute pancreatitis. Infection of the pancreatic and peripancreatic necrosis occurs in about 20–40% of patients with severe acute pancreatitis, and is associated with worsening organ dysfunctions. While most patients with sterile necrosis can be managed nonoperatively, patients with infected necrosis usually require an intervention that can be percutaneous, endoscopic, or open surgical. These guidelines present evidence-based international consensus statements on the management of severe acute pancreatitis from collaboration of a panel of experts meeting during the World Congress of Emergency Surgery in June 27–30, 2018 in Bertinoro, Italy. The main topics of these guidelines fall under the following topics: Diagnosis, Antibiotic treatment, Management in the Intensive Care Unit, Surgical and operative management, and Open abdomen.

Keywords: Acute pancreatitis, Necrosectomy, Infected necrosis, Open abdomen, Consensus statement

Introduction

Acute pancreatitis is an inflammatory condition of the pancreas most commonly caused by bile stones or excessive use of alcohol. In most patients, the disease takes a mild course, where moderate fluid resuscitation, management of pain and nausea, and early oral feeding result in rapid clinical improvement.

The severe form comprising about 20–30% of the patients is a life-threatening disease with hospital mortality rates of about 15% [1]. The most commonly used classification system for acute pancreatitis is the 2012 revision of the Atlanta classification and definitions based on international consensus [2]. This classification identifies two phases (early and late). Severity is classified as mild, moderate, or severe. The mild form (interstitial edematous pancreatitis) has no organ failure, local or systemic complications, and usually resolves in the first week. If there is transient (less than 48 h) organ failure, local complications or exacerbation of co-morbid disease, it is classified as moderate. Patients with persistent (more than 48 h) organ failure have the severe form of the disease.

Infection of the pancreatic and peripancreatic necrosis occurs in about 20–40% of patients with severe acute pancreatitis, and is associated with worsening organ dysfunctions. In a systematic review and meta-analysis totaling 6970 patients, the mortality rate in patients with infected necrosis and organ failure was 35.2% while concomitant sterile necrosis and organ failure was associated with a mortality of 19.8%. If the patients had infected necrosis without organ failure, the mortality was 1.4% [3].

According to the updated Atlanta classification 2012, the peripancreatic collections associated with necrosis are acute necrotic collection (ANC) and walled-off necrosis (WON) [2]. ANC is a collection seen during the first 4 weeks and containing variable amount of fluid and necrotic tissue involving the pancreatic parenchyma...
and/or peripancreatic tissues. WON is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis with a well-defined, enhancing inflammatory wall. The maturation takes usually 4 weeks or more after the onset of acute pancreatitis.

Currently, several trends in the management of severe acute pancreatitis have changed our clinical practices; early enteral feeding, selective role of prophylactic antibiotics, avoiding surgery in patients with sterile necrosis, more conservative approach to infected necrosis with delayed intervention, whether endoscopic or surgical, and management of biliary pancreatitis. The aim of these guidelines is to present evidence-based international consensus statements on the management of severe acute pancreatitis from collaboration of a panel of experts meeting during the World Congress of Emergency Surgery in June 27–30, 2018 in Bertinoro, Italy.

**Methods**

These guidelines have been created by international collaboration and discussion among an expert panel of clinicians, practicing in the field of emergency surgery and managing patients with severe acute pancreatitis. These consensus guidelines have been facilitated by the World Society of Emergency Surgery, and are an update of the 2014 World Society of Emergency Surgery (WSES) position paper on this topic [4].

The statements are formulated and graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) hierarchy of evidence from Guyatt and colleagues [5], summarized in Table 1.

For clarity, the statements and discussions have been divided into five topics: Diagnosis, Antibiotic treatment, Management in the Intensive Care Unit (ICU), Surgical and operative management, and Open abdomen.

**Results**

**Diagnosis**

Questions:

1. Which are the criteria to establish the diagnosis of severe acute pancreatitis?

2. What is the appropriate imaging work-up in case of suspected severe acute pancreatitis? What is the

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**Table 1** Grading of Recommendations Assessment, Development and Evaluation (GRADE) hierarchy of evidence from Guyatt et al. [5]

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses or imprecise conclusions) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, Low-quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
</tr>
</tbody>
</table>
role of magnetic resonance imaging (MRI), computed tomography (CT) scan, ultrasound (US), endoscopic ultrasound (EUS), and other ancillary tests?
3. Which laboratory parameters should be considered in the diagnostic process?
4. How do different etiologies affect the diagnostic workup?
5. Which scores are indicated for risk assessment?
6. What is the timing and the suitable test for early follow-up imaging?

**Statements (severity grading)**

1. Severe acute pancreatitis is associated with persistent organ failure (cardiovascular, respiratory, and/or renal), and high mortality. Both new classification systems, Revised Atlanta Classification and Determinant-based Classification of Acute Pancreatitis Severity, are similar in establishing the diagnosis and severity of acute pancreatitis (1C).
2. Patients who have persistent organ failure with infected necrosis have the highest risk of death (1C).
3. Patients with organ failures should be admitted to an intensive care unit whenever possible (1C).

**Discussion** Acute pancreatitis (AP) represents a disease characterized by acute inflammation of the pancreas and histologically acinar cell destruction [6]. The diagnosis of AP requires at least the presence of two of the three following criteria: (i) abdominal pain consistent with the disease, (ii) biochemical evidence of pancreatitis (serum amylase and/or lipase greater than three times the upper limit of normal), and (iii) characteristic findings from abdominal imaging [2].

Most patients (80–85%) will develop a mild disease course (self-limited, mortality <1–3%), but around 20% will have a moderate or severe episode of AP, with a mortality rate from 13 to 35% [7, 8]. Thus, it is important to diagnose (or better predict) an episode of severe acute pancreatitis (SAP), and to identify the patients with high risk of developing complications.

During almost 20 years, the 1992 Atlanta Classification has been used, but some of the definitions and the classifications have been confusing [9]. In a revision of 447 articles, Bollen et al. found that alternative definitions of the 1992 Atlanta Classification were used in more than half of the studies, and that definitions are often used erroneously [9].

Important insights on the management of AP, better understanding of the pathophysiology of organ failure and necrotizing pancreatitis, improved diagnostic imaging, minimally invasive techniques, and studies showing that patients in the severe group of the 1992 Atlanta Classification comprise subgroups with very different outcomes, were indications that a more accurate classification is warranted. In a review in 2004, Johnson et al. reported that persistent organ failure (POF) for more than 48 h in the first week is strongly associated with the risk of death or local complications [10]. They used a previous database of 290 patients with predicted SAP recruited from 78 hospitals through 18 centers in the UK, and also cited that resolution of organ failure within 48 h suggests a good prognosis.

A retrospective study of 759 patients with AP performed by the University of Edinburgh found that 25.4% of the patients with persistent systemic inflammatory response syndrome (SIRS) died, compared with 8% with transient SIRS and 0.7% without SIRS [11].

These and other studies showed that organ failure is central to the definition of SAP. If organ failure persists for more than 48 h, the patient is at high risk of death (one out of three) and a “severe” category can be established. Also, it is important to remind that a period of illness with a marked inflammatory response (SIRS) preceded the organ failure, and if SIRS is present, the patient is at risk of progression to organ failure, and every attempt should be made to restore normality as soon as possible [12].

Almost simultaneously in 2012, two new classifications systems of AP were published: Determinant-Based Classification of Acute Pancreatitis Severity (DBC) and the Revised Atlanta Classification 2012 (RAC) [2, 13]. The novel DBC was based on a global web-based survey and a dedicated international symposium with contributors from different disciplines: E-mail invitations were delivered to 528 pancreatologists from 55 countries, and 240 pancreatologists from 49 countries participated in the survey. During the 2011 World Congress of the International Association of Pancreatology (Kochi, India), around 100 participants discussed the proposed classification and tried to agree on the definitions [13].

The RAC was generated by an iterative, web-based consultation process incorporating responses from the members of 11 national and international pancreatic societies. Revisions were made in response to comments, and the web-based consultation was repeated three times. The final consensus was reviewed, and only statements based on published evidence were retained [2]. The RAC is a broader overview than DBC: in addition to severity classification, it provides a clear definition of diagnosing AP, highlights the onset of pain as an important reference point, and defines individual local complications as well as interstitial and necrotizing pancreatitis [2, 14]. The RAC has three categories: mild, moderately severe, and severe, according to organ failure and local...
or systemic complications. The DBC added a fourth category: critical, based on two main determinants of mortality: (peri)pancreatic necrosis and organ failure (Table 2).

Subsequently, Bansal et al. in a cohort of 248 patients found that RAC and DBC are similar in ICU admission, need of percutaneous drainage, need for surgery, and in-hospital mortality. The critical category in DBC identified the most severe disease [15]. Nawaz et al. enrolled prospectively 256 patients, and assigned a severity category for all three classifications: RAC, DBC, and Atlanta 1992. They found that RAC and DBC severity categories accurately reflected clinical outcomes and were superior to Atlanta 1992 (evaluating mortality, ICU admission, ICU length of stay) [16].

Two years later, a retrospective study of 395 patients in China, with an overall 8.9% in-hospital mortality, found similar results. The authors found that all three classification systems (RAC, BDC, and Atlanta 1992) accurately classify the severity of AP. However, the RAC and the DBC performed better than the Atlanta 1992, and they were comparable in predicting long-term clinical prognosis, major complications, and clinical interventions [17].

Choi et al. studying 553 patients with AP admitted to a single center during the 7-year period, validated the RAC correlating well with clinical outcome, despite not considering infected necrosis. However, patients in the severe group and with infected necrosis (classified as critical in DBC) should be considered separately from those without it (the mortality rate increased fourfold: up to 32%) [18]. Another study analyzed 543 episodes of AP from 459 patients in a prospective cohort of patients. They found that the different categories of severity for each classification system were associated with statistically significant and clinically relevant differences in length of hospital stay, need for admission to the intensive care unit, nutritional support, invasive treatment, and in-hospital mortality. In addition, the direct comparison between categories of both classifications (after unifying the severe and critical category of the DBC) yielded no significant differences [19].

In general, patients with organ failure (accurately defined utilizing one of the established criteria or scoring systems) need an urgent transfer to an ICU. Accordingly, it may be unnecessary to transfer patients with transient organ failure to either a tertiary medical center or an ICU. Nevertheless, to confirm persistent organ failure, it needs to be documented for over 48 h.

**Statements (imaging)**

1. On admission, ultrasound (US) should be performed to determine the etiology of acute pancreatitis (biliary) (1C).
2. When doubt exists, computed tomography (CT) provides good evidence of the presence or absence of pancreatitis (1C).
3. All patients with severe acute pancreatitis need to be assessed with contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (MRI). Optimal timing for first the CE-CT assessment is 72–96 h after onset of symptoms (1C).
4. Magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound should be considered to screen for occult common bile duct stones in patients with unknown etiology (1C).

**Discussion** On admission, the etiology of AP should be determined, to project the need of definitive treatment (e.g., gallstone disease) and to avoid recurrence (e.g., alcohol intake, hypertriglyceridemia) [20]. The treatment and follow-up depend on the etiology of the AP. A transabdominal US should be performed on admission

<table>
<thead>
<tr>
<th>Revised Atlanta Classification (RAC)</th>
<th>Determinant-based classification (DBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild acute pancreatitis (AP)</td>
<td>Mild AP</td>
</tr>
<tr>
<td>No organ failure</td>
<td>No organ failure AND</td>
</tr>
<tr>
<td>No local or systemic complications</td>
<td>No (peri)pancreatic necrosis</td>
</tr>
<tr>
<td>Moderately severe AP</td>
<td>Moderate AP</td>
</tr>
<tr>
<td>Transient organ failure (&lt; 48 h)</td>
<td>Transient organ failure AND/OR</td>
</tr>
<tr>
<td>Local or systemic complications</td>
<td>Sterile (peri)pancreatic necrosis</td>
</tr>
<tr>
<td>Severe AP</td>
<td>Severe AP</td>
</tr>
<tr>
<td>Persistent single or multiple organ failure (&gt; 48 h)</td>
<td>Persistent organ failure OR</td>
</tr>
</tbody>
</table>

| Critical AP | Infected (peri)pancreatic necrosis |

---

**Table 2** Definition of severity in acute pancreatitis
(to perform cholecystectomy for biliary pancreatitis when appropriate). Almost all the AP guidelines worldwide (based on revisions and meta-analyses) recommend performing US on admission or in the first 48 h [7, 8, 20–23].

In the majority of patients with AP, CT is not required [24]. The extension of the (peri)pancreatic necrosis may be detected with a contrast-enhanced CT (CECT) after 72 h from the onset of AP [20]. Concerns have been raised over post-contrast acute kidney injury (AKI). A recent meta-analysis with 28 observational studies and over 100,000 participants found no evidence to support the association of contrast with AKI, renal replacement therapy, or mortality [25]. However, there are no comparative studies in patients with severe acute pancreatitis or sepsis, and therefore, caution should be applied.

Early CT scan will not show necrotic/ischemic areas, and will not modify the clinical management during the first week of the illness. However, when the diagnosis is uncertain, CT should be considered, especially to rule out secondary perforation peritonitis or mesenteric ischemia. It also shows active hemorrhage and thrombosis associated with pancreatitis [21, 22].

CECT has been shown to yield an early overall detection rate of 90% with close to 100% sensitivity after 4 days for pancreatic necrosis [26]. Balthazar et al. established a CT severity index (Table 3) that graded pancreatitis based on the degree of inflammation, presence of fluid collections, and extent of necrosis: a higher score is associated with increased morbidity and mortality [26–28].

CECT is the imaging modality of choice for diagnosis, staging, and detection of complications of acute pancreatitis, and has major roles in the evaluation of patients with known or suspected AP: (i) diagnosis, (ii) staging of the severity, and (iii) detection of complications, particularly the identification and quantification of (peri)pancreatic necrosis [20, 24, 26]. However, frequent repeat CT scans increase the total radiation dose and have limited effect in subsequent decision-making [29].

MRI is preferable to CECT in patients with allergy to iodinated contrast, in patients with renal impairment/insufficiency (unenhanced MRI), in young or pregnant patients to minimize radiation exposure in order to identify nonliquefied material (e.g., debris or necrotic tissue), but is less sensitive than CT for detecting gas in fluid collections [24, 26]. CT without contrast is an alternative for the first two patient groups, if MRI is not available.

When US does not show gallstones, sludge, or biliary obstruction and in the absence of cholangitis and/or abnormal liver function tests suggesting biliary obstruction, magnetic resonance cholangio-pancreatography (MRCP) or endoscopic ultrasound (EUS) rather than diagnostic endoscopic retrograde cholangiopancreatography (ERCP) should be used to screen for occult choledocholithiasis, if no other etiology can be established [20, 24]. In a retrospective cohort studying 221 patients, MRCP has a sensitivity of 97.98% and specificity of 84.4% for choledocholithiasis avoiding the need for invasive imaging in most patients with suspected choledocholithiasis [30].

### Table 3 CT Severity Index (Modified from: Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990; 174:331–6 [27])

<table>
<thead>
<tr>
<th>CT grade</th>
<th>Grade score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>Normal pancreas</td>
</tr>
<tr>
<td>B</td>
<td>1</td>
<td>Pancreatic enlargement</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>Pancreatic inflammation and/or peripancreatic fat</td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>Single peripancreatic fluid collection</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>$\geq 2$ fluid collections and/or retroperitoneal air</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% of necrosis</th>
<th>Necrosis score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>Uniform pancreatic enhancement</td>
</tr>
<tr>
<td>$&lt; 30%$</td>
<td>2</td>
<td>Non-enhancement of region(s) of gland equivalent in size of pancreatic head</td>
</tr>
<tr>
<td>$30–50%$</td>
<td>4</td>
<td>Non-enhancement of 30–50% of the gland</td>
</tr>
<tr>
<td>$&gt; 50%$</td>
<td>6</td>
<td>Non-enhancement of over 50% of the gland</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CT Severity Index</th>
<th>Morbidity</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2–3</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>4–6</td>
<td>35%</td>
<td>6%</td>
</tr>
<tr>
<td>7–10</td>
<td>92%</td>
<td>17%</td>
</tr>
</tbody>
</table>

CT severity Index = grade score (0–4) + necrosis score (0–6)
Statements (diagnostic laboratory parameters)

1. The cut-off value of serum amylase and lipase is normally defined to be three times the upper limit.
2. C-reactive Protein level $\geq 150$ mg/l at third day can be used as a prognostic factor for severe acute pancreatitis (2A).
3. Hematocrit $> 44\%$ represents an independent risk factor of pancreatic necrosis (1B).
4. Urea $> 20$ mg/dl represents itself as an independent predictor of mortality (2B).
5. Procalcitonin is the most sensitive laboratory test for detection of pancreatic infection, and low serum values appear to be strong negative predictors of infected necrosis (2A).
6. In the absence of gallstones or significant history of alcohol use, serum triglyceride and calcium levels should be measured. Serum triglyceride levels over 11.3 mmol/l (1000 mg/dl) indicate it as the etiology (2C).

Discussion Serum pancreatic enzyme measurement is the “gold standard” for the diagnosis of AP [31]. In an episode of AP, amylase, lipase, elastase, and trypsin are released into the bloodstream at the same time but the clearance varies depending on the timing of blood sampling. Amylase is an enzyme secreted by the pancreas, and also salivary glands, small intestine, ovaries, adipose tissue, and skeletal muscles. There are two major isoforms of amylase: pancreatic and salivary, and the leading function is digestion of starch, glycogen, and related polyand oligosaccharides, by hydrolysis [32]. In AP, serum amylase levels usually rise within 6 to 24 h, peak at 48 h, and decrease to normal or near normal levels over the next 3 to 7 days [23, 32, 33].

Lipase is another enzyme secreted by the pancreas. AP is the main reason for an increase in lipase, and many investigators emphasize that lipase is more specific, but can be found elevated also in non-pancreatic diseases such as renal disease, appendicitis, acute cholecystitis, chronic pancreatitis, bowel obstruction, etc. [23]. In AP, serum lipase remains elevated for a longer period than serum amylase. It rises within 4 to 8 h, peaks at 24 h, and decreases to normal or near normal levels over the next 8 to 14 days [32, 33].

Trypsinogen is the zymogen of the pancreatic enzyme trypsin. In AP, the serum and urinary concentrations of trypsinogen usually rise to high levels within a few hours and decrease in 3 days [32, 33].

Collectively, serum lipase is considered a more reliable diagnostic marker of AP than serum amylase. No single test shows optimal diagnostic accuracy, but most current guidelines and recommendations indicate that lipase should be preferred over total and p-amylase [32]. The main reasons supporting lipase over both types of amylase for the diagnosis of acute pancreatitis include higher sensitivity and larger diagnostic window [32]. A Cochrane revision with the aim to compare the diagnostic accuracy of different pancreatic enzymes in the diagnosis of AP showed a sensitivity and specificity of 72% and 93% for serum amylase, and 79% and 89% for serum lipase, respectively [33].

Chang et al. found in a meta-analysis including 13 studies that trypsinogen-2 dipstick test is a rapid and non-invasive bedside test with sensitivity 82% and specificity 94% for AP [34].

Numerous biomarkers have been studied as potential early predictors of the severity of AP so that treatment can be optimally tailored to prevent complications [34, 35]. At this moment, no laboratory test is practically available or consistently accurate to predict severity in patients with AP [23].

In the absence of gallstones or significant history of alcohol use, serum triglyceride should be measured and considered to be the etiology if the value is $> 11.3$ mmol/l ($> 1000$ mg/dl) [23].

Many textbooks consider the C-reactive protein (CRP) as the gold standard for disease severity assessment [36]. Using a cut-off value from 110 to 150 mg/l, the sensitivity and specificity ranged from 38 to 61%, and 89 to 90%, respectively, at the time of hospital admission [36]. The major drawback of CRP is that peak levels are reached only after 48 to 72 h.

In a prospective study of 175 patients divided into mild and non-mild acute pancreatitis according to the Atlanta classification, CRP and IL-6 combined demonstrated good discriminative capacity with an area under the curve of 0.803 [37].

Resistin is a newly identified peptide hormone, secreted specifically by adipocytes that can cause obesity and hypertriglyceridemia, due to its association with insulin resistance. Studies have revealed that resistin is also an important cytokine in inflammatory reactions, and in the regulation of other cytokines [38]. In a prospective observational study, resistin levels were better for predicting SAP than CRP or WBC levels on day 3, and better than CRP levels for predicting the development of necrosis [38]. A retrospective cohort study from data from 90 patients found that resistin has similar accuracy with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score in predicting POF, and leptin has a weak correlation with POF [39].

Other laboratory findings used to characterize an episode of SAP are BUN $> 20$ mg/dl ($> 7.14$ mmol/l) or rising BUN, hematocrit (HCT) $> 44\%$ or rising HCT, lactate dehydrogenase (LDH), and procalcitonin for predicting infected necrosis in patients with confirmed pancreatic necrosis [36, 40–43]. A procalcitonin value of
3.8 ng/ml or higher within 96 h after onset of symptoms indicated a pancreatic necrosis with a sensitivity and specificity of 93% and 79% [36, 42]. Serum lactate level on admission predicts severe AP, death, and ICU admission, but should be considered suboptimal as a single marker [44].

**Statements (diagnostics in idiopathic pancreatitis)**

1. In idiopathic pancreatitis, biliary etiology should be ruled out with two ultrasound examinations, and if needed MRCP and/or endoscopic ultrasound EUS, to prevent recurrent pancreatitis (2B).

**Discussion** Idiopathic AP is defined as pancreatitis with no etiology established after initial laboratory and imaging tests. In patients with idiopathic AP, at least two US examinations should be performed to rule out biliary etiology [31]. Following that, CE-CT and EUS, after the acute phase is over, are the next steps to assess micro-lithiasis, neoplasm, or chronic pancreatitis. If EUS is negative, MRI should be performed to identify morphologic abnormalities [31]. Laparoscopic cholecystectomy seems to prevent recurrent idiopathic acute pancreatitis; however, there is currently insufficient evidence to support this approach routinely [45].

**Statement (risk scores)**

1. There are no “gold standard” prognostic score for predicting severe acute pancreatitis. Probably the bedside index of severity of acute pancreatitis (BISAP) score is one of the most accurate and applicable in everyday clinical practice because of the simplicity and the capability to predict severity, death, and organ failure as well as the APACHE-II (very complex) and other scores (1B).

**Discussion** Several scoring systems have been developed to predict SAP, but evidence on their predictive performance is variable [46, 47]. Currently, no systematic review has included studies assessing the accuracy of different clinical scoring systems used to predict severity and mortality in people with acute pancreatitis. Cochrane Database of Systematic Reviews is developing a protocol to synthesize studies evaluating the predictive accuracy of clinical scoring systems (measured on admission and up to 48 h following admission) [46].

Most prediction scores in AP have focused on death as an outcome. With the overall mortality declining over the past decades, it should be considered whether death should remain as the principal outcome to predict pancreatitis [48]. Another aspect is that more or less all severity scores take more than 24 h to stratify the patients, and probably that represent a loss of time in some critically ill patients [48]. A retrospective cohort study from UK conducted in 159 ICUs evaluating 2,462 patients admitted to ICU with SAP showed that 75% of the patients who required intensive care were transferred to the ICU within the first 72 h of admission to hospital, with a median time-to-transfer of 24 h after admission [49].

Over time, most scores were based on patient demographics, clinical features, laboratory parameters, or imaging modalities, and were assessed on admission or within 48 h: Ranson criteria (1974), Glasgow-Imrie score (1978), Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS II) (1984), Sequential Organ Failure Assessment (SOFA), CT severity index (CTSI), Bedside Index of Severity in Acute Pancreatitis (BISAP) score (2008), Japanese Severity Score [46].

The predictors (or potential predictors) present in almost all of the scoring systems mentioned above include age, organ failure or immunocompromise, previous history of chronic disease, temperature, blood pressure, pulse rate, respiratory rate, body mass index, consciousness level, presence of peritonitis, presence of acute renal failure, blood white cell count, blood hematocrit, blood platelet count, blood glucose, blood urea nitrogen, serum creatinine, serum aspartate transaminase, serum lactate dehydrogenase, serum calcium, serum electrolytes, serum bilirubin, plasma albumin, oxygen saturation, pH, and base deficit, and multiple imaging modalities principally CT.

The APACHE II score evaluates the chronic health score and 12 physiologic measurement, but is not specific for AP, and is not designed for day to day evaluation in any patient. The advantages of this score are that it is a widely validated instrument and can be done at any time, but it has disadvantages; i.e., cumbersome and not all parameters are routinely collected [48]. In a study of 81 consecutive patients with AP, Thandassery et al. found that independent predictors of occurrence of infected necrosis were hypotension and APACHE II score at 24 h of hospital admission [50].

A study of 161 patients evaluated the assessment and comparison of the early predictability of various parameters most widely used in AP. They found the significant cutoff values for prediction of severe AP were Ranson ≥ 3, BISAP ≥ 2, APACHE-II ≥ 8, CTSI ≥ 3, and CRP at 24 h ≥ 21 mg/dl (> 210 mg/l). They concluded that different scoring systems showed similar predictive accuracy for severity of AP, but that APACHE-II demonstrated the highest accuracy for the prediction of SAP [51].
The PPV for the Ranson score ranges from 28.6 to 49% (sensitivity 75–87%, specificity 68–77.5%), for the Glasgow score from 59 to 66% (sensitivity 61–71%, specificity 88–89%), for the APACHE II score, 55.6% after 48 h (sensitivity 83.3%, specificity 91%), and for the APACHE-O score 54–80% (sensitivity 69–74%, specificity 86–90%). All these scores can only be assessed after 48 h, and thus do not enable risk stratification on admission. Despite their weaknesses, these scores are still useful to prove or exclude severe disease [31].

BISAP, a recently developed prognostic scoring system, has been proposed as a simple method for prediction of severe AP compared to traditional scoring systems. BISAP represent an acronym of the parameters evaluated in the score (Table 3) [48].

The BISAP score was derived using data from a population of 17,992 patients and validated on a population of 18,256 patients in the USA [52]. It has similar accuracy to the APACHE-II score for predicting death and is a very simplified scoring system that can be easily applied in the earliest phases. One of the key points of this study is that it was able to identify patients at increased risk of mortality prior to the onset of organ failure [52]. A retrospective analysis of 303 patients revealed that BISAP predicts severity, death, and especially organ failure (OF) in AP as well as APACHE-II does, and better than Ranson criteria, CT-severity index, CRP, hematocrit, and BMI. A BISAP score of two was a statistically significant cutoff value for the diagnosis of severe acute pancreatitis, organ failure, and mortality [53] (Table 4).

Multiple studies cite that BMI, obesity, and or overweight are independent risk factors for developing severe AP, local complications, or death [54, 55]. A study performed in two hospitals from Nanjing, China, using a cohort of 1073 patients to develop a new score and 326 patients to validate it, confirmed that changes in intra-abdominal pressure (IAP) and BMI were significantly associated with the severity of AP [46]. In addition, they found that the new modeling using BMI and changes in IAP has better sensitivity and specificity (77.6% and 82.6%) than APACHE-II (73.1% and 81.7%), BISAP (68.7% and 76.2%), CTSI (70.6% and 78.5%), and Ranson’s score (68.5% and 75.9%), respectively [55].

**Table 4** Bedside index of severity of acute pancreatitis (BISAP) score [48]

<table>
<thead>
<tr>
<th>BISAP: score one point for each of the following criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea nitrogen level &gt; 8.9 mmol/L</td>
</tr>
<tr>
<td>Impaired mental status</td>
</tr>
<tr>
<td>Systemic inflammatory response syndrome is present</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
</tr>
<tr>
<td>Pleural effusion on radiography</td>
</tr>
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*Statements (follow-up imaging)*

1. In severe acute pancreatitis (computed tomography severity index ≥ 3), a follow-up CECT scan is indicated 7–10 days from the initial CT scan (1C).

2. Additional CE-CT scans are recommended only if clinical status deteriorates or fails to show continued improvement, or when invasive intervention is considered (1C).

*Discussion* Patients with mild AP do not need a CT in the majority of cases. These patients will require further CT only if there is a change in the patient’s clinical status that suggests a new complication [20].

Routine follow-up CT (e.g., weekly or every 10 days) is advocated in several guidelines, but lack evidence to justify this practice. The vast majority of complications in a patient with AP/SAP can be suspected by clinical or laboratory assessment [20]. Therefore, in SAP, additional follow-up scans are recommended only if the patient’s clinical status deteriorates or fails to show continued improvement [21, 31].

The resolution of the CT manifestations of (peri)pancreatic inflammation virtually always lag behind the improving clinical status of the patient. Thus, if the patient shows an improving clinical status, additional follow-up scans during hospitalization are recommended only if the patient’s clinical status deteriorates or fails to show continued improvement.

*Antibiotic treatment*

Questions

1. Which are the indications for an antimicrobial therapy in case of severe acute pancreatitis?

2. Is antibiotic prophylaxis effective in sterile severe acute pancreatitis?

3. What is the correct timing to introduce an antimicrobial therapy?

4. Which antimicrobial regimen should be used?

5. What is the correct duration of antimicrobial therapy?

*Statement (prophylactic antibiotics)*

1. Recent evidences have shown that prophylactic antibiotics in patients with acute pancreatitis are not associated with a significant decrease in mortality or morbidity. Thus, routine prophylactic antibiotics are no longer recommended for all patients with acute pancreatitis (1A).

*Discussion* The use and efficacy of prophylactic antibiotic therapy in acute pancreatitis has long been a point
of controversy. Prophylaxis refers to the administration of antibiotics in patients when no clinical infection is present with the intent to prevent pancreatic infection. Although early trials suggested that administration of antibiotics might prevent infectious complications in patients with sterile necrosis [56], subsequent, better-designed trials have consistently failed to confirm an advantage. Recent evidences have shown that prophylactic antibiotics in patients with acute pancreatitis are not associated with a significant decrease in mortality or morbidity [57–61]. Thus, routine prophylactic antibiotics for all patients with acute pancreatitis are no longer recommended.

**Statement (infected necrosis and antibiotics)**

1. Antibiotics are always recommended to treat infected severe acute pancreatitis. However the diagnosis is challenging due to the clinical picture that cannot be distinguished from other infectious complications or from the inflammatory status caused by acute pancreatitis (2A).
2. Serum measurements of procalcitonin (PCT) may be valuable in predicting the risk of developing infected pancreatic necrosis (1B).
3. A CT-guided fine-needle aspiration (FNA) for Gram stain and culture can confirm an infected severe acute pancreatitis and drive antibiotic therapy but is no longer in routine use (1B).

**Discussion**

Antibiotics are always recommended to treat infected acute pancreatitis. However, diagnosis of infected pancreatitis is challenging due to the clinical picture that cannot be distinguished from other infectious complications or from the inflammatory status caused by acute pancreatitis. The timing of infection in pancreatic necrosis is variable and unpredictable and peaks in the second to fourth week after the onset of pancreatitis. Clinical signs may be very sensitive yet are not specific enough [62, 63].

A limited number of smaller studies evaluated C-reactive protein (CRP). Conversely, PCT has been investigated as an effective predictor for the severity of acute pancreatitis and the risk of developing infected pancreatitis. PCT is the inactive 116 amino acid propeptide of the biologically active hormone calcitonin, which was first described to have significantly increased concentrations in patients with bacterial and fungal infections [64].

Several studies have demonstrated that serum measurements of PCT may be valuable in predicting the risk of developing infected pancreatic necrosis [65–68].

The diagnostic tool of choice remains CT-guided FNA of the pancreatic necrotic areas. A CT-guided FNA for Gram stain and culture can guide clinicians in choosing an appropriate individualized antibiotic regimen [69, 70]. However, because of the high rate of false negative findings, some centers have abandoned the routine use of FNA.

The presence of gas in the retroperitoneal area is considered indicative of infected pancreatitis in the context of severe acute pancreatitis, but it is only present in a limited number of patients [62].

**Statement (type of antibiotics)**

1. In patients with infected necrosis, antibiotics known to penetrate pancreatic necrosis should be used (1B).
2. In patients with infected necrosis, the spectrum of empirical antibiotic regimen should include both aerobic and anaerobic Gram-negative and Gram-positive microorganisms. Routine prophylactic administration of antifungal is not recommended in patients with infected acute pancreatitis, although *Candida* spp. are common in patients with infected pancreatic necrosis and indicate patients with a higher risk of mortality (1B).

**Discussion**

Aminoglycoside antibiotics (e.g., gentamicin and tobramycin) in standard intravenous dosages fail to penetrate into the pancreas in sufficient tissue concentrations to cover the minimal inhibitory concentration (MIC) of the bacteria that are commonly found in secondary pancreatic infections [71].

Acyclureidopenicillins and third-generation cephalosporins have an intermediate penetration into pancreas tissue and are effective against gram-negative microorganisms and can cover the MIC for most gram-negative organisms found in pancreatic infections [72]. Among these antibiotics, only piperacillin/tazobactam is effective against gram-positive bacteria and anaerobes. Quinolones (ciprofloxacin and moxifloxacin) and carbapenems both show good tissue penetration into the pancreas the additional benefit of excellent anaerobic coverage [73–76]. However, because of quinolones high rate of resistance worldwide, quinolones should be discouraged and used only in patients with allergy to beta-lactam agents. Carbapenems due to the spread of carbapenem resistant *Klebsiella pneumoniae* should be always optimized and should be used only in very critically ill patients.

Metronidazole, with its bactericidal spectrum focused almost exclusively against anaerobes, also shows good penetration into the pancreas.

Pathogenesis of secondary bacterial pancreatic infection is still debated. Pathogens can reach the pancreas through the hematogenous pathway, via the biliary
system, ascending from the duodenum via the main pancreatic duct, or through transmural colonic migration via translocation of the colonic bacteria [77].

Most pathogens in pancreatic infection are gastrointestinal Gram-negative bacteria (*Escherichia coli*, *Proteus*, *Klebsiella pneumonia*), which occur via disruption of the intestinal flora and damage to the bowel mucosa. Impaired body defenses predispose to translocation of the gastrointestinal organisms and toxins with subsequent secondary pancreatic infection. However, Gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus faecalis*, *Enterococcus*), anaerobes, and, occasionally, fungi have also been found [78].

Fungal infection is a serious complication of acute pancreatitis with an associated increase in morbidity and mortality [79]. *Candida albicans* is the most frequent organism encountered, followed by *Candida tropicalis* and *Candida krusei*. Although fungal infections complicating acute pancreatitis generally arise proportionately to the extent of pancreatic necrosis, there is not enough data to support the prevention of fungal infections and therefore is not recommended.

**Intensive care unit**

Questions:

1. Which are the indications for intensive care unit (ICU) admission?
2. When is fluid resuscitation indicated and which fluid should be used? What is the optimal fluid infusion rate and response measurement for initial resuscitation? What is the preferred pharmacologic approach to persistent shock?
3. What is the correct approach for pain control?
4. Which are the indications for mechanical ventilation?
5. What is the medical approach to the abdominal compartment syndrome? What is the role of medications such as Gabexate Mesilate and somatostatin analogues?
6. Enteral nutrition: which are the indications, what type of nutrition should be used, and which is the best way to administer enteral nutrition?

**Discussion** The worldwide heterogeneity in intensive and intermediate care unit settings makes it difficult to define universal pathways. There is no single marker able to define the severity of the illness. Several scoring system should be used to assess the severity in a different phase, place, and patient.

Extensive fluid administration, adequate pain management with potentially harmful strategies, and organ function evaluation during initial treatment are the reason why continuous vital signs monitoring is crucial, whatever the setting is. Persistent organ dysfunction despite adequate fluid resuscitation needing specific organ support is usually delivered only in ICUs [11, 80].

**Statement (fluid resuscitation)**

1. Early fluid resuscitation is indicated to optimize tissue perfusion targets, without waiting for hemodynamic worsening. Fluid administration should be guided by frequent reassessment of the hemodynamic status, since fluid overload is known to have detrimental effects. Isotonic crystalloids are the preferred fluid (1B).

**Discussion** The decrease in mortality observed over the last decade might be due to the prevention of pancreatic necrosis by maintenance of microcirculation due to more extensive fluid resuscitation. Data on the amount of fluid needed to prevent necrosis or to improve outcome are contradictory and the volume must be adjusted to the patient's age, weight, and pre-existing renal and/or cardiac conditions [81].

Hematocrit, blood urea nitrogen, creatinine, and lactate are laboratory markers of volemia and adequate tissue perfusion, and should be monitored. Ringer's lactate may be associated with anti-inflammatory effect, but the evidence for superiority of Ringer's lactate vs. normal saline based on randomized trials is weak [82–84]. It could be better in correcting the potassium level. The value of early goal-directed therapy in patients with acute pancreatitis remains unknown [81, 85].

**Statement (pain control)**

1. No evidence or recommendation about any restriction in pain medication is available. Non-steroidal anti-inflammatory drugs (NSAID) should be avoided in acute kidney injury (AKI). Epidural analgesia should be an alternative or an agonist with intravenous analgesia, in a multimodal approach. Patient-controlled analgesia (PCA) should be integrated with every described strategy. (1C) Dilaudid is preferred over morphine or fentanyl in the non-intubated patient.
Discussion Pain is the cardinal symptom of acute pancreatitis and its relief is a clinical priority. All patients with acute pancreatitis must receive some form of analgesia in the first 24 h of hospitalization in order not to compromise patient's quality of life. In most institutions, dilaudid is preferred over morphine or fentanyl in the non-intubated patient. Epidural analgesia may be considered for those patients with severe and acute critical pancreatitis who require high doses of opioids for an extended period [63].

Despite some evidence from RCTs, there remains uncertainty about the preferred analgesic and the best method of administration. That is why the best current recommendation now is to adhere to the most current acute pain management guidelines in the perioperative setting [63].

Statement (mechanical ventilation)

1. Mechanical ventilation must be instituted if oxygen supply, even with high flow nasal oxygen, or continuous positive airway pressure became ineffective in correcting tachypnea and dyspnea. Both non-invasive and invasive techniques can be used, but invasive ventilation is mandatory when bronchial secretions clearance start to be ineffective and/or the patient is tiring of predicted to tire. Lung-protective strategies should be used when invasive ventilation is needed (1C).

Discussion There are no issues for the management of respiratory failure specific to this topic. Oxygen supply, even with high flow or continuous positive pressure devices, could become insufficient in supporting respiratory failure. Different levels of tachypnea and dyspnea are only partially justified by hypoxia. Pain, possible intra-abdominal hypertension and pleural effusion, can induce these symptoms despite adequate arterial oxygenation. Increased systemic permeability could precipitate pulmonary edema after fluid resuscitation [86, 87].

Statement (increased intra-abdominal pressure)

1. Limitation of sedation, fluids, and vasoactive drugs to achieve resuscitative goals at lower normal limits is suggested. Deep sedation and paralysis can be necessary to limit intra-abdominal hypertension if all other nonoperative treatments including percutaneous drainage of intraperitoneal fluid are insufficient, before performing surgical abdominal decompression (1B).

Discussion Increased systemic permeability induced by systemic inflammation and therapeutic attempts such as fluid resuscitation and vasoactive drugs are associated with gut failure and worsening of intra-abdominal pressure. Excessive sedation can further worsen gut dysfunction with subsequent increase in intra-abdominal pressure. Limiting “usual ICU medications” when side effects overcome benefits is crucial [88].

Statement (pharmacological treatment)

1. No specific pharmacological treatment except for organ support and nutrition should be given (1B).

Discussion Despite a lot of research, no effective pharmacological treatment has been found [89].

Statement (enteral nutrition)

1. Enteral nutrition is recommended to prevent gut failure and infectious complications. Total parenteral nutrition (TPN) should be avoided but partial parenteral nutrition integration should be considered to reach caloric and protein requirements if enteral route is not completely tolerated. Both gastric and jejunal feeding can be delivered safely (1A).

Discussion Enteral feeding maintains the gut mucosal barrier, prevents disruption, and prevents the translocation of bacteria that seed pancreatic necrosis. In most institutions, continuous infusion is preferred over cyclic or bolus administration. Enteral nutrition as compared with total parenteral nutrition decreases infectious complications, organ failure, and mortality [90]. In a multicenter, randomized study comparing early nasoenteric tube feeding within 24 h after randomization to an oral diet initiated 72 h after presentation to the emergency department with necrotizing pancreatitis, early nasoenteric feeding did not reduce the rate of infection or death. In the oral diet group, 69% of the patients tolerated an oral diet and did not require tube feeding [91].

Surgical and operative management

Questions:

1. Which are the indications for emergent ERCP in case of severe acute pancreatitis?
2. Which is the correct operative/surgical strategy in severe acute pancreatitis?
3. Which are the indications for percutaneous/ endoscopic drainage of pancreatic collections (i.e., sterile necrosis, infected necrosis, others)?
4. Which are the indications for surgical intervention?
5. What is the timing for surgery and what is the appropriate surgical strategy (i.e., laparoscopy vs.
laparotomy, intraperitoneal vs. extraperitoneal, early vs. delayed)?
6. When is cholecystectomy recommended and what is the correct timing?

Statements (indications for emergent ERCP)

1. Routine ERCP with acute gallstone pancreatitis is not indicated (grade 1A).
2. ERCP in patients with acute gallstone pancreatitis and cholangitis is indicated (grade 1B).
3. ERCP in acute gallstone pancreatitis with common bile duct obstruction is indicated (grade 2B).
4. ERCP in patients with predicted severe acute gallstone pancreatitis without cholangitis or common bile duct obstruction cannot be recommended at this time (grade 2B).

Discussion

A systematic review of seven randomized controlled trials (RCT) comprising 757 participants found no evidence to support routine ERCP for all patients with acute gallstone pancreatitis (AGP) [92]. There was no evidence to suggest that the results were dependent on the predicted severity of AGP. However, concerns have been raised of study design limitations, lack of pooled sample size with predicted severe AGP, and ERCP timing and technique. In the same meta-analysis, among trials that included patients with cholangitis, the early routine ERCP significantly reduced mortality as well as local and systemic complications.

In patients with biliary obstruction, early routine ERCP was associated with a significant reduction in local complications and a non-significant trend toward reduction of systemic complications. In cases of predicted severe AGP, the guidelines are controversial [93]. This systematic review studied eight meta-analyses and 12 guidelines and concluded that consensus is lacking on routine ERCP with predicted severe AGP. An on-going RCT, the APEC trial, is designed to answer this question [94]. The recruitment has ended but the results have not yet been published.

Statements (indications for percutaneous/endoscopic drainage of pancreatic collections)

1. Clinical deterioration with signs or strong suspicion of infected necrotizing pancreatitis is an indication to perform intervention (percutaneous/endoscopic drainage)

After 4 weeks after the onset of the disease:

- On-going gastric outlet, biliary, or intestinal obstruction due to a large walled off necrotic collection
- Disconnected duct syndrome
- Symptomatic or growing pseudocyst

Discussion

The evidence of indications is based on understanding the natural course of the disease, mechanism-based reasoning, and non-randomized studies. Interventions for necrotizing pancreatitis should preferably be done when the necrosis has become walled-off, usually after 4 weeks after the onset of the disease [2].

Signs or strong suspicion of infected necrosis in a symptomatic patient requires intervention, although a small number of patients have been shown to recover with antibiotics only [1]. When a patient deteriorates a step-up approach starting with percutaneous or endoscopic drainage is indicated [20, 95–97].

A majority of patients with sterile necrotizing pancreatitis can be managed without interventions [1]. However, it should be noted that nearly half of patients operated due to on-going organ failure without signs of infected necrosis have a positive bacterial culture in the operative specimen [98]. Therefore, interventions should be considered when organ dysfunctions persist for more than 4 weeks.

Walled off necrotic collections or pseudocysts may cause symptoms and/or mechanical obstruction and if they do not resolve when inflammation ceases, a step up approach is indicated. A symptomatic disconnected pancreatic duct results in a peripancreatic collection and is an indication for interventions [99, 100].

Statements (indications for surgical intervention)

The following are indications for surgical intervention:

- As a continuum in a step-up approach after percutaneous/endoscopic procedure with the same indications
- Abdominal compartment syndrome
- Acute on-going bleeding when endovascular approach is unsuccessful
- Bowel ischaemia or acute necrotizing cholecystitis during acute pancreatitis
- Bowel fistula extending into a peripancreatic collection
Discussion

The evidence of indications is based on understanding the natural course of the disease, mechanism-based reasoning, and non-randomized studies. When percutaneous or endoscopic strategies fail to improve the patient, further surgical strategies should be considered. Abdominal compartment syndrome should first be managed by conservative methods [101]. Surgical decompression by laparostomy should be considered if conservative methods are insufficient [102].

Bleeding complications in acute severe pancreatitis may warrant surgical interventions if endovascular approach is unsuccessful. Bowel- and other extrapancreatic complications are relatively rare but may require surgical interventions.

**Statement (timing of surgery)**

1. Postponing surgical interventions for more than 4 weeks after the onset of the disease results in less mortality (2B).

Discussion

Early surgery was compared to late surgery in a recent systematic review and meta-analysis from the Eastern Association for the Surgery of Trauma [103]. The study consisted of nine studies, of which one was a randomized controlled study. Timing of operative interventions was compared in three different cut-offs (72 h, 12 days, and 30 days). In all cut-offs, late surgery resulted in a clear survival benefit. With delayed surgery, the demarcation of necrosis from vital tissue occurs resulting in less injuries to vital tissues. Therefore, in late surgery, there is less bleeding and the necrosectomy is more effective.

It is not known how long surgery can be postponed, if the patient can tolerate it, and will the longer delay result in more complications, such as increased rate of bowel fistulas or intestinal obstruction. If emergency surgery is needed earlier for other indications, such as abdominal compartment syndrome or bowel necrosis, drainage or necrosectomy is not routinely recommended [20, 97].

**Statements (surgical strategy)**

1. In infected pancreatic necrosis, percutaneous drainage as the first line of treatment (step-up approach) delays the surgical treatment to a more favorable time or even results in complete resolution of infection in 25–60% of patients and it is recommended as the first line of treatment (1A).
2. Minimally invasive surgical strategies, such as transgastric endoscopic necrosectomy or video-assisted retroperitoneal debridement (VARD), result in less postoperative new-onset organ failure but require more interventions (1B).
3. Considering mortality, there is insufficient evidence to support open surgical, mini-invasive, or endoscopic approach (1B).
4. In selected cases with walled-off necrosis and in patients with disconnected pancreatic duct, a single-stage surgical transgastric necrosectomy is an option (2C).
5. A multidisciplinary group of experts should individualize surgical treatment taking local expertise into account (2C)

Discussion

A systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis consisted of 11 studies and 384 patients [97]. Infected necrosis was proven in 71% and 56% of patients did not require surgery after percutaneous drainage. In addition, percutaneous drainage allows delaying the later possible surgical intervention to a more favorable time.

An important question is what the preferred strategy is when percutaneous drainage does not result in resolution of the infection. The management options include open surgery, mini-invasive surgery, endoscopic surgery, and a combination of these. It is generally assumed that open surgery causes a more severe inflammatory response. There are various RCTs and a review comparing different strategies [104–106]. In summary, minimally invasive strategies (e.g., minimally invasive step-up approach, video-assisted retroperitoneal debridement, VARD, or endoscopic) result in less new-onset organ failure but require more interventions. However, no differences in mortality have been found. These conclusions are supported by a systematic review [107]. When interpreting the results, it should be noted that there is significant heterogeneity in patients, organ failures, and size as well as localization of necrosis. In addition, surgical techniques and indications for interventions are not uniform.

In a series of 178 selected cases with walled-off necrosis, 96% of the patients underwent a single-stage surgical transgastric necrosectomy with postoperative mortality and morbidity of 2% and 38%, respectively [108]. It is also a good option in patients with a disconnected duct syndrome.

When considering mortality, it is important to notice that pancreatitis-associated mortality is mostly not caused by infected necrosis. Therefore, in future studies, other outcomes measures should be considered. These outcome measures should be able to detect complete resolution of symptoms, quality of life, time to return to normal daily activities or work, and need for further interventions. Local expertise on different surgical
approaches should be taken into account, since only a small percentage of patients require surgery and even in large centers the number of operations remains small. We recommend that a local multidisciplinary group of experts should individualize surgical strategy.

**Statements (timing of cholecystectomy)**

1. Laparoscopic cholecystectomy during index admission is recommended in mild acute gallstone pancreatitis (1A).
2. When ERCP and sphincterotomy are performed during the index admission, the risk for recurrent pancreatitis is diminished, but same admission cholecystectomy is still advised since there is an increased risk for other biliary complications (1B).
3. In acute gallstone pancreatitis with peripancreatic fluid collections, cholecystectomy should be deferred until fluid collections resolve or stabilize and acute inflammation ceases (2C).

**Discussion** Two different systematic reviews state that index admission cholecystectomy for mild AGP is safe [109, 110]. In order to decrease the length of stay and the overall costs, cholecystectomy may be performed as early as the second hospital day, as long as the patient is clinically improving [111, 112]. Routine intraoperative cholangiography seems to be unnecessary in patients with mild gallstone pancreatitis and normalizing bilirubin levels [113]. If ERCP was performed during the index admission, the risk for recurrent biliary events, especially recurrent AGP, was diminished but still higher than same-admission cholecystectomy. A multicenter RCT with 266 patients concluded that interval cholecystectomy resulted in more gallstone-related complications, especially recurrent pancreatitis and colics, without increased cholecystectomy-related complications [114]. There is a single retrospective study of timing of cholecystectomy in patients with moderate to severe AGP with peripancreatic fluid collections [115]. This study reported more complications after early cholecystectomy.

**Open abdomen**

**Questions**

1. Which are the indications for open abdomen in case of severe acute pancreatitis?
2. What is the best temporary abdominal closure system for open abdomen?
3. What is the correct timing for dressing changes?
4. What is the correct timing for abdominal closure?

**Statements (open abdomen)**

1. In patients with severe acute pancreatitis unresponsive to conservative management of IAH/ACS, surgical decompression and use of open abdomen are effective in treating the abdominal compartment syndrome (2C).
2. We suggest that clinicians should be cautious not to over-resuscitate patients with early SAP and measure intra-abdominal pressure regularly (1C).
3. We suggest that the open abdomen (OA) be avoided if other strategies can be used to mitigate or treat severe intra-abdominal hypertension in SAP (1C).
4. We recommend not to utilize the OA after necrosectomy for SAP (unless severe IAH mandates OA as a mandatory procedure) (1C).
5. We recommend not to debride or undertake early necrosectomy if forced to undertake an early OA due abdominal compartment syndrome or visceral ischemia (1A).

**Discussion** The potential rationale for potentially utilizing OA management in severe acute pancreatitis (SAP) patients has historically been to potentially mitigate IAH/ACS, improve the drainage of inflammatory ascites, to allow potential pancreatic lavage, and to potentially allow easier relaparotomy with repeated necrosectomy [116–118].

However, in SAP, there is no level 1 evidence regarding the efficacy of the open abdomen for SAP, with no randomized controlled trials (RCTs) and no meta-analyses. There was a published protocol for such a study [119], but the reviewers could recover no evidence that this study was ever conducted.

As the next best level of evidence, there are existing consensus recommendations from the World Society of Emergency surgery [120], and the International Association of Pancreatology/American Pancreatic Association [20], that both recommend medical and minimally invasive management of severe intra-abdominal hypertension (IAH) leading to the abdominal compartment syndrome (ACS) as per the abdominal compartment syndrome management algorithms [101]. However, recognizing that established overt ACS is universally fatal if untreated, open decompressive laparotomy (DCL) will be required and is recommended if less invasive measures are not effective. When DCL is performed, the retroperitoneal cavity and the lesser omental sac should be left intact to reduce the risk of infecting peripancreatic and pancreatic necrosis [20, 121].

Related to this main recommendation, there are corollary statements that relate to the basic principles that over-zealous fluid resuscitation appears to be closely
related to IAH/ACS occurrence in severe shock and that early necrosectomy is not warranted in SAP. A now classic study noted that early (< 72 h) versus late (> 12 days) necrosectomy had a 56% in early interventions to 27% in late operations, and the intraoperative blood loss was substantially reduced by a delayed approach, results that only continued to improve with continued refinements in surgery and critical care [122–124].

**Statements (open abdomen management and temporary abdominal closure)**

1. We recommend the use of negative pressure peritoneal therapy for OA management (1B).
2. We suggest fascial traction be added to NPWT methods (2B).
3. We suggest that further controlled studies be conducted on intra-peritoneal osmotic therapies in SAP (no recommendation)

**Discussion** There were no RCTs or meta-analyses that directly presented comparative evidence regarding OA techniques in SAP, thus all evidence will be indirect related to the study of the OA in other related settings such as intra-peritoneal sepsis [125, 126], or mixed trauma-medical populations [127–130] with methodological concerns.

The study of Pliakos is notable because the randomized inclusion of fascial traction sutures in addition to peritoneal vacuum therapy was significantly associated with demonstrated superiority concerning a shorter open abdomen duration, reduced number of dressing changes, reduced re-exploration rate, higher successful abdominal closure rate, and reduced enteroatmospheric fistulae [125]. A RCT comparing active negative pressure peritoneal therapy versus more passive pressure demonstrated a mortality benefit with enhanced peritoneal pressure [129], corroborating non-randomized results [130], but a biological mechanism was not obvious. Several meta-analyses including non-randomized trial data have been conducted without clear superiority being demonstrated of any one method [131, 132]. The most contemporary of these did conclude “Although the best results in terms of achieving delayed fascial closure and risk of enteroatmospheric fistula were shown for NPWT with continuous fascial traction, the overall quality of the available evidence was poor, and uniform recommendations cannot be made” [131].

A final therapy to be carefully considered in OA management is that of direct peritoneal resuscitation (DPR), the intra-peritoneal instillation of dialysate fluid, which has been shown efficacious in trauma populations [133]. In a RCT from Smith and colleagues, intra-abdominal complications (8% vs. 18%), abscess rates (3% vs. 14%), and 30-day mortality were lower despite similar injury severity scores (13% vs. 28%; \( p = 0.06 \)) [20]. As there is no direct evidence in SAP patients, no recommendation was made concerning DPR.

**Statement (timing of dressing changes)**

1. Open abdomen re-exploration should be conducted no later than 24–48 h after the index and any subsequent operation, with the duration from the previous operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (1C).

**Discussion** There are no RCTs or meta-analyses concerning the timing of when a patient with an open abdomen should be taken back to the operating room specifically when the OA indication was SAP, nor for any other indication actually. Nor do other guidelines from recognized societies give evidence on when re-operation with an OA should take place [101, 131, 134, 135]. However, in one review, re-exploration performed more than 48 h after the initial operation resulted in a significantly higher mortality rate; and the lowest mortality rate (9%) was achieved in patients who underwent reoperation within 48 h [136].

Contemporary data indicate a linear correlation exists between days of OA and serious complications such as enterocutaneous fistula development [137]. Another prospective series noted that specifically, each hour delay in return to the operating room 24 h after initial laparotomy, and there was a 1.1% decrease in primary fascial closure, and a trend toward increased intra-abdominal complications after 48 h [138].

In the absence of any new data, the SAP OA reviewers suggest adopting the previous contemporary WSES OA management guidelines statement to maintain consistency across WSES sanctioned recommendations until new data warrants potential revisions [120]. As overall outcomes are markedly improved by avoiding early and un-necessitated pancreatic interventions [124], surgeons should resist any temptations to “mess with the pancreas” that might be presented in the course of a reoperation for the OA that would not be available in less complex cases of SAP.

**Statements (timing for abdominal closure)**

1. Early fascial and/or abdominal definitive closure should be the strategy for management of the open abdomen once any requirements for on-going resuscitation have ceased, the source control has been definitively reached, no concern regarding intestinal viability persist, no further surgical re-exploration is
needed, and there are no concerns for abdominal compartment syndrome (1B).

**Discussion** At the risk of possibly being considered facetious, the writing team emphasizes the importance of trying to optimize preventive strategies for IAH though careful and diligent resuscitation, early introduction of medical and minimally invasive management of IAH \[101, 139, 140\], to attempt to avoid progression to the ACS with a requirement for DCL.

Delayed fascial closure has been defined as formal fascial obtained seven or more days after the index OA procedure \[141\]. It has become apparent that complications are much higher and primary fascial closure much lower in those who undergo late versus early closure, although this may also be related to patient factors in uncontrolled non-randomized trials. Meta-analysis has however revealed that compared with delayed abdominal closure, early PFC was associated with reduced mortality and complication rate \[142\]. The former World Society of the Abdominal Compartment Syndrome thus recommended that among ICU patients with OAs, conscious and/or protocolized efforts be made to obtain early or at least same-hospital-stay abdominal fascial closure \[101\].

Similar to the preceding question, until new data regarding definitive OA closure in SAP or any other conditions becomes available, the reviewers suggest adopting the previous contemporary WSES management guidelines statement to maintain consistency across WSES sanctioned recommendations until new data warrants potential revisions \[120\].

**Conclusions** These guidelines present evidence-based international consensus statements on the management of severe acute pancreatitis from collaboration of a panel of experts. It contains 55 statements on diagnosis, management in the ICU, surgical and operative management, open abdomen, and antibiotic treatment. For some of the statements such as severity grading, imaging, use of prophylactic antibiotics and most aspect of the management in the ICU, the evidence is strong. For others, such as laboratory diagnostics and surgical strategies, for example, the evidence is quite weak requiring further studies. With accumulating knowledge, the statements need to be regularly updated.

**Abbreviations**


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**Ethics approval and consent to participate**

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**Consent for publication**

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The authors declare that they have no competing interests.

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**References**


Guidelines in the management of obstructing cancer of the left colon: consensus conference of the world society of emergency surgery (WSES) and peritoneum and surgery (PnS) society

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Abstract

Background: Obstructive left colon carcinoma (OLCC) is a challenging matter in terms of obstruction release as well as oncological issues. Several options are available and no guidelines are established. The paper aims to generate evidenced based recommendations on management of OLCC.

Methods: The PubMed and Cochrane Library databases were queried for publications focusing on OLCC published prior to April 2010. A extensive retrieval, analyses, and grading of the literature was undertaken. The findings of the research were presented and largely discussed among panelist and audience at the Consensus Conference of the World Society of Emergency Surgery (WSES) and Peritoneum and Surgery (PnS) Society held in Bologna July 2010. Comparisons of techniques are presented and final committee recommendation are enounced.

Results: Hartmann’s procedure should be preferred to loop colostomy (Grade 2B). Hartmann’s procedure offers no survival benefit compared to segmental colonic resection with primary anastomosis (Grade 2C+); Hartmann’s procedure should be considered in patients with high surgical risk (Grade 2C). Total colectomy and segmental colectomy with intraoperative colonic irrigation are associated with same mortality/morbidity, however total colectomy is associated with higher rates impaired bowel function (Grade 1A). Segmental resection and primary anastomosis either with manual decompression or intraoperative colonic irrigation are associated with same mortality/morbidity rate (Grade 1A). In palliation stent placement is associated with similar mortality/morbidity rates and shorter hospital stay (Grade 2B). Stents as a bridge to surgery seems associated with lower mortality rate, shorter hospital stay, and a lower colostomy formation rate (Grade 1B).

Conclusions: Loop colostomy and staged procedure should be adopted in case of dramatic scenario, when neoadjuvant therapy could be expected. Hartmann’s procedure should be performed in case of high risk of anastomotic dehiscence. Subtotal and total colectomy should be attempted when cecal perforation or in case of synchronous colonic neoplasm. Primary resection and anastomosis with manual decompression seems the procedure of choice. Colonic stents represent the best option when skills are available. The literature power is relatively poor and the existing RCT are often not sufficiently robust in design thus, among 6 possible treatment modalities, only 2 reached the Grade A.

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**Background**

The majority of cases of acute colonic obstruction is secondary to colorectal cancer. Up to 20% of patients with colonic cancer present with symptoms of acute obstruction [1-4]. Emergency surgery for acute colonic obstruction is associated with a significant risk of mortality and morbidity and with a high percentage of stoma creation (either temporary or permanent) [1,2,5,6]. Whereas right-sided colonic obstructions are usually treated by one-stage resection with primary anastomosis for all patients but the frailest [1], controversy continues to revolve around emergency management of obstructed left colon cancer (OLCC).

Indeed several options for OLCC are available (Figure 1):

1) loop colostomy (C) or loop ileostomy and subsequent resection (2 or 3 staged procedure)
2) primary resection with end colostomy: Hartmann’s procedure (HP);
3) primary resection and anastomosis (PRA):
   a. total/subtotal colectomy (TC)
   b. segmental colectomy, (SC)
      i. with intra-operative colonic irrigation (ICI)
      ii. without intra-operative colonic irrigation (manual decompression, MD)
4) endoscopic colonic stenting by self-expanding metallic stents (SEMS):
   a. palliation
   b. bridge to surgery

The consensus conference aimed to evaluate available literature to generate evidenced based recommendations on management of OLCC. It must be stated, in advance, that suggestions coming from this study are not substitute of the clinical judgement.

**Methods**

The PubMed and Cochrane Library databases were queried for publications focusing on OLCC published prior to April 2010. The following Mesh headings were used: ‘colonic neoplasm’, ‘intestinal obstruction’, ‘stents’, ‘colectomy’. Also, text terms were used in combination such as: ‘colonic obstruction’, ‘colonic stents’, ‘Hartmann’s operation’, ‘colonic irrigation’, ‘colostomy’, ‘anastomosis’. There was no language restriction. The ‘Related Articles’ function in PubMed was used and the references of the retrieved articles were reviewed. Initially the Chairman (AL) and the committee members (BF, CV, LA, RA, TJ) collaborated to the preparation of a preliminary statements. Subsequently, the Chairman, the committee members and world renowned experts in the field met for a consensus conference on OLCC during the 1st World Congress of World Society of Emergency Surgery and the IX Meeting of Peritoneum and Surgery (PnS) Society (Bologna, Italy, July 2010). During the consensus conference each committee member presented a summary of evidence available for each of the treatment options outlined in Figure 1. The data available from literature review were analyzed and graded according to the level of evidence.
validated by the American College of Chest Physicians (ACCP) systems (Table 1) [7,8]. Those presentations served to launch a discussion on optimal management of OLCC. Following exhaustive discussion the panel was asked to agree on final recommendations.

The coordinators (FL, PM) merged the committee preliminary statements with the observations and recommendations from the panel, and had the responsibility of summarizing the discussion on standards of treatment for OLCC that are presented in this manuscript.

Results

Loop colostomy (C) with staged procedure vs Hartmann’s procedure (HP)

Loop colostomy is a historical component of the staged therapeutic schema for OLCC. During the first stage, the obstruction is managed by the colostomy. The second stage takes place a few weeks later when the tumour is resected and the colostomy is closed (two stage procedure) or, alternatively, the colostomy can be closed at a third stage. There is only one RCT study, by Kromborg et al in 1995, comparing emergency colostomy with three stages procedure (58 patients) versus HP (63 patients) for OLCC. The authors showed no difference in terms of mortality (8/58 vs. 8/63 patients) and morbidity rate, recurrence rate and cancer specific survival; the overall length of hospital stay was shorter in the resection group [9]. However this RCT has some important limitations due to methodological flaws: no prior sample size estimation; a 15-year accrual period; procedures being performed by 36 attending and training surgeons; incomplete follow up; heterogeneous underlying pathology (with non-malignant strictures accounting for 14% of cases).

Previously Fielding et al. in 1979 published a prospective non-randomised study (PNRS) which showed the same mortality rate for both groups [10]; however the study was affected by strong bias selection. A Cochrane systematic review in 2008 by De Salvo rt al, compared staged procedure vs. primary resection, and found similar mortality with either strategy [11]. It should be noted that the Kronborg study was excluded for methodological weaknesses. In theory, several benefits might be associated with creation of a loop colostomy: it provides colonic decompression; minimizes surgical trauma; reduces the risk of contamination from unprepared bowel; allows staging and multidisciplinary evaluation prior to definitive treatment.

Our literature review reveals that C does not provide any short- or long-term benefit over the HP whereas the multiple operations are associated with longer overall hospital stay: 49 days in group C vs. 35 days in HP group (p = 0.01); finally the staged approach shows a not significant tendency to expose the patient to a higher cumulative morbidity as a result of multiple operations[9].

Recommendation: HP should be preferred to C for OLCC, since C appears to be associated with longer overall hospital stay and need for multiple operations

Table 1 Grades of Recommendations according to the American College of Chest Physicians (ACCP) 78

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Methodological strength of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Risk/benefit clear</td>
<td>Randomized controlled trials (RCTs) without important limitations</td>
<td>Strong recommendation, can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1 B</td>
<td>Risk/benefit clear</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws)</td>
<td>Strong recommendations, likely to apply to most patients</td>
</tr>
<tr>
<td>1 C+</td>
<td>Risk/benefit clear</td>
<td>No RCTs but RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies</td>
<td>Strong recommendation, can apply to most patients in most circumstances</td>
</tr>
<tr>
<td>1 C</td>
<td>Risk/benefit clear</td>
<td>Observational studies</td>
<td>Intermediate strength recommendation; may change when stronger evidence available</td>
</tr>
<tr>
<td>2A</td>
<td>Risk/benefit unclear</td>
<td>RCTs without important limitations</td>
<td>Intermediate strength recommendation, best action may differ depending on circumstances or patients’ or societal values</td>
</tr>
<tr>
<td>2 B</td>
<td>Risk/benefit unclear</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws)</td>
<td>Weak recommendation, alternative approaches likely to be better for some patients under some circumstances</td>
</tr>
<tr>
<td>2 C</td>
<td>Risk/benefit unclear</td>
<td>Observational studies</td>
<td>Very weak recommendations; other alternatives may be equally reasonable</td>
</tr>
</tbody>
</table>
but not with a reduction in peri-operative morbidity (Grade of recommendation 2B).

Advice: the role of staged procedure, with preference at the two stages operation, should be considered (a) in a clinical situation where a surgical approach like “damage control” could be applied as happens in trauma scenario (b) when neoadjuvant multimodality therapy can be expected, or (c) unresectable disease.

Hartmann’s procedure (HP) vs. primary resection and anastomosis (PRA)

There are no RCTs comparing HP and PRA; thus neither grade A and B evidence are available.

In 2004 Meyer et al by a prospective non randomized multicenter study compared, in emergency scenario, 213 patients undergoing HP to 340 patients undergoing PRA for OLCC. The mortality rate in the case of palliation for HP and PRA respectively was 33% vs. 39% and in case of curative intent for HP and PRA respectively 7,5% vs. 9,2%, however both of them without statistical difference; also the morbidity rate was not significantly different among groups; finally the HP was the most frequent surgical option [6]. The authors made a substantial effort in planning the study, collecting and analyzing data, however the number of participating institutions was very high (309) and heterogeneous spanning from regional to university hospitals. Finally among prospective non randomized and retrospective studies the rates of anastomotic leak in patients with OLCC treated with PRA range from 2,2% to 12% [5,6,12-14], which are similar to those reported for elective surgery ranging from 1,9% to 8% [15-18].

Furthermore our literature review suggests that HP might be associated with worse long-term outcomes. Villar et al. in 2005 published a prospective non randomized study comparing HP in 20 patients to PRA in 35 patients divided into ICI/SC or TC: they reported 5-year overall survival of 38% and 41-45% for HP and PRA (divided into subgroups) respectively; however this difference was likely the result of selection bias as anastomosis was likely avoided in higher-risk patients [12,14].

The absence of anastomosis makes HP a technically easier operation and obviously eliminates the risk of colon dehiscence in a already complex scenario such as occurs in high grade obstruction: thus HP still remains an option also suitable by less experienced and non-specialist surgeons. The main disadvantages of HP is the need for a second major operation to reverse the colostomy, which will be also associated with a risk of anastomotic dehiscence similar to PRA. Furthermore, it is somewhat disappointing to observe that the stoma reversal rate is only 20% in those patients with colon cancer [12,19]. PRA offers the advantages of a definite procedure without need for further surgery. Its main disadvantages are related to the increased technical challenge and to the potential higher risk of anastomotic leakage that occurs in the emergency setting.

Although PRA appears, at least in theory, more appealing than HP in OLCC, several parameters (patient and surgeon related) should be taken in consideration prior to choose the surgical procedure [5,14,20].

Risk stratification is at the base of patient selection. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) study of large bowel obstruction caused by colorectal cancer identified four important predictors of outcome - age, ASA grade, operative urgency, and Dukes’ stage [5]. Similar results were shown by other studies [14,20]. Recent large studies demonstrated that mortality rate after PRA of obstructive right colon cancer is higher than mortality after HP for OLCC [5,14,21], whereas one study did not show any difference [22]. This findings could be explained by the fact that almost all patients with right-sided obstruction are treated by one stage resection and anastomosis, whereas patients with OLCC are carefully selected according to risk.

Keeping in mind these considerations the HP could be appropriate for patients deemed to be at high risk. Moreover the same considerations could explain the results of a questionnaire survey of American Gastrointestinal Surgeons in 2001 who responded that 67% would perform HP and 26% a simple colostomy in the high-risk patient [23]. Otherwise we should assume a lack of adherence to the literature evidence in the clinical practice or difficulty in changing from surgical tradition.

The experience and subspecialty of surgeon seems to be a primary factor in the choice of anastomosis or end colostomy. It has been shown that primary anastomosis is more likely to be performed by colorectal consultants rather than general surgeons, and by consultants rather than unsupervised trainees [20]. The ACPGBI study has shown that the mortality rate following surgery was similar between ACPGBI and non-ACPGBI members [5]. This result can be challenged as the study was done on a voluntary basis. The Large Bowel Cancer Project showed that registrars had a higher mortality rate than consultants after primary resection for obstruction in the late 1970 s, and this result has remained unchanged 20 years later in the Zorcolo study [1,20]. Other studies have also shown that unsupervised trainees had significantly greater morbidity, mortality and anastomotic dehiscence rates [10,24].

Recommendation: HP offers no overall survival benefit compared to segmental colonic resection with primary anastomosis in OLCC (Grade of recommendation 2C+); HP should be considered in patients with high surgical risk (Grade of recommendation 2C)
Primary resection and anastomosis (PRA): total or subtotal colectomy (TC) vs. segmental colectomy (SC)

There is only one RCT, write out SCOTIA study group (Subtotal Colectomy versus on Table Irrigation and Anostomosis) in 1995, that compared the TC (47 patients) vs. SC (44 patients) and ICI. There were no differences in mortality, overall morbidity and rates of single complications (superficial and deep surgical site infections, anastomotic leakage). In regard of long-term outcomes, patients undergoing TC were noted to have a statistically higher number of daily bowel movements compared to ICI/SC. The authors concluded that SC following ICI should be therefore preferred to TC [25].

Another non-randomised study comparing the two techniques did not show any difference in mortality but showed significantly more surgical postoperative complications in the ICI group and in particular superficial surgical site infections [26].

TC as a one-stage resection anastomosis in OLCC allows the surgeon to encompass a massively distended and faecal-loaded colon [27,28]; moreover the proximal colon dilatation makes difficult the detection of synchronous cancer and so TC could bypass the need for further operation especially in severely ill patients. However we can’t extend the use of TC as a prophylaxis of future malignancy outside hereditary tumours syndromes [27].

In the 1980 s, segmental colectomy with ICI was suggested as an alternative operation. It has the benefit of making an anastomosis on a prepared bowel and preserving the normal colon. The main concerns are the prolonged operative time, the risk of spillage and contamination, and the need for increased expertise [25].

Absolute indications for STC in OLCC are right colon ischemia, cecal serosa tears or perforation, and synchronous proximal malignant tumours which occur in 3 to 10% of cases [27]; it is a one stage radical oncological resection with advantages to treat synchronous proximal tumours, prevent metastachous cancer, to avoid stoma creation and to remove the colon as a septic content; but the major disadvantages are resection of healthy colon, resulting in poor functional results with many patients complaining of diarrhoea afterwards [25,27,28].

| Recommendation: | TC for OLCC (without cecal perforation or evidence of synchronous right colonic cancers) should not longer be preferred to SC with ICI, since the two procedures are associated with same mortality/morbidity, while TC is associated with higher rates impaired bowel function (Grade of recommendation 1A). |

Primary resection and anastomosis (PRA): Segmental colectomy (SC) with intraoperative colonic irrigation (ICI) vs. Segmental colectomy (SC) with manual decompression (MD)

Lim et al in 2005 published the only RCT comparing ICI (24 patients) with MD (25 patients) in OLCC. They concluded that MD is a shorter and simpler procedure than ICI, and offers similar results in terms of mortality, morbidity or anastomotic leak rates, but the study was underpowered [29].

On average, the ICI increases duration of surgery by an hour, although this time can improve with increasing experience. To overcome the problems of ICI, various studies suggested segmental resection and primary anastomosis with MD only, as an safe alternative [29-32]. This idea was supported by various RCTs comparing mechanical bowel preparation, with no preparation in elective open colonic surgery.

The results were separately examined in a Cochrane systematic review of 9 RCTs [15] and in a metaanalysis of 7 RCTs [33]. Both studies concluded that there is no convincing evidence that mechanical bowel preparation is associated with reduced rates of anastomotic leakage after elective colorectal surgery.

Finally in 2009 Kam et al published a systematic review on ICI vs. MD in left-sided colorectal emergencies: they included 1 RCT, 1 prospective comparative trial and 5 prospective descriptive case series and concluded that, although the power of studies is poor and large-scale prospective randomized trial is desirable, no statistical significance could be shown between the two procedures [34].

| Recommendation: | during segmental resection and primary anastomosis for OLCC (without cecal perforation or evidence of synchronous right colonic cancers), either MD or ICI can be performed as the two techniques are associated with same mortality/morbidity rate. The only significant difference is that MD is a shorter and simpler procedure. Either procedure could be performed, depending of the experience/preference of the surgeon (Grade of recommendation 1A). |

Endoscopic Colonic Stents (SEMS)

Colonic stents were introduced in the 1990 s and have been used for palliation or as a bridge to surgery: following release of the obstruction with an endoscopic stent the patient is properly staged and offered multidisciplinary treatment and eventually elective or semi-elective surgery [35].

| A) Palliation: endoscopic colonic stents (SEMS) vs. colostomy (C) | There are three RCTs comparing colostomy vs. SEMS for palliation of malignant colonic obstruction [36-38]. Xinopoulos et al in 2004 randomized 30 patients. In the SEMS group placement of the stent was achieved in 93.3% (14/15 pt); there was no mortality. In 57% (8/14) of patients in which the stent was successfully placed, colonic obstruction was permanently released (i.e. until death). Mean survival was 21.4 month in SEMS group and 20.9 months in C group. Mean |

http://www.wjes.org/content/5/1/29
hospital stay was quite high in both groups and significantly higher in group C: 28 days vs. 60 days. This study presented several limitations, and the small sample size might have limited the ability to discern differences between groups [36]

Fiori et al in 2004 randomized 22 patients to either C or SEMS: mortality was 0% in both groups, morbidity was similar. SEMS group had shorter time to oral intake, restoration of bowel function, and hospital stay. This study was also limited by the small simple size and by the lack of follow up [37].

The Dutch Stent-in I multicenter RCT was planned to randomized patients with incurable colorectal cancer to SEMS or surgery: the study was terminated prematurely after enrolling 21 patients because four stent-related delayed perforations resulting in three deaths among 10 patients in the SEMS group. There are no clear explanation for such a high perforation rate; the authors pointed out that limited safety data existed fort he stent used in their study (WallFlex, Boston Scientific Natick, MA) [38]. Indeed, subsequent studies of Wallflex stent for colonic obstruction reported a perforation rate of about 5% [39-42] which is in line with what commonly observed with other stents [42].

The feasibility, safety, and efficacy of SEMS have been analyzed by retrospective studies. There are four systematic reviews analysing the outcome of SEMS for large bowel obstruction with the Sebastian study being the most complete and focused one [43-46]. He retrieved 54 studies with a total of 1198 patients and the median rates were: technical success 94%, the clinical success 91%, the colonic perforation 3.76%, the stent migration 10%, the re-obstruction 10%, stent-related mortality 1% [44]. These studies have shown that colonic stenting is a relatively safe technique with high success rates.

The influence of colonic stents on oncologic outcomes has been questioned but no exhaustive answer is available. Indeed, several studies suggested that primary tumour resection with palliative intent, would prolong survival in patients with stage IV colorectal cancer [47,48]. However the power of these retrospective studies is poor due to the study design, no uniform adjuvant therapies among groups, and the bias to compare unrectsectable stage IV cancer patients with resectable stage IV cancer patients.

On the other hand, several comparative, retrospective studies did not show any significant difference in term of overall survival after 3 and 5 years of follow up, between emergency surgery and stent placement [49,50].

Colonic stents have an attractive role in a multimodality approach to obstructive colon cancer; however close clinical observation is required: for example there is one literature report that colonic stent may increase the risk of colon perforation in patients who are candidates for bevacizumb: thus according to authors alternative treatments to SEMS in these patients should be considered [51].

**Recommendation:** in facilities with capability for stent placement, SEMS should be preferred to colostomy for palliation of OLCC since stent placement is associated with similar mortality/morbidity rates and shorter hospital stay (Grade of recommendation 2B).

**Advice:** authors cautiously suggest to consider alternative treatments to stent in patients eligible for further bevacizumab-based therapy

**B) Bridge to surgery: endoscopic colonic stents and planned surgery vs. emergency surgery**

Cheung et al. recently published a RCT comparing endolaparoscopic approach (24 pts) vs. conventional open surgery (24 pts). In patients who were randomized to the endolaparoscopic group, an SEMS placement for colon decompression was attempted within 24-30 hours from admission and an elective laparoscopic-assisted colectomy was performed within two weeks following SEMS placement. Patients who were randomized to the open surgery group underwent emergency HP or TC with ICI on the same day of admission. Over a 3-years period, 50 patients were enrolled and 48 were available for the final analysis (24 in the open surgery group and 24 in the endolaparoscopic group). Overall, only 6 of 11 patients undergo HP had subsequent reversal; PRA was conducted in 13 patients all but two without covering stoma; two patients experienced anastomotic leak (2 out of 11, 18.8%) requiring end colostomy and one of these had subsequent reversal; thus 1-stage operation was performed successfully in 38% and 75% avoided a permanent colostomy. Colon decompression by SEMS was achieved in 83% of patients while the 17% had HP At the time of planned surgery, 67% of patients in the endolaparoscopic group had successful 1-stage operations performed and the 4 remaining patients had diverting ileostomy (33%); finally in the endolaparoscopic group no one was given a permanent stoma. Furthermore, patients randomized to the endolaparoscopic group compared to emergency surgery had significantly greater successful 1-stage operation (16 vs. 9, \( p = 0.04 \)), less cumulative blood loss (50 ml vs. 200, \( p = 0.01 \)), less wound infection (2 vs. 8, \( p = 0.04 \)), reduced incidence of anastomotic leak (0 vs. 2, \( p = 0.045 \)), and greater lymph-node harvest (23 vs. 11, \( p = 0.05 \)).

Cheung and colleagues suggest that colon decompression provides time for resuscitation, adequate staging, bowel preparation and safer, minimally-invasive elective resection. Indeed, the rate of primary anastomosis is twice that following emergent surgery, and the stoma rate and the postoperative complications are significantly reduced [52].
Observational studies comparing SEMS followed by planned surgery with emergency surgery (HP, or PRA). Martinez-Santos in a prospective non-randomised study comparing 43 patients in the SEMS group with 29 patients in emergency surgery group reports a 95% technical success rate of SEMS; however only 26 patient in the SEMS group had a further surgical operation: at the time of planned surgery for SEMS the comparison of median rate between SEMS vs. emergency surgery shows: primary anastomosis was 84.6% vs. 41.4% with p = 0.0025; morbidity was 40% vs.62% p = 0.054; ICU stay was 0.3 vs.2.9 days p = 0.015; reintervention was 0% vs. 17% p = 0.014; mortality was 9% vs. 24% however without reaching statistical significance [53]. However the study is somewhat confusing because it include also a large population of palliative SEMS (14) and the two population in SEMS are sometime mixed and then compared to emergency surgery group. Similar results are reported also in less robust retrospective studies [50,54].

Finley in 2007 performed a meta-analysis of non-randomised studies that compared SEMS and open surgery for malignant large bowel obstruction: SEMS was attempted in 244 out of 451 patients (54,1%) with a success rate of 92.6%; mortality occurred in 14 (5.7%) in SEMS and in 25 (12.1%; p = 0.03) in emergency surgery [55]. This metaanalysis however was likely impaired by the heterogeneity of studies, since both patients stented for palliation or as a bridge to surgery were included. In this meta-analysis mortality rate for stenting (5.7%) was much higher than the 0.6% rate reported in a large systematic review [45].

Little is known on oncologic outcomes of using SEMS as a bridge to elective surgery. A recent paper recommended that surgery should be scheduled shortly after stent insertion because the risk of tumour seeding from perforation and dislocation of stent [56]. However selection bias of indication and timing of stenting could explain the high level of complications reported with SEMS and consequently the advice of authors regarding long-term survival [57]. Finally there is no study available comparing survival in SEMS versus other surgical options.

The cost effectiveness of SEMS is an important parameter as stents are very expensive. It is thought that their cost is offset by the shorter hospital stay and the lower rate of colostomy formation. Two decision analysis studies from the US and Canada calculated the cost-effectiveness of two competing strategies - colonic stent versus emergency primary resection for OLCC [58,59]. Both concluded that colonic stent followed by elective surgery is more effective and cost efficient than emergency surgery. A small retrospective study from the UK in 1998 showed that palliative stenting compared to surgical decompensation allows saving a mean of £1769, whereas the stenting as a bridge to elective resection vs. emergency HP followed by elective reversal saved a mean of £685 [60]. A RCT from Greece comparing SEMS and colostomy for palliation of patients with inoperable malignant partial colonic obstruction showed very small difference in the costs, with the stent group being 6.9% (132 euros) more expensive per patient [36]. Another study from Switzerland reported SEMS to be 19.7% less costly than surgery [61]. None of these studies incorporated the hidden costs of stoma bags used in the community. Although stents seem to be cost effective, results are difficult to compare because costs calculations vary in different health care systems, costs differ for palliation and bridge to surgery, and the cost of stents is likely to decrease over time.

**Recommendation:** SEMS should be used as a bridge to elective surgery in referral centre hospitals with specific expertise and in selected patients mainly as their use seems associated with lower mortality rate, shorter hospital stay, and a lower colostomy formation rate (Grade of recommendation 1B).

**Conclusions**

This consensus conference aimed to analyze the available scientific evidence on treatment modalities for OLCC and how this is implemented in clinical practice. The goal of the authors was to offer practical and scientifically supported suggestion to manage OLCC.

The committee made every effort to collect and classify the best available scientific evidence on treatment of OLCC (Table 2). Subsequently, the audit and panel discussion played a pivotal role in the statement declarations.

All the participants at consensus conference agree that the literature power is relatively poor and the existing RCT are often not sufficiently robust in design thus, among 6 possible treatment modalities, only 2 reached the Grade A.

To help in decision making the authors wish to suggest surgeons to consider 3 further key points approaching OLCC: patient stratification according to the ACPGBI rules; clinical environment; surgeon skill.

The target as usual is to offer the best option for the patient; starting from this point of view also historical surgical option could still play a valid role. The staged procedure, with preference to the two stages, should be reserved when multimodality therapy is expected or in case of “dramatic” scenarios.

PRA with manual decompresion is a safe option and appears to be associated with best outcomes. HP might still have a role in patients at high risk for anastomotic dehiscence. TC is an appealing option in case of synchronous polyps or cancer and/or impending or actual perforation of the right colon. SEMS represent a valuable option both for palliation and as a bridge to elective surgery. Obviously high clinical and technical expertise...
Table 2 Evidences used for the present Consensus Conference

<table>
<thead>
<tr>
<th>Evidence type</th>
<th>C vs. HP</th>
<th>HP vs. PRA</th>
<th>TC vs. SC</th>
<th>SC+ICI vs. SC+MD</th>
<th>SEPS vs. C in palliation</th>
<th>SEPS + surgery vs. surgery</th>
<th>Total of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>1 (9)</td>
<td>0</td>
<td>1 (25)</td>
<td>1 (29)</td>
<td>3 [36-38]</td>
<td>1 [52]</td>
<td>9</td>
</tr>
<tr>
<td>PNRS/OS</td>
<td>1 (10)</td>
<td>6 [5,6,12-14,23]</td>
<td>1 (26)</td>
<td>3 [30-32]</td>
<td>0</td>
<td>3 [50,53,54]</td>
<td>14</td>
</tr>
<tr>
<td>CSR</td>
<td>1 (11)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SR</td>
<td>0</td>
<td>0</td>
<td>1 [34]</td>
<td>4 [43-46]</td>
<td>0</td>
<td>5</td>
<td>5</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1 [55]</td>
<td>1</td>
</tr>
<tr>
<td>Cost analysis</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>[references]</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

is mandatory to safely and successfully treat colonic obstruction by stents: due to this consideration routine use in practice is still limited.

However we strongly support a judicious application of the procedure and encourage increased use of stents after adequate training in referral hospitals with a goal of further testing this modality.

List of abbreviations


Acknowledgements

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Authors’ contributions

LA: conception and design of the study; organiser of the consensus conference; preparation of the draft; he merged the committee preliminary statements with the observations and recommendations from the panel, he summarised the discussion on standards of treatment for OLCC; manuscript preparation and review. FC: conception and design of the study, organiser of the consensus conference; manuscript review. SD: manuscript review. BF, CV, LA, RA, TIJ: preparation of the draft inclusive of preliminary statements, manuscript review. PAD: conception of the study; organiser of the consensus conference; main contributor to critical discussion of the draft. ARE, SPH, JM, MEE: main contributors to critical discussion of the draft, manuscript review. FL: preparation of the draft inclusive of preliminary statements. He merged the committee preliminary statements with the observations and recommendations from the panel, he summarized the discussion on standards of treatment for OLCC; manuscript preparation and review. All Authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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References

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Liver trauma: WSES 2020 guidelines


Abstract

Liver injuries represent one of the most frequent life-threatening injuries in trauma patients. In determining the optimal management strategy, the anatomic injury, the hemodynamic status, and the associated injuries should be taken into consideration. Liver trauma approach may require non-operative or operative management with the intent to restore the homeostasis and the normal physiology. The management of liver trauma should be multidisciplinary including trauma surgeons, interventional radiologists, and emergency and ICU physicians. The aim of this paper is to present the World Society of Emergency Surgery (WSES) liver trauma management guidelines.

Keywords: Liver trauma, Adult, Pediatric, Minor, Moderate, Severe, Classification, Guidelines, Surgery, Hemorrhage, Operative management, Non-operative management, Interventional, Radiology, Intensive care

Background

Liver trauma is one of the most common abdominal lesions in severely injured trauma patients [1]. Diagnosis and treatment of hepatic trauma has evolved with the use of modern diagnostic and therapeutic tools [2–4]. Until two to three decades ago, most cases with blunt abdominal trauma and possible injury in parenchymatous organs were managed by exploratory laparotomy [5]. Several innovative multimodal approaches as EVTM (endovascular trauma and bleeding management) have allowed to greatly increase the likelihood of non-operative management (NOM) for selected patients. Nowadays, even borderline patients or transient responder, without other indications for laparotomy, may be considered for NOM in selected and well-developed trauma centers. This advanced strategy necessitates a multidisciplinary approach to deal with the complexity of moderate and severe liver injury. The majority of patients admitted with liver injuries have minor or moderate injuries (WSES I, II, III) (AAST-OIS I, II, or III) and are successfully treated by NOM. In contrast, one third of severe injuries (WSES IV, V) (AAST-OIS IV, V) allow for NOM [6]. In pediatric patients, NOM should be considered the optimal management approach. In determining the optimal treatment strategy, the anatomical description of liver lesions is fundamental but not sufficient. In fact, the decision whether patients need to be managed operatively or undergo NOM is based mainly on the hemodynamic status, associated injuries, and on the anatomical liver injury grade.

The aim of this manuscript is to present the updated World Society of Emergency Surgery (WSES) liver trauma management guidelines.
Notes on the use of the guidelines
The guidelines are evidence-based, with the grade of recommendation based on the evidence. The guidelines present the diagnostic and therapeutic methods for optimal management of liver trauma. The practice guidelines promulgated in this work do not represent a standard of practice. These are suggested plans of care, based on best available evidence and the consensus of experts, but they do not exclude other approaches as being within the standard of practice. For example, they should not be used to compel adherence to a given method of medical management, which method should be finally determined after taking account of the conditions at the relevant medical institution (staff levels, experience, equipment, etc.), and the characteristics of the individual patient. However, responsibility for the results of treatment rests with those who are directly engaged therein, and not with the consensus group.

Methods
A computerized search was done by the bibliographer in different databanks (MEDLINE, Scopus, EMBASE). Citations were included for the period between January 1990 and October 2019 using the primary search strategy: liver, injuries, trauma, hepatic, adult, pediatric, hemodynamic instability/stability, angioembolization, management, nonoperative, conservative, operative, surgery, diagnosis, and follow-up, combined with AND/OR. No search restrictions were imposed. The dates were selected to allow comprehensive published abstracts of clinical trials, consensus conference, comparative studies, congresses, guidelines, government publication, multicenter studies, systematic reviews, meta-analysis, large case series, original articles, and randomized controlled trials. Case reports and small case series were excluded. Narrative review articles were also analyzed to determine if other cited studies should be included.

The level of evidence (LE) was evaluated using the GRADE system [7] (Table 1).

A group of experts in the field coordinated by a central coordinator was contacted to express their evidence-based opinion on several issues about the pediatric (< 16 years old) and adult liver trauma [8, 9]. Hepatic trauma was assessed by the anatomy of the injury, type of injury (blunt and penetrating injury), management (conservative and operative management), and type of patient (adults, pediatrics). Through the Delphi process, different issues were discussed in subsequent rounds. The central coordinator assembled the different answers derived from each round. Each version was then revised and improved. An expert group discussed the definitive version. The final version about on agreement was reached resulted in the present manuscript. Statements are summarized in Table 4.

Definitions
In adult patients, hemodynamic instability is considered the condition in which admission systolic blood pressure is < 90 mmHg with clinical evidence of hemorrhagic shock with skin vasoconstriction (cool, clammy, decreased capillary refill), altered level of consciousness and/or shortness of breath, or > 90 mmHg but requiring bolus infusions/transfusions and/or vasopressor drugs and/or admission base excess (BE) > -5 mmol/l or transfusion requirement of at least > 4 units of packed red blood cells within the first 8 h. Transient responder patients (adult and pediatric) are those showing an initial response to adequate fluid resuscitation, but then subsequent signs of ongoing blood loss and perfusion deficits. These patients have an initial response to therapy but do not reach sufficient stabilization to undergo endovascular procedures or NOM.

In pediatric patients, hemodynamic stability is considered a systolic blood pressure of 70 mmHg plus twice the child’s age in years. An acceptable hemodynamic status in children is considered a positive response to fluid resuscitation: 2 boluses of 20 mL/kg of crystalloid replacement should be administered before blood replacement leading to heart rate reduction, cleared sensorium, return of peripheral pulses, normal skin color, increase in blood pressure and urinary output, and an increase in warmth of the skin in the extremities. Clinical judgment however is fundamental in evaluating pediatric patients.

WSES classification
The WSES classification (Table 2) divides liver injuries into four classes considering the AAST-OIS classification (Table 3) and the hemodynamic status (Table 4):

- Minor (WSES grade I)
- Moderate (WSES grade II)
- Severe (WSES grade III and IV)

Minor hepatic injuries:

- WSES grade I includes AAST-OIS grade I–II hemodynamically stable lesions.

Moderate hepatic injuries:

- WSES grade II includes AAST-OIS grade III hemodynamically stable lesions.

Severe hepatic injuries:

- WSES grade III includes AAST-OIS grade IV–V hemodynamically stable lesions.
- WSES grade IV includes AAST-OIS grade I–VI hemodynamically unstable lesions.
<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
</table>
| 1A                           | Strong recommendation, high-quality evidence  
Benefits clearly outweigh risk and burdens, or vice versa | RCTs without important limitations or overwhelming evidence from observational studies  
RCTs without important limitations or overwhelming evidence from observational studies | Strong recommendation, applies to most patients in most circumstances without reservation                                              |
| 1B                           | Strong recommendation, moderate-quality evidence  
Benefits clearly outweigh risk and burdens, or vice versa | RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses, or imprecise conclusions) or exceptionally strong evidence from observational studies | Strong recommendation, applies to most patients in most circumstances without reservation                                              |
| 1C                           | Strong recommendation, low-quality or very low-quality evidence  
Benefits clearly outweigh risk and burdens, or vice versa | Observational studies or case series  
Observational studies or case series | Strong recommendation but subject to change when higher quality evidence becomes available                                             |
| 2A                           | Weak recommendation, high-quality evidence  
Benefits closely balanced with risks and burden | RCTs without important limitations or overwhelming evidence from observational studies  
RCTs without important limitations or overwhelming evidence from observational studies | Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values                          |
| 2B                           | Weak recommendation, moderate-quality evidence  
Benefits closely balanced with risks and burden | RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies | Weak recommendation, best action may differ depending on the patient, treatment circumstances, or social values                          |
| 2C                           | Weak recommendation, low-quality or very low-quality evidence  
Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced | Observational studies or case series  
Observational studies or case series | Very weak recommendation; alternative treatments may be equally reasonable and merit consideration                                    |
Based on the present classification, we suggest two management algorithms: one general (Fig. 1) and one specifically dedicated to hemodynamically unstable patients (Fig. 2).

**Diagnosis**

- The diagnostic methods on admission are determined by the hemodynamic status (GoR 1A).
- Extended-focused abdominal sonography for trauma (E-FAST) is rapid in detecting intra-abdominal free fluid (GoR 1A).
- CT scan with intravenous contrast is the gold standard in hemodynamically stable trauma patients (GoR 1A).
- Careful physical examination is of paramount importance in determining the need for exploratory laparotomy [10]. E-FAST is useful and generally reliable in trauma in general. However, abdominal ultrasound may be falsely negative due to clotted blood or suboptimal quality views [11–13]. In the pediatric population, reported sensitivity and specificity ranges from 42 to 52% and 96 to 98%, with a negative predicting value for intra-abdominal fluid of 93–96% [8, 9, 14–16]. The low sensitivity of E-FAST in hemodynamically stable pediatric patients may warrant further investigation, specifically contrast-enhanced ultrasound (US) or abdomen/pelvis CT scan or magnetic resonance, in hemodynamically stable pediatric patients with a high degree of suspicion for intra-abdominal injury (abnormal physical examination, abnormal laboratory values, or other radiologic studies).

Computed tomography (CT) scan is considered the gold standard in trauma imaging assessment with a sensitivity and specificity approaching 96–100% [17–19]. CT must be immediately available and performed only in hemodynamically stable or stabilized patients or in those who transiently responded to fluid resuscitation in special circumstances and under the supervision of the trauma team [20, 21]. Delayed-phase CT helps in differentiating patients with active bleeding from those with contained vascular injuries [22]. This data is important to reduce the risk of discrepancy between CT scan images and angiographic images (only 47% of patients have a confirmation of the CT findings at angiography) [22]. Active contrast extravasation is a sign of active hemorrhage [23]. CT scan may help in subsequent

### Table 2 WSES liver trauma classification

<table>
<thead>
<tr>
<th>WSES grade</th>
<th>AAST</th>
<th>Hemodynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>I-II</td>
<td>Stable</td>
</tr>
<tr>
<td>Moderate</td>
<td>III</td>
<td>Stable</td>
</tr>
<tr>
<td>Severe</td>
<td>IV-V</td>
<td>Stable</td>
</tr>
<tr>
<td>Severe</td>
<td>I-VI</td>
<td>Unstable</td>
</tr>
</tbody>
</table>

### Table 3 AAST liver trauma classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Injury Type</th>
<th>Injury Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Haematoma</td>
<td>Subcapsular &lt; 10% surface</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>Capsular tear &lt; 1cm parenchymal depth</td>
</tr>
<tr>
<td>II</td>
<td>Haematoma</td>
<td>Subcapsular 10-50% surface area; intraparenchymal, &lt; 10cm diameter</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>1-3cm parenchymal depth, &lt; 10 cm in length</td>
</tr>
<tr>
<td>III</td>
<td>Haematoma</td>
<td>Subcapsular &gt; 50% surface area or expanding, ruptured subcapsular or parenchymal haematoma. Intraparenchymal haematoma &gt; 10cm</td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>&gt; 3cm parenchymal depth</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>Parenchymal disruption 25-75% of hepatic lobe</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>Parenchymal disruption involving &gt; 75% of hepatic lobe</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Juxtavenous hepatic injuries i.e retrohepatic vena cava/central major hepatic veins</td>
</tr>
<tr>
<td>VI</td>
<td>Vascular</td>
<td>Hepatic avulsion</td>
</tr>
<tr>
<td></td>
<td>Advance one grade for multiple injuries up to grade III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AAST liver injury scale (1994 revision)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4 Statements summary

<table>
<thead>
<tr>
<th>Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic procedures</strong></td>
</tr>
<tr>
<td>- The diagnostic methods on admission are determined by the hemodynamic status (GoR 1A).</td>
</tr>
<tr>
<td>- E-FAST is rapid in detecting intra-abdominal free fluid (GoR 1A).</td>
</tr>
<tr>
<td>- CT scan with intravenous contrast is the gold standard in hemodynamically stable trauma patients (GoR 1A).</td>
</tr>
<tr>
<td><strong>Non-operative management (NOM)</strong></td>
</tr>
<tr>
<td>- NOM should be the treatment of choice for all hemodynamically stable minor (WSES I) (AAST I–II), moderate (WSES II) (AAST III), and severe (WSES III) (AAST IV–V) injuries in the absence of other internal injuries requiring surgery (GoR 2A).</td>
</tr>
<tr>
<td>- In patients considered transient responders with moderate (WSES II) (AAST III) and severe (WSES III) (AAST IV–V) injuries, NOM should be considered only in selected settings provided the immediate availability of trained surgeons, operating room, continuous monitoring ideally in an ICU or ER setting, access to angiography, angiography/angiembolization, blood and blood products, and in locations where a system exists to quickly transfer such patients to higher level of care facilities (GoR 2B).</td>
</tr>
<tr>
<td>- A CT scan with intravenous contrast should always be performed in patients being considered for NOM (GoR 2A).</td>
</tr>
<tr>
<td>- AG/AE may be considered as a first-line intervention in hemodynamically stable patients with arterial blush on CT scan (GoR 2B).</td>
</tr>
<tr>
<td>- In hemodynamically stable children, the presence of contrast blush on CT scan is not an absolute indication for AG/AE (GoR 2B).</td>
</tr>
<tr>
<td>- Serial clinical evaluations (physical exams and laboratory testing) must be performed to detect a change in clinical status during NOM (GoR 2A).</td>
</tr>
<tr>
<td>- NOM should be attempted in the setting of concomitant head trauma and/or spinal cord injuries with reliable clinical exam, unless the patient could not achieve specific hemodynamic goals for the neurotrauma and the instability might be due to intra-abdominal bleeding (GoR 2B).</td>
</tr>
<tr>
<td>- Intensive care unit admission in isolated liver injury may be required only for moderate (WSES II) (AAST III) and severe (WSES III) (AAST IV–V) lesions (GoR 2B).</td>
</tr>
<tr>
<td>- In selected cases where an intra-abdominal injury is suspected in the days after the initial trauma, interval laparoscopic exploration may be considered as an extension of NOM and a means to plan patient management in a step-up treatment strategy (GoR 2C).</td>
</tr>
<tr>
<td>- In low-resource settings, NOM could be considered in patients with hemodynamic stability without evidence of associated injuries, with negative serial physical examinations and negative imaging and blood tests (GoR 2C).</td>
</tr>
<tr>
<td><strong>Operative management (OM)</strong></td>
</tr>
<tr>
<td>- Hemodynamically unstable and non-responder patients (WSES IV) should undergo OM (GoR 2A).</td>
</tr>
<tr>
<td>- Primary surgical intention should be to control the hemorrhage and bile leak and initiation of damage control resuscitation as soon as possible (GoR 2A).</td>
</tr>
<tr>
<td>- Major hepatic resections should be avoided at first and only considered in subsequent operations, in a resectional debridement fashion in cases of large areas of devitalized liver tissue done by experienced surgeons (GoR 2B).</td>
</tr>
<tr>
<td>- Angioembolization is a useful tool in case of persistent arterial bleeding after non-hemostatic or damage control procedures (GoR 2A).</td>
</tr>
<tr>
<td>- Resuscitative endovascular balloon occlusion of the aorta (i.e., REBOA) may be used in hemodynamically unstable patients as a bridge to other more definitive procedures for hemorrhage control (GoR 2B).</td>
</tr>
<tr>
<td><strong>Short- and long-term follow-up</strong></td>
</tr>
<tr>
<td>- Intrahepatic abscesses may be successfully treated with percutaneous drainage (GoR 2A).</td>
</tr>
<tr>
<td>- Delayed hemorrhage without severe hemodynamic compromise may be managed at first with AG/AE (GoR 2A).</td>
</tr>
<tr>
<td>- Hepatic artery pseudoaneurysm should be managed with AG/AE to prevent rupture (GoR 2A).</td>
</tr>
<tr>
<td>- Symptomatic or infected bilomas should be managed with percutaneous drainage (GoR 2A).</td>
</tr>
<tr>
<td>- Combination of percutaneous drainage and endoscopic techniques may be considered in managing post-traumatic biliary complications not suitable for percutaneous management alone (GoR 2B).</td>
</tr>
<tr>
<td>- Lavage/drainage and endoscopic stenting may be considered as the first approach in delayed post-traumatic biliary fistula without any other indication for laparotomy (GoR 2B).</td>
</tr>
<tr>
<td>- Laparoscopy as initial approach should be considered in cases of delayed surgery, so as to minimize the invasiveness of surgical intervention and to tailor the procedure to the lesion (GoR 2B).</td>
</tr>
<tr>
<td><strong>Thrombo-prophylaxis, feeding, and mobilization</strong></td>
</tr>
<tr>
<td>- Mechanical prophylaxis is safe and should be considered in all patients with no absolute contraindication (GoR 2A).</td>
</tr>
<tr>
<td>- LMWH-based prophylaxis should be started as soon as possible following trauma and may be safe in selected patients with liver injury treated with NOM (GoR 2B).</td>
</tr>
<tr>
<td>- In those patients taking anticoagulants, individualization of the risk-benefit balance of anticoagulant reversal is suggested (GoR 1C).</td>
</tr>
<tr>
<td>- Early mobilization should be achieved in stable patients (GoR 2A).</td>
</tr>
<tr>
<td>- In the absence of contraindications, enteral feeding should be started as soon as possible (GoR 2A).</td>
</tr>
</tbody>
</table>

Surgical procedures and angiography/angiembolization (AG/AE) [24–32].

Diagnostic peritoneal lavage (DPL) should be considered diagnostic modality in low-resource settings, where CT scan or US is not promptly available [33]. It should be considered in the presence of massive subcutaneous emphysema in a shocked patient in whom ultrasound cannot be done and/or in the presence of free peritoneal fluid without solid organ injury in a hemodynamically stable patient. The possibility of DPL-related complications (up to 2%) should be considered [33].

**Non-operative management**

- NOM should be the treatment of choice for all hemodynamically stable minor (WSES I) (AAST I–
II), moderate (WSES II) (AAST III), and severe (WSES III) (AAST IV–V) injuries in the absence of other internal injuries requiring surgery (GoR 2A).

- In patients considered transient responders with moderate (WSES II) (AAST III) and severe (WSES III) (AAST IV–V) injuries, NOM should be considered only in selected settings provided the immediate availability of trained surgeons, operating room, continuous monitoring ideally in an ICU or ER setting, access to angiography, angioembolization, blood, and blood products, and in locations where a system exists to quickly transfer such patients to higher level of care facilities (GoR 2B).

- A CT scan with intravenous contrast should always be performed in patients being considered for NOM (GoR 2A).

- AG/AE may be considered as a first-line intervention in hemodynamically stable patients with arterial blush on CT scan (GoR 2B).

- In hemodynamically stable children, the presence of contrast blush on CT scan is not an absolute indication for AG/AE (GoR 2B).

- Serial clinical evaluations (physical exams and laboratory testing) must be performed to detect a change in clinical status during NOM (GoR 2A).

- NOM should be attempted in the setting of concomitant head trauma and/or spinal cord injuries with reliable clinical exam, unless the patient could not achieve specific hemodynamic goals for the neurotrauma and the instability might be due to intra-abdominal bleeding (GoR 2B).

- Intensive care unit admission in isolated liver injury may be required only for moderate (WSES II) (AAST III) and severe (WSES III) (AAST IV–V) lesions (GoR 2B).

- In selected cases where an intra-abdominal injury is suspected in the days after the initial trauma, interval laparoscopic exploration may be considered as an extension of NOM and a means to

---

Fig. 1 Liver trauma management algorithm (SW: stab wound. Number sign indicates wound exploration near the inferior costal margin should be avoided if not strictly necessary. Asterisk indicates angioembolization should be always considered for adults, only in selected patients and in selected centers for pediatrics)
plan patient management in a step-up treatment strategy (GoR 2C).

- In low-resource settings, NOM could be considered in patients with hemodynamic stability without evidence of associated injuries, with negative serial physical examinations and negative imaging and blood tests (GoR 2C).

Absolute requirements for NOM are hemodynamic stability and absence of other lesions requiring surgery [9, 15, 34–39]. In hemodynamically stable patients without other associated injuries requiring OM, NOM is considered the standard of care [8, 14, 15]. The concept is valid for both: blunt (BT) and penetrating trauma (PT). Attempting NOM in moderate (WSES II) (AAST-OIS III) and severe (WSES III) (AAST-OIS IV–V) blunt or penetrating injuries requires the ability to diagnose all associated injuries and to provide intensive management (continuous clinical monitoring, serial hemoglobin monitoring, and around-the-clock availability of trained surgeons, CT scanning, angiography, OR, and blood and blood products) [16, 40–44].

As a general consideration, great attention should be paid in selecting PT for NOM especially in the case of gunshot wound (GSW) and even more if thoraco-abdominal. They should be considered for NOM only in centers with experience in dealing with PT. Even in patients presenting with stable conditions and with no evidence of other intra-abdominal/internal injuries, interval laparoscopy should be always considered in order to confirm the absence of other injuries requiring surgical repair.

In PT, NOM feasibility has been reported [35–37, 45–49] with 50% and 85% success rate of NOM for stab wounds (SW) in anterior and posterior abdomen respectively [34, 50]. Similar managing strategy can be applied to GSWs [35, 45]. Necessary distinction between low- and high-energy penetrating trauma however is mandatory when deciding for OM or NOM. Low-energy PT (SW and low-energy GSW) may be safely treated...
with NOM at first, provided the patient is hemodynamically stable and no other injuries require surgery. In considering NOM, interval laparoscopy should be considered to rule out missed intra-abdominal injuries. High-energy GSW and other ballistic injuries are less amenable to NOM, and in 90% of cases, OM is required [34, 36, 51]. In abdominal GSWs, up to 25% of non-therapeutic laparotomy has been reported [51], confirming the need to have strict selection criteria for OM or NOM even in the GSW cohort. Associated head and spinal cord injuries (that preclude affordable clinical examination) and significant reduction in hemoglobin requiring > 4 units of blood transfusion in the first 8 h [34, 45] have been suggested as predictive criteria of NOM failure in abdominal GSWs.

Patient selection is influenced by the diagnostic capability and accuracy. In fact, the accuracy of CT scan in SWs has been questioned [37, 50]. Even in the presence of a negative CT scan, exploratory laparoscopy/laparotomy may be necessary [37]. Interval laparoscopy is a useful tool to be considered in obese patients or in the presence a long and tangential wound tract or when the trajectory is difficult to determine on CT scan [34, 37]. In anterior abdominal SW, local wound exploration (LWE) is generally accurate in evaluating penetration depth; small external wounds may be enlarged for precise LWE and determination of anterior fascia violation [34, 35]. LWE, however, may be misleading, and patients should be admitted for observation if equivocal. Wounds close to the inferior costal margin should be evaluated by LWE with caution and only if strictly necessary.

GSWs undergoing NOM may warrant a CT scan to determine the trajectory [45, 51]. CT scan specificity and sensitivity of 96% and 90.5% respectively for GSWs requiring laparotomy have been reported [52]. The gold standard to decide for OM or NOM remains the clinical examination [34, 51] associated with laboratory and radiological evaluation. Strict clinical and hemoglobin evaluation should be done (every 6 h for at least 24 h); after index CT scan allowing for NOM, serial ecograpical evaluation may be utilized to help in defining patient clinical evolution. Once stabilized, patients are usually transferred from ICU to the ward [35, 45, 50].

NOM is contraindicated if free intra- or retroperitoneal air, free intra-peritoneal fluid in the absence of solid organ injury, localized bowel wall thickening, bullet tract close to hollow viscus with surrounding hematoma [46], and in high-energy penetrating trauma are detected at CT scan.

In selected centers, AE is considered as an “extension” of NOM in patients with liver injuries presenting with ongoing resuscitative needs [9, 53, 54]. If required, AE can be safely repeated.

In children, the use of primary hepatic AE has been reported rarely and is debated even in the presence of arterial blush where it seems to increase NOM failure rates [55], or according to some studies, it does not correlate with decrease odds of laparotomy [30]. In the pediatric population, AE use is associated with older age and is not completely defined in terms of efficacy and cost-effectiveness, especially in low-resource settings [30, 55–61]. Some authors, however, identify the presence of active contrast extravasation as an independent predictor for pseudoaneurysm (PSA) formation in children, regardless of injury grade. This suggests a thorough follow-up during NOM of these patients, so to obtain an early identification and angiographic treatment of PSA [62].

The biggest risk of NOM in penetrating trauma is a missed abdominal injury, especially hollow viscus perforation [34, 46]. However, no increase in mortality rates with missed hollow viscus perforation has been reported in patients without peritonitis on admission [63]. As a counterpart, non-therapeutic laparotomy leads to an increase in morbidity [63]. Moreover, OM in penetrating liver injuries has a higher liver-related complication rate (50–52%) compared to blunt injuries [34, 46].

During NOM for liver injuries, no standard early follow-up and monitoring protocols exist in adult or in children [34]. Serial clinical evaluation and hemoglobin measurement represent the cornerstone in evaluating NOM patients [14]. Besides, US may represent an affordable tool during early follow-up. Presence of large subcapsular hematomas is not a strict indication for OM, but a higher risk of NOM failure exists. In any case, these patients should undergo serial blood test: increasing levels of transaminases could indicate the presence of intrahepatic parenchymal ischemia or rare cases of torsion of suprahepatic veins [64]. ICU admission may be indicated for moderate (WSES II) (AAST III) and severe (WSES III–IV) (AAST IV–V) liver trauma in order to reduce the mortality risk [26].

If available, interval laparoscopy during NOM provides important information about the evolution of the injury. Laparoscopy should be considered an important tool in the NOM of liver injuries, and it could be used as a bridge strategy to plan an immediate or subsequent laparoscopic/laparotomy intervention [65].

Particular attention should be paid in managing hemodynamically stable patients with liver trauma associated with spinal trauma (ST) and severe traumatic brain injury (STBI). In blunt trauma, NOM should apply to all patients with no other indication to laparotomy. However, the optimal management of concomitant STBI and/or ST and penetrating liver injuries is debated and OM in general could be suggested as safer [45, 48, 66].
Patients affected by neurotrauma (i.e., spinal cord or moderate-severe traumatic brain injury) in fact, for several instances, differ from the others because they need a higher perfusion pressure to adequately supply oxygen to the brain and to the spinal cord to reduce the subsequent burden of disability and mortality. A disruption of the normal blood flow regulation in the central nervous system (CNS) characterizes the trauma and eventually leads to a blood flow dependent on perfusion pressure in ischemic tissue [67]. Specific hemodynamic goals for ST and STBI are defined as SBP > 110 mmHg and/or a CPP between 60 and 70 mmHg in the case of moderate/severe TBI and an MBP > 80 mmHg in case of ST [68, 69]. To date, no study specifically addressed the NOM of abdominal solid organ injuries in the neuro-trauma patient, and several authors have considered it an exclusion criterion from NOM [45, 48, 70]. However, since the first goal is to have a stable patient with adequate perfusion pressure, there is no rationale in denying NOM to these patients, as long as the specific hemodynamic goals are met.

Operative management

- Hemodynamically unstable and non-responder patients (WSES IV) should undergo OM (GoR 2A).
- Primary surgical intention should be to control the hemorrhage and bile leak and initiation of damage control resuscitation as soon as possible (GoR 2A).
- Major hepatic resections should be avoided at first and only considered in subsequent operations, in a resectional debridement fashion in cases of large areas of devitalized liver tissue done by experienced surgeons (GoR 2B).
- Angioembolization is a useful tool in case of persistent arterial bleeding after non-hemostatic or damage control procedures (GoR 2A).
- Resuscitative endovascular balloon occlusion of the aorta (i.e., REBOA) may be used in hemodynamically unstable patients as a bridge to other more definitive procedures for hemorrhage control (GoR 2B).

At laparotomy, if no major bleeding is present, compression alone or electrocautery, bipolar devices, argon beam coagulation, topical hemostatic agents, simple suture of the hepatic parenchyma, or omental patching may be sufficient to stop the bleeding [34, 66, 71–73].

In case of major hemorrhage, more aggressive procedures including manual compression and hepatic packing, ligation of vessels in the wound, hepatic debridement and finger fracture, balloon tamponade, shunting procedures, or hepatic vascular isolation and exclusion may be used [64, 74]. Of paramount importance is to provide simultaneous intraoperative intensive resuscitation with early institution of a massive transfusion protocol (MTP) aiming to maintain organ perfusion and ultimately reverse all trauma-induced physiological derangements [34, 71, 73, 75].

In case of evident injury to the proper hepatic artery, an attempt to control and repair it should be made. If not effective or not possible, selective hepatic artery ligation should be considered as a viable option. If the injury is on the right or left branches of the proper hepatic artery, selective ligation is advisable. If the right or common hepatic artery must be ligated, cholecystectomy should be performed to avoid gallbladder necrosis [2, 76]. If the patient’s condition allows for it, post-operative AE represents a viable alternative allowing hemorrhage control while reducing complications [34, 66, 71, 77]. Hepatic artery ligation increases the risk of hepatic necrosis, abscesses, and biloma formation [34].

Portal vein injuries should be repaired primarily. Portal vein main branch ligation should not be considered and should be avoided because of the high risk of liver necrosis or massive bowel edema. If no other option exists, ligation can be used, but only in patients with an intact hepatic artery. Liver packing or liver resection should be preferred to ligation in case of lobar or segmental/subsegmental portal venous branch injuries [34, 76].

Whenever Pringle maneuver or arterial control fails and bleeding persists, the presence of an aberrant hepatic artery should be considered. If the bleeding comes from behind the liver, retro-hepatic caval or hepatic vein injury should be highly suspected [34, 77]. Three viable options exist for the management of retrohepatic caval/ suprahepatic venous injuries: (1) tamponade with hepatic packing, (2) direct repair (with or without vascular isolation), and (3) lobar resection [38, 78–80]. Liver packing is the least risky method to temporarily deal with severe venous injuries [34, 66, 81–83]. Direct venous repair is difficult especially in non-experienced hands, with high mortality rates [34, 66].

Different techniques of hepatic vascular exclusion with shunting procedures have been described, most of them anecdotally. The veno-veno bypass (femoral vein and inferior mesenteric vein to axillary or jugular vein by pass) and the use of fenestrated stent grafts are the most frequently used [66, 71, 76, 84]. The atrio-caval shunt bypasses the retro-hepatic cava blood through the right atrium using a chest tube put into the inferior vena cava. Mortality rates in such a complicated situations are very high and usually related to the fact that the decision to perform the shunt is made late in the case [71]. Complete vascular exclusion of the liver is generally poorly tolerated in the unstable patient with major blood loss [34].
Resuscitative endovascular balloon occlusion of the aorta (REBOA) catheter in zone I should be considered if despite all damage control procedures, there is still active surgical bleeding. Simultaneously, the large high flow femoral venous catheter should be exchanged over a guide wire to an introducer with the aim of floating up and inflating a resuscitative endovascular balloon occlusion of the retro-hepatic vena cava (REBOVC) at the level of the retro-hepatic vena cava. The goal is to achieve proximal and distal vascular control of a possible retro-hepatic/supra-hepatic vessel injury with the REBOVC and ultimately obtaining complete combined endovascular/open liver isolation with the Pringle maneuver. A supra-diaphragmatic central venous access must be obtained prior to inflating the REBOA/REBOVC [85–91].

In cases of liver avulsion or total crush injury, when a total hepatic resection is indicated, hepatic transplantation has been described [76]. A retrospective study based on the European Liver Transplant Registry identifies an ISS score less than 33 for recipient selection, so to avoid futile procedures [92].

Anatomic hepatic resection may seldom be considered as a surgical option [6, 93, 94]. In unstable patients and during damage control surgery, it should be avoided, but in case of need, a non-anatomic resection is safer and easier [34, 66, 71, 76]. For staged liver procedures, either anatomic or non-anatomic resections may be safely performed by experienced surgeons [76].

Temporary abdominal closure may be indicated if the risk of abdominal compartment syndrome is high or in those situation where a “second look” operation is needed [71–73].

Two principal indications for post-operative angiography-embolization (AG-AE) have been proposed: (1) after initial operative hemostasis, in stable or stabilized patients with contrast blush at completion CT scan; and (2) as adjunctive hemostatic tool in patients with uncontrolled suspected arterial bleeding despite emergency laparotomy and hemostasis attempt [34, 54, 95–99]. Recent evidence suggests that routine use of immediate post-damage control hepatic angiography reduces mortality in grade IV/V hepatic injuries [100].

Complications

- Intrahepatic abscesses may be successfully treated with percutaneous drainage (GoR 2A).
- Delayed hemorrhage without severe hemodynamic compromise may be managed at first with AG/AE (GoR 2A).
- Hepatic artery pseudoaneurysm should be managed with AG/AE to prevent rupture (GoR 2A).
- Symptomatic or infected bilomas should be managed with percutaneous drainage (GoR 2A).
- Combination of percutaneous drainage and endoscopic techniques may be considered in managing post-traumatic biliary complications not suitable for percutaneous management alone (GoR 2B).
- Laparoscopic lavage/drainage and endoscopic stenting may be considered as the first approach in delayed post-traumatic biliary fistula without any other indication for laparotomy (GoR 2B).
- Laparoscopy as initial approach should be considered in cases of delayed surgery, so as to minimize the invasiveness of surgical intervention and to tailor the procedure to the lesion (GoR 2B).

In blunt hepatic trauma, particularly after high-grade injury, complications occur in 12–14% of patients [9, 66]. Diagnostic tools for complications after NOM include clinical examination, blood tests, ultrasound, and CT scan. Routine follow-up with CT scan is not necessary unless there is clinical suspicion of a complication [6, 9, 66]. In the presence of abnormal inflammatory response, abdominal pain, fever, jaundice, or drop of hemoglobin level, repeated CT scan is recommended [9]. Bleeding, abdominal compartment syndrome, infections (abscesses and other infections), biliary complications (bile leak, hemobilia, biloma, biliary peritonitis, biliary fistula), and liver necrosis are the most frequent complications associated with NOM [16, 66]. Ultrasound is useful in the assessment of bile leak/biloma in grade IV–V injuries, especially with a central laceration.

Re-bleeding or secondary hemorrhage is the most frequently reported complications after NOM as in subcapsular hematoma or pseudo-aneurysm (PSA) rupture (range 1.7–5.9%) with a mortality rate up to 18% [9, 66, 101, 102]. In the majority of cases (69%), “late” bleeding can be treated non-operatively [9, 66].

Hepatic artery PSA is a rare complication with a prevalence of 1% [103]. Asymptomatic PSA should be treated as early as possible with AE because of the high risk of rupture and the associated high morbidity [34, 104, 105]. In patients with melena or hematemia following liver trauma, bleeding from the ampulla of Vater (hemobilia) is highly suggestive of ruptured intrahepatic PSA [106, 107]. AE is the treatment of choice [6, 34, 66]. In the presence of intrahepatic bilio-venous fistula (frequently associated with bilemia), endoscopic retrograde cholangiopancreatography (ERCP) represents an effective tool [108].

Biliary complications include biloma, biliary fistula, bilhemia, and bile peritonitis (incidence 2.8–30%) [8, 40]. Most traumatic bilomas regress spontaneously. Enlarging, symptomatic or infected bilomas can be successfully managed with percutaneous drainage. Percutaneous drainage may be combined with therapeutic ERCP with
eventual endobiliary stent placement [9, 101, 109–111]. Bile peritonitis has been usually treated with laparotomy. Combination of laparoscopic irrigation/drainage and endoscopic bile duct stent placement may represent a valid alternative [101, 102, 112, 113]. Abscesses are rare after NOM and usually happen in severe lesions (prevalence 0.6–7%) [9, 66, 114–117]. CT scan or ultrasound-guided percutaneous drainage is the treatment of choice with high success rate and no reported mortality [106]. In the presence of necrosis and devascularization of hepatic segments, surgical management may be indicated whenever affecting patient condition [34, 66].

Generally, once stabilization of traumatized patient is obtained, late complications should be managed preferentially by minimally invasive procedures. Laparoscopy and endoscopy are part of this approach, which became possible in a delayed surgery setting [64, 65, 118, 119].

**Thromboprophylaxis, feeding, and mobilization**

- Mechanical prophylaxis is safe and should be considered in all patients with no absolute contraindication (GoR 2A).
- LMWH-based prophylaxis should be started as soon as possible following trauma and may be safe in selected patients with liver injury treated with NOM (GoR 2B).
- In those patients taking anticoagulants, individualization of the risk-benefit balance of anticoagulant reversal is suggested (GoR 1C).
- Early mobilization should be achieved in stable patients (GoR 2A).
- In the absence of contraindications, enteral feeding should be started as soon as possible (GoR 2A).

Venous thromboembolism (VTE) is one of the great risks of trauma victims, because patients enter a hypercoagulation state within 48 h from injury [120–122]. More than 50% of patients without thrombo-prophylaxis may develop deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE) which carries a mortality rate up to 50% [120, 121]. PE is the third leading cause of death in trauma patients.

No differences in complication, mortality, and NOM failure rate were demonstrated when thromboprophylaxis was administered within and after 48 and 72 h from the initial injury in patients without STBI and BST [123–125]. Early mobilization is not related to NOM failure and secondary bleeding [126]. However, VTE rates seem to be over fourfold when LMWH is administered > 72 h from admission [120].

In patients taking anticoagulants, it is important to evaluate the eventual need for reversal therapy in order to balance the risk of bleeding against the benefit of preventing thrombotic complications. Poor outcomes derive from the failure to restore the anticoagulation as soon as possible [127].

Early enteral feeding is associated with improved clinical outcomes when administered within the first 72 h from admission in ICU [128], and it should be delayed only in cases of uncontrolled shock, use of vasopressor therapy, uncontrolled hypoxaemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate > 500 ml/6 h, bowel ischemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access [129]. Oral intake, when possible, should be initiated after 24–48 h from the traumatic event.

**Follow-up**

Mandatory late follow-up imaging is not indicated, and it should be used only if the patient’s clinical condition and/or symptoms indicating a complication require it for diagnosis. The majority of liver lesions heal in about 4 months [14, 66]. After moderate and severe liver injuries, patients may usually resume normal physical activities after 3–4 months.

During the recovery phase, patients should be encouraged to not remain alone for long periods and to return immediately to the hospital in case of increasing abdominal pain, lightheadedness, nausea, or vomiting [14, 34].

**Conclusions**

Management of liver trauma is multidisciplinary. When feasible, non-operative management should always be considered as the first option in adult and in the pediatric populations. For this reason, clinical condition, anatomical injury grade, and associated injuries should be considered together in deciding the best treatment option.

**Abbreviations**

NOM: Non-operative management; OM: Operative management; AAST: American Association for Surgery for Trauma; WSES: World Society of Emergency Surgery; PTS: Panamerican Trauma Society; ATLS: Advanced trauma life support; ERCP: Endoscopic retrograde cholangiopancreatography; BLT: Blunt liver trauma; SW: Stab wounds; GSW: Gunshot wound; DCS: Damage control surgery; OR: Operating room; AG: Angiography; AE: Angioembolization; EVTM: Endovascular bleeding and trauma management; STBI: Severe traumatic brain injury; ST: Spine trauma; CNS: Central nervous system; PSA: Pseudoaneurysm; REBOA: Resuscitative endovascular balloon occlusion of the aorta; MTP: Massive transfusion protocol

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None

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Splenic trauma: WSES classification and guidelines for adult and pediatric patients


Abstract

Spleen injuries are among the most frequent trauma-related injuries. At present, they are classified according to the anatomy of the injury. The optimal treatment strategy, however, should keep into consideration the hemodynamic status, the anatomic derangement, and the associated injuries. The management of splenic trauma patients aims to restore the homeostasis and the normal physiopathology especially considering the modern tools for bleeding management. Thus, the management of splenic trauma should be ultimately multidisciplinary and based on the physiology of the patient, the anatomy of the injury, and the associated lesions. Lastly, as the management of adults and children must be different, children should always be treated in dedicated pediatric trauma centers. In fact, the vast majority of pediatric patients with blunt splenic trauma can be managed non-operatively. This paper presents the World Society of Emergency Surgery (WSES) classification of splenic trauma and the management guidelines.

Keywords: Spleen, Trauma, Adult, Pediatric, Classification, Guidelines, Embolization, Surgery, Non-operative, Conservative

Background

The management of splenic trauma has changed considerably in the last few decades especially in favor of non-operative management (NOM). NOM ranges from observation and monitoring alone to angiography/angioembolization (AG/AE) with the aim to preserve the spleen and its function, especially in children. These considerations were carried out considering the immunological function of the spleen and the high risk of immunological impairment in splenectomized patients. In contrast with liver traumatic injuries, splenic injuries can be fatal not only at the admission of the patient to the Emergency Department (ED), but also due to delayed subcapsular hematoma rupture or pseudoaneurism (PSA) rupture. Lastly, overwhelming post-splenectomy infections (OPSI) are a late cause of complications due to the lack of the immunological function of the spleen. For these reasons,
standardized guidelines in the management of splenic trauma are necessary.

The existing classification of splenic trauma considered the anatomical lesions (Table 1). However, patients’ conditions may lead to an emergent transfer to the operating room (OR) without the opportunity to define the grade of the splenic lesions before the surgical exploration. This confirms the primary importance of the patient’s overall clinical condition in these settings. In addition, the modern tools in bleeding management have helped in adopting a conservative approach also in severe lesions. Trauma management must be multidisciplinary and requires an assessment of both the anatomical injury and its physiologic effects. The present guidelines and classification reconsider splenic lesions in the light of the physiopathologic status of the patient associated with the anatomic grade of injury and the other associated lesions.

Notes on the use of the guidelines
The guidelines are evidence-based, with the grade of recommendation also based on the evidence. The guidelines present the diagnostic and therapeutic methods for optimal management of spleen trauma. The practice guidelines promulgated in this work do not represent a standard of practice. They are suggested plans of care, based on best available evidence and the consensus of experts, but they do not exclude other approaches as being within the standard of practice. For example, they should not be used to compel adherence to a given method of medical management, which method should be finally determined after taking account of the conditions at the relevant medical institution (staff levels, experience, equipment, etc.) and the characteristics of the individual patient. However, responsibility for the results of treatment rests with those who are directly engaged therein, and not with the consensus group.

Methods
A computerized search was done by the bibliographer in different databanks (MEDLINE, Scopus, EMBASE) citations were included for the period between January 1980 and May 2016 using the primary search strategy: spleen, injuries, trauma, resuscitation, adult, pediatric, hemodynamic instability/stability, angioembolization, management, infection, follow-up, vaccination, and thrombo-prophylaxis combined with AND/OR. No search restrictions were imposed. The dates were selected to allow comprehensive published abstracts of clinical trials, consensus conference, comparative studies, congresses, guidelines, government publication, multicenter studies, systematic reviews, meta-analysis, large case series, original articles, and randomized controlled trials. Case reports and small cases series were excluded. Narrative review articles were also analyzed to determine other possible studies. Literature selection is reported in the flow chart (Fig. 1). The Level of evidence (LE) was evaluated using the GRADE system [1] (Table 2).

A group of experts in the field coordinated by a central coordinator was contacted to express their evidence-based opinion on several issues about the pediatric (<15 years old) and adult splenic trauma. Splenic trauma were divided and assessed as type of injury (blunt and penetrating injury) and management (conservative and operative management). Through the Delphi process, the different issues were discussed in subsequent rounds. The central coordinator assembled the different answers derived from each round. Each version was then revised and improved. The definitive version was discussed during the WSES World Congress in May 2017 in Campinas, Brazil. The final version about which the agreement was reached resulted in present paper.

WSSES classification
The WSES position paper suggested to group splenic injury into minor, moderate, and severe. This classification has not previously been clearly defined by the literature. Frequently low-grade AAST lesions (i.e., grades I–III) are considered as minor or moderate and treated with NOM. However, hemodynamically stable patients with high-grade lesions could be successfully treated non-operatively, especially exploiting the more advanced tools for bleeding management. On the other hand, “minor” lesions associated with hemodynamic instability often must be treated with

Table 1 AAST Spleen Trauma Classification

<table>
<thead>
<tr>
<th>Grade</th>
<th>Injury description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma Subcapsular, &lt; 10% surface area</td>
</tr>
<tr>
<td></td>
<td>Laceration Capsular tear, &lt; 1 cm parenchymal depth</td>
</tr>
<tr>
<td>II</td>
<td>Hematoma Subcapsular, 10–50% surface area</td>
</tr>
<tr>
<td></td>
<td>Intraparenchymal, &lt; 5 cm diameter</td>
</tr>
<tr>
<td></td>
<td>Laceration 1–3 cm parenchymal depth not involving a perichymal vessel</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma Subcapsular, &gt; 50% surface area or expanding</td>
</tr>
<tr>
<td></td>
<td>Ruptured subcapsular or parenchymal hematoma</td>
</tr>
<tr>
<td></td>
<td>Intraparenchymal hematoma &gt; 5 cm</td>
</tr>
<tr>
<td></td>
<td>Laceration &gt; 3 cm parenchymal depth or involving trabecular vessels</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration Laceration of segmental or hilar vessels producing major devascularization (&gt; 25% of spleen)</td>
</tr>
<tr>
<td>V</td>
<td>Laceration Completely shatters spleen</td>
</tr>
<tr>
<td></td>
<td>Vascular Hilar vascular injury which devascularized spleen</td>
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</table>
OM. This demonstrates that the classification of spleen injuries into minor and major must consider both the anatomic AAST-OIS classification and the hemodynamic status.

The WSES classification divides spleen injuries into three classes:

- Minor (WSES class I)
- Moderate (WSES classes II and III)
- Severe (WSES class IV)

The classification considers the AAST-OIS classification and the hemodynamic status and is the same for adult and pediatric patients. Table 3 explains the classification with the different key points of treatment differentiated within adult and pediatric patients; Table 4 resumes the guidelines statements.

Minor spleen injuries:
- **WSES class I** includes hemodynamically stable AAST-OIS grade I–II blunt and penetrating lesions.

Moderate spleen injuries:
- **WSES class II** includes hemodynamically stable AAST-OIS grade III blunt and penetrating lesions.
- **WSES class III** includes hemodynamically stable AAST-OIS grade IV–V blunt and penetrating lesions.

Severe spleen injuries:
- **WSES class IV** includes hemodynamically unstable AAST-OIS grade I–V blunt and penetrating lesions.
Based on the present classification, WSES suggests two management algorithms for both adult and pediatric patients explained in Figs. 2 and 3.

**Adult patients**

**Physiopathology of injuries**

Some mechanisms of injuries are similar between children and adults like motor vehicle crashes and pedestrian accidents, while others like motorcycle accidents, sport injuries, gunshot or stab-related injuries, and assaults are more frequent in adults [2]

A few authors consider a normal hemodynamic status in adults when the patient does not require fluids or blood to maintain blood pressure, without signs of hypoperfusion; hemodynamic stability in adults as a counterpart is the condition in which the patient achieve a constant or an amelioration of blood pressure after fluids with a blood pressure > 90 mmHg and heart rate < 100 bpm; hemodynamic instability in adults is the condition in which the patient has an admission systolic blood pressure < 90 mmHg, or > 90 mmHg but requiring bolus infusions/transfusions and/or vasopressor drugs and/or admission base excess (BE) > −5 mmol/l and/or shock index > 1 [3, 4] and/or transfusion requirement of at least 4–6 units of packed red blood cells within the first 24 h [5]. The 9th edition of the Advanced Trauma Life Support (ATLS) definition considers as “unstable” the patient with the following: blood pressure < 90 mmHg and heart rate > 120 bpm, with evidence of skin vasoconstriction (cool, clammy, decreased capillary refill), altered level of consciousness and/or shortness of breath [5]. Moreover, transient responder patients (those showing an initial response to adequate fluid resuscitation and then signs of ongoing loss and perfusion deficits) and, more in general, those responding to therapy but not amenable of sufficient stabilization to be undergone to interventional radiology treatments, are to be considered as unstable patients. In the management of severe bleeding, the early evaluation and correction of the trauma-induced coagulopathy remains a main cornerstone. Physiologic impairment is frequently associated with aggressive resuscitation and the activation and deactivation of several procoagulant and anticoagulant factors contributes to the insurgence of trauma-induced coagulopathy. The application of massive transfusion protocols (MTP) is of paramount importance. The advanced tailored evaluation of the patient’s coagulative asset is clearly demonstrated as fundamental in driving the

**Table 2 GRADE system to evaluate the level of evidence and recommendation**

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses or imprecise conclusions) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
</tr>
</tbody>
</table>
Table 3  WSES Spleen Trauma Classification for adult and pediatric patients

<table>
<thead>
<tr>
<th>WSES class</th>
<th>Mechanism of injury</th>
<th>AAST</th>
<th>Hemodynamic status&lt;sup&gt;a, b&lt;/sup&gt;</th>
<th>CT scan</th>
<th>First-line treatment in adults</th>
<th>First-line treatment in pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>WSES I</td>
<td>Blunt/penetrating</td>
<td>I–II</td>
<td>Stable</td>
<td>Yes + local exploration in SW&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NOM&lt;sup&gt;c&lt;/sup&gt; + serial clinical/laboratory/radiological evaluation</td>
</tr>
<tr>
<td>Moderate</td>
<td>WSES II</td>
<td>Blunt/penetrating</td>
<td>III</td>
<td>Stable</td>
<td>Consider angiography/angioembolization</td>
<td>Consider angiography/angioembolization</td>
</tr>
<tr>
<td></td>
<td>WSES III</td>
<td>Blunt/penetrating</td>
<td>IV–V</td>
<td>Stable</td>
<td>NOM&lt;sup&gt;c&lt;/sup&gt; + serial clinical/laboratory/radiological evaluation</td>
<td>All angiography/angioembolization + serial clinical/laboratory/radiological evaluation</td>
</tr>
<tr>
<td>Severe</td>
<td>WSES IV</td>
<td>Blunt/penetrating</td>
<td>I–V</td>
<td>Unstable</td>
<td>No</td>
<td>OM</td>
</tr>
</tbody>
</table>

<sup>a</sup> Hemodynamic instability in adults is considered the condition in which the patient has an admission systolic blood pressure < 90 mmHg with evidence of skin vasoconstriction (cool, clammy, decreased capillary refill), altered level of consciousness and/or shortness of breath, or > 90 mmHg but requiring bolus infusions/transfusions and/or vasopressor drugs and/or admission base excess (BE) > − 5 mmol/l and/or shock index > 1 and/or transfusion requirement of at least 4–6 units of packed red blood cells within the first 24 h; moreover, transient responder patients (those showing an initial response to adequate fluid resuscitation, and then signs of ongoing loss and perfusion deficits) and more in general those responding to therapy but not amenable of sufficient stabilization to be undergone to interventional radiology treatments.

<sup>b</sup> Hemodynamic stability in pediatric patients is considered systolic blood pressure of 90 mmHg plus twice the child's age in years (the lower limit is inferior to 70 mmHg plus twice the child's age in years, or inferior to 50 mmHg in some studies). Stabilized or acceptable hemodynamic status is considered in children with a positive response to fluid resuscitation: 3 boluses of 20 mL/kg of crystalloid replacement should be administered before blood replacement; positive response can be indicated by the heart rate reduction, the sensorium clearing, the return of peripheral pulses and normal skin color, an increase in blood pressure and urinary output, and an increase in warmth of extremity. Clinical judgment is fundamental in evaluating children.

<sup>c</sup> NOM should only be attempted in centers capable of a precise diagnosis of the severity of spleen injuries and capable of intensive management (close clinical observation and hemodynamic monitoring in a high dependency/intensive care environment, including serial clinical examination and laboratory assay, with immediate access to diagnostics, interventional radiology, and surgery and immediately available access to blood and blood products or alternatively in the presence of a rapid centralization system in those patients amenable to be transferred.

<sup>d</sup> Wound exploration near the inferior costal margin should be avoided if not strictly necessary because of the high risk to damage the intercostal vessels.
Table 4 Statement summary

<table>
<thead>
<tr>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic procedures</strong></td>
<td>The role of E-FAST in the diagnosis of pediatric spleen injury is still unclear (GoR 1A).</td>
</tr>
<tr>
<td>-The choice of diagnostic technique at admission must be based on the hemodynamic status of the patient (GoR 1A).</td>
<td>-A positive E-FAST examination in children should be followed by an urgent CT in stable patients (GoR 1B).</td>
</tr>
<tr>
<td>-E-FAST is effective and rapid to detect free fluid (GoR 1A).</td>
<td>-Complete abdominal US may avoid the use of CT in stable patients (GoR 1B).</td>
</tr>
<tr>
<td>-CT scan with intravenous contrast is the gold standard in hemodynamically stable or stabilized trauma patients (GoR 1A).</td>
<td>-Contrast-enhanced CT scan is the gold standard in pediatric splenic trauma (GoR 1A). Doppler US and contrast-enhanced US are useful to evaluate splenic vascularization (GoR 1B).</td>
</tr>
<tr>
<td>-Doppler US and contrast-enhanced US are useful to evaluate splenic vascularization and in follow-up (GoR 1B).</td>
<td>-CT scan is suggested in children at risk for head and thoracic injuries, need for surgery, recurrent bleeding, and if other abdominal injuries are suspected (GoR 1A).</td>
</tr>
<tr>
<td>-Injury grade on CT scan, extent of free fluid, and the presence of PSA do not predict NOM failure or the need of OM (GoR 1B).</td>
<td>-Injury grade on CT scan, free fluid amount, contrast blush, and the presence of pseudoaneurysm do not predict NOM failure or the need for OM (GoR 1B).</td>
</tr>
</tbody>
</table>

**Non-operative management**

- **General indications**
  - NOM is recommended as first-line treatment for hemodynamically stable pediatric patients with blunt splenic trauma (GoR 2A). Patients with moderate-severe blunt and all penetrating splenic injuries should be considered for transfer to dedicated pediatric trauma centers after hemodynamic stabilization (GoR 2A).
  - NOM of spleen injuries in children should be considered only in an environment that provides capability for patient continuous monitoring, angiography, and trained surgeons, an immediately available OR and immediate access to blood and blood products or alternatively in the presence of a rapid centralization system in those patients amenable to be transferred (GoR 2A).
  - NOM should be attempted even in the setting of concomitant head trauma; unless the patient is unstable, this might be due to intra-abdominal bleeding (GoR 2B). Blunt trauma
  - Blunt splenic injuries with hemodynamic stability and absence of other internal injuries requiring surgery, should undergo an initial attempt of NOM irrespective of injury grade (GoR 2A).
  - NOM of moderate or severe spleen injuries should be considered only in an environment that provides capability for patient intensive monitoring, AG/AE, an immediately available OR and immediate access to blood and blood products or alternatively in the presence of a rapid centralization system and only in patients with stable or stabilized hemodynamic and absence of other internal injuries requiring surgery (GoR 2A).
  - NOM in splenic injuries is contraindicated in the setting of unresponsive hemodynamic instability or other indicates for laparotomy (peritonitis, hollow organ injuries, bowel evisceration, impalement) (GoR 1A).
  - In patients being considered for NOM, CT scan with intravenous contrast should be performed to define the anatomic spleen injury and identify associated injuries (GoR 2A).
  - AG/AE may be considered the first-line intervention in patients with hemodynamic stability and arterial blush on CT scan irrespective from injury grade (GoR 2B).
  - Strong evidence exists that age above 55 years old, high ISS, and moderate to severe splenic injuries are prognostic factors for NOM failure. These patients require more intensive monitoring and higher index of suspicion (GoR 2B).
  - Age above 55 years old alone, large hemoperitoneum alone, hypotension before resuscitation, GCS < 12 and low-hematocrit level at the admission, associated abdominal injuries, blush at CT scan, anticoagulation drugs, HIV disease, drug addiction, cirrhosis,


- **Blunt/penetrating trauma**
  - Patients with hemodynamic stability and absence of other abdominal organ injuries requiring surgery should undergo an initial attempt of NOM irrespective of injury grade (GoR 2A).
  - NOM of moderate or severe spleen injuries should be considered only in an environment that provides capability for patient intensive monitoring, AG/AE, an immediately available OR and immediate access to blood and blood products or alternatively in the presence of a rapid centralization system and only in patients with stable or stabilized hemodynamic and absence of other internal injuries requiring surgery (GoR 2A).
  - NOM in splenic injuries is contraindicated in the setting of unresponsive hemodynamic instability or other indicates for laparotomy (peritonitis, hollow organ injuries, bowel evisceration, impalement) (GoR 1A).
  - In patients being considered for NOM, CT scan with intravenous contrast should be performed to define the anatomic spleen injury and identify associated injuries (GoR 2A).
  - AG/AE may be considered the first-line intervention in patients with hemodynamic stability and arterial blush on CT scan irrespective from injury grade (GoR 2B).
  - Strong evidence exists that age above 55 years old, high ISS, and moderate to severe splenic injuries are prognostic factors for NOM failure. These patients require more intensive monitoring and higher index of suspicion (GoR 2B).
  - Age above 55 years old alone, large hemoperitoneum alone, hypotension before resuscitation, GCS < 12 and low-hematocrit level at the admission, associated abdominal injuries, blush at CT scan, anticoagulation drugs, HIV disease, drug addiction, cirrhosis,
Table 4 Statement summary (Continued)

<table>
<thead>
<tr>
<th>The role of angiography/angioembolization (AG/AE)</th>
<th>AG/AE may be performed in hemodynamically stable and rapid responder patients with moderate and severe lesions and in those with vascular injuries at CT scan (contrast blush, pseudo-aneurysms and arterio-venous fistula) (GoR 2A).</th>
</tr>
</thead>
<tbody>
<tr>
<td>-In patients with bleeding vascular injuries and in those with intraperitoneal blush, AG/AE should be performed as part of NOM only in centers where AG/AE is rapidly available. In other centers and in case of rapid hemodynamic deterioration, OM should be considered (GoR 2B).</td>
<td></td>
</tr>
<tr>
<td>-In case of absence of blush during angiography, if blush was previously seen at CT scan, proximal angioembolization could be considered (GoR 2C).</td>
<td></td>
</tr>
<tr>
<td>-AG/AE should be considered in all hemodynamically stable patients with WSES grade III lesions, regardless with the presence of CT blush (GoR 1B).</td>
<td></td>
</tr>
<tr>
<td>-AG/AE could be considered in patients undergone to NOM, hemodynamically stable with signs of persistent hemorrhage regardless with the presence of CT blush once excluded extra-splenic source of bleeding (GoR 1C).</td>
<td></td>
</tr>
<tr>
<td>-Hemodynamically stable patients with WSES grade II lesions without blush should not underwent routine AG/AE but may be considered for prophylactic proximal embolization in presence of risk factors for NOM failure (GoR 2B).</td>
<td></td>
</tr>
<tr>
<td>-In the presence of a single vascular abnormality (contrast blush, pseudo-aneurysms, and arterio-venous fistula) in minor and moderate injuries, the currently available literature is inconclusive regarding whether proximal or distal embolization should be used. In the presence of multiple splenic vascular abnormalities or in the presence of a severe lesion, proximal or combined AG/AE should be used, after confirming the presence of a permissive pancreatic vascular anatomy (GoR 1C).</td>
<td></td>
</tr>
<tr>
<td>-In performing, AG/AE coils should be preferred to temporary agents (GoR 1C).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operative management (OM)</th>
<th>OM should be performed in patients with hemodynamic instability and/or with associated lesions like peritonitis or bowel evisceration or impalement requiring surgical exploration (GoR 2A).</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OM should be performed in moderate and severe lesions even in stable patients in centers where intensive monitoring cannot be performed and/or when AG/AE is not rapidly available (GoR 2A).</td>
<td></td>
</tr>
<tr>
<td>-Splenectomy should be performed when NOM with AG/AE failed, and patient remains hemodynamically unstable or shows a significant drop in hematocrit levels or continuous transfusion are required (GoR 2A).</td>
<td></td>
</tr>
<tr>
<td>-During OM, salvage of at least a part of the spleen is debated and could not be suggested (GoR 2B).</td>
<td></td>
</tr>
<tr>
<td>-Laparoscopic splenectomy in early trauma scenario in bleeding patients could not be recommended (GoR 2A).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short- and long-term follow-up</th>
<th>Clinical and laboratory observation associated to bed rest in moderate and severe lesions is the cornerstone in the first 48–72 h follow-up (GoR 1C).</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CT scan repetition during the admission should be considered in patients with moderate and severe lesions or in decreasing hematocrit, in presence of vascular anomalies or underlying splenic pathology or coagulopathy, and in neurologically impaired patients (GoR 2A).</td>
<td></td>
</tr>
<tr>
<td>-In hemodynamically stable children without drop in hemoglobin levels for 24 h, bed rest should be suggested (GoR 2B).</td>
<td></td>
</tr>
<tr>
<td>-The risk of pseudo-aneurysm after splenic trauma is low, and in most of cases, it resolves spontaneously (GoR 2B).</td>
<td></td>
</tr>
<tr>
<td>-Angioembolization should be taken into consideration when a pseudoaneurysm is found (GoR 2B).</td>
<td></td>
</tr>
</tbody>
</table>
administration of blood products, coagulation factors, and drugs [6–9].

Diagnostic procedures:

- **The choice of diagnostic technique at admission must be based on the hemodynamic status of the patient (GoR 1A).**
- **E-FAST is effective and rapid to detect free fluid (GoR 1A).**
- **CT scan with intravenous contrast is the gold standard in hemodynamically stable or stabilized trauma patients (GoR 1A).**
- **Doppler US and contrast-enhanced US are useful to evaluate splenic vascularization and in follow-up (GoR 1B).**
- **Injury grade on CT scan, extent of free fluid, and the presence of PSA do not predict NOM failure or the need of OM (GoR 1B).**

Extended focused assessment sonography for trauma (E-FAST) and ultrasonography (US) have replaced diagnostic peritoneal lavage (DPL) management of abdominal trauma in present days [5, 10, 11]. Studies have shown a sensitivity up to 91% and a specificity up to 96% also for a small fluid amount [12, 13].

Nevertheless, 42% of false-negative have been reported [10]. This might be due to the 20% of cases in which no significant extravasation of blood is present in splenic trauma or in injuries near the diaphragm [10, 12, 13].

**Contrast-enhanced US (CEUS)** increases the visualization of a variety of splenic injuries and complications [12].

**Doppler US (DUS)** has been reported as safe and effective in evaluating PSA or blush previously found at CT scan [14].

Contrast tomography (CT) scan is considered the gold standard in trauma with a sensitivity and specificity for splenic injuries near to 96–100% [10, 15, 16]. However, Carr et al. [10] reported that CT scan can underestimate splenic injuries at ilium. CT must be rapidly available and must be performed only in hemodynamically stable patients or in those responding to fluid resuscitation [17, 18]. However, in some centers, there is the possibility to perform a fast-track CT scan that seems to permit to expand the criteria for performing CT scan in trauma patients. Delayed-phase CT helps in differentiating patients with active bleeding from those with contained vascular injuries [19]. This is important to reduce the risk of discrepancy between CT scan images

Table 4 Statement summary (Continued)

<table>
<thead>
<tr>
<th>Thrombo-prophylaxis</th>
<th>In the presence of underlying splenic pathology or coagulopathy and in neurologically impaired patients CT follow-up is to be considered after the discharge (GoR 2B).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Activity restriction may be suggested for 4–6 weeks in minor injuries and up to 2–4 months in moderate and severe injuries (GoR 2C).</td>
</tr>
<tr>
<td>Infections prophylaxis in asplenic and hyposplenic adult and pediatric patients</td>
<td>US (DUS, CEUS) follow-up seems reasonable to minimize the risk of life-threatening hemorrhage and associated complications in children (GoR 1B).</td>
</tr>
<tr>
<td></td>
<td>After NOM in moderate and severe injuries, the reprise of normal activity could be considered safe after at least 6 weeks (GoR 2B).</td>
</tr>
<tr>
<td>US (DUS, CEUS) follow-up seems reasonable to minimize the risk of life-threatening hemorrhage and associated complications in children (GoR 1B).</td>
<td></td>
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Contrast-enhanced US (CEUS) increases the visualization of a variety of splenic injuries and complications [12].

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and angio images (only 47% of patients have a confirmation of the CT findings at angio) [19]. Active contrast extravasation is a sign of active hemorrhage [20]. The use of CT helps in surgical procedure and in AG/AE to be more selective [21, 22]. Contrast blush occurs in about 17% of cases and has been demonstrated to be an important predictor of failure of NOM (more than 60% of patients with blush failed NOM). Its absence on initial CT scan in high-grade splenic injuries does not definitively exclude active bleeding and should not preclude AG/AE [15, 23, 24]. Federle et al. showed that the hematoperitoneum quantification is not related to the risk of NOM failure [20].

**Non-operative management**

**Blunt and penetrating trauma:**

- Patients with hemodynamic stability and absence of other abdominal organ injuries requiring surgery should undergo an initial attempt of NOM irrespective of injury grade (GoR 2A).
- NOM of moderate or severe spleen injuries should be considered only in an environment that provides capability for patient intensive monitoring, AG/AE, an immediately available OR and immediate access to blood and blood product or alternatively in presence of a rapid centralization system and only in patients with

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**Fig. 2** Spleen Trauma Management Algorithm for Adult Patients. (SW stab wound, GSW gunshot wound. *NOM should only be attempted in centers capable of a precise diagnosis of the severity of spleen injuries and capable of intensive management (close clinical observation and hemodynamic monitoring in a high dependency/intensive care environment, including serial clinical examination and laboratory assay, with immediate access to diagnostics, interventional radiology, and surgery and immediately available access to blood and blood products or alternatively in the presence of a rapid centralization system in those patients amenable to be transferred; @ Hemodynamic instability is considered the condition in which the patient has an admission systolic blood pressure < 90 mmHg with evidence of skin vasoconstriction (cool, clammy, decreased capillary refill), altered level of consciousness and/or shortness of breath, or > 90 mmHg but requiring bolus infusions/transfusions and/or vasopressor drugs and/or admission base excess (BE) > −5 mmol/l and or shock index > 1 and or transfusion requirement of at least 4–6 units of packed red blood cells within the first 24 h; moreover, transient responder patients (those showing an initial response to adequate fluid resuscitation, and then signs of ongoing loss and perfusion deficits) and more in general those responding to therapy but not amenable of sufficient stabilization to be undergone to interventional radiology treatments. # Wound exploration near the inferior costal margin should be avoided if not strictly necessary because of the high risk to damage the intercostal vessels.)
stable or stabilized hemodynamic and absence of other internal injuries requiring surgery (GoR 2A).

– NOM in splenic injuries is contraindicated in the setting of unresponsive hemodynamic instability or other indications for laparotomy (peritonitis, hollow organ injuries, bowel evisceration, impalement) (GoR 1A).

– In patients being considered for NOM, CT scan with intravenous contrast should be performed to define the anatomic spleen injury and identify associated injuries (GoR 2A).

– AG/AE may be considered the first-line intervention in patients with hemodynamic stability and arterial blush on CT scan irrespective from injury grade (GoR 2B).

– Strong evidence exists that age above 55-years old, high ISS, and moderate to severe splenic injuries are prognostic factors for NOM failure. These patients require more intensive monitoring and higher index of suspicion (GoR 2B).

– Age above 55 years old alone, large hemoperitoneum alone, hypotension before resuscitation, GCS < 12, and low hematocrit level at the admission, associated abdominal injuries, blush at CT scan, anticoagulation drugs, HIV disease, drug addiction, cirrhosis, and need for blood transfusions should be taken into account, but they are not absolute contraindications for NOM (GoR 2B).
- In WSES classes II–III spleen injuries with associated severe traumatic brain injury, NOM could be considered only if rescue therapy (OR and/or AG/AE) is rapidly available; otherwise, splenectomy should be performed (GoR 1C).

**Blunt trauma**

NOM is considered the gold standard for the treatment of patients with blunt splenic trauma (BST) who are hemodynamically stable after an initial resuscitation, in the absence of peritonitis and associated injuries requiring laparotomy [15, 25–28]. In high-volume centers with all facilities, the successful rate of attempted NOM is near 90% [29]. The advantages of NOM over OM were described as lower hospital costs, avoidance of non-therapeutic laparotomies, lower rates of intra-abdominal complications and of blood transfusions, lower mortality and the maintenance of the immunological function, and the prevention of OPSI [27, 30, 31]. Other guidelines have agreed the non-indication of routine laparotomy in hemodynamically stable patients with blunt splenic injury [32, 33].

NOM failure rate is reported to be between 4 and 15% [15, 29, 34–44]. Several risk factors of NOM failure have been reported [15, 29, 34–54].

In several studies, hemodynamic status at the admission has not been considered a significant prognostic indicator for NOM failure and, for this reason, should not be considered an absolute contraindication for NOM [15, 29, 36, 40, 41]. Others reported that the need for red cell transfusions in ED or during the first 24 h [40, 48], hemoglobin and hematocrit levels at admission [40], HIV disease, cirrhosis, and drug addiction [55–57] could affect the outcome after NOM.

The presence of a blush at CT scan has been considered a risk factor for NOM failure only in studies in which AG/AE was not adopted [46, 53]. In addition, the extension of hemoperitoneum at imaging alone cannot be considered an absolute contraindication for NOM [15, 19, 20, 40, 54].

In AAST-OIS injury grades above IV, the failure rate of NOM reaches 54.6% [49], while according to other studies, patients with III–V injury grades could achieve a 87% of success rate [15, 49].

Patients with higher ISS were more likely to fail NOM. According to the literature, two ISS values which were significantly associated with the failure of NOM were above 15 [40] or 25 [37]. This finding is in agreement with the increased risk of associated lesions in higher ISS.

NOM failure in case of missed concomitant abdominal injuries is reported in 1–2.5% of cases [38, 41, 47, 48, 51, 58].

GCS score below 12 alone should not be considered a contraindication for NOM as these patients can be successfully managed non-operatively with a reported overall NOM failure rate near 4.5% [15, 29, 40, 49].

The risk of NOM failure in patients older than 55 years is still debated. A few studies [15, 35, 37, 38, 41, 44, 52, 54] found older age to be a significant prognostic factor for NOM failure [15]. On the other hand, other studies [29, 39, 43, 45, 50] did not find significant differences between patients ≤55 and >55 years. It has been suggested that age>55 years could be a risk factor for NOM failure only in high AAST-OIS injury grades [36, 38, 49]. Furthermore, the failure of NOM in older patients has been found to be associated with higher mortality rates and longer length of hospital stay than patients <55 years [44].

Some authors suggested a primary OM in the presence of hypotension in the ED, more than five red blood cell transfusions, GCS <11, high ISS, abdominal AIS ≥3, age >55, and spleen AAST-OIS injury grade >3. However, it has also been demonstrated that NOM could be successful also in high-risk patients without an increase in complications or mortality rates related to delayed operative interventions [15, 52].

According to larger studies on patients with BST [29], in level I trauma centers, NOM success rate is higher than in level II or III centers. Nevertheless, some authors stated that this might not be associated with the failure of NOM [42, 49].

Finally, severe unstable spleen injuries could ideally benefit from a resuscitation in a hybrid OR with trauma surgeons, in order to increase the spleen salvage rate [59–61].

**Penetrating trauma**

Laparotomy has been the gold standard in penetrating abdominal trauma. Several studies demonstrated as the rate of negative laparotomy ranges between 9 and 14% [62, 63]. For the last 20 years, there has been an increased number of approaches with NOM for gunshot and stab injuries [64, 65].

Carlin et al. in a large series compared penetrating splenic trauma (248 patients) with blunt trauma and found that mortality was not significantly different [66]. However, when the authors compared GSW and SW versus blunt splenic trauma, they found a significant difference in mortality (24 versus 15%, p = 0.02). Pancreatic, diaphragmatic, and colic injuries significantly increase the rate of OM approach and mortality for septic complications. The associated pancreatic injuries require frequently spleno-pancreatectomy [66]. Demetriades et al. showed in a prospective study with 225 patients with penetrating splenic injury, the direct relationship between the degree of injury and the possibility of NOM vs. emergency laparotomy [67]. Emergency laparotomy rate was 33% in grade I lesions, and it could increase up
to 84% in the grade IV; all splenectomies were in injuries with grade III or higher.

Indication to angiography and angioembolization:

- AG/AE may be performed in hemodynamically stable and rapid responder patients with moderate and severe lesions and in those with vascular injuries at CT scan (contrast blush, pseudo-aneurysms and arterio-venous fistula) (GoR 2A).
- In patients with bleeding vascular injuries and in those with intraperitoneal blush, AG/AE should be performed as part of NOM only in centers where AG/AE is rapidly available. In other centers and in case of rapid hemodynamic deterioration, OM should be considered (GoR 2B).
- In case of absence of blush during angiography, if blush was previously seen at CT scan, proximal angioembolization could be considered (GoR 2C).
- AG/AE should be considered in all hemodynamically stable patients with WSES class III lesions, regardless the presence of CT blush (GoR 1B).
- AG/AE could be considered in patients undergone to NOM, hemodynamically stable with sings of persistent hemorrhage regardless the presence of CT blush once excluded extra-splenic source of bleeding (GoR 1C).
- Hemodynamically stable patients with WSES class II lesions without blush should not underwent routine AG/AE but may be considered for prophylactic proximal embolization in presence of risk factors for NOM failure (GoR 2B).
- In presence of a single vascular abnormality (contrast blush, pseudo-aneurysms and arterio-venous fistula) in minor and moderate injuries the currently available literature is inconclusive regarding whether proximal or distal embolization should be used. In presence of multiple splenic vascular abnormalities or in presence of a severe lesion, proximal or combined AG/AE should be used, after confirming the presence of a permissive pancreatic vascular anatomy (GoR 1C).
- In performing AG/AE coils should be preferred to temporary agents (GoR 1C).

The reported success rate of NOM with AG/AE ranges from 86 to 100% with a success rate of AG/AE from 73 to 100% [68–78]. In a large study, Haan et al. suggested that indications to AG/AE were pseudo-aneurysms (PSA) or active bleeding at admission CT scan, significant hemoperitoneum, and high-grade splenic injury [68–70]. More than 80% of grade IV–V splenic injuries were successfully managed non-operatively with AG/AE. A large multicenter study [76] on 10,000 patients found that AG/AE was associated with a reduced odds of splenectomy and that the earlier AG/AE was performed; the less number of patients had splenectomy. A multi-institutional study by Banerjee et al. demonstrated that level I trauma center that had AG/AE rates greater than 10% had significantly higher spleen salvage rates and fewer NOM failure, especially for AAST-OIS grade III–IV injured spleen. AG/AE was also found as an independent predictor of spleen salvage and mortality reduction [78, 79].

A few meta-analyses showed a significant improvement in NOM success following introduction of AG/AE protocols (OR 0.26, 95% CI 0.13–0.53, p < 0.002) [54, 80–82]. The failure rate without AG/AE is significantly higher than with AG/AE in AAST-OIS grade IV–V injuries (43.7 vs. 17.3%, p = 0.035, and 83.1 vs. 25.0%, p = 0.016, respectively) [80].

Specific CT findings can help in the therapeutic decision, and they are correlated with outcomes. As such, patients with PSA and arterovenous fistula showed higher NOM failure rates [21, 22, 53, 83–90].

NOM failure in the presence of contrast blush treated without AG/AE ranges between 67 and 82% [53, 85]. Shanmuganathan et al. reported an 83% accuracy of blush in predicting the need for AG/AE [86]. Marmery et al. showed a 4% of active bleeding vascular injuries in AAST-OIS grade I–II splenic injuries [21, 87]. Intraperitoneal splenic blush exhibited a significantly higher percentage of hemodynamic deterioration during the time required for AG/AE than intra-parenchymal bleedings (p < 0.001), suggesting intraperitoneal blush as an independent risk factor for OM [88].

Between 2.3 and 47% CT detected, contrast blush could not be confirmed at the subsequent angiography [89, 90]. The presence of a vascular injury is significantly associated with the splenic injury grade (p < 0.0001) [21]. Moreover an analysis on 143 patients with blush at CT scan suggested that an angiographic procedure without embolization increases twofold the risk of re-bleeding and NOM failure [90].

The indication for routine prophylactic AG/AE in high-grade splenic injuries is a matter of controversy [23, 68, 70, 74, 85, 91–93]. Several retrospective and prospective studies recommended the use of AG/AE in all hemodynamically stable patients with high-grade splenic injuries [23, 91–93]. NOM failure rates both with and without prophylactic AG/AE for high-grade injuries are 0–42% vs. 23–67%, respectively [23, 68, 70, 74, 85, 91].

Controversies exist regarding which kind of lesions should be considered as “high-grade” (AAST III–V or IV–V grade) and should undergo routine AG/AE [23, 68, 91, 92]. It has been reported that NOM could fail in up to 3% of grade III lesions without blush with no AG/AE [23]. Furthermore, no outcome deterioration (in terms of NOM failure, rate of re-bleeding,
complications, and mortality) was detected after excluding grade III injuries from routine AG/AE protocol [91]. Therefore, considering the AG/AE-related morbidity of 47% (versus 10% related to NOM without AG/AE) [93] and the fact that widening the selection criteria for AG/AE from grades IV–V to grades III–V may slightly decrease the overall NOM failure rate, patients with grade III lesions without blush should not undergo routine AG/AE.

To date, no randomized comparing proximal and distal embolization are available [94]. In a meta-analysis including 15 retrospective studies, proximal and distal embolization was found to be equivalent with regard to the incidence of major infarctions, infections, and major re-bleeding [95]. However, a significant higher rate of overall minor complications was found after distal AE (2.8–11.6% versus 15.9–25.2%) [95].

Several studies analyzed the morbidity related to AG/AE, to OM, and to NOM without AG/AE [23, 68, 70, 96–103]. The AG/AE major morbidity rates range from 3.7 to 28.5% including re-bleeding, total or subtotal splenic infarction, splenic abscesses, acute renal insufficiency, pseudocysts, and puncture-related complications. The rates for minor morbidities range from 23 to 61%, and they included fever, pleural effusion, coil migration, and partial splenic infarction [70, 96, 102, 103]. All studies [97, 98, 101], but one [93] reported significantly higher complication rates in patients undergone OM (increased rate of death, infectious complications, pleural drainage, acute renal failure, and pancreatitis). In particular, the incidence of infectious complications was significantly higher in the splenectomy group (observation 4.8%, AG/AE 4.2%, splenorrhaphy 10.5%, splenectomy 32.0%, p = 0.001) [98].

Some studies analyzed the cost of NOM and AG/AE [104]. They observed that NOM is safe and cost effective, and AG/AE is similar to surgical therapy with regard to cost.

Lastly, AG/AE does not seem to totally compromise the splenic function, and even in presence of an elevated leukocyte and platelet counts, no significant differences in immunoglobulin titers were found between splenic artery AG/AE patients and controls [91]. The spleen due to its intense vascularization could assure the necessary blood to continue its immunological function.

Operative management
Blunt trauma and penetrating:

- **OM should be performed in patients with hemodynamic instability and/or with associated lesions like peritonitis or bowel evisceration or impalement requiring surgical exploration (GoR 2A).**
- **OM should be performed in moderate and severe lesions even in stable patients in centers where intensive monitoring cannot be performed and/or when AG/AE is not rapidly available (GoR 2A).**
- **Splenectomy should be performed when NOM with AG/AE failed and patient remains hemodynamically unstable or shows a significant drop in hematocrit levels or continuous transfusion are required (GoR 2A).**
- **During OM, salvage of at least a part of the spleen is debated and could not be suggested (GoR 2B).**
- **Laparoscopic splenectomy in early trauma scenario in bleeding patients could not be recommended (GoR 2A).**

Operative management (OM) of splenic injuries should be performed in non-responder hemodynamic instable patients. This condition is frequently observed in high- ISS trauma, in high-grade lesions, and in patients with associated lesions. However, it can be also required in low volume trauma centers or peripheral centers where no intensive care unit or intensive monitoring can be achieve [13, 105, 106]. It has been reported that isolated splenic injury is about 42% of all abdominal trauma [107]. Multiple injuries are reported near 20–30% [107–109]. No sufficient data are available about concomitant vascular and splenic injuries. Associated hollow viscous injuries could be found in 5% of cases; the severity of splenic injury seems to be related to the incidence of hollow viscous injury (1.9, 2.4, 4.9, and 11.6% in minor, moderate, major, and massive injuries, respectively) [110].

The use of splenectomy is decreasing, and the use of splenorrhaphy is rarely adopted (35–24% and 6–1%, respectively) [108, 111]. The attempt to perform a partial splenic salvage is reported in 50–78% of cases, but when NOM fails, splenectomy is the preferred treatment [108, 111].

Laparoscopic splenectomy for trauma is reported only in some cases of hemodynamically stable low-moderate grade splenic injuries [112, 113].

The use of splenic autologous transplantation (i.e., voluntarily leaving pieces of spleen inside the abdomen), to avoid infective risk from splenectomy, has been investigated, but no reduction of morbidity or mortality has been demonstrated [114].

The reported overall hospital mortality of splenectomy in trauma is near 2%, and the incidence of post- operative bleeding after splenectomy, ranges from 1.6 to 3%, but with mortality near to 20% [115].

Spleen injuries with concomitant spinal and brain injuries
Particular attention should be posed in managing hemodynamically stable patients with blunt spinal trauma (BST) and severe traumatic brain injury (STBI).
A recent study in patients with concomitant spinal and/or brain associated to AAST-OIS grade IV–V spleen injuries reported a general survival benefit of immediate splenectomy over NOM [116]. However, in centers where AG/AE is available (having therefore a lower NOM failure rate of high-grade splenic injuries), immediate splenectomy in patients with severe brain injury does not seem to be associated with an improved survival benefit regardless the grade of injury [116]. It must be highlighted that the differences in definition of hemodynamic instability may represent a bias in this cohort of patients as a few “unstable” patients might have undergone NOM. This data strongly emphasizes the dangers related to poor patient selection for NOM in BST and STBI [34, 49].

**Thrombo-prophylaxis in splenic trauma:**

- Mechanical prophylaxis is safe and should be considered in all patients without absolute contraindication to its use (GoR 2A).
- Spleen trauma without ongoing bleeding is not an absolute contraindication to LMWH-based prophylactic anticoagulation (GoR 2A).
- LMWH-based prophylactic anticoagulation should be started as soon as possible from trauma and may be safe in selected patients with blunt splenic injury undergone to NOM (GoR 2B).
- In patient with oral anticoagulants the risk-benefit balance of reversal should be individualized (GoR 1C).

Trauma patients are at high risk of venous thromboembolism (VTE); the transition to a hyper-coagulation state occurs within 48 h from injury [117–119]. Without any prophylaxis, more than 50% may experience deep vein thrombosis (DVT) which substantially increases the risk of pulmonary embolism (PE) whose mortality is about 50% [117, 118]. In trauma patients surviving beyond the first 24 h, PE is the third leading cause of death. Even with chemical prophylaxis, DVT can be detected in 15% of patients. There are currently no standards for the initiation of prophylactic anticoagulation in trauma patients with blunt spleen injuries. A survey-based analysis from ASST reported a growing use of heparin according to the increasing grade of the splenic lesion, and on the contrary, an increasing use of low-molecular-weight heparin (LMWH) in low-grade lesions [120]. Heparin and LMWH can be combined with mechanical prophylaxis; however, mechanical prophylaxis alone in high-grade lesions seems to be preferred by surgeons compared with heparin. Eberle et al. [121] and Alejandro et al. [119] demonstrated no differences between VTE prophylaxis administered within and after 72 and 48 h from trauma respectively, with highest rate of failure in patients with high-grade splenic injury. Bellal et al. [122] found no difference in hemorrhagic complication and NOM failure rate in patients with early (< 48 h), intermediate (48–72 h), and late (> 72 h) VTE prophylaxis. These considerations are referred to selected patients, particularly those without significant head and spinal injuries. As a counterpart, Rostas et al. [117] show that VTE rates were over fourfold greater when LMWH was administered after 72 h from admission.

When trauma occurs in patients under anticoagulants, it is important to consider, if it is necessary, the reversal of their effects in order to avoid thrombotic complications. However, failing to resume anticoagulation in a timely fashion is associated with poor outcomes [123]. Short- and long-term follow-up in NOM (blunt and penetrating)

- Clinical and laboratory observation associated to bed rest in moderate and severe lesions is the cornerstone in the first 48–72 h follow-up (GoR 1C).
- CT scan repetition during the admission should be considered in patients with moderate and severe lesions or in decreasing hematocrit, in the presence of vascular anomalies or underlying splenic pathology or coagulopathy, and in neurologically impaired patients (GoR 2A).
- In the presence of underlying splenic pathology or coagulopathy and in neurologically impaired patients CT follow-up is to be considered after the discharge (GoR 2B).
- Activity restriction may be suggested for 4–6 weeks in minor injuries and up to 2–4 months in moderate and severe injuries (GoR 2C).

Splenic complications after blunt splenic trauma range between 0 and 7.5% with a mortality of 7–18% in adults [13]. In children, these incidences are lower [124–127]. The 19% of splenic-delayed ruptures happen within the first 48 h, more frequently between 4 and 10 days after trauma. The risk of splenectomy after discharge ranges between 3 and 146 days after injury, and the rate of re-admission for splenectomy was 1.4% [128]. Savage et al. [129] showed that approximately 2% of patients discharged with a non-healed spleen required late intervention. Savage et al. [129] found an average of healing in grades I–II of 12.5 days with a complete healing after 50 days while in grades III–V, 37.2 and 75 days, respectively. In 2–2.5 months, regardless of severity of spleen injury, the 84% of patients presented a complete healing [129]. As a counterpart, Crawford et al. suggested that an early discharge is safe because late failure occurs infrequently [56, 130]. Mortality of late rupture ranges from 5 to 15% compared with 1% mortality in case of
acute rupture [40, 131]. In any case, patients undergone NOM should be counseled to not remain alone or in isolated places for the first weeks after the discharge and they should be warned regarding the alert symptoms.

Radiological follow-up is used, but there are not clear information regarding the timing and type of imaging (CT vs. US); thus, imaging follow-up is usually based on clinical judgment and has been widely debated [18, 34, 40, 125, 132–134]. Management strategies that use patient education are more cost effective than to undergo imaging all patients until splenic complete healing.

In the short course (first 24–72 h), observation remains an essential part of low-grade splenic injury (AAST I–II grade); after the admission CT scan, serial abdominal examinations, and hematocrit determination every 6 h are necessary [18]. Clancy et al. [125] showed as PSA were found in patients with grade II, even months after trauma, so they recommended CT scan at 36–72 h in all injuries [129, 131, 132]. Some authors suggest to repeat CT scan only in patients with decreasing hematocrit, in AAST grades III–IV, in patients with subcapsular hematoma, or underlying splenic pathology or coagulopathy, as also in neurologically impaired patients [135].

In the intermediate-long course recent reports recommended that routine post-discharge follow-up abdominal CT is not necessary in low-grade (AAST grade I or II) injuries [132].

More than 50% of patients present a healing at CT scan after 6 weeks, and subsequent image follow-up seems to have no clinical utility [24, 135]. Complete healing of almost all grades is observed 3 months after injury. Lynch et al. [136], in a prospective study, showed that mean time to US healing in AAST grade I, II, III, and IV injuries was 3.1, 8.2, 12.1, and 20.7 weeks, respectively. Soffer D. et al. [14] suggest a DUS for splenic lesion follow-up. Some authors have suggested the use of magnetic resonance images [18].

The role of radiological follow-up before returning to normal activity remains controversial. According to some authors, the return to normal activity can occur 3 weeks after splenectomy, and after 2.5–3 months after NOM [126, 134, 136, 137]. Other authors suggested activity restriction of 2 weeks for mild injuries with a return to full activity after 6 weeks, and up to 4–6 months for patients with more severe injuries [120, 129].

**Pediatric patients**

**Pediatric splenic trauma**

The spleen is the most commonly injured solid organ in pediatric blunt trauma patients (25–30%) [2, 138]. The age limit for pediatric patients is considered for present guidelines to be < 15 years old. While non-operative management of splenic trauma is the mainstay in children, the available clinical guidelines are not universally applied. In urban pediatric hospitals where resources facilitate the non-operative approach, the likelihood of splenic preservation with NOM ranges from 95 to 100% [139].

The Eastern Association for the Surgery of Trauma (EAST) recommends NOM in blunt splenic trauma in all hemodynamically stable children irrespective of the AAST injury grade [140, 141]. The same guidelines recommend a “less is more” approach with respect to imaging studies during admission and follow-up, aiming to reduce the use of CT scan and radiation exposure [140, 142].

NOM seems to be more effective in children, and therefore, it is more commonly used in these patients compared to adults NOM of pediatric splenic trauma which is also associated with reduced cost and lengths of hospital stay, less need for blood transfusions, vaccinations, and antibiotic therapy, as well as higher immunity and reduced rate of infections [142–146].

Even though it is not clear why NOM outcomes are superior in children compared with adults, this phenomenon may be related to certain unique pediatric characteristics (e.g., thicker splenic capsule, higher proportion of myoepithelial cells, more efficient contraction, and retraction of the splenic arterioles [147–152]).

**Clinical presentation in splenic pediatric trauma**

The mechanisms of trauma are similar in children and adults. These include motor vehicle and pedestrian injuries as well as sports-related injuries, bicycle injuries, and child abuse [2].

Pediatric injuries differ from adult trauma as the elastic pediatric rib cage may cause a transmission of force into the abdominal compartment [151].

Trauma in neonates represents a rare but unique diagnostic challenge since shock and abdominal rigidity or altered mental status may be the only indications of underlying abdominal injury [2].

In adolescents, the signs of splenic trauma may include the left upper quadrant pain associated with referred left shoulder pain hypovolemic shock or generalized abdominal pain [2].

**Definition of the hemodynamic status in children**

According to ATLS, the normal systolic blood pressure in children is 90 mmHg plus twice the child’s age in years (the lower limit is inferior to 70 mmHg plus twice the child’s age in years, or inferior to 50 mmHg in some studies) [5]. Severe blood loss is defined as blood loss greater than 45% of the circulating volume and results in hemodynamic instability. Nevertheless, clinical judgment remains the most important factor in diagnosing an ongoing bleeding [153].
For fluid resuscitation, three boluses of 20 mL/kg of crystalloid replacement should be administered before blood replacement [5, 153]. Massive transfusion protocol in children should be applied with a ratio of 1:1:1 [153]. Transfusion triggers have been debated, and although, there are no class I data to support a specific numerical threshold, it is generally agreed that transfusion should be considered when hemoglobin is less than 7 g/dL [153].

Effective resuscitation is classically indicated by reduction of the heart rate, improved mental status, return of peripheral pulses and normal skin color, increase in blood pressure, and urinary output, as well as increase in extremity warmth [5].

Even though the benefit of thromboelastography (TEG) has not been confirmed in children, recent ATOMAC guidelines suggested that it may be useful in these patients as well (based on adult data) [153].

Diagnostic procedures:

- **The role of E-FAST in the diagnosis of pediatric spleen injury is still unclear (GoR 1A).**
- **A positive E-FAST examination in children should be followed by an urgent CT in stable patients (GoR 1B).**
- **Complete abdominal US may avoid the use of CT in stable patients (GoR 1B).**
- **Contrast-enhanced CT scan is the gold standard in pediatric splenic trauma (GoR 1A).**
- **Doppler US and contrast-enhanced US are useful to evaluate splenic vascularization (GoR 1B).**
- **CT scan is suggested in children at risk for head and thoracic injuries, need for surgery, recurrent bleeding, and if other abdominal injuries are suspected (GoR 1A).**
- **Injury grade on CT scan, free fluid amount, contrast blush, and the presence of pseudo-aneurysm do not predict NOM failure or the need for OM (GoR 1B).** **Thoracic X-ray at the admission is recommended in the ATLS guidelines [2, 5].**

**Ultrasonography (US)** is the less invasive and is considered the gold standard in trauma, according to the ATLS guidelines especially in Europe [5, 154]. The additional use of DUS or CEUS is helpful and can increase sensitivity for the evaluation of splenic flow and injuries [2]. In patients with low clinical suspicion for splenic trauma, US and CEUS may allow to avoid CT scan [2]. The routine use of CEUS can improve the search of PSA [155].

**FAST (Focused Assessment with Sonography for Trauma):** The role of FAST for the diagnosis of spleen injury in children is still unclear. Recent Pediatric Emergency Care Applied Research Network (PECARN) data suggest that only 13.7% of pediatric trauma patients with a suspicion of intra-abdominal injuries undergo FAST examination [156]. The sensitivity of this imaging modality in children ranges from 50 to 92%, with a comprehensive meta-analysis suggesting the sensitivity to be around 66% [157–159].

The specificity of this exam is also quite low, and therefore, in a hemodynamically stable patient, a positive FAST examination should be followed by an urgent CT. Bedside FAST may have utility in hemodynamically unstable patients to rapidly identify or rule out intraperitoneal hemorrhage when patients cannot undergo CT.

**Contrast-enhanced computer tomography (CT)** is the gold standard for the evaluation of blunt abdominal trauma [2, 5]. However, patients should be hemodynamically stable, as well as cooperative or sedated. Of note, surgeons should interpret CT findings cautiously before opting for OM because more than 50% of children present with grade III–IV lesions [2, 160]. Taking into account the radiation risk in children, low-dose protocols are preferred (3–6 mSv instead of 11–24 mSv) [2, 5]. APSA guidelines recommend CT scanning in children at risk for injuries that might be missed by FAST, need for surgery, recurrent bleeding, and when other abdominal injuries (such as pancreatic or hollow viscous injury) are suspected [142].

**Non-operative management in splenic injury:**

- **NOM is recommended as first-line treatment for hemodynamically stable pediatric patients with blunt splenic trauma (GoR 2A).**
- **Patients with moderate-severe blunt and all penetrating splenic injuries should be considered for transfer to dedicated pediatric trauma centers after hemodynamic stabilization (GoR 2A).**
- **NOM in children should be considered only in an environment that provides capability for patient continuous monitoring, angiography, trained surgeons, an immediately available OR and immediate access to blood and blood products or alternatively in the presence of a rapid centralization system in those patients amenable to be transferred (GoR 2A).**
- **NOM should be attempted even in the setting of concomitant head trauma; unless the patient is unstable, and this might be due to intra-abdominal bleeding (GoR 2B).**

**Blunt splenic injury:**

- **Blunt splenic injuries with hemodynamic stability and absence of other internal injuries requiring surgery should undergo an initial attempt of NOM irrespective of injury grade (GoR 2A).**
Overall, the majority (72.5%) of NOM failures peaks at 4 h and then declines over 36 h from admission. There is evidence suggesting that the rate of NOM failure has been shown to range from 2 to 5% [174, 175]. Of note, children with splenic injury have a greater chance to undergo splenectomy or laparotomy in general if treated in an adult trauma center [171, 173].

Mooney et al. and Todd et al. demonstrated that children treated in adult trauma centers [145, 162, 168] – patients treated in dedicated centers were demonstrated to have higher probability to undergo NOM than those treated in adult trauma centers [145, 162, 168–172]. Pediatric trauma patients treated in dedicated centers were demonstrated to have higher probability to undergo NOM than those treated in adult trauma centers [145, 162, 168–170]. Mooney et al. and Todd et al. demonstrated that children with splenic injury have a greater chance to undergo splenectomy or laparotomy in general if treated in an adult trauma center [171, 173].

NOM failure rates for pediatric splenic trauma have been shown to range from 2 to 5% [174, 175]. Of note, there is evidence suggesting that the rate of NOM failure peaks at 4 h and then declines over 36 h from admission [174]. Overall, the majority (72.5%) of NOM failures seem to occur during the first week after trauma, with 50% of them happening within the first 3–5 days [37].

Finally, there are no granular data validating NOM for penetrating spleen injury in children. However, reports on successful non-operative management of isolated penetrating spleen injuries in hemodynamically stable pediatric patients do exist [176–178].

**The role of angiography/angioembolization (AG/AE):**

- The vast majority of pediatric patients do not require AG/AE for CT blush or moderate to severe injuries (GoR 1C).
- AG/AE may be considered in patients undergone to NOM, hemodynamically stable with signs of persistent hemorrhage not amenable of NOM, regardless the presence of CT blush once excluded extra-splenic source of bleeding (GoR 1C).
- AG/AE may be considered for the treatment of post-traumatic splenic pseudo-aneurysms prior to patient discharge (GoR 2C).
- Patients with more than 15 years old should be managed according to adults AG/AE-protocols (GoR 1C).

The role of AG/AE in the management of pediatric splenic trauma is controversial, and its use varies widely among institutions [164, 179, 180].

Even though AG/AE appears to be a safe intervention, the vast majority of retrospective observational data show that very few pediatric patients with contrast extravasation may benefit from embolization [153, 181].

Therefore, AG/AE may only be considered in carefully selected patients, such as those with high-grade injuries, transient response to resuscitation, and/or persistent blood requirements [182]. Similarly, the role of embolization in the management of pediatric splenic pseudo-aneurysms is also unclear. Of note, PSAs often undergo spontaneous thrombosis and could resolve without any interventions [133, 144, 155, 180, 183]. Some authors proposed a distinction between adolescent of more than 13–15 years old, for which should be applied the adult protocol for AG/AE, and children of less than 13–15 years old that are more vulnerable to OPSI [184, 185]. Moreover, Skattum et al. suggested that if a patient aged less than 15 years old is found to have a PSA on admission CT, contrast-enhanced ultrasound should be performed prior to discharge. If at that time PSA is still present, embolization should be considered [184].

Mortality and major complications are rarely reported following AG/AE [180, 184, 186, 187]. Nevertheless, a post-embolization syndrome (PES), consisting of abdominal pain, nausea, ileus, and fever, seems to occur in 90% of children undergoing AG/AE. This syndrome is usually
self-limited and tends to resolve spontaneously in 6 to 9 days [188]. In addition, pleural effusion (9%), pneumonia (9%), and coil migration (4.5%) can also be seen after splenic embolization [184].

Overall, AG/AE seems to preserve splenic function without lasting complications, but most children do not need this intervention [179, 189, 190].

Operative management in blunt and penetrating injuries:

- **Patients should undergo to OM in case of hemodynamic instability, failure of conservative treatments, severe coexisting injuries necessitating intervention and peritonitis, bowel evisceration, impalement (GoR 2A).**
- **Splenic preservation (at least partial) should be attempted whenever possible (GoR 2B).**

Indications for laparotomy include hemodynamic instability, ongoing blood loss, or evidence of hollow viscous injury [153, 161, 191–194]. Of note, ATOMAC guidelines recommend surgery if transfusion of 40 mL/kg of all blood products within 24 h (or more than 4 units of blood) fails to stabilize the patient hemodynamically [146, 153]. One percent (1%) of pediatric patients who undergo immediate OM are re-admitted for intestinal obstruction within a year [194]. In most cases of OM, splenic partial preservation is possible. Indeed, partial (subtotal) splenectomy or splenorrhaphy are safe and viable alternatives to total splenectomy and can be performed even in high-grade injuries [193, 195–197].

**Splenectomy associated with head injuries**

Head injury is an important cause of morbidity and mortality in trauma patients of all ages (50–60%). Importantly, head injuries can also result in altered mental status, which can complicate the process of clinical evaluation [198]. Especially in the setting of concurrent head injury, blood pressure and heart rate are poor markers of hemorrhagic shock in pediatric patients [153]. Nevertheless, an analysis of the National Pediatric Trauma Registry suggested that the association of altered mental status from head injury with spleen injuries should not impact the decision for observational management in pediatric patients (<19 years old) [198].

**Short- and long-term follow-up in splenic trauma (blunt and penetrating):**

- The risk of pseudo-aneurysm after splenic trauma is low, and in most of cases, it resolves spontaneously (GoR 2B).
- Angioembolization should be taken into consideration when a pseudoaneurysm is found (GoR 2B).
- US (DUS, CEUS) follow-up seems reasonable to minimize the risk of life-threatening hemorrhage and associated complications in children (GoR 1B).
- After NOM in moderate and severe injuries, the reprise of normal activity could be considered safe after at least 6 weeks (GoR 2B).

No definitive data exist regarding complication rate and short- and long-term follow-up, and no clear indications regarding the most cost-effective imaging technique (US, DUS, CEUS, CT scan). Initial APSA guidelines [142] recommended bed rest for a number of days equal to the grade of injury plus 1 day [142]. However, recent studies suggest a shorter bed rest of one night in solitary grade I–II splenic trauma and two nights for patients with more severe injuries (grade ≥III) and stable hemoglobin level [199]. Longer admission should be considered in patients with lower hemoglobin levels on admission, higher injury grade, suspicious of other abdominal injuries (as pancreatic or small bowel injuries), blush on the CT scan, bicycle handlebar injuries, recurrent abdominal, or patients at risk for missed injuries [153, 165].

US or CEUS or DUS follow-up seems reasonable to minimize the risk of life-threatening hemorrhage and its associated complications [200]. General surgeons tend to perform routinely imaging follow-up for children differently from pediatric surgeons that only in 5% of cases suggest imaging follow-up [145, 165, 201].

The APSA guidelines [142] recommended 2–5 months of “light” activity before restart with normal activities and recommended 3 week–3 months of limited activity at home. Some authors suggested the reprise of normal activity even after 4 weeks after III–IV grade injuries. In fact, the risks of delayed splenic rupture and post-traumatic pseudocysts seem to be increase within the first 3 weeks (incidence 0.2 and 0.3%, respectively) [142, 202]. Canadian guidelines suggested a discharge at home after reprise and good toleration of oral intake, able mobilization, and analgesia with oral medications without images before discharge [160]. They reported a 32% of children that did not have any images follow-up without any complications and a restriction of activity no more than 6–8 weeks with a length of activity restriction modulated on the grade of injury [160]. The use of CEUS can improve the diagnosis of PSA that can be found in all grades of injury [155].

Patients and parents psychological involvement after trauma can be related with abdominal pain; for this
reason, family and patient education post-discharge should be considered to reduce readmission rate [203].

Infection prophylaxis in asplenic and hyposplenic adult and pediatric patients:

- **Patients should receive immunization against the encapsulated bacteria (Streptococcus pneumoniae, Haemophilus influenzae, and Neisseria meningitidis)** (GoR 1A).
- **Vaccination programs should be started no sooner than 14 days after splenectomy or spleen total vascular exclusion** (GoR 2C).
- **In patients discharged before 15 days after splenectomy or angioembolization, where the risk to miss vaccination is deemed high, the best choice is to vaccinate before discharge** (GoR 1B).
- **Annual immunization against seasonal flu is recommended for all patients over 6 months of age** (GoR 1C).
- **Malaria prophylaxis is strongly recommended for travelers** (GoR 2C).
- **Antibiotic therapy should be strongly considered in the event of any sudden onset of unexplained fever, malaise, chills, or other constitutional symptoms, especially when medical review is not readily accessible** (GoR 2A).
- **Primary care providers should be aware of the splenectomy/angioembolization** (GoR 2C).

OPSI are defined as fulminant sepsis, meningitis, or pneumonia triggered mainly by *Streptococcus pneumoniae* (50% of cases) [204, 205] followed by *H. influenzae* type B and *N. meningitidis*. OPSI is a medical emergency. The risks of OPSI and associated death are highest in the first year after splenectomy, at least among young children, but remain elevated for more than 10 years and probably for life. The incidence of OPSI is 0.5–2%; the mortality rate is from 30 to 70%, and most death occurs within the first 24 h. Only prompt diagnosis and immediate treatment can reduce mortality [2, 204, 206, 207]. Asplenic/hyposplenic children younger than 5 years old have a greater overall risk of OPSI with an increased death compared with adults [204, 208]. The risk is more than 30% in neonates [2]. Evidence exist regarding the possible maintaining of the function by the embolized spleen (hyposplenic patients) however is reasonable to consider it as less effective and proceed with vaccination as well [179, 189, 190].

Vaccination against flu is recommended annually for asplenic/hyposplenic patients over 6 months of age. Prevention of influenza may decrease the risk of secondary bacterial infection, including pneumococcal infection [207, 208].

Ideally, the vaccinations against *S. pneumoniae*, *H. influenzae* type B, and *N. meningitidis* should be given at least 2 weeks before splenectomy [2]. Patients should be informed that immunization can only reduce the incidence of OPSI (vaccines so far available do not allow an exhaustive coverage neither for *S. pneumoniae*—23 of 90 serotypes are included—nor for *N. meningitidis*—5 of 6 serotypes) (Table 5).

In traumatic patients, the correct time for vaccination should be not less than 14 days after splenectomy; in fact, before 14 days, the antibody response is supposed to be suboptimal [204, 206, 209]; after that interval, the earlier the better. In asplenic/hyposplenic patients discharged before 15 days, where the risk to miss the vaccination is deemed high, the first vaccines should be given before discharge [206, 210]. The Centre for Disease Control in 2016 proposed the last updated recommendations [211]. Most episodes of severe infections occur within the first 2 years after splenectomy, and for this reason, some authors recommend at least 2 years of prophylactic antibiotics after splenectomy. However, the duration of antibiotic prophylaxis is controversial.

Community physicians should be aware of the asplenic/hyposplenic condition, in order to provide them with the most appropriate level of care.

Asplenic/hyposplenic patients should be given an antibiotic supply in the event of any sudden onset of unexplained fever, malaise, chills, or other constitutional symptoms, especially when medical review is not readily accessible. The recommended options for emergency standby in adults include the following: (a) Amoxycillin, 3 g starting dose followed by 1 g, every 8 h; (b) Levofloxacin 500 mg every 24 h or Moxifloxacin 400 mg every 24 h (for beta-lactam allergic patients).

The recommended emergency standby treatment in children is Amoxycillin 50 mg/Kg in three divided daily doses. For beta-lactam allergic patients, an alternative should be proposed by a specialist (fluoroquinolones are generally contraindicated in children, but due to the possible severity of OPSI, they might still be considered).

Antibiotic prophylaxis is necessary in patients with asplenia/hyposplenia who are bitten by dogs and other animals because of increased risk of severe sepsis (Amoxycillin/Clavulanic acid for 5 days) [205, 207, 208].

If the patient is being treated in an outpatient setting, he/she should be referred immediately to the nearest emergency department. Clinical deterioration can be rapid even after antibiotic administration. Antibiotics should be modified once blood culture results become available [208]. Failures of antibiotic prophylaxis have been reported, so patients should be warned that prophylaxis reduces but does not abolish the risk of sepsis.
Due to the increased risk of severe malaria, asplenic/hyposplenic travelers to endemic areas should receive an adequate pre-departure counseling, regarding both measures aimed at reducing the exposure to mosquitoes’ bites and chemoprophylaxis.

**Conclusions**

The management of spleen trauma must be multidisciplinary and must keep into consideration the physiological and anatomical derangement together with the immunological effects. Critical and operative decisions can be taken more effectively if both anatomy of injury and its physiological effects, and the associated lesions are considered especially considering the modern tools for integrated bleeding management. The treatment algorithm must differ within adults, and children these lasts should always be treated in dedicated trauma centers.

**Abbreviations**

AAST: American Association for Surgery for Trauma; AG/AE: Angiography/angioembolization; AIS: Abbreviated injury score; AMX: Amoxicillin; AMX/CLA: Amoxicillin/clavulanic; APSA: American Pediatric Surgical Association; ATLS: Advanced Trauma Life Support; BE: Base excess; BST: Blunt spinal trauma; CEUS: Contrast-enhanced US; CT: Computerized tomography; DPL: Diagnostic peritoneal lavage; DUS: Doppler US; DVT: Deep venous thrombosis; EAST: Eastern Association for the Surgery of Trauma; ED: Emergency Department; E-FAST: Extended focused assessment sonography for trauma; GCS: Glasgow Coma Scale; ICU: Intensive Care Unit; ISS: Injury severity score; LE: Level of evidence; LMWH: Low-molecular-weight heparin; LOS: Length of hospital stay; MTP: Massive transfusion protocols; NOM: Non-operative management; OIS: Organ Injury Scale;


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Pelvic trauma: WSES classification and guidelines

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Abstract

Complex pelvic injuries are among the most dangerous and deadly trauma related lesions. Different classification systems exist, some are based on the mechanism of injury, some on anatomic patterns and some are focusing on the resulting instability requiring operative fixation. The optimal treatment strategy, however, should keep into consideration the hemodynamic status, the anatomic impairment of pelvic ring function and the associated injuries. The management of pelvic trauma patients aims definitively to restore the homeostasis and the normal physiopathology associated to the mechanical stability of the pelvic ring. Thus the management of pelvic trauma must be multidisciplinary and should be ultimately based on the physiology of the patient and the anatomy of the injury. This paper presents the World Society of Emergency Surgery (WSES) classification of pelvic trauma and the management Guidelines.

Keywords: Pelvic, Trauma, Management, Guidelines, Mechanic, Injury, Angiography, REBOA, ABO, Preperitoneal pelvic packing, External fixation, Internal fixation, X-ray, Pelvic ring fractures

Background

Pelvic trauma (PT) is one of the most complex management in trauma care and occurs in 3% of skeletal injuries [1–4]. Patients with pelvic fractures are usually young and they have a high overall injury severity score (ISS) (25 to 48 ISS) [3]. Mortality rates remain high, particularly in patients with hemodynamic instability, due to the rapid exsanguination, the difficulty to achieve hemostasis and the associated injuries [1, 2, 4, 5]. For these reasons, a multidisciplinary approach is crucial to manage the resuscitation, to control the bleeding and to manage bones injuries particularly in the first hours from trauma. PT patients should have an integrated management between trauma surgeons, orthopedic surgeons, interventional radiologists, anesthesiologists, ICU doctors and urologists 24/7 [6, 7].

At present no comprehensive guidelines have been published about these issues. No correlation has been demonstrated to exist between type of pelvic ring anatomical lesions and patient physiologic status. Moreover the management of pelvic trauma has markedly changed throughout the last decades with a significant improvement in outcomes, due to improvements in diagnostic and therapeutic tools. In determining the optimal treatment strategy, the anatomical lesions classification should be supplemented by hemodynamic status and associated injuries. The anatomical description of pelvic ring lesions is fundamental in the management algorithm but not definitive. In fact, in clinical practice the first decisions are based mainly on the clinical conditions and the associated injuries, and less on the pelvic ring lesions. Ultimately, the management of trauma requires an assessment of the anatomical injury and its physiologic effects.

This paper aims to present the World Society of Emergency Surgery (WSES) classification of pelvic trauma and the treatment Guidelines.
WSES includes surgeons from whole world. This Classification and Guidelines statements aim to direct the management of pelvic trauma, acknowledging that there are acceptable alternative management options. In reality, as already considered for other position papers and guidelines, not all trauma surgeons work in the same conditions and have the same facilities and technologies available [8].

Notes on the use of the guidelines
The Guidelines are evidence-based, with the grade of recommendation also based on the evidence. The Guidelines present the diagnostic and therapeutic methods for optimal management of pelvic trauma. The practice Guidelines promulgated in this work do not represent a standard of practice. They are suggested plans of care, based on best available evidence and the consensus of experts, but they do not exclude other approaches as being within the standard of practice. For example, they should not be used to compel adherence to a given method of medical management, which method should be finally determined after taking account of the conditions at the relevant medical institution (staff levels, experience, equipment, etc.) and the characteristics of the individual patient. However, responsibility for the results of treatment rests with those who are directly engaged therein, and not with the consensus group.

Methods
Eight specific questions were addressed regarding the management of PT assessing the main problems related to the hemodynamic and the mechanical status:

- 1Which are the main diagnostic tools necessary prior to proceed in hemodynamically unstable PT?
- 2Which is the role of pelvic binder in hemodynamically unstable pelvic fracture?
- 3Which is the role of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) in hemodynamically unstable pelvic trauma?
- 4Which patients with hemodynamically unstable PT warrant preperitoneal pelvic packing?
- 5Which patients with hemodynamically unstable pelvic ring injuries require external pelvic fixation?
- 6Which patients with hemodynamically unstable PT warrant angioembolization?
- 7What are the indications for definitive surgical fixation of pelvic ring injuries?
- 8What is the ideal time-window to proceed with definitive internal pelvic fixation?

A computerized search was done by the bibliographer in different databanks (MEDLINE, SCOPUS, EMBASE) citations were included for the period between January 1980 to December 2015 using the primary search strategy: pelvis, pelvic, injuries, trauma, resuscitation, sacral, bone screws, fractures, external fixation, internal fixation, anterior and posterior fixation, hemodynamic instability/stability, packing, pubic symphysis, angioembolization, pelvic binder/binding, aortic, balloon, occlusion, resuscitative, definitive, stabilization combined with AND/OR. No search restrictions were imposed. The dates were selected to allow comprehensive published abstracts of clinical trials, consensus conference, comparative studies, congresses, guidelines, government publication, multicenter studies, systematic reviews, meta-analysis, large case series, original articles, randomized controlled trials. Case reports and small cases series were excluded. No randomized controlled trials were found. Narrative review articles were also analyzed to determine other possible studies. Literature selection is reported in the flow chart (Fig. 1). The Level of Evidence (LE) was evaluated using the GRADE system [9] (Table 1).

The discussion of the present guidelines has been realized through the Delphi process. A group of experts in the field coordinated by a central coordinator was contacted separately to express their evidence-based opinion on the different questions about the hemodynamically and mechanically unstable pelvic trauma management. Pelvic trauma patterns were differentiated into hemodynamically and mechanically stable and unstable ones. Conservative and operative management for all combinations of these conditions were evaluated. The central coordinator assembled the different answers derived from the first round and drafted the first version that was subsequently revised by each member of an enlarged expert group separately. The central coordinator addressed the definitive amendments, corrections and concerns. The definitive version about which the agreement was reached consisted in the published guidelines.

Mechanisms of injuries
Principal mechanisms of injuries that cause a pelvic ring fracture are due to a high energy impact as fall from height, sports, road traffic collision (pedestrian, motorcyclist, motor vehicle, cyclist), person stuck by vehicles [1, 5]. Ten to fifteen percent of patients with pelvic fractures arrive to the ED in shock and one third of them will die reaching a mortality rate in the more recent reports of 32% [10]. The causes of dying are represented in the major part by uncontrolled bleeding and by patient’s physiologic exhaustion.

Anatomy of pelvis and pelvic injuries
Pelvic ring is a close compartment of bones containing urogenital organs, rectum, vessels and nerves. Bleeding from pelvic fractures can occur from veins (80%) and
from arteries (20%) [7, 11]. Principal veins injured are presacral plexus and prevesical veins, and the principals arteries are anterior branches of the internal iliac artery, the pudendal and the obturator artery anteriorly, and superior gluteal artery and lateral sacral artery posteriorly [7, 11]. Others sources of bleeding include bones fractures [1]. Among the different fracture patterns affecting the pelvic ring each has a different bleeding probability. No definitive association between fracture pattern and bleeding exist but some pattern as APC III are associated to a greater transfusion rate according to some studies [12]. Part of the bleeding is from the bones as clearly showed since 1973. The necessity to fix the bones fractures by repositioning them has been explained by Huittimen et al. [13]. In cases of high-grade injuries, thoraco-abdominal associated injuries can occur in 80%, and others local lesions such as bladder, urethra (1.6-25% of cases), vagina, nerves, sphincters and rectum (18–64%), soft tissues injuries (up to 72%). These injuries should be strongly suspected particularly in patients with perineal hematoma or large soft tissue disruption [1, 3, 14]. These patients need an integrate management with other specialists. Some procedures like supra-pubic catheterization of bladder, colostomy with local debridement and drainage, and antibiotic prevention are important to avoid aggravating urethral injuries or to avoid fecal contamination in case of a digestive tract involvement [1]. Although these conditions must be respected and kept in mind the first aim remains the hemodynamic and pelvic ring stabilization.

**Physiopathology of the injuries**

The lesions at the level of the pelvic ring can create instability of the ring itself and a consequent increase in the internal volume. This increase in volume, particular in open book lesions, associated to the soft tissue and vascular disruption, facilitate the increasing hemorrhage in the retroperitoneal space by reducing the tamponing effect (pelvic ring can contain up to a few liters of blood) and can cause an alteration in hemodynamic status [7, 15]. In the management of severely injured and bleeding patients a cornerstone is represented by the early evaluation and correction of the trauma induced coagulopathy. Resuscitation associated to physiologic impairment and to suddenly activation and deactivation of several procoagulant and anticoagulant factors contributes to the insurance of this
frequently deadly condition. The massive transfusion protocol application is fundamental in managing bleeding patients. As clearly demonstrated by the literature blood products, coagulation factors and drugs administration has to be guided by a tailored approach through advanced evaluation of the patient’s coagulative asset [16–22]. Some authors consider a normal hemodynamic status when the patient does not require fluids or blood to maintain blood pressure, without signs of hypoperfusion; hemodynamic stability as a counterpart is the condition in which the patient achieves a constant or an amelioration of blood pressure after fluids with a blood pressure >90 mmHg and heart rate <100 bpm [23]; hemodynamic instability is the condition in which the patient has an admission systolic blood pressure <90 mmHg, or > 90 mmHg but requiring bolus infusions/transfusions and/or vaso-pressor drugs and/or admission base deficit (BD) >6 mmol/l and/or shock index > 1 [24, 25] and/or transfusion requirement of at least 4–6 Units of packed red blood cells within the first 24 hours [5, 16, 26]. The Advanced Trauma Life Support (ATLS) definition considers as “unstable” the patient with: blood pressure <90 mmHg and heart rate > 120 bpm, with evidence of skin vasoconstriction (cool, clammy, decreased capillary refill), altered level of consciousness and/or shortness of breath [26]. The present classification and guideline utilize the ATLS definition. Some authors suggested that the sacroiliac joint disruption, female gender, duration of hypotension, an hematocrit of 30% or less, pulse rate of 130 or greater, displaced obturator ring fracture, a pubic symphysis diastasis can be considered good predictors of major pelvic bleeding [2, 15, 27]. However unfortunately the extent of bleeding is not always related with the type of lesions and there is a poor correlation between the grade of the radiological lesions and the need for emergent hemostasis [7, 15, 28].

**WSES Classification**

The anatomical description of pelvic ring lesions is not definitive in the management of pelvic injuries. The classification of pelvic trauma into minor, moderate and severe considers the pelvic ring injuries anatomic classification (Antero-Posterior Compression APC; Lateral Compression LC; Vertical Shear VS; CM: Combined Mechanisms) and more importantly, the hemodynamic
status. As already stated the ATLS definition considers as “unstable” the patient with: blood pressure < 90 mmHg and heart rate > 120 bpm, with evidence of skin vasoconstriction (cool, clammy, decreased capillary refill), altered level of consciousness and/or shortness of breath [26].

The WSES Classification divides Pelvic ring Injuries into three classes:

- **Minor** (WSES grade I) comprising hemodynamically and mechanically stable lesions
- **Moderate** (WSES grade II, III) comprising hemodynamically stable and mechanically unstable lesions
- **Severe** (WSES grade IV) comprising hemodynamically unstable lesions independently from mechanical status.

The classification (Table 2) considers the Young-Burges classification (Fig. 2), the hemodynamic status and the associated lesions.

**Minor pelvic injuries:**

- **WSES grade I** (should be formatted in bold and cursive as the other grade of classification) includes APC I, LC I hemodynamically stable pelvic ring injuries.

**Moderate pelvic injuries:**

- **WSES grade II** includes APC II – III and LC II - III hemodynamically stable pelvic ring injuries.
- **WSES grade III** includes VS and CM hemodynamically stable pelvic ring injuries.

**Severe pelvic injuries:**

- **WSES grade IV** includes any hemodynamically unstable pelvic ring injuries.

Basing on the present classification WSES indicates a management algorithm explained in Fig. 3.

**Principles and cornerstones of the management**

The management of pelvic trauma as for all the other polytraumatized patients needs to pose in definitive the attention in treating also the physiology; decisions can be more effective when combining evaluation of anatomy, mechanical consequences of injury and their physiological effects. During daily clinical practice the first decisions are based mainly on the clinical conditions and the associated injuries, and less on the pelvic ring lesions. The management of trauma in fact aims firstly to restore the altered physiology. The main aims of proper PT management are bleeding control and stabilization of the hemodynamic status, restoring of the eventual coagulation disorders and the mechanical integrity and stability of the pelvic ring, and preventing complications (septic, urogenital, intestinal, vascular, sexual functions, walking) (×9); then to definitively stabilize the pelvis.

**Recommendations for diagnostic tools use in Pelvic Trauma**

- **- The time between arrival in the Emergency Department and definitive bleeding control should be minimized to improve outcomes of patients with hemodynamically unstable pelvic fractures [Grade 2A].**
- **- Serum lactate and base deficit represent sensitive diagnostic markers to estimate the extent of traumatic-haemorrhagic shock, and to monitor response to resuscitation [Grade 1B].**
- **- The use of Pelvic X-ray and E-FAST in the Emergency Department is recommended in hemodynamic and mechanic unstable patients with pelvic trauma**

<table>
<thead>
<tr>
<th>WSES grade</th>
<th>Young-Burges classification</th>
<th>Haemodynamic</th>
<th>Mechanic</th>
<th>CT-scan</th>
<th>First-line Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINOR</td>
<td>WSES grade I</td>
<td>APC I – LC I</td>
<td>Stable</td>
<td>Stable</td>
<td>Yes</td>
</tr>
<tr>
<td>MODERATE</td>
<td>WSES grade II</td>
<td>LC II/III - APC II/III</td>
<td>Stable</td>
<td>Unstable</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>WSES grade III</td>
<td>VS - CM</td>
<td>Stable</td>
<td>Unstable</td>
<td>Yes</td>
</tr>
<tr>
<td>SEVERE</td>
<td>WSES grade IV</td>
<td>Any</td>
<td>Unstable</td>
<td>Any</td>
<td>No</td>
</tr>
</tbody>
</table>
and allows to identify the injuries that require an early pelvic stabilization, an early angiography, and a rapid reductive maneuver, as well as laparotomy [Grade 1B].

- Patients with pelvic trauma associated to hemodynamic normality or stability should undergo further diagnostic workup with multi-phasic CT-scan with intravenous contrast to exclude pelvic hemorrhage [Grade 1B].

- CT-scan with 3-Dimensional bones reconstructions reduces the tissue damage during invasive procedures, the risk of neurological disorders after surgical fixation, operative time, and irradiation and the required expertise [Grade 1B].

- Retrograde urethrogram or/and urethrocystogram with contrast CT-scan is recommended in presence of local perineal clinical hematoma and pelvic disruption at Pelvic X-ray [Grade 1B].

- Perineal and a rectal digital examination are mandatory in case of high suspicious of rectal injuries [Grade 1B].

- In case of a positive rectal examination, proctoscopy is recommended [Grade 1C].

Diagnostic workup strategies in the emergency room must be standardized and streamlined in order to avoid an unnecessary delay to definitive bleeding control, the time between trauma and operating room has been shown to inversely correlate with survival in patients with traumatic pelvic hemorrhage [29].

Sensitive laboratory markers of acute traumatic hemorrhage include serum lactate and base deficit by arterial blood gas analysis [29]. In contrast, hemoglobin level and hematocrit do not represent sensitive early markers of the extent of traumatic hemorrhagic shock [29]. As coagulopathic patients with traumatic hemorrhagic shock form unstable pelvic ring injuries have a significantly increased post-injury mortality [16], the presence of coagulopathy should be determined early by "point-of-care" bedside testing using Thromboelastography (TEG) or Rotational Thromboelastometry (ROTEM), which allow targeted resuscitation with blood products and improved post-injury survival rates [17, 19–22]. At first, the evaluation of a PT should be based on the mechanism of injury (particularly in case of high-energy impact, more frequent in blunt trauma) and physical examination to search a pelvic ring deformity or instability, a pelvic or perineal hematoma, or a rectal/urethral bleeding [1]. Lelly maneuver can be useful in evaluating the pelvic ring stability but it should be done cautiously because it can sometime increase the bleeding by dislocating bones margin. In case of hemodynamic instability, particularly in blunt trauma, chest and pelvic x-rays and extended focused assessment for sonographic evaluation of trauma patients (E-FAST) are performed according to ATLS protocols. Chest X-rays and E-FAST are performed to exclude others sources of hemorrhage in the thorax and in the abdomen [1, 7, 30, 31]. The Eastern Association for the Surgery of Trauma guidelines [2]
reported that E-FAST is not enough sensitive to exclude a pelvic bleeding, however it could be considered adequate to exclude the need for a laparotomy in unstable patients.

**Pelvic X-ray (PXR)** in hemodynamically unstable patients helps in identifying life-threatening pelvic ring injuries [18, 32, 33]. It is important but its execution must not delay in proceeding with life-saving maneuvers. Sensitivity and sensibility rates are low (50–68% and 98% respectively) and the false negative rates are high (32%) [23, 34]. For these reason some authors suggested to abandon PXR in case of stable patients [11, 23, 34]. The principal injuries related with hemodynamic instability are sacral fractures, open-book injuries and vertical-shear injuries (APC II-III, LC II-III and VS) [34]. To clearly define injury pattern, it is fundamental to achieve early pelvic stabilization and to early plan for the subsequent diagnostic-therapeutic approach. Moreover PXR is important to evaluate the hip dislocation in order to provide a prompt reductive maneuver [34]. However PXR alone does not predict mortality, hemorrhage or need for angiography [2]. In hemodynamically normal patients with nor pelvic instability nor hip dislocation nor positive physical examination scheduled for CT-scan PXR could be omitted [11].

At the end of primary evaluation a radiological workup is performed. In case of hemodynamic normality or stability **Computed Tomography (CT)** is the gold standard with a sensitivity and specificity for bones fractures of 100% [1, 23, 34]. The main two factors that are important to plan a correct decision-making process and to steer the angiography are the presence at CT of intra-
venous contrast extravasation and the pelvic hematoma size [2, 35]. CT has an accuracy of 98% for identifying patients with blush, however an absence of blush in contrast CT does not always exclude an active pelvic bleeding [2, 28]. In presence of a pelvic hematoma ≥500 cm³ an arterial injury should be strongly suspected even in absence of a visible contrast blush [2]. CT is useful also to evaluate any injuries of other organs, retroperitoneum, and bones but also to better decide the subsequent surgical management [34]. A recent study supports the use of a multidetector CT with a three phases protocol (arterial, portal and delayed phase) with a subsequent digital subtraction angiography (DSA) in case of suspect of arterial hemorrhage so as to better evaluate bleeding or hematoma [35]. This protocol could significantly reduce the rate of subsequent interventions due to others hemorrhagic foci [35].

**CT with 3-Dimensional bone reconstruction** is helpful reducing tissue damage during invasive procedure, reducing the subjective expertise required from clinical staff and improving patient recovery times [36]. Chen and coll. reported successful rates of screw positioning in 93.8% of cases after 3D CT reconstruction, particularly in patients with sacral fractures and ilio-sacral joint dislocations [36]. This approach permits to also reduce the neurological disorders after surgical fixation, operative times, and irradiation.

In 7-25% of pelvic ring fractures lower urinary tract and urethra are damaged. However the diagnosis of urethral injuries remains difficult at the initial evaluation and about 23% of them are missed [14]. Clinical signs suggesting a urethral injury are perineal/scrotal hematoma, blood from the urethral meatus, the presence of a high-riding or non-palpable prostate at rectal exploration, the presence of an unstable pelvic fracture. The insertion of a transurethral catheter without other previous investigations in patients with a pelvic injury could be associated with severe complications: either acute like complete transection of the urethra, or chronic like stricture formation, impotence and urinary incontinence [14]. For this reason ATLS guidelines, the World Health Organization and some authors [14] suggested a **retrograde urethrogram (RUG)** prior the urethral catheterization. RUGs is recommended when local clinical signs or a disruption in the PXR are found, particularly in the presence of higher degree of soft tissue disruption, bone displacement, or multiple fractures [14]. In case a positive of RUG or when high suspicion of urethral injury are present, a suprapubic catheter with delayed cystogram is recommended [14]. Magnetic resonance images seem promising to detect type of injuries and could be a useful tool in combination with RUGs or in alternative but only in stable patients [14]. However the sequence between RUG and **urethrocytogram with contrast CT** is controversial [2]. Performing a RUG before CT could increase the rate of indeterminate and false-negative CT-scans [2]. For this reason when hemodynamic status permits in case of suspected urethral injuries the late contrast CT-scan with a urologic study is recommended [2].

The high incidence of ano-rectal lesions (18–64%) requires careful study of the ano-rectal region. At first a **perineal and a rectal digital examination** to detect blood, rectal wall weakness and non-palpable prostate should be done. In case of positive rectal examination a **rigid proctoscopy** should be strongly considered [3].

Tile Classification and Young and Burgess Classification (Fig. 2) are the most commonly used classifications for pelvic ring injuries. These classifications are based on the direction of forces causing fracture and the associated instability of pelvis with four injury patterns: lateral compression, antero-posterior compression (external rotation), vertical shear, combined mechanism [12]. The Young and Burgess classification is more beneficial for specialists, as a counterpart the second seems to be more easily remembered and applied.

**Role of pelvic binder in hemodynamically unstable pelvic fractures**

- - The application of non-invasive external pelvic compression is recommended as an early strategy to stabilize the pelvic ring and decrease the amount of pelvic haemorrhage in the early resuscitation phase [Grade 1A].
- - Pelvic binders are superior to sheet wrapping in the effectiveness of pelvic haemorrhage control [Grade 1C].
- - Non-invasive external pelvic compression devices should be removed as soon as physiologically justifiable, and replaced by external pelvic fixation, or definitive pelvic stabilization, if indicated [Grade 1B].
- - Pelvic binders should be positioned cautiously in pregnant women and elderly patients [Grade 2A].
- - In a patient with pelvic binder whenever it’s possible, an early transfer from the spine board reduces significantly the skin pressure lesions [Grade 1A].

Pelvic binder (PB) could be a “home-made” (as a bed-sheet) or commercial binder (as T-POD® (Bio Cybernetics Inter-national, La Verne, CA, USA), SAM-Sling® (SAM Medical Products, Newport, OR, USA), Pelvi Binder® (Pelvic Binder Inc., Dallas, TX, USA)). Nowadays, according to ATLS guidelines PB should be used before mechanical fixation when there are signs of a pelvic ring fracture [26]. The PB right position should be around the great trochanter and the symphysis pubis to
apply a pressure to reduce pelvic fracture and to adduct lower limbs in order to decrease the pelvic internal volume. Commercial pelvic binders are more effective in control pelvic bleeding than the “home-made” ones [36]. However in low resources setting or in lacking of commercial devices, “home-made” pelvic binder can be effectively and safely used.

PB is a cost-effective and a non-invasive tool that could be used by physicians and volunteers during the maneuvers aiming to stabilize a trauma patient, particularly in the immediate resuscitative period and the pre-hospital setting [1, 28, 37]. Sometimes PB can be used as bridge to definitive mechanical stabilization in those patients hemodynamically stable and mechanically unstable with no other lesions requiring treatment and with a negative CT-scan; those patients in many cases can proceed directly to definitive mechanical stabilization. Biomechanical studies on cadaver showed an effective pelvic volume reduction with an improved hemorrhage control [38–41]. These data are confirmed in vivo [42–44]. The Eastern Association for Surgery for Trauma’s pelvic trauma guidelines reporting data from the large retrospective study of Croce et al. recommended the use of PB to reduce a pelvic unstable ring [2, 42]. The use of PB alone doesn’t seem to reduce mortality [2, 42]. Authors reported a decrease in used units of blood from 17.1 to 4.9 ($p = 0.0001$) in the first 24 h, and from 18.6 to 6 after 48 h in patients treated with external fixation and PB, respectively [42]. However, comparing PB with external pelvic fixation in patients with sacroiliac fractures, Krieg et al. found a higher transfusion needs in the first 24 and 48 h in patients who underwent external fixation [43].

Some complications could occur if the binder is not removed rapidly and if it’s over-tightened: PB should not be kept for more than 24–48 h. Skin necrosis and pressure ulcerations could be increased by PB continuous application of a pressure above 9.3 kPa for more than 2–3 h [40]. As the long-term effects of pelvic binder remain unclear at present, including the potential risk of soft tissue complications from prolonged compression [45], the general recommendation is to remove pelvic binders as soon as physiologically justifiable [26], and to consider replacing binders by external pelvic fixation.

In elderly patients, even a minor trauma could cause major pelvic fractures or bleedings due to the bones fragility and the decrease in function of regulation systems as the vasospasm [46]. Lateral compression fracture pattern is more frequent, and fractures are usually not displaced. For this reason angiography seems to have more hemostatic effect than PB [44].

Even in pregnant women, the pelvis can be closed with internal rotation of the legs and PB positioning [47].

Role of REBOA in hemodynamic unstable pelvic ring injuries

- Resuscitative thoracotomy with aortic cross-clamping represents an acute measure of temporary bleeding control for unresponsive patients “in extremis” with exsanguinating traumatic hemorrhage. [Grade 1A]
- REBOA technique may provide a valid innovative alternative to aortic cross-clamping [Grade 2B].
- In hemodynamic unstable patients with suspected pelvic bleeding (systolic blood pressure <90 mmHg or non-responders to direct blood products transfusion), REBOA in zone III should be considered as a bridge to definitive treatment [Grade 2B].
- In major trauma patients with suspected pelvic trauma, arterial vascular access via femoral artery (e.g. 5Fr) introducer might be considered as the first step for eventually REBOA placement [Grade 2C].
- Partial-REBOA or/and intermittent-REBOA should be considered to decrease occlusion time and ischemic insult [Grade 2C].

Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) has emerged in recent years as alternative to emergent Resuscitative thoracotomy (RT) in hemodynamic unstable trauma patients [48–51]. The usage of REBOA and other Endo-Vascular hybrid Trauma Management (EVTM) methods is increasing worldwide in general trauma care including pelvic bleeding and now a part of the clinical praxis and guidelines in major trauma centers [6, 48–50, 52–58]. Several retrospective publications on REBOA in trauma care came lately from Japan, where REBOA has been practiced widely in the last 10–15 years but there are only few series concentrating on pelvic bleeding and REBOA [53, 57, 59, 60]. The method itself though, as a bleeding control method, has been used widely in endovascular surgery under the name Aortic Balloon Occlusion (ABO) [61–64]. REBOA is described as a “bridge to surgery” method and in pelvic bleeding as an alternative for RT with following open surgery or embolization (or both) for definitive bleeding control. REBOA can be placed in Zone I (supra-renal or descending aorta) or Zone III (infra-renal) but preferably not in zone II (para-renal) due to risk of visceral organ ischemia. It’s been speculated that Zone III REBOA be optimal for pelvic bleeding as the ischemic insult on visceral organs is prevented and long occlusion time (4–6 h) is possible [48, 49, 52]. Trauma patients though, might have multiple injuries and unclear source of bleeding upon arrival, which makes it challenging to decide if Zone III REBOA is suitable for hemodynamic stabilization. In the majority of reported series, REBOA was placed in zone I first and
then redeployed in Zone III. REBOA seems to elevate the systolic blood pressure in bleeding patients while preserving carotid and coronary flow and this data is confirmed in animal studies though there is no clear evidence of mortality benefit in the reported literature [49, 65–68]. One must consider though that the reported usage of REBOA is a mixture of different bleeding mechanism and localizations as there is not enough data of isolated pelvic bleedings reported [57, 59]. New information from the AORTA, ABOTrauma Registry and DIRECT IABO studies show preliminary beneficial results in trauma patients and some evidence that zone III REBOA as well as partial-REBOA and intermittent-REBOA might have positive effect on survival rates [54]. Zone III REBOA seems to have some benefits as time gain for surgical strategic consideration by temporary hemodynamic stabilization. It also allows time for fluid replacement as well as preparation of bleeding control procedures (surgery/angiography or hybrid procedures) [49, 52, 54, 69]. REBOA is highly dependent on a functional femoral artery access and its early establishment might be of considerable value [52, 70]. REBOA for pelvic bleeding in hemodynamic unstable patients has the advantage of being a minimal invasive procedure with less metabolic and surgical burden on the trauma patient but this is only based on expert opinion and animal experiments rather than firm data [66, 68, 71–74]. Its usage is though increasing dramatically worldwide, especially in the USA despite lack of high quality evidence and prospective trials and RCT data are needed. Two important factors to consider when using REBOA in pelvic bleeding are:

- the vascular access for REBOA, because of a functional femoral artery access must be gained first and it’s still remained to be answered who should do it and at what stage and localization should it be done. As a main rule only qualified experienced people should do this; as a counterpart however any surgeon who also does ICU or vascular should be facile at these. Lastly it must be kept in mind that having an arterial line bring some additional issues to manage: on one hand when placed it needs to be connected to ulterior lines (i.e. fluids, cable, etc.) on the other hand it also provides the most accurate blood pressure readings.

- the estimated source of bleeding is crucial for determination of REBOA zone placement. For pelvic bleeding, zone III is postulated to be preferred [48, 49, 52].

Moreover there are some major limitations to REBOA. As mentioned, REBOA is only a temporary solution and a definitive bleeding control must follow. One of the major problems of REBOA is the ischemia-reperfusion organ injury followed by multiple organ failure that might be prevented by short REBOA time, intermittent REBOA (iREBOA), Zone III REBOA and new methods as partial REBOA (pREBOA) described lately [67, 75, 76].

The insertion of REBOA is not free from risks. During maneuvers inside emergency room in a hemodynamically unstable patient, it can be time-consuming to obtain percutaneous, or US guided, or surgically exposed femoral access. Vascular injuries can be present in severe pelvic injuries or otherwise produced particularly in elderly with calcific vessels and, nowadays, most trauma surgeons reserve REBOA only in patients in extremis, with multiple sites of bleeding, as a bridge to more definitive damage control surgical techniques.

Finally, a new evolving concept is the EvndoVascular hybrid Trauma Management (EVTM) that takes into considerations early vascular arterial access, REBOA, embolization and stent-grafts for bleeding control with hybrid (Open and endovascular) procedures. This concept takes into consideration all the above in the initial treatment of trauma patients and can finally suggest to take into account the presence of a vascular surgeon in the team managing selected politraumatized patients [52, 69, 70].

Role of Pre-peritoneal Pelvic Packing in hemodynamically unstable pelvic fractures

- Patients with pelvic fracture-related hemodynamic instability should always be considered for pre-peritoneal pelvic packing, especially in hospitals with no angiography service [Grade 1C].

- Direct preperitoneal pelvic packing represents an effective surgical measure of early haemorrhage control in hypotensive patients with bleeding pelvic ring disruptions [Grade 1B].

- Pelvic packing should be performed in conjunction with pelvic stabilization to maximize the effectiveness of bleeding control [Grade 2A].

- Patients with pelvic fracture-related hemodynamic instability with persistent bleeding after angiography should always be considered for pre-peritoneal pelvic packing [Grade 2A].

- Pre-peritoneal pelvic packing is an effective technique in controlling hemorrhage in patients with pelvic fracture-related hemodynamic instability undergone prior anterior/C-clamp fixation [Grade 2A].

The main source of acute retroperitoneal hemorrhage in patients with hemodynamically unstable pelvic ring disruptions is attributed to venous bleeding in 80%–90% of all cases, originating from presacral and paravesical venous plexus and from bleeding cancellous bone surfaces from sacral and iliac fractures and sacro-ilial joint
disruptions [77]. Only 10%–20% of all pelvic bleeding sources are arterial [77]. Arterial bleeding may be predominant in patients with persistent hemodynamic instability after mechanical stabilization [78]. Moreover, when arterial bleeding is present, the likelihood of concomitant venous bleeding is close to 100% [46, 79]. Since venous bleeding sources are inadequately managed by angio-embolization, studies have shown that the traditional ATLS-guided management of hemodynamically unstable pelvic ring injuries with angio-embolization results in poor patient outcomes with high post-injury mortality rates greater than 40% [80, 81]. The notion of a mainly venous retroperitoneal bleeding source in pelvic fractures provides the main rationale for pelvic packing for acute surgical hemorrhage control [4, 82].

Pre-peritoneal pelvic packing (PPP) has become a commonly used technique to control bleeding in hemodynamically unstable pelvic fractures in recent years. PPP has been reported to be a quick and easy-to-perform technique [4, 79] and it could be accomplished both in the emergency department (ED) and the operating room [4]. In experienced hands it can be completed with a minimal operative blood loss in less than 20 min [79, 83]. Since its first description by Hannover and Zurich groups in patients with pelvic ring injuries, outcomes have been improved by early surgical “damage control” intervention, including temporary external stabilization of unstable pelvic fractures, transabdominal pelvic packing, and surgical bleeding control [84–86].

More recently, the concept of “direct” preperitoneal pelvic packing (PPP) was described in Denver using a distinct surgical technique by a separate suprapubic midline incision that allows a direct retroperitoneal approach to the space of Retzius [83]. The modified PPP technique allows for more effective packing within the concealed preperitoneal space with three laparotomy pads for each side of the bladder in the retroperitoneal space packed below the pelvic brim towards the iliac vessels [79, 83, 87], without the necessity of opening the retroperitoneal space [82, 83]. With this technique, a midline laparotomy can be performed through a separate incision proximal to the suprapubic approach, if indicated for associated intra-abdominal injuries [88]. The separate incision technique has been shown to be safe with regard to preventing cross-contamination from intra-abdominal injuries to the retroperitoneal space and thereby decreasing the risk of postoperative infections after pelvic packing and subsequent pelvic fracture fixation [88]. PPP revision should be done within 48–72 h.

Retrospective observational studies revealed that the implementation of standardized multidisciplinary clinical guidelines that include early surgical management with pelvic external fixation and direct PPP for hypotensive patients with hemodynamical and mechanical unstable pelvic ring injuries led to a significant decrease of transfused blood products and to a significantly decreased post-injury mortality [5, 6, 87]. More recent observational studies confirmed the notion that extraperitoneal pelvic packing is a safe and fast procedure associated with a significantly reduced mortality in hemodynamically unstable patients with pelvic fractures, compared to patients managed by conventional measures without pelvic packing [89–91].

In hemodynamically and mechanically unstable pelvic fractures, PPP should be performed along with external fixation [46, 56, 79]. Cothren et al. showed that external fixation and PPP could be sufficient to control bleeding in severely injured patients with pelvic fractures, reporting that only 13% of patients required a subsequent angioembolization for an arterial blush [82]. In very sick patients, pelvic ring stabilization can be rapidly obtained by pelvic binder, with posterior compression using rolled surgical towels under the binder in sacro-iliac disruption [92].

Subsequent (secondary) angioembolization is recommended in the selected cohort of patients with ongoing hemorrhage and/or transfusion requirements after the pelvic packing procedure [4, 29, 56, 79, 87, 93]. The need for angioembolization following PPP has been reported to be between 13 and 20% [56, 87, 91]. However, Totterman et al. reported that 80% of patients who underwent PPP had positive findings for arterial injury at angiography [94].

PPP has been proposed as an alternative to angiography [79, 87, 91, 93]. Some papers [87, 91, 93] compared the use of PPP vs. Angioembolization. In a recent a prospective quasi-randomized trial Li et al. [91] showed that time-to-procedure and procedure time were significantly shorter in the PACK group than in the ANGIO one. The need for packed red cells in the first 24 h after procedure, the need for complementary procedures (angiography or PPP), mortality rates did not differ between the two groups [91]. Present guidelines recommend considering angiography and PPP as complementary procedures.

Role of external pelvic fixation in hemodynamic unstable pelvic ring injuries

- External pelvic fixation provides rigid temporary pelvic ring stability and serves as an adjunct to early haemorrhage control in hemodynamically unstable pelvic ring disruptions [Grade 1A].
- External pelvic fixation is a required adjunct to preperitoneal pelvic packing to provide a stable counterpressure for effective packing [Grade 2A].
- Anterior “resuscitation frames” through iliac crest or supra-acetabular route provide adequate temporary
pelvic stability in APC-II/-III and LC-II/-III injury patterns. A posterior pelvic C-clamp can be indicated for hemorrhage control in “vertical shear” injuries with sacroiliac joint disruptions [Grade 2A].

- Pelvic C-clamp application is contraindicated in comminuted and transfemoral sacral fractures, iliac wing fractures, and LC-type pelvic ring disruptions [Grade 2B].

The biomechanics of pelvic ring injuries and the underlying trauma mechanism dictate the need for external fixation [58, 95]. Pelvic ring disruptions in hemodynamically unstable patients should be temporarily stabilized to prevent further hemorrhage and to support measures of hemorrhage control, including angiography and pelvic packing [28, 46, 58, 96, 97]. The rationale for acute external pelvic fixation consists of (1) reducing the intrapelvic volume in “open book” equivalent injuries to decrease the retroperitoneal bleeding space, and (2) to provide a stable counter-pressure to the “packed” lap sponges for effective pelvic packing. For example, pelvic packing is not effective in absence of adequate counterpressure by posterior pelvic elements, which requires external fixation for unstable pelvic ring disruptions [56, 87, 98]. The technical aspects of decision-making for the modality of “damage control” external fixation for unstable pelvic ring injuries have been described elsewhere [58]. In essence, the indication and technique of pelvic external fixation can be guided by the Young & Burgess fracture classification [58, 99]. Unstable antero-posterior compression (APC-II/APC-III) and lateral compression injuries (LC-II/LC-III) injuries are ideally managed by anterior resuscitation frames, using iliac crest or supra-acetabular Schanz pin application. While the iliac crest route is technically less demanding and allows a faster “damage control” application, the pull-out resistance of Schanz pins in the iliac crest is very low and therefore associated with a higher risk of failure of reduction and fixation. In contrast, supra-acetabular frames require diligent pin placement under radiographic control using a C-arm, however, these frames have a very high pull-out resistance due to the solid supra-acetabular surgical corridor [58]. In contrast to rotationally unstable APC and LC-type injuries, vertically unstable pelvic ring disruptions, such as “vertical shear” (VS) injuries, are best stabilized by a posterior C-clamp [84, 86, 100–103]. Of note, the trauma surgeon must be aware of inherent risks and potential technical complications using the C-clamp due to the learning curve and required experience for safe application [104, 105]. Contraindications for the application of a pelvic C-clamp include comminuted and transfemoral sacral fractures, fractures of the iliac wing, and lateral compression-type injuries [58]. For these reasons, C-clamp is not used in many trauma centers.

Role of Angioembolization in hemodynamic unstable pelvic fractures

- Angioembolization is an effective measure of hemorrhage control in patients with arterial sources of retroperitoneal pelvic bleeding [Grade 1A].

- CT-scan demonstrating arterial contrast extravasation in the pelvis and the presence of pelvic hematoma are the most important signs predictive of the need for angioembolization [Grade 1C].

- After pelvic stabilization, initiation of aggressive hemostatic resuscitation and exclusion of extra-pelvic sources of blood loss, patients with pelvic fractures and hemodynamic instability or evidence of ongoing bleeding should be considered for pelvic angiography/angioembolization [Grade 2A].

- Patients with CT-scan demonstrating arterial contrast extravasation in the pelvis may benefit from pelvic angiography/angioembolization regardless of hemodynamic status [Grade 2A].

- After extra-pelvic sources of blood loss have been ruled out, patients with pelvic fractures who have undergone pelvic angiography with or without angioembolization, with persisting signs of ongoing bleeding, should be considered for repeat pelvic angiography/angioembolization [Grade 2B].

- Elderly patients with pelvic fractures should be considered for pelvic angiography/angioembolization regardless of hemodynamic status [Grade 2C].

Since the 1980s, percutaneous trans-catheter angioembolization has been shown to represent an effective nonsurgical measure of acute bleeding control in hemodynamically unstable pelvic fractures [106–109]. Most published clinical guidelines recommend the use of early angioembolization, in conjunction with external pelvic fixation if indicated, as the main measure of acute bleeding control [10, 46, 93, 110–117]. As a counterpart it is important to consider a number of factors that are critical to decision-making. The exclusive use of angioembolization has been associated with a high mortality in patients with bleeding pelvic fractures [118], which was significantly reduced by application of a combined protocol with initial preperitoneal pelvic packing and subsequent (secondary) angioembolization, if indicated [28, 56, 79, 86, 89]. It has been estimated that 85% of pelvic bleeding originates from bone, soft tissues, or major venous structures [2]. In addition, as many as 90% of patients with unstable pelvic fractures will have significant associated injuries. Bleeding in the abdomen, chest, or extremities will contribute to shock and may
require more urgent control than the pelvic bleeding. Thus, the fundamental management principles include aggressive hemostatic resuscitation, bony stabilization of the pelvis, and identification and management of extra-pelvic bleeding. Management guidelines that emphasize these principles demonstrate improved outcomes [6, 16, 46, 116]. Pelvic Angiography/Angioembolization (AG/AE) is expected to benefit only a small minority of patients, and therefore should be employed once extrapelvic and non-arterial sources of bleeding are controlled [2]. Arterial contrast extravasation seen on CT scan is a good indicator of the need for pelvic AG/AE [114]. In contrast, fracture pattern alone has not been predictive of who will require angiography [119]. Pelvic AG/AE is very effective in controlling hemorrhage. However, some patients will continue to bleed and repeat AG/AE has been found to be an effective strategy [115]. Elderly patients have been found to require AG/AE more frequently than younger adults, regardless of apparently normal hemodynamics at presentation, even in mechanical stable-low risk fractures. Therefore, AG/AE should be considered in these patients even when there is low suspicion of pelvic bleeding [120].

**Indications for definitive surgical fixation of pelvic ring injuries**

- Posterior pelvic ring instability represents a surgical indication for anatomic fracture reduction and stable internal fixation. Typical injury patterns requiring surgical fixation include rotationally unstable (APC-II, LC-II) and/or vertically unstable pelvic ring disruptions (APC-III, LC-III, VS, CM) [Grade 2A].

- Selected lateral compression patterns with rotational instability (LC-II, L-III) benefit from adjunctive, temporary external fixation, in conjunction to posterior pelvic ring fixation [Grade 2A].

- Pubic symphysis plating represents the modality of choice for anterior fixation of “open book” injuries with a pubic symphysis diastasis > 2.5 cm (APC-II, APC-III) [Grade 1A].

- The technical modality of posterior pelvic ring fixation remains a topic of debate, and individual decision-making is largely guided by surgeons’ preference. Spinopelvic fixation has the benefit of immediate weight bearing in patients with vertically unstable sacral fractures [Grade 2C].

- Patients hemodynamically stable and mechanically unstable with no other lesions requiring treatment and with a negative CT-scan can proceed directly to definitive mechanical stabilization [Grade 2B].

Pelvic ring injuries with rotational or vertical instability require surgical fixation with the goal of achieving anatomic reduction and stable fixation as a prerequisite for early functional rehabilitation. There is general consensus that pelvic ring disruptions with instability of posterior elements require internal fixation [95, 121]. Trauma mechanism-guided fracture classifications, including the widely used Young & Burgess system, provide guidance for surgical indications for pelvic fracture fixation [58, 122]. For example, stable fracture patterns, such as antero-posterior compression type 1 (APC-I) and lateral compression type 1 (LC-1) injuries are managed non-operatively, allowing functional rehabilitation and early weight bearing [123, 124]. In contrast, rotationally unstable APC-II/APC-III (“open book”) injuries and LC-II fracture patterns (“crescent fracture”), as well as rotationally and vertically unstable LC-III (“windswept pelvis”), “vertical shear” (VS), and “combined mechanism” (CM) fracture patterns require definitive internal fixation [123, 124]. Multiple technical modalities of surgical fixation have been described, including open reduction and anterior plating of pubic symphysis disruptions, minimal-invasive percutaneous iliosacral screw fixation for unstable sacral fractures and iliosacral joint disruptions, plating of iliac wing fractures, and spinopelvic fixation (named “triangular osteosynthesis” in conjunction with iliosacral screw fixation) or tension band plating for posterior pelvic ring injuries, including vertically unstable sacral fractures [125–133]. In addition, selected lateral compression (LC) type injuries are occasionally managed with temporary adjunctive external fixators for 6 weeks post injury, to protect from rotational instability of the anterior pelvic ring [58, 134]. Minimal invasive anterior “internal fixators” have been recently described as an alternative technical option [135]. The ultimate goal of internal fixation of unstable pelvic ring injuries is to allow early functional rehabilitation and to decrease long-term morbidity, chronic pain and complications that have been historically associated with prolonged immobilization [136, 137].

**Ideal time-window to proceed with definitive internal pelvic fixation**

- Hemodynamically unstable patients and coagulopathic patients “in extremis” should be successfully resuscitated prior to proceeding with definitive pelvic fracture fixation [Grade 1B].

- Hemodynamically stable patients and “borderline” patients can be safely managed by early definitive pelvic fracture fixation within 24 h post injury [Grade 2A].

- Definitive pelvic fracture fixation should be postponed until after day 4 post injury in physiologically deranged polytrauma patients [Grade 2A].
The timing of definitive internal fixation of unstable pelvic ring injuries remains a topic of debate [138–145]. Most authors agree that patients in severe traumatic-hemorrhagic shock from bleeding pelvic ring disruptions are unlikely candidates for early definitive pelvic fracture fixation, due to the inherent risk of increased mortality from exsanguinating hemorrhage and the “lethal triad” of coagulopathy, acidosis and hypothermia [22, 146]. A prospective multicenter cohort study revealed a significantly increased extent of blood loss and increased interleukin (IL-6 and IL-8) serum levels, reflective of an exacerbated systemic inflammatory response, in politrauma patients who underwent early pelvic fracture fixation on the first or second day post injury [147]. The early timing and short duration of initial pelvic stabilization revealed to have a positive impact on decreasing the incidence of multiple organ failure (MOF) and mortality [148]. Furthermore, post-injury complication rates were shown to be significantly increased when definitive pelvic ring fixation was performed between days 2 and 4, and decreased when surgery was delayed to days 6 to 8 post injury [149]. Many authors concur with the traditional concept of initial “damage control” external fixation of hemodynamically unstable pelvic ring injuries, and delayed definitive internal fixation after day 4, subsequent to successful resuscitative measures [28, 41, 58, 95, 118, 150–152]. The use of such definitions and classification systems can provide guidance for future stratification of unstable politrauma patients with pelvic ring injuries requiring “damage control” resuscitative measures compared to stable or “borderline” patients who may be safely amenable to early total care by definitive pelvic fracture fixation [141, 146]. In this regard, multiple observational cohort studies from the orthopedic trauma group at MetroHealth in Cleveland have shown that early pelvic fracture fixation in stable or borderline resuscitated patients within 24 h of admission reduces the risk of complications and improves outcomes [139, 141, 144, 145]. Recently, a new definition of politrauma has been proposed by an international consensus group, which is based on injury severity and derangement of physiological parameters [153]. This new politrauma definition in conjunction with recently established grading systems [141] may provide further guidance towards the “ideal” timing of definitive pelvic fracture fixation, pending future validation studies.

**Damage Control Orthopedics in Severe Head Injuries**

Severe head injuries are common in politrauma patients with concomitant pelvic injuries. No definitive guidelines exist regarding severe head injuries and pelvic fixation. One of the main issues is that pelvic fracture associated bleeding and consequent coagulopathy leads to a deterioration of the head injury through secondary bleeding and subsequent progression of hemorrhagic contusions in a risky vicious circle. For these reasons the acute definitive hemorrhage control and prevention and prompt reversal of coagulopathy is essential. Careful monitoring of brain injuries, potential early re-scanning with perfusion CT-scan is helpful. In the major part of the trauma centers patients are treated according to the indications of the neurosurgery team [150]. On one hand several articles suggested that early fracture fixation might be deleterious in patients with brain injury especially if old-aged, on the other hand however some trials didn’t confirm these concerns suggesting that outcomes are worse in patients who do not have early skeletal stabilization [44, 154–156]. Usually neurosurgeons are very concerned for the possible additional brain injury deriving from blood pressure fluctuations during orthopedic fixative surgery [150]. This in general leads to several doubts and additional delay to let the patients being considered suitable for operating room [150]. The potential benefit of damage control orthopedics interventions and the minimal physiologic insult of placing an external fixator allows for almost all patients with closed head injuries to be appropriate for at least external fixation [150]. However no definitive indications can be obtained from the literature.

**Morbidity, mortality and outcomes**

Complications with important functional limitations are present especially in patients with open PT who may have chronic sequelae as fecal and urinary incontinence, impotence, dyspareunia, residual disability in physical functions, perineal and pelvic abscess, chronic pain and vascular complications as embolism or thrombosis [1, 3].

The majority of deaths (44.7%) occurred on the day of trauma and the main factors that correlate with mortality are increasing age, ISS, pelvic ring instability, size and contamination of the open wound, rectal injury, fecal diversion, numbers of blood units transfused, head Abbreviated Injury Scale (AIS), admission base deficit [3, 5].

Lastly, a recent study reported the impact given by the multidisciplinary approach resulting in an improvement in performance and in patient outcomes [5]. At first a defined decision making algorithm reduce significantly \( p = 0.005 \) the time from hospital arrival and bleeding control in the theatre with PPP [5]. Furthermore the definition of a massive hemorrhage protocol reduced significantly the use of liquids administered prior blood transfusions and rationalized the use of packed red cells and fresh frozen plasma (ratio 2:1) starting within the first hours following injury [5]. Moreover a dedicated pelvic orthopedic surgeons can improve \( p = 0.004 \) the number of patients that undergoing definitive unstable pelvic fractures repair with a consequently improvement in outcome [5]. Similar data about the importance of the
adherence to defined guidelines have been reported by Balogh et al. [16] and recently confirmed by the multi-institutional trial by Costantini et al. [10].

Conclusions

the management of pelvic trauma must keep into consideration the physiological and mechanical derangement. Critical and operative decisions can be taken more effectively if both anatomy of injury and its physiological and mechanical effects are considered.

Abbreviations

ABO: Aortic Balloon Occlusion; AE: Angiembolization; AG: Angiography; AIF: Abbreviated Injury Score; APP: Anterior Posteriour Compression; ATLS: Advanced Trauma Life Support; BD: Base Deficit; BPA: Beat Per Minute; CM: Combined Mechanism; CT: Computed Tomography; DSA: Digital Subtraction Angiography; ED: Emergency Department; E-FAST: Extended Focused Assessment with Sonography for Trauma; ETV/M: Endovascular Trauma Management; ICU: Intensive Care Unit; IREBOA: Intermittent Resuscitative Endo Vascular Balloon Occlusion; ISS: Injury Severity Score; LC: Lateral Compression; LE: Level of Evidence; MOP: Multi-Organ Failure; NOM: Non-Operative Management; OM: Operative Management; PB: Pelvic Binder; PPI: Pre-peritoneal Pelvic Packing; PREBOA: Partial Resuscitative Endo Vascular Balloon Occlusion; PT: Pelvic Trauma; PXR: Pelvic X-ray; RCT: Randomized Controlled Trial; RIEBOA: Resuscitative Endo Vascular Balloon Occlusion; RTOM: Rotational Thromboelastometry; RUG: Retrograde Urethrogram; TEG: Thromboelastography; VS: Vertical Shear; WSES: World Society of Emergency Surgery

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Competing interest

All authors declare to have no competing interests.

Consent for publication

Not applicable.

Ethics Approval and Consent to Participate

Not applicable.

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Abstract

Damage control resuscitation may lead to postoperative intra-abdominal hypertension or abdominal compartment syndrome. These conditions may result in a vicious, self-perpetuating cycle leading to severe physiologic derangements and multiorgan failure unless interrupted by abdominal (surgical or other) decompression. Further, in some clinical situations, the abdomen cannot be closed due to the visceral edema, the inability to control the compelling source of infection or the necessity to re-explore (as a “planned second-look” laparotomy) or complete previously initiated damage control procedures or in cases of abdominal wall disruption. The open abdomen in trauma and non-trauma patients has been proposed to be effective in preventing or treating deranged physiology in patients with severe injuries or critical illness when no other perceived options exist. Its use, however, remains controversial as it is resource consuming and represents a non-anatomic situation with the potential for severe adverse effects. Its use, therefore, should only be considered in patients who would most benefit from it. Abdominal fascia-to-fascia closure should be done as soon as the patient can physiologically tolerate it. All precautions to minimize complications should be implemented.

Keywords: Open abdomen, Laparostomy, Non-trauma, Trauma, Peritonitis, Pancreatitis, Vascular emergencies, Intra-abdominal infection, Fistula, Nutrition, Re-exploration, Reintervention, Closure, Biological, Synthetic, Mesh, Technique, Timing, Guidelines
Background
Damage control management (DCM) of severely injured or physiologically deranged patients is considered by many to consist of damage control resuscitation (DCR) and damage control surgery (DCS). Use of DCM in patients with deranged physiology may trigger intra-abdominal hypertension (IAH) or abdominal compartment syndrome (ACS) that may aggravate physiologic derangement or multiorgan failure (MOF) in a vicious circle unless interrupted by abdominal decompression (surgical or other) [1, 2]. Further, in other clinical situations, the abdomen cannot be closed due to visceral edema, the inability to completely control the compelling source of infection or to the necessity to re-explore (in a “planned re-look laparotomy”) or to complete DCS procedures or in cases of abdominal wall damage. Although open abdomen (OA) has been proposed to be effective in preventing or treating deranged physiology in patients with severe injuries or critical illness, it must be recognized as a non-anatomic situation that has potential for severe side effects while increasing resource utilization [3].

The World Society for Emergency Surgery (WSES) accepted the definitions of IAH, ACS, and related conditions published by the World Society Abdominal Compartment Syndrome in 2013 (WSACS) [2–4] (Fig. 1).

OA management consists of intentionally leaving the abdominal fascial edges of the paired rectus abdominis muscles un-approximated (laparostomy) in order to truncate operation, prevent IAH/ACS, and facilitate re-exploration without damaging the abdominal fascia [3]. Temporary abdominal closure (TAC) refers to the method for providing protection to the abdominal viscera during the time the fascia remains open [2, 5]. Patients undergoing OA management are at risk of developing entero-atmospheric fistula (EAF) and a “frozen abdomen,” intra-abdominal abscesses, and lower rates of definitive fascial closure [6, 7]. The risk-benefit ratio must be kept in mind in using OA. It should not be performed liberally. Measures to mitigate complications are necessary. In all patients with an OA, every effort should be exerted to achieve primary fascial closure (i.e., fascia-to-fascia closure of the abdominal wall within the index hospitalization) as soon as the patient can physiologically tolerate it [3].

Purpose and use of this guideline
The guidelines are evidence-based, with the grades of recommendation, based on the evidence. These guidelines present methods for optimal management of open abdomen in trauma and non-trauma patients. They do not represent a standard of practice. They are suggested plans of care, based on best available evidence and a consensus of experts. They, however, do not exclude other approaches as being within a standard of practice. For example, they should not be used to compel adherence to a given method of medical management, which should be finally determined after taking into account conditions at the relevant medical institution (staff levels, experience, equipment, etc.) and the characteristics of the individual patient. The responsibility for the results, however, rests with the engaging practitioners and not aged therein, and not the consensus group.

Methods
A computerized search was performed in MEDLINE, EMBASE, and Scopus by an information scientist/librarian for the time range of January 1980 to August 2017. The terms open abdomen, laparostomy, injuries, trauma, peritonitis, pancreatitis, vascular, ischemia, resuscitation, adult, management, infection, intensive care unit, anastomosis, vasopressors, and follow-up in various combinations with the use of the Boolean operators “AND” and “OR” were used. No search restrictions were imposed. The dates were selected to allow comprehensive published abstracts of clinical trials, consensus conferences, comparative studies, congresses, guidelines, government publications, multicenter studies, systematic reviews, meta-analyses, large case series, original articles, and randomized controlled trials. Case reports and small case series were excluded. We also analyzed the reference lists of relevant narrative review articles identified during the search to identify any studies that may have been missed.

For each article, we subsequently applied a level of evidence (LE) using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [8] (Table 1). The full GRADE process was not used, as this system is difficult to apply when scant evidence exists. A group of experts in the field of OA management, coordinated by a central coordinator, were subsequently convened in order to elicit their evidence-based opinions on certain key clinical questions relating to the OA. Through a Delphi process, the clinical questions were discussed in rounds.

<table>
<thead>
<tr>
<th>IAH grade</th>
<th>IAP [mmHg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>12 - 15</td>
</tr>
<tr>
<td>Grade II</td>
<td>16 - 20</td>
</tr>
<tr>
<td>Grade III</td>
<td>21 - 25</td>
</tr>
<tr>
<td>Grade IV</td>
<td>&gt; 25</td>
</tr>
<tr>
<td>ACS</td>
<td>&gt; 20 with new organ disfunction/failure</td>
</tr>
</tbody>
</table>

Fig. 1 WSACS grading of intra-abdominal hypertension (IAH) (IAP intra-abdominal pressure, ACS abdominal compartment syndrome) [4]
The central coordinator assembled the different answers derived from each round. Each version was then revised and improved through iterative evaluation. The final version about which the agreement was reached resulted in the comments and recommendations made in the present guideline. Statements have been summarized in Table 2.

**Indications**

**Trauma patients**

*Persistent hypotension, acidosis (pH < 7.2), hypothermia (temperature < 34°C) and coagulopathy are strong predictors of the need for abbreviated laparotomy and open abdomen in trauma patients (Grade 2A)*

*Risk factors for abdominal compartment syndrome such as damage control surgery, injuries requiring packing and planned reoperation, extreme visceral or retroperitoneal swelling, obesity, elevated bladder pressure when abdominal closure is attempted, abdominal wall tissue loss and aggressive resuscitation are predictors of the necessity for open abdomen in trauma patients (Grade 2B)*

*Decompressive laparotomy is indicated in abdominal compartment syndrome if medical treatment has failed after repeated and reliable IAP measurements (Grade 2B)*

*The inability to definitively control the source of contamination or the necessity to evaluate bowel perfusion may be an indicator to leave the abdomen open in post-traumatic bowel injuries (Grade 2B)*

Severely injured patients with hemodynamic instability are at higher risk of ACS for several reasons (i.e., aggressive resuscitation, ischemia-reperfusion injury, visceral or retroperitoneal swelling, recurrent bleeding, and intraperitoneal packing) [9–12].
**Table 2** Summary of statements

<table>
<thead>
<tr>
<th>Indications</th>
<th>Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma patients</strong></td>
<td>Persistent hypotension, acidosis (pH &lt; 7.2), hypothermia (temperature &lt; 34°C) and coagulopathy are strong predictors of the need for abbreviated laparotomy and open abdomen in trauma patients (Grade 2A)</td>
</tr>
<tr>
<td></td>
<td>Risk factors for abdominal compartment syndrome such as damage control surgery, injuries requiring packing and planned reoperation, extreme visceral or retroperitoneal swelling, obesity, elevated bladder pressure when abdominal closure is attempted, abdominal wall tissue loss and aggressive resuscitation are predictors of the necessity for open abdomen in trauma patients (Grade 2B)</td>
</tr>
<tr>
<td></td>
<td>Decompressive laparotomy is indicated in abdominal compartment syndrome if medical treatment has failed after repeated and reliable IAP measurements (Grade 2B)</td>
</tr>
<tr>
<td></td>
<td>The inability to definitively control the source of contamination or the necessity to evaluate the bowel perfusion may be an indicator to leave the abdomen open in post-traumatic bowel injuries (Grade 2B)</td>
</tr>
<tr>
<td><strong>Non-trauma patients</strong></td>
<td>Decompressive laparotomy is indicated in abdominal compartment syndrome if medical treatment has failed after repeated and reliable IAP measurements (Grade 2B)</td>
</tr>
<tr>
<td><strong>➢ Peritonitis</strong></td>
<td>The open abdomen is an option for emergency surgery patients with severe peritonitis and severe sepsis/septic shock under the following circumstances: abbreviated laparotomy due to the severe physiological derangement, the need for a deferred intestinal anastomosis, a planned second look for intestinal ischemia, persistent source of peritonitis (failure of source control), or extensive visceral oedema with the concern for development of abdominal compartment syndrome (Grade 2C).</td>
</tr>
<tr>
<td><strong>➢ Vascular emergencies</strong></td>
<td>The open abdomen should be considered following management of hemorrhagic vascular catastrophes such as ruptured abdominal aortic aneurysm (Grade 1C)</td>
</tr>
<tr>
<td></td>
<td>The open abdomen should be considered following surgical management of acute mesenteric ischemic insults (Grade 2C).</td>
</tr>
<tr>
<td><strong>➢ Pancreatitis</strong></td>
<td>In patients with severe acute pancreatitis unresponsive to step-up conservative management surgical decompression and open abdomen are effective in treating abdominal compartment syndrome (Grade 2C).</td>
</tr>
<tr>
<td></td>
<td>Leaving the abdomen open after surgical necrosectomy for infected pancreatic necrosis is not recommended except in those situations with high risk factors to develop abdominal compartment syndrome (Grade 1C)</td>
</tr>
</tbody>
</table>

**Management**

<table>
<thead>
<tr>
<th>Trauma and non-trauma patients</th>
<th>The role of Damage Control Resuscitation in OA management is fundamental and may influence outcome (Grade 2A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU management</td>
<td>A multidisciplinary approach is encouraged, especially during the patient's ICU admission (Grade 2A)</td>
</tr>
<tr>
<td></td>
<td>Intra-abdominal pressure measurement is essential in critically ill patients at risk for IAH/ACS (Grade 1B)</td>
</tr>
<tr>
<td></td>
<td>Physiologic optimization is one of the determinants of early abdominal closure (Grade 2A)</td>
</tr>
<tr>
<td></td>
<td>Inotropes and vasopressors administration should be tailored according to patient condition and performed surgical interventions (Grade 1A)</td>
</tr>
<tr>
<td></td>
<td>Fluid balance should be carefully scrutinized (Grade 2A)</td>
</tr>
<tr>
<td></td>
<td>High attention to body temperature should be given, avoiding hypothermia (Grade 2A)</td>
</tr>
<tr>
<td></td>
<td>In presence of coagulopathy or high risk of bleeding the negative pressure should be down regulated balancing the therapeutic necessity of negative pressure and the hemorrhage risk (Grade 2B).</td>
</tr>
<tr>
<td>Technique for temporary abdominal closure</td>
<td>Negative pressure wound therapy with continuous fascial traction should be suggested as the preferred technique for temporary abdominal closure (Grade 2B).</td>
</tr>
<tr>
<td></td>
<td>Temporary abdominal closure without negative pressure (e.g., Bogota bag) can be applied in low resource settings accepting a lower delayed fascial closure rate and higher intestinal fistula rate (Grade 2A).</td>
</tr>
<tr>
<td></td>
<td>No definitive recommendations can be given about temporary abdominal closure with NPWT in combination with fluid instillation even if it seems to improve results in trauma patients (Not grades).</td>
</tr>
<tr>
<td>Re-exploration before definitive closure</td>
<td>Open abdomen re-exploration should be conducted no later than 24-48 hours after the index and any subsequent operation, with the duration from the previous operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (Grade 1C).</td>
</tr>
<tr>
<td></td>
<td>The abdomen should be maintained open if requirements for on-going resuscitation and/or the source of contamination persists, if a deferred intestinal anastomosis is needed, if there is the necessity for a planned second look for ischemic intestine and lastly if there are concerns about abdominal compartment syndrome development (Grade 2B).</td>
</tr>
<tr>
<td>Nutritional support</td>
<td>Open abdomen patients are in a hyper-metabolic condition; immediate and adequate nutritional support is mandatory (Grade 1C).</td>
</tr>
<tr>
<td></td>
<td>Open abdomen techniques result in a significant nitrogen loss that must be replaced with a balanced nutrition regimen (Grade 1C).</td>
</tr>
</tbody>
</table>
In fact, the post-traumatic physiological derangements and the consequent DCM expose patients at risk for increased intra-abdominal pressure. Risk factors associated with ACS requiring an OA after trauma, indicating a higher need for OA, are acidosis with $\text{pH} \leq 7.2$, lactate levels $\geq 5 \text{ mmol/L}$, base deficit (BD) $\geq -6$ in patients older than 55 years or $\geq -15$ in patients younger than 55 years, core temperature $\leq 34^\circ \text{C}$, systolic pressure $\leq 90$, severe hypovolemic shock, and patients with a hematocrit $\leq 25$

### Table 2 Summary of statements (Continued)

<table>
<thead>
<tr>
<th>Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early enteral nutrition should be started as soon as possible in presence of viable and functional gastrointestinal tract (Grade 1C).</td>
</tr>
<tr>
<td>Enteral nutrition should be delayed in patients with an intestinal tract in discontinuity (temporarily stapled stumps), or in situations of a high output fistula with no possibility to obtain feeding access distal to the fistula or with signs of intestinal obstruction (Grade 2C).</td>
</tr>
<tr>
<td>Oral feeding is not contraindicated and should be used where possible (Grade 2C).</td>
</tr>
<tr>
<td><strong>Definitive closure</strong></td>
</tr>
<tr>
<td><strong>Trauma and non-trauma patients</strong></td>
</tr>
<tr>
<td><strong>Open abdomen definitive closure</strong></td>
</tr>
<tr>
<td>Early fascial and/or abdominal definitive closure should be the strategy for management of the open abdomen once any requirements for on-going resuscitation have ceased, the source control has been definitively reached, no concern regarding intestinal viability persist, no further surgical re-exploration is needed and there are no concerns for abdominal compartment syndrome (Grade 1B).</td>
</tr>
<tr>
<td><strong>Non-mesh-mediated techniques</strong></td>
</tr>
<tr>
<td>Primary fascia closure is the ideal solution to restore the abdominal closure (2A).</td>
</tr>
<tr>
<td>Component separation is an effective technique; however it should not be used for fascial temporary closure. It should be considered only for definitive closure (Grade 2C).</td>
</tr>
<tr>
<td>Planned ventral hernia (skin graft or skin closure only) remains an option for the complicated open abdomen (i.e. in the presence of entero-atmospheric fistula or in cases with a protracted open abdomen due to underlying diseases) or in those settings where no other alternatives are viable (Grade 2C).</td>
</tr>
<tr>
<td><strong>Mesh-mediated techniques</strong></td>
</tr>
<tr>
<td>The use of synthetic mesh (polypropylene, polytetrafluoroethylene (PTFE) and polyester products) as a fascial bridge should not be recommended in definitive closure interventions after open abdomen and should be placed only in patients without other alternatives (Grade 1B).</td>
</tr>
<tr>
<td>Biologic meshes are reliable for definitive abdominal wall reconstruction in the presence of a large wall defect, bacterial contamination, comorbidities and difficult wound healing (Grade 2B).</td>
</tr>
<tr>
<td>Non–cross-linked biologic meshes seem to be preferred in sublay position when the linea alba can be reconstructed. (Grade 2B).</td>
</tr>
<tr>
<td>Cross-linked biologic meshes in fascial-bridge position (no linea alba closure) maybe associated with less ventral hernia recurrence (Grade 2B).</td>
</tr>
<tr>
<td>NPWT can be used in combination with biologic mesh to facilitate granulation and skin closure (Grade 2B).</td>
</tr>
<tr>
<td><strong>Complications management</strong></td>
</tr>
<tr>
<td><strong>Trauma and non-trauma patients</strong></td>
</tr>
<tr>
<td>Preemptive measures to prevent entero-atmospheric fistula and frozen abdomen are imperative (i.e. early abdominal wall closure, bowel coverage with plastic sheets, omentum or skin, no direct application of synthetic prosthesis over bowel loops, no direct application of NPWT on the viscera and deep burying of intestinal anastomoses under bowel loops) (Grade 1C).</td>
</tr>
<tr>
<td>Entero-atmospheric fistula management should be tailored according to patient conditions, fistula output and position and anatomical features (Grade 1C).</td>
</tr>
<tr>
<td>In the presence of entero-atmospheric fistula the caloric intake and protein demands are increased; the nitrogen balance should be evaluated and corrected and protein supplemented (Grade 1C).</td>
</tr>
<tr>
<td>Nutrition should be reviewed and optimized upon recognition of entero-atmospheric fistula (Grade 1C).</td>
</tr>
<tr>
<td>Entero-atmospheric fistula effluent isolation is essential for proper wound healing. Separating the wound into different compartments to facilitate the collection of fistula output is of paramount importance (Grade 2A).</td>
</tr>
<tr>
<td>In the presence of entero-atmospheric fistula in open abdomen, negative pressure wound therapy makes effluent isolation feasible and wound healing achievable (Grade 2A).</td>
</tr>
<tr>
<td>Definitive management of entero-atmospheric fistula should be delayed to after the patient has recovered and the wound completely healed (Grade 1C).</td>
</tr>
</tbody>
</table>
70 mmHg, estimated blood loss ≥ 4 L during the operation and/or transfusion requirement ≥ 10 U of packed red blood cells in the pre- or pre- and intraoperative settings, and severe coagulation derangements (INR/PT > 1.5 times normal, with or without a concomitant PTT > 1.5 times normal) [10, 13–17].

Other recognized risk factors for IAH should be kept into consideration: obesity, pancreatitis, hepatic failure/cirrhosis, positive end-expiratory pressure > 10 cm H₂O, respiratory failure, acute respiratory distress syndrome [18].

All non-surgical treatment should be implemented to prevent or reduce IAH before proceeding to surgical decompression (i.e., nasogastric and colonic decompression, prokinetic agents, adequate patient positioning and avoidance of constrictive dressings, eventual escharotomy and percutaneous decompression, adequate mechanical ventilation, analgesia, sedation and neuromuscular blockade, balanced fluid resuscitation, eventual diuretic therapy and continuous veno-venous hemofiltration/ultrafiltration, and vasoactive medications).

Moreover, failure to definitively control the source of infection at the index operation or the necessity to check bowel perfusion during DCM or abdominal wall tissue loss represents indications to OA management in traumatic abdominal injuries [3, 11].

**Non-trauma patients**

*Decompressive laparotomy is indicated in abdominal compartment syndrome if medical treatment has failed after repeated and reliable IAP measurements (Grade 2B)*

**Peritonitis**

*The open abdomen is an option for emergency surgery patients with severe peritonitis and severe sepsis/septic shock under the following circumstances: abbreviated laparotomy due to severe physiological derangement, the need for a deferred intestinal anastomosis, a planned second look for intestinal ischemia, persistent source of peritonitis (failure of source control), or extensive visceral oedema with the concern for development of abdominal compartment syndrome (Grade 2C).*

Some patients suffering from severe peritonitis may experience a disease progression to septic shock with no room for definitive surgical procedures [3, 19]. In these cases, surgical operation should be abbreviated even in advanced age [20]. In hypotensive patients requiring high-dose vasopressors or inotropes infusion intestinal continuity restoration may be deferred [21]. In incomplete source control or in the presence of visceral edema and/or decreased abdominal wall compliance primary complete fascia closure should not be attempted because of the high risk of IAH/ACS [22]. In all these situations, the abdomen may be left open. However, there is no definitive data regarding the use of the OA in the face of severe peritonitis and therefore, caution should be exercised when using OA in these circumstances.

**Vascular emergencies**

*The open abdomen should be considered following management of hemorrhagic vascular catastrophes such as ruptured abdominal aortic aneurysm (Grade 1C)*

*The open abdomen should be considered following surgical management of acute mesenteric ischemic insults (Grade 2C).*

Up to 20% of patients experiencing a ruptured AAA repair develop ACS. Mortality is high (30–50%) and is almost doubled in presence of ACS [23, 24]. OA reduces the ACS incidence [25]. No definitive indications to OA exist; the relative indications to OA are massive resuscitation, deranged physiology, fascial tension at closure, use of balloon occlusion of the aorta, and blood loss > 5 L [25–27].

Advanced age is not a contraindication to DCM [20]. ACS can occur even after endovascular repair (EVAR), and the major risk factor appears to be massive resuscitation [23]. Risk of graft infection due to OA management has been demonstrated to be low [28].

The use of OA after perfusion restoration in a patient with acute mesenteric ischemia as in occlusive proximal or distal superior mesenteric artery emboli, watershed necrosis after AAA repairs (open or endovascular), and non-occlusive mesenteric ischemia (e.g., post-arrest or resuscitation from shock/arrest) should be considered in case of deranged physiology and bowel edema and necessity to perform a second look or delayed anastomosis [29–31].

Mesenteric venous thrombosis requiring laparotomy does not routinely mandate OA as often as mesenteric ischemia [32]; however, the risk of IAH/ACS imposes attention to IAP.

**Pancreatitis**

*In patients with severe acute pancreatitis unresponsive to step-up conservative management surgical decompression and open abdomen open are effective in treating abdominal compartment syndrome (Grade 2C)*

*Leaving the abdomen open after surgical necrosectomy for infected pancreatic necrosis is not recommended except in those situations with high risk factors to develop abdominal compartment syndrome (Grade 1C)*
MOF is the factor mainly associated with mortality in acute pancreatitis (AP) especially when infected necrosis [33–37] is present. As in many other conditions, secondary IAH/ACS may aggravate MOF in a vicious circle [38]. IAH/ACS should be prevented and treated as far as it is possible with non-surgical measures. Surgical decompression is the last but effective tool; it should not be delayed in case of ACS [4, 39]. Pancreatic necrosis may become infected after the first week [40]. The presence of organ failure, early bacteremia, and the extent of pancreatic necrosis are factors associated with infection [40]. Surgical necrosectomy should be considered when more conservative management as percutaneous drainage fails [41]. In case of necrosectomy, OA may be considered, but it is not mandatory. It should be considered only if risks for IAH/ACS exist.

Management

Trauma and non-trauma patients

ICU management

The role of Damage Control Resuscitation in OA management is fundamental and may influence outcome (Grade 2A)

A multidisciplinary approach is encouraged, especially during the patient's ICU admission (Grade 2A)

Intra-abdominal pressure measurement is essential in critically ill patients at risk for IAH/ACS (Grade 1B)

Physiologic optimization is one of the determinants of early abdominal closure (Grade 2A)

Inotropes and vasopressors administration should be tailored to patient's condition and performed surgical interventions (Grade 1A)

Fluid balance should be carefully scrutinized (Grade 2A)

High attention to body temperature should be given, avoiding hypothermia (Grade 2A)

In presence of coagulopathy or high risk of bleeding the negative pressure should be down regulated balancing the therapeutic necessity of negative pressure and the hemorrhage risk (Grade 2B).

The initial management is fundamental. DCR is part of DCM utilized in treating severely injured and severely physiologically deranged patients. It passes through some cornerstone actions as volume resuscitation, reversal of coagulopathy, correction of acidosis, and all the other pertinent resuscitative measures aiming to restore the normal physiology. The fluid status, nutrition, and respiratory mechanics should also be kept into consideration in managing OA. In fact the possibility of recurrent ACS with its related high mortality is to be posed into consideration [42–44].

Abdominal pressure should be measured in all patients at risk of developing IAH/ACS; in fact, it has been demonstrated that clinical examination is inaccurate in diagnosing IAH/ACS [45]. As a general principle, it should be measured every 12 h and every 4–6 h once ACS/IAH has been detected or if organ failure happens. Physiology optimization is necessary to allow early abdominal closure. In fact, prolonged OA may delay extubation, increase the risk for EAF and frozen abdomen, and increase complications [46].

Multidisciplinary collaboration with all teams managing the patient is required for optimal care of OA patients. The real extent of heat loss in OA and a temporary abdominal dressing cannot be quantified. It is well known that patient physiology is impaired by hypothermia and its related hypo-perfusion effects such as heart function depression, reduced oxygen delivery, coagulation cascade alteration, and acidosis.

In trauma patients, the “lethal triad” should be rapidly interrupted [47–53]. It is well known that mortality increases in trauma patients with significant core-body temperature drop [54]. Commercial NPWT systems significantly reduce heat loss but the non-commercial ones still maintain a reduced heat isolation capacity. For this reason, the heat loss control is of paramount importance especially in those settings where non-commercial systems are utilized.

During ICU stay, it is important to ensure analgesia over hypnosis and consider multimodal analgesia to reduce opioid infusion, trying to keep the patient “awake” but well adapted to mechanical ventilation. Moreover, protective mechanical ventilation strategies should be adopted. Fluid balance is important as well in OA management and should be carefully scrutinized to avoid over- or under- resuscitation. Careful monitoring and maintenance of adequate urinary output could help in evaluating adequacy of resuscitation effects. Continuous monitoring of cardiac output (CO), targeting at low/normal values, is essential to avoid fluid overload and vasopressor abuse. If increasing vasopressors induce low CO, and fluid responsiveness is transient, consider to target treatments (included inotropes) to the best compromise between MAP, CO, and fluid amount. High-rate maintenance fluid infusions should be avoided. As a counterpart, whenever possible, frequent, small-volume fluid boluses
should be preferred. Hypertonic crystalloid and colloid-based resuscitation seem to decrease the risk of iatrogenic, induce resuscitation, and increase IAP [55]. Daily patient weights may help in evaluating fluid retention.

Inotrope infusion should be balanced keeping in mind the patients’ condition, the performed surgical procedures, and the necessity to prevent further complications due to their overuse [56, 57].

Volumetric-based monitoring technologies can be very useful in hemodynamic evaluation during DCR phases in critically ill patients. In fact, the elevated intra-abdominal and intra-thoracic pressure can impair the real value of the measurements obtained with traditional pressure-based parameters such as pulmonary artery occlusion pressure and central venous pressure [58–60]. The alteration of these parameters can potentially lead to wrong decisions as regards the correct fluid status and as a consequence the necessary amount of fluid to be administered. This balance is essential also to optimize the surgical success of primary fascial closure [12, 61, 62].

**Technique for temporary abdominal closure**

Negative pressure wound therapy with continuous fascial traction should be suggested as the preferred technique for temporary abdominal closure (Grade 2B).

Temporary abdominal closure without negative pressure (e.g. Bogota bag) can be applied in low resource settings accepting a lower delayed fascial closure rate and higher intestinal fistula rate (Grade 2A).

No definitive recommendations can be given about temporary abdominal closure with NPWT in combination with fluid instillation even if it seems to improve results in trauma patients (Not graded).

Several strategies to maintain the OA have been described. They result in different delayed fascial closure rate and EAF risk. In general, negative pressure associated to a dynamic component (mesh-mediated fascial traction or dynamic sutures) allows to reach the best results in terms of delayed fascial closure, but dynamic sutures result more often in fistula [3]. Negative pressure without a dynamic component (Barker’s VAC or commercial products) results in a moderate delayed fascial closure rate and a fistula rate similar to mesh closure without negative pressure [3].

Recent data from the International Register of Open Abdomen (IROA study) showed that different techniques of OA resulted in different results according to the treated disease [63] (trauma and severe peritonitis) and if treated with or without negative pressure in terms of abdominal closure and mortality rate. The results favored the non-negative pressure systems in trauma and negative pressure temporary closure in severe peritonitis patients [46]. Also, recent contradictory data from a single-center RCT showed that NPWT and fluid instillation seemed to improve outcomes in trauma patients in terms of early and primary closure [64].

Another important issue in OA management is the necessity to balance the antimicrobial therapy in relation to positive cultures of intra-abdominal fluids. Two options are generally followed without any strong literature evidence: treating all the cultured organisms (with high proportions of staphylococci, candida, and MDR Gram-negative bacilli including *Pseudomonas*) or a “wait and see” strategy. WSES suggests to follow guidelines for intra-abdominal infections [65].

### Re-exploration before definitive closure

Open abdomen re-exploration should be conducted no later than 24-48 hours after the index and any subsequent operation, with the duration from the previous operation shortening with increasing degrees of patient non-improvement and hemodynamic instability (Grade 1C).

The abdomen should be maintained open if requirements for on-going resuscitation and/or the source of contamination persists, if a deferred intestinal anastomosis is needed, if there is the necessity for a planned second look for ischemic intestine and lastly if there are concerns about abdominal compartment syndrome development (Grade 2B).

Indications to re-explore an OA may vary between trauma and non-trauma patients. In general, the patient’s non-improvement possibly is due to an intra-abdominal reason. No definitive data regarding the timing of re-operation in OA patients exist [6, 66]. It is generally recommended that OA patients should be re-explored 24–72 h after the initial or any subsequent surgical intervention [2, 67, 68]. Some data regarding trauma patients showed that the time of re-exploration reduces the primary fascial closure rate of 1.1% for each hour after the first 24 h after the index operation [69]. Moreover, increased complication rate was observed in patients having the first re-operation after 48 h [3, 69].

In non-trauma patients, the indication to re-explore the abdominal cavity are less definite and usually are due to the necessity to continue DCM, to the impossibility to definitively control the source of infection or to the necessity to re-asses the bowel vascularization or lastly, to concerns regarding the possibility of ACS [2, 3, 20, 70].
Even though there is some evidence that OA may be justified in severely injured or physiologically deranged patients with the aim to manipulate the systemic immune response and ameliorate the biomediator burden, no definitive statement can be made [3, 71–75].

**Nutritional support**

*Open abdomen patients are in a hyper-metabolic condition; immediate and adequate nutritional support is mandatory (Grade 1C).*

*Open abdomen techniques result in a significant nitrogen loss that must be replaced with a balanced nutrition regimen (Grade 1C).*

*Early enteral nutrition should be started as soon as possible in the presence of viable and functional gastrointestinal tract (Grade 1C).*

*Enteral nutrition should be delayed in patients with an intestinal tract in discontinuity (temporarily closed loops), or in situations of a high output fistula with no possibility to obtain feeding access distal to the fistula or with signs of intestinal obstruction (Grade 2C).*

*Oral feeding is not contraindicated and should be used where possible (Grade 2C).*

Malnutrition is a risk factor for poor outcomes [76]. Critically ill patients with OA are in a hyper-catabolic state with an estimated nitrogen loss of almost 2 g/L of abdominal fluid output. Abdominal fluid evacuation is to be measured in order to adjust nutritional integrations [77]. In case of EAF, nitrogen loss greatly increases. Parenteral nutrition should be started as soon as possible. Once the resuscitation is almost complete and the GI tract is viable, enteral nutrition (EN) should be started. Relative contraindication to EN is a viable bowel shorter than 75 cm [78].

Polymeric formula supplying a daily intake of 20- to 30-kcal/kg non-protein calories with 1.5- to 2.5-g/kg proteins is usually sufficient to maintain a positive nitrogen balance.

EN starting within the first 24–48 h improves wound healing and fascial closure rate, decreases catabolism, reduces pneumonia and fistula rate, preserves GI tract integrity, and finally reduces complications, length of hospital stay, and costs [79–81]. Compared to prolonged total parenteral nutrition, early EN decreases septic complications especially in abdominal trauma and traumatic brain injuries [3, 79, 82, 83].

**Patient mobilization**

*No recommendations can be made about early mobilization of patients with open abdomen (Not graded).*

No definite evidence exists regarding the optimal timing for mobilization of patients with OA [84]. Prolonged bed rest is associated with a significant increase in morbidity. Mobilization occurring within the first 2-5 days of ICU admission is defined “early” [85] and it is associated with positive effects on outcomes [86–90].

OA patients with NPWT may be “early” mobilized by active or passive transfer thanks to the provisional abdominal wall function supplied by NPWT systems [3].

**Definitive closure**

*Open abdomen definitive closure*

*Fascia and/or abdomen should be definitively closed as soon as possible (Grade 1C).*

*Early fascial and/or abdominal definitive closure should be the strategy for management of the open abdomen once any requirements for on-going resuscitation have ceased, the source control has been definitively reached, no concern regarding intestinal viability persist, no further surgical re-exploration is needed and there are no concerns for abdominal compartment syndrome (Grade 1B).*

The priority in order to reduce mortality, complications, and length of stay linked to the OA should be the early definitive abdominal closure [10, 91, 92]. Major factors influencing early definitive closure are postoperative ICU management and the TAC technique [93]. Early fascial closure is commonly defined as occurring within 4–7 days from the index operation [21]. In contrast to trauma patients, those affected by abdominal sepsis usually experience a lower rate of early fascial closure [94] even though continuous fascial traction seems to increase this rate [95]. Fascial closure should be attempted as soon as the source of infection is controlled [96].

Solutions to definitively close an open abdomen

In case of prolonged OA, fascia retraction and large abdominal wall defects requiring complex abdominal wall reconstruction may occur. In contaminated fields, the complication risk in abdominal wall definitive closure is increased [92, 97–99].
Techniques used to definitively close the abdomen are principally divided into non-mesh and mesh mediated.

Non-mesh-mediated closure techniques

Primary fascia closure is the ideal solution to restore the abdominal closure (2A).

Component separation is an effective technique; however it should not be used for fascial temporary closure. It should be considered only for definitive closure (Grade 2C).

Planned ventral hernia (skin graft or skin closure only) remains an option for the complicated open abdomen (i.e. in the presence of entero-atmospheric fistula or in cases with a protracted open abdomen due to underlying diseases) or in those settings where no other alternatives are viable (Grade 2C).

Abdominal component separation should be considered an elective procedure for ventral hernia repair [100]. In fact, it should not be used during the OA management but reserved to the definitive closure interventions. At a delayed time point, very good results reaching up to 75% of fascial closure rate have been reported [101]. The separation of components can be approached anteriorly or posteriorly [102, 103].

Planned ventral hernia represents a valid alternative to cover abdominal viscera and to prevent EAF. In fact, in cases of persistent contamination, several comorbidities or in severely ill patients, with or without sufficient skin to cover the abdominal wall defect, delaying the eventual synthetic prosthetic reconstruction may be a safer option. The decision either to close the skin or to perform vascularized flaps, pedicled flaps in small-/mid-sized defects, or free flaps such as tensor fasciae latae for extensive thoraco-abdominal defects is usually taken, considering the wound conditions, the dimension of the skin defect, and the center facilities [13].

Mesh-mediated closure techniques

The use of synthetic mesh (polypropylene, polytetrafluoroethylene (PTFE) and polyester products) as a fascial bridge should not be recommended in definitive closure interventions after open abdomen and should be placed only in patients without other alternatives (Grade 1B).

Biologic meshes are reliable for definitive abdominal wall reconstruction in the presence of a large wall defect, bacterial contamination, comorbidities and difficult wound healing (Grade 2B).

Non–cross-linked biologic meshes seem to be preferred in sublay position when the linea alba can be reconstructed. (Grade 2B).

Cross-linked biologic meshes in fascial-bridge position (no linea alba closure) maybe associated with less ventral hernia recurrence (Grade 2B).

NPWT can be used in combination with biologic mesh to facilitate granulation and skin closure (Grade 2B).

Several data exist regarding the abdominal wall closure after OA [104, 105]. Non-absorbable synthetic materials (i.e., polypropylene mesh) in a bridging position (i.e., no linea alba closure), where no native tissue protect viscera, may induce several local side effects (adhesions, erosions, and fistula formation) [106–111]. Synthetic meshes in contaminated fields are not recommended by guidelines in emergency abdominal wall reconstruction [112].

Biological prostheses (BP) were designed to perform as permanent surgical prosthesis in abdominal wall repair, minimizing mesh-related complications. Non-cross-linked biologic mesh is easily integrated, with reduced fibrotic reaction and lesser infection and removal rate [113].

BP can be used as a bridge for large abdominal wall defects [114–127]; however, the long-term outcome of a bridging non-cross-linked BP is laxity of the abdominal wall and a high rate of recurrent ventral hernia [113]. As a consequence, non-cross-linked BP should be used in a sublay position (i.e., with linea alba closure) and cross-linked ones should be preferred when the fascial bridge is needed [128–130]. BP could also tolerate adjunctive NPWT to facilitate wound healing, granulation, and skin closure [131–133].

Complication management

Preemptive measures to prevent entero-atmospheric fistula and frozen abdomen are imperative (i.e. early abdominal wall closure, bowel coverage with plastic sheets, omentum or skin, no direct application of synthetic prosthesis over bowel loops, no direct application of NPWT on the viscera and deep burying of intestinal anastomoses under bowel loops) (Grade 1C).

Entero-atmospheric fistula management should be tailored according to patient condition, fistula output and position and anatomical features (Grade 1C).
In the presence of entero-atmospheric fistula the caloric intake and protein demands are increased; the nitrogen balance should be evaluated and corrected and protein supplemented (Grade 1C).

Nutrition should be reviewed and optimized upon recognition of entero-atmospheric fistula (Grade 1C).

Entero-atmospheric fistula effluent isolation is essential for proper wound healing. Separating the wound into different compartments to facilitate the collection of fistula output is of paramount importance (Grade 2A).

In the presence of entero-atmospheric fistula in open abdomen, negative pressure wound therapy makes effluent isolation feasible and wound healing achievable (Grade 2A).

Definitive management of entero-atmospheric fistula should be delayed to after the patient has recovered and the wound completely healed (Grade 1C).

Risk factors for frozen abdomen and EAF in OA are delayed abdominal closure, non-protection of bowel loops during OA, presence of bowel injury and repairs or anastomosis, colon resection during DCS, the large fluid resuscitation volume (> 5 L/24 h), the presence of intra-abdominal sepsis/abscess, and the use of polypropylene mesh directly over the bowel [66, 134–139]. All risk factors often linked as a “vicious cycle” may contribute to the development of frozen abdomen and EAF. Complications increase mortality, length of stays, and costs [140]. Some preemptive measures to prevent this complication are early abdominal wall closure, bowel coverage with plastic sheets, omentum or skin, no direct application of synthetic prosthesis on bowel, no direct application of NPWT on the viscera, and intestinal anastomosis deep burying under bowel loops [73, 141, 142]. EAF can be classified based on the output: low (< 200 mL/day), moderate (200–500 mL/day), and high (> 500 mL/day) [143]; usually, the greater the output, the higher the difficulty in managing the EAF [144, 145]. In EAF management, the definition of characteristics and anatomical features are extremely important in planning the best treatment [146]. The intra-abdominal situation can be classified according to the WSACS classification (Fig. 2) [147]. Nutrition plays a pivotal role in EAF management. While early EN improves outcomes [81, 148–151], it may increase EAF output even if it seems not to impair final outcomes [152, 153]. Spontaneous closure of an EAF is quite impossible; for this reason, the treatment should try to isolate the fistula effluent to allow granulation tissue formation around [3]. Many different effective techniques have been described with no definitive results [138, 144, 145, 154–157]. NPWT in all its variants is effective and the most accepted technique [3]. It often allows EAF isolation, adequate wound management, re-epithelialization, and eventual subsequent skin graft with the final conversion of the EAF into a sort of enterostomy. EAF definitive treatment (i.e., fistula closure and abdominal wall reconstruction) should be postponed at least of 6 months and only after the patient and the wound healed completely [3].

Conclusions
Open abdomen in trauma and non-trauma patients is dramatically effective in facing the deranged

<table>
<thead>
<tr>
<th>BJORK CLASSIFICATION 2009</th>
<th>BJORK CLASSIFICATION 2016</th>
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<tbody>
<tr>
<td>GRADE</td>
<td>DESCRIPTION</td>
</tr>
<tr>
<td>A</td>
<td>Clean OA without adherence between bowel and abdominal wall or fixity</td>
</tr>
<tr>
<td>B</td>
<td>Contaminated OA without adherence/fixity</td>
</tr>
<tr>
<td>C</td>
<td>Enteric leak, no fixation</td>
</tr>
<tr>
<td>2 A</td>
<td>Clean OA developing adherence/fixity</td>
</tr>
<tr>
<td>B</td>
<td>Contaminated OA developing adherence/fixity</td>
</tr>
<tr>
<td>C</td>
<td>Enteric leak, developing fixation</td>
</tr>
<tr>
<td>3 A</td>
<td>OA complicated by fistula formation</td>
</tr>
<tr>
<td>B</td>
<td>Contaminated, frozen abdomen</td>
</tr>
<tr>
<td>4</td>
<td>Frozen OA with adherent/fixated bowel; unable to close surgically; with or without fistula</td>
</tr>
</tbody>
</table>

Fig. 2 Open Abdomen classification according to Björck et al. [147]
physiology of severe injuries or critical illness when no other perceived options exist. Its use remains very controversial and is a matter of great debate, as it is a non-anatomic situation with potential severe side effects and increased resource utilization. Moreover, the lack of definitive data demands carefully tailoring its use to each single patient, taking care to not over-use it. Abdominal closure attempt should be done as soon as the patient can physiologically tolerate it. All possible precautions should be implemented to minimize complications. Results improve proportionate to the clinicians’ team’s experience with the intricacies of open abdomen management.

Abbreviations

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Special thanks to Ms. Franca Boschini (Bibliographer, Medical Library, Papa Giovanni XXIII Hospital, Bergamo, Italy) for the precious bibliographical work.

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2017 update of the WSES guidelines for emergency repair of complicated abdominal wall hernias


Abstract

Emergency repair of complicated abdominal wall hernias may be associated with worsened outcome and a significant rate of postoperative complications. There is no consensus on management of complicated abdominal hernias. The main matter of debate is about the use of mesh in case of intestinal resection and the type of mesh to be used. Wound infection is the most common complication encountered and represents an immense burden especially in the presence of a mesh. The recurrence rate is an important topic that influences the final outcome. A World Society of Emergency Surgery (WSES) Consensus Conference was held in Bergamo in July 2013 with the aim to define recommendations for emergency repair of abdominal wall hernias in adults. This document represents the executive summary of the consensus conference approved by a WSES expert panel. In 2016, the guidelines have been revised and updated according to the most recent available literature.

Keywords: Hernia repair, Emergency surgery, Incarcerated hernia, Strangulated hernia, Mesh repair, Biologic mesh, Bowel resection, Infected field, Contaminated wound, Abdominal wall hernia

Background

A large number of abdominal hernias require emergency surgery. However, these procedures may be associated with poor prognosis and a significant rate of postoperative complications [1].

Abdominal hernias may be classified as groin hernias (femoral or inguinal) and ventral hernias (umbilical, epigastric, Spigelian, lumbar, and incisional).

An incarcerated hernia is a hernia in which the content has become irreducible due to a narrow opening in the abdominal wall or due to adhesions between the content and the hernia sac. Moreover, intestinal obstruction may complicate an incarcerated hernia. A strangulated hernia occurs when the blood supply to the contents of the hernia (e.g. omentum, bowel) is compromised [2]. Strangulated hernias remain a significant challenge, as they are sometimes difficult to diagnose by physical examination and require urgent surgical intervention. Early surgical intervention of a strangulated
hernia with obstruction is crucial as delayed diagnosis can result in the need for bowel resection with prolonged recovery and increased complication rate. Strangled hernias may lead to bacterial translocation and intestinal wall necrosis (potentially resulting in bowel perforation). This condition significantly increases the risks in emergency hernia repair that may lead to an increased incidence of surgical site contamination and recurrence.

An interesting topic is the use of laparoscopy in emergency hernia repair. However, its role in acute settings is not well established yet.

Bacteria inherently colonize all surgical wounds, but not all of these contaminations ultimately lead to infection. In most patients, infection does not occur because innate host defences are able to eliminate microbes at the surgical site. However, there is some evidence that the implantation of foreign materials, such as prosthetic mesh, may lead to a decreased threshold for infection [3].

While many factors can influence surgical wound healing and postoperative infection, bacterial burden is the most significant risk factor. According to the likelihood and degree of wound contamination at the time of operation, the Centers for Disease Control and Prevention (CDC) wound classification stratifies the wound as follows [4]:

- Class I = clean wounds
- Class II = clean-contaminated wounds
- Class III = contaminated wounds
- Class IV = dirty or infected wounds (Table 1)

The choice of technique repair is based on the contamination of the surgical field, the size of the hernia, and the experience of the surgeon.

In clean-contaminated, contaminated, and dirty surgical procedures, the polymicrobial aerobic and anaerobic flora closely resemble the normal endogenous microflora of the gastrointestinal (GI) tract and are the most frequently observed pathogens. The contaminating pathogens in GI surgery include gram-negative bacilli (e.g. *Escherichia coli*) and gram-positive microbes, such as enterococci and anaerobic organisms. A classification scheme has been demonstrated in multiple studies to predict the relative probability that a given wound will become infected [5, 6].

Several studies show clear advantages of mesh use in elective cases, where infection is uncommon [7]. Mesh is easy to use, has low complication rates, and significantly reduces the rate of hernia recurrence. However, few studies have investigated the outcome of mesh use in an emergency setting, where there is often surgical field contamination due to bowel involvement [8, 9].

The use of biological mesh has many advantages, including a decreased immune response, as well as decreased incidence of fistulae formation, fibrosis, and erosions.

There is, however, a paucity of high-quality evidence on the superiority of biological mesh, and it is still a very expensive device [10].

The role of local anaesthesia in the treatment of complicated inguinal and femoral hernia needs to be taken into consideration because of its multiple advantages, especially in patients with multiple comorbidities.

A World Society of Emergency Surgery (WSES) Consensus Conference was held in Bergamo in July 2013, during the 2nd Congress of the World Society of Emergency Surgery with the goal of defining recommendations for emergency repair of abdominal wall hernias in adults. This document represents the executive summary of the consensus conference approved by a WSES expert panel. In 2017, the guidelines have been revised and updated according to the most recent available literature (Appendix).

**Materials and methods**

A computerized search was done by the bibliographer in different databases (MEDLINE, Scopus, Embase), and

<table>
<thead>
<tr>
<th>Table 1 Surgical wound classification [4]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I/clean</strong></td>
</tr>
<tr>
<td>An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria</td>
</tr>
<tr>
<td><strong>Class II/clean-contaminated</strong></td>
</tr>
<tr>
<td>An operative wound in which the respiratory, alimentary, genital, or urinary tract is entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered</td>
</tr>
<tr>
<td><strong>Class III/contaminated</strong></td>
</tr>
<tr>
<td>Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g. open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered are included in this category</td>
</tr>
<tr>
<td><strong>Class IV/dirty-infected</strong></td>
</tr>
<tr>
<td>Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation</td>
</tr>
</tbody>
</table>
citations were included for the period between January 2000 and December 2016 using the primary search strategy: hernia, groin, inguinal, femoral, crural, umbilical, epigastric, spigelian, ventral, incisional, incarcerated, strangulated, acute, emergency, repair, suture, mesh, direct, synthetic, polypropylene, prosthetic, biologic, SSI, wound infection, bowel resection, intestinal resection, complication, morbidity, recurrence, timing, laparoscopy combined with AND/OR. No search restrictions were imposed. The dates were selected to allow comprehensive published abstracts of clinical trials, consensus conference, comparative studies, congresses, guidelines, government publication, multicenter studies, systematic reviews, meta-analysis, large case series, original articles, and randomized controlled trials. Narrative review articles were also analysed to determine other possible studies. Recommendation guidelines are evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE), a hierarchical, evidence-based rubric [11, 12] summarized in Table 2.

The guidelines statements have been issued to each class according to the CDC wound classification (Table 1).

In 2016, the guidelines have been revised and updated by the WSES working group on emergency repair of complicated abdominal wall hernias according to the most recent literature available.

**Recommendations**

**Timing of intervention**

Patients should undergo emergency hernia repair immediately when intestinal strangulation is suspected (grade 1C recommendation).

Systemic inflammatory response syndrome (SIRS), contrast-enhanced CT findings, as well as lactate, serum creatinine phosphokinase (CPK), and D-dimer levels are predictive of bowel strangulation (grade 1C recommendation).

Unfortunately, morbidity and mortality rates remain high for patients who undergo emergency repair of abdominal hernias. Early diagnosis of strangulated obstruction may be difficult, and delayed diagnosis can lead to septic complications. However, in the case of suspected bowel strangulation, the benefits outweigh the risks of surgery and patients should undergo immediate surgical intervention.

A recent study performed by Martínez-Serrano et al. prospectively analysed morbidity and mortality rates following emergency hernia repair. The study population included 244 patients with complicated abdominal wall hernias requiring surgical repair. In this study, the patients were treated according to standardized protocols with detailed actions taken during the pre-, intra-, and postoperative periods. Clinical outcomes were compared retrospectively to that of 402 patients who had undergone similar procedures before the development and implementation of the protocols outlined in the study. Results showed higher rates of mortality in patients with acute complication as their first hernia-related symptom and whose treatment was delayed for more than 24 h. Thus, the authors concluded that early detection of complicated abdominal hernias may be the best means of reducing the rate of mortality [13].

Similar results were achieved in the study published in 2014 by Koizumi et al., retrospectively analysing the clinical course and outcomes in 93 patients with strangulated inguinal end femoral hernias. The results demonstrated how the elapsed time from onset to surgery was the most important prognostic factor ($P < 0.005$) [14].

In 2007, Derici et al. published a retrospective study using univariate and multivariate analyses to investigate factors affecting morbidity and mortality rates in cases of incarcerated abdominal wall hernias [15]. Using the univariate analysis, results showed that symptomatic periods lasting longer than 8 h, the presence of comorbid disease, high American Society of Anesthesiologists (ASA) scores, the use of general anaesthesia, the presence of strangulation, and the presence of necrosis significantly affect mortality rates. In contrast, advanced age, the presence of comorbid diseases, high ASA scores, the presence of strangulation, the presence of necrosis, and hernia repair with graft were found to significantly affect mortality rates by univariate analysis; the presence of necrosis, however, was the only factor that appeared to significantly affect mortality rates based on multivariate analysis [16].

A retrospective study evaluated the risk factors associated with bowel resection and treatment outcome in patients with incarcerated groin hernias. The study analysed 182 adult patients with incarcerated groin hernias who underwent emergency hernia repair in the 10-year period from January 1999 to June 2009. Of these patients, bowel resection was required in 15.4% of cases (28/182). A logistic regression model identified three independent risk factors for bowel resection: lack of health insurance (odds ratio (OR) = 5, $P = 0.005$), obvious peritonitis (OR = 11.52, $P = 0.019$), and femoral hernia (OR = 8.31, $P < 0.001$) [17].

Many authors reported that early detection of progression from an incarcerated hernia to a strangulated hernia is difficult to achieve by either clinical or laboratory means, which presents a large challenge in early diagnosis [18–20]. Signs of SIRS including fever, tachycardia, and leukocytosis, as well as abdominal wall rigidity, are considered common indicators of strangulated obstruction. However, an investigation by Sarr et al. demonstrated that the combination of four classic signs of strangulation—continuous abdominal
<table>
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<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
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<tr>
<td>1A</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
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<tr>
<td>1B</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses, or imprecise conclusions) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
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<tr>
<td>1C</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but subject to change when higher-quality evidence becomes available</td>
</tr>
<tr>
<td>2A</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, the best action may differ depending on the patient, treatment circumstances, or social values</td>
</tr>
<tr>
<td>2B</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, the best action may differ depending on the patient, treatment circumstances, or social values</td>
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<tr>
<td>2C</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
<td>Very weak recommendation; alternative treatments may be equally reasonable and merit consideration</td>
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RCTs randomized controlled trials
pain, fever, tachycardia, and leukocytosis—could not distinguish strangulated from simple obstructions [18]. Furthermore, Shatlla et al. reported a low incidence of these classical findings and stated that their presence indicated an advanced stage of strangulation, which would be of limited value for early diagnosis [19]. In 2004, Tsumura et al. published a retrospective study investigating SIRS as a predictor of strangulated small bowel obstruction. Multivariate analysis revealed that the presence of SIRS alongside abdominal muscle guarding was independently predictive of strangulated small bowel obstruction [21].

Among possible diagnostic tests, CPK appears to be a relatively reliable indicator of early intestinal strangulation [22, 23]. Icoz et al. published a prospective study investigating the relevance of serum D-dimer measurement as a potential diagnostic indicator of strangulated intestinal hernia. The authors concluded that D-dimer assays should be performed on patients presenting with intestinal emergencies to better evaluate and predict ischemic events. Despite having low specificity, elevated D-dimer levels measured upon admission were found to correlate strongly with intestinal ischaemia [24].

In 2012, an interesting retrospective study examining whether various laboratory parameters could predict the viability of strangulation in patients with bowel obstruction was published. Forty patients diagnosed with bowel strangulation operated within 72 h of the start of symptoms were included in the study. Lactate level was the only laboratory parameter significantly associated with a lack of viability ($P < 0.01$, Mann–Whitney U test). Other laboratory data did not show statistically significant associations. The authors concluded that an arterial blood lactate level of 2.0 mmol/L or greater was a useful predictor of non-viable bowel strangulation [25].

Early diagnostic methods to detect bowel strangulation have advanced substantially following the development and refinement of radiological techniques, such as computed tomography (CT) scanning [26]. Jancelewicz et al. published a retrospective analysis demonstrating that CT findings of reduced wall enhancement were the most significant independent predictor of bowel strangulation, with 56% sensitivity and 94% specificity. By contrast, elevated white blood cell (WBC) count and guarding on physical examination were only moderately predictive. It should be noted, however, that an elevated WBC was the only variable found to be independently predictive of bowel strangulation in patients with small bowel obstruction [27].

In 2014, Kahramanca et al. retrospectively analysed the role of WBC count and fibrinogen as predictive factors of incarcerated abdominal hernia. Comparing 100 patients with incarcerated hernia with 100 patients with uncomplicated hernia, the results showed that high levels of WBC and fibrinogen were significantly predictive of morbidity and cost burden ($P < 0.001$) [28].

**Laparoscopic approach**

Diagnostic laparoscopy may be a useful tool with the target of assessing bowel viability after spontaneous reduction of strangulated groin hernias (grade 2B recommendation).

Repair of incarcerated hernias—both ventral and groin—may be performed with a laparoscopic approach in the absence of strangulation and suspicion of the need of bowel resection, where an open pre-peritoneal approach is preferable (grade 2C recommendation).

Few studies have focused on the laparoscopic approach to hernia repair in an emergency setting. In 2004, Landau and Kyzer published a retrospective study investigating the use of laparoscopy in the repair of incarcerated incisional and ventral hernias. The authors argued that laparoscopic repair was feasible and could be safely used to treat patients presenting with incarcerated incisional and ventral hernias [29].

In 2007, a series of patients with large irreducible groin hernias (omentoceles), treated by laparoscopy without conversions, was published. The authors described a technique to facilitate complete removal of the hernia contents. A laparoscopic transperitoneal repair for large irreducible scrotal hernias, removing as much omentum as possible, was performed. Then, a small groin incision was made to excise the adherent omentum from the distal sac [30].

Another retrospective study published in 2008 investigated the role of laparoscopy in the management of incarcerated (non-reducible) ventral hernias. The authors concluded that laparoscopic repair of ventral abdominal wall hernias could be safely performed with low subsequent complication rates, even in the event of an incarcerated hernia. Careful bowel reduction with adhesiolysis and mesh repair in an uncontaminated abdomen (without inadvertent enterotomy) using a 5-cm-mesh overlap was an important factor predictive of successful clinical outcome [31].

In 2009, a retrospective study investigating laparoscopic techniques used to treat incisional hernias in an emergency setting was published. The results of this series also demonstrated the feasibility of laparoscopic surgery to treat incarcerated incisional hernias in an emergency setting [32].

Additionally, a systematic literature review performed in 2009 identified articles reporting on laparoscopic treatment, reduction, and repair of incarcerated or strangulated inguinal hernias from 1989 to 2008. It included seven articles on this topic, reporting on 328 cases treated with total extraperitoneal (TEP) or transabdominal preperitoneal (TAPP) repair. Laparoscopy can also...
be used to resect bowel, if necessary, or to repair an occult contralateral hernia, present in 11.2–50% of cases. The authors concluded that the laparoscopic repair is a feasible procedure with acceptable results; however, its efficacy needs to be studied further, ideally with larger, multicentre randomized controlled trials [33].

The retrospective 4-year analysis of 188 patients who underwent emergency surgical repair of strangulated groin hernias (57 laparoscopic and 131 open, including one and ten bowel resections, respectively, \( P = 0.117 \)) revealed a significant lower wound infection rate \( (P < 0.018) \) in the laparoscopic group, without a higher recurrence rate \( (P < 0.815) \) [34].

Hernioscopy is a mixed laparoscopic–open surgical technique for incarcerated inguinal hernias. Specifically, it is effective in evaluating the viability of the herniated loop, thus avoiding unnecessary laparotomy [35].

A prospective randomized study in 2009 aimed to evaluate the impact of hernia sac laparoscopy on the morbidity and mortality of cases with a spontaneous reduction of the strangulated hernia content before the assessment of its viability. Ninety-five patients were randomly assigned to two groups: group A (21 patients managed using hernia sac laparoscopy) and group B (20 patients managed without laparoscopy). The median hospital stay was 28 h for group A and 34 h for group B. Four patients of group B had major complications, whereas there was none observed in group A. Two unnecessary laparotomies and two deaths occurred in group B. The authors concluded that hernia sac laparoscopy seems to be an accurate and safe method of preventing unnecessary laparotomy, and in high-risk patients, it contributes to decreased morbidity [36].

**Emergency hernia repair in “clean surgical field” (CDC wound class I)**

The use of mesh in clean surgical fields (CDC wound class I) is associated with lower recurrence rate, if compared to tissue repair, without an increase in the wound infection rate. Prosthetic repair with a synthetic mesh is recommended for patients with intestinal incarceration and no signs of intestinal strangulation or concurrent bowel resection (clean surgical field) (grade 1A recommendation).

**Ventral hernias**

For patients with intestinal incarceration and no signs of intestinal strangulation or concurrent bowel resection, the surgical field is presumed clean and the infectious risk for synthetic mesh is low. The absence of intestinal wall ischaemia makes patients less prone to bacterial translocation.

Advantages have demonstrated using a mesh for hernia repair in clean fields; such advantages include low rate of long-term complications and reduction of recurrence [37–42].

A wide variety of small-sized retrospective studies comparing mesh use to suture repair in the treatment of acute irreducible hernias have been published [39, 43, 44]. The prospective randomized trial by Abdel-Baki et al. compared the use of mesh repair (group 1, 21 patients) and tissue repair (group 2, 21 patients) in 42 cases with acute para-umbilical hernia. The wound infection rate between the two groups was not statistically significant. At follow-up (mean 16 ± 5.5 months), there were four recurrences in group 2 (4/21, 19%) and no recurrences in group 1 (\( P < 0.05 \)) [42].

The prospective 6-year study by Abd Ellatif et al. included 115 patients who underwent acutely incarcerated abdominal wall hernia repair. The results showed low rates of wound infection (4.3%) and recurrence (4.3%), with a mean follow-up of 42 months. The authors therefore concluded that mesh hernioplasty is crucial to prevent recurrence and that it is safe for repairing acutely incarcerated hernias [45].

**Groin hernias**

The retrospective study by Venara et al. compared the 30-day outcome after acute hernia (inguinal, femoral, and umbilical) repair with or without mesh. The study included 166 patients, of which 64 were treated with and 102 without mesh repair. Among the 64 patients who underwent mesh repair, four patients had concomitant bowel resection. Among the 102 patients who underwent primary repair, 21 patients had concomitant bowel resection. The mesh repair was neither related to a significant increase of complications \( (P = 0.89) \) nor related to surgical site infection (SSI) \( (P = 0.95) \), overall morbidity \( (OR = 1.5, CI = 95\%, P = 0.458) \), and major complications \( (OR = 1.2, CI = 95\%, P = 0.77) \) [37].

A recent prospective study included 202 patients with acutely incarcerated groin hernias. The results showed extremely low rates of wound infection, mesh infections, and recurrence. The authors concluded that the use of mesh in incarcerated hernias is safe [46].

**Emergency hernia repair in “clean-contaminated surgical field” (CDC wound class II)**

For patients having a complicated hernia with intestinal strangulation and/or concomitant need of bowel resection without gross enteric spillage (clean-contaminated surgical field, CDC wound class II), emergent prosthetic repair with a synthetic mesh can be performed (without any increase in 30-day wound-related morbidity) and is associated with a significant lower risk of recurrence, regardless the size of hernia defect (grade 1A recommendation).
The use of prosthetic grafts in clean-contaminated settings is seldom described. Most studies on the subject focus on elective repair.

**Ventral hernias**

In 2000, Mandalà et al. published a series of patients with incisional hernias treated with non-absorbable prostheses and associated visceral surgery. The low incidence of suppurrative complications, with neither removal of the patch nor recurrences in the short term, showed that non-absorbable mesh repair in potentially contaminated fields was safe [47].

Retrospective studies by Vix et al., Birolini et al., and Geisler et al. report wound-related morbidity rates of 10.6, 20, and 7%, respectively, following mesh use in both clean-contaminated and contaminated procedures [48–50].

The retrospective study by Campanelli et al. analysed ten prosthetic hernia repairs in potentially contaminated fields and reported no major or minor complications after a 21-month follow-up period [51].

On the other hand, in 2010, Xourafas et al. retrospectively examined the impact of mesh use on ventral hernia repairs with simultaneous bowel resections attributable to either cancer or bowel occlusion. Researchers found a significantly higher incidence of postoperative infection in patients with a prosthetic mesh compared to those without mesh. According to the multivariate regression analysis, prosthetic mesh use was the only significant risk factor, irrespective of other variables such as drain use, defect size, or type of bowel resection [52].

The large-sized US National Surgical Quality Improvement Program (NSQIP) study by Choi et al., analysed and compared postoperative outcome following ventral hernia repair, in the 5-year period from 1 January 2005 to 4 April 2010, including 6721 clean-contaminated cases, of which 3879 underwent mesh repair and 2842 underwent non-mesh repair. The results did not show a significant statistical difference in the rate of deep incisional SSI and return to OR within 30 days, between the mesh and non-mesh groups [53].

One of the few available studies investigating acute hernia repair is the small-sized retrospective analysis by Nieuwenhuizen et al. including 23 patients who underwent acute hernia repair with intestinal resection, and surprisingly, it revealed a higher incidence of wound infection in the primary suture group (5/14, 35%) than in the mesh group (2/9, 22%) [54].

Another retrospective analysis of emergency prosthetic repair of incarcerated incisional hernias with simultaneous bowel resection in potentially contaminated fields including 60 patients demonstrated that the intestinal resection was associated with high rates of wound infection (38%) [55].

The prospective 6-year study by Abd Ellatif et al. included 163 patients who underwent acutely incarcerated abdominal wall hernia mesh repair, of which 48 required intestinal resection and anastomosis and 155 did not. No significant difference was found in terms of postoperative morbidities, wound infection, and recurrence rate between the two groups. The authors therefore concluded that mesh hernia repair is crucial to prevent recurrence and that it is safe for repairing acutely incarcerated hernias, even in case of intestinal resection [45].

In 2013, a prospective study to present a 7-year experience with the use of prosthetic mesh repair in the management of the acutely incarcerated and/or strangulated ventral hernias was published. Resection–anastomosis of non-viable small intestine was performed in 18 patients (23%) and was not regarded as a contraindication for prosthetic repair [43].

Haskins et al. evaluated the outcomes after emergency ventral hernia repair in 1357 patients with CDC wound class II from the American College of Surgeons (ACS) NSQIP database and did not find any statistical significance in wound-related or additional 30-day patient morbidity or mortality, between mesh and non-mesh emergency ventral hernia repair. The authors concluded that emergency ventral hernia repair with a mesh can be safely performed without an increase in wound-related or additional early patient morbidity or mortality in CDC wound class II [56].

The randomized trial by Kassem and El-Haddad compared the use of onlay polypropylene mesh positioned and supported by omentum and/or peritoneum versus inlay implantation of polypropylene-based composite mesh in 60 patients with complicated wide-defect ventral hernias, including 12 bowel resections. Postoperatively, seven patients developed a wound infection (11.6%) and two patients developed a recurrence (3%), after 3 and 8 months, respectively [57].

**Groin hernias**

Some studies have asserted that prosthetic repair of abdominal hernias can be safely performed alongside simultaneous colonic operations. Such joint procedures, they argue, exhibit acceptable rates of infectious complications and recurrence, and consequently, they stated that there is insufficient evidence to advocate the avoidance of prosthetic mesh in clean-contaminated fields, assuming that the appropriate technique is used [44, 58].

Also, the results of the retrospective study by Ueda et al. including 27 patients operated for strangulated groin hernia with small bowel resection (ten patients
with mesh and 17 without mesh) did not show any statistically significant differences in terms of morbidity between the two groups and led to the conclusion that strangulated inguinal hernia cannot be considered a contraindication to the mesh repair even in case of intestinal resection [59].

A recent prospective study by Bessa et al. enrolled 234 patients with acutely or strangulated groin hernias of which 34 underwent resection and anastomosis of non-viable intestine. The results did not show any significant difference \( P = 0.7 \) in the rate of wound or mesh infection between hernias with viable versus non-viable contents. The authors concluded that the presence of non-viable intestine could not be regarded as a contraindication for prosthetic repair [46].

In the retrospective study by Venara et al. including a subgroup of 25 patients who underwent acute hernia repair with concomitant bowel resection (four with mesh repair and 21 with primary repair), bowel resection appeared to be a risk factor for overall postoperative complications \( P > 0.0001 \) and major complications \( P = 0.003 \), but not for postoperativeSSI \( P = 0.42 \). The authors concluded that mesh repair appeared to be safer in the treatment of incarcerated hernia, since after multivariate analysis, mesh placement was not a significant predictor of postoperative complication \( P = 0.458 \) [37].

In 2014, a SR and meta-analysis including nine studies has been published, investigating the optimal technique to treat strangulated inguinal hernia (mesh vs non-mesh repair). The wound infection rate has been found to be lower in the mesh group than in the control group \( OR = 0.46, CI = 95\%, P = 0.07 \). The recurrence rate was found to be lower in the mesh repair group \( OR = 0.2, CI = 95\%, P = 0.02 \). Nonetheless, the authors concluded that the study did not allow to currently recommend the use of mesh in case of bowel resection, despite the finding of similar SSI rates with either mesh repair or non-mesh techniques, when comparing bowel resection and no bowel resection \( OR = 1.50, P = 0.73 \) [60].

**Emergency hernia repair in “contaminated-dirty surgical field” (CDC wound classes III and IV)**

For stable patients with strangulated hernia with bowel necrosis and/or gross enteric spillage during intestinal resection (contaminated, CDC wound class III) or peritonitis from bowel perforation (dirty surgical field, CDC wound class IV), primary repair is recommended when the size of the defect is small \(<3\text{ cm})\); when direct suture is not feasible, a biological mesh may be used for repair (grade 2C recommendation).

The choice between a cross-linked and a non-cross-linked biological mesh should be evaluated depending on the defect size and degree of contamination (grade 2C recommendation).

If a biological mesh is not available, either polyglactin mesh repair or open wound management with delayed repair may be a viable alternative (grade 2C recommendation).

In cases of bacterial peritonitis, patients must undergo contaminated surgical intervention, which means that the surgical field is infected and the risk of surgical site infection is very high.

High infection rates are reported after emergency hernia repairs with a polypropylene mesh of CDC wound class III. A retrospective study by Kelly and Behrman reported a 21% infection rate in a series of emergency and elective incisional hernia repairs [61]. Recently, a retrospective study by Carbonell et al. investigated open ventral hernia repairs performed with a polypropylene mesh in the retro-rectus position in clean-contaminated and contaminated fields: the 30-day surgical site infection rate was 7.1 and 19.0%, respectively [62].

Some authors investigated the use of absorbable prosthetic materials [64]. However, the use of absorbable prostheses exposes the patient to an inevitable hernia recurrence. These meshes, once implanted, induce an inflammatory reaction that, through a hydrolytic reaction, digests and removes and digests the implanted prosthetic material completely. In this case, the high risk of hernia recurrence is explained by the complete dissolution of the prosthetic support [63].

Biological mesh prosthetics are most commonly used in infected fields involving large, complex abdominal wall hernia repairs. The use of biological mesh, which becomes vascularized and remodelled into autologous tissue after implantation, may offer a low-morbidity alternative to prosthetic mesh products in these complex settings, with good results also in immune-compromised patients [64]. By incorporating a biological mesh, surgeons hope to provide a collagen-based extracellular matrix scaffold by which host fibroblasts can induce angiogenesis and deposit new collagen. The non-synthetic material of biological mesh makes it less susceptible to infection, and several biological grafts are available in the current market. The classification of biological meshes is based on the species of origin (allogenic or xenogenic), the type of collagen matrix utilized (dermis, pericardium, or intestinal submucosa), the decellularization process, the presence or absence of cross-linkage, temperature-related storage requirements, and the use of rehydration [65]. On the basis
of either the presence or not of the cross-linking, biological prostheses are divided into two subgroups: the partially remodelling ones (cross-linked) and the completely remodelling ones (not cross-linked). Thanks to the presence of additional links, the partially remodelling ones resist better and for a longer period to mechanical stress [64].

Many retrospective studies have explored the promising role of biological mesh in contaminated fields, but most of these investigations did not focus on emergency repair of incarcerated hernias [66–86]. Although a biological mesh in these situations is safe, long-term durability has still not been demonstrated [87–89].

A recent multicentre large-sized retrospective study compared suture, synthetic mesh, and biologic matrix in contaminated ventral hernia repair. On multivariate analysis, a biologic matrix was associated with a non-significant reduction in both SSI and recurrences, whereas a synthetic mesh was associated with fewer recurrences compares to suture and non-significant increase in SSI [90].

A prospective study by Catena et al. published in 2007 focused on complicated incisional hernia repair using mesh prosthetics made of porcine dermal collagen (PDC). Incisional hernioplasty using PDC grafts was found to be a safe and efficient approach to difficult contaminated cases [81].

Coccolini et al. published the results of the first 193 patients of the Italian Register of Biological Prosthesis (IRBP) [86]. This prospective multicentre study suggests the usefulness, versatility, and ease of using biological prostheses in many different situations, including contaminated surgical fields.

The literature review by Coccolini et al. covered the use of biological meshes for abdominal reconstruction in emergency and elective setting in transplanted patients and reported a complication rate of 9.4% [84].

In 2014, Han et al. published a retrospective study including 63 patients who underwent emergency surgery for acute incarcerated abdominal wall hernias with human acellular dermal matrix (ADM) repair with a very low rate of infection (1.6%) as well as recurrences (15.9%) in a follow-up of 43 months. Bowel resection, performed in 33 patients, did not significantly affect the bulge and recurrence rate (P = 0.262). Interestingly, multivariate analysis demonstrated three factors to be significantly related to bulge and recurrence: BMI (P = 0.008), defect size (P = 0.016), and numbers of biological meshes used (P = 0.027) [91].

The systematic review by Lee et al. included a total of 32 studies regarding the use of synthetic and biologic materials for abdominal wall reinforcement in contaminated fields. In contaminated and/or dirty fields, wound infection rates were similar, but pooled hernia rates were 27.2% (95% CI = 9.5–44.9) with biological and 3.2% (95% CI = 0.0–11.0) with synthetic non-absorbable meshes. Other outcomes were comparable [92].

The recent multicentre prospective observational study by De Simone et al. included 71 patients who underwent emergency ventral hernia repair with a biological mesh. The surgical field resulted contaminated in 27 patients (38%), potentially contaminated in 19 patients (26.7%), and dirty in 25 patients (35.2%). Early postoperative (3rd–7th postoperative days) wound infection occurred in 21 patients (29.57%). High ASA score (≥3) (OR = 2.82, CI = 1.85–6.43, P = 0.03), smoking (OR = 4.1, CI = 1.73–6.35, P = 0.02), diabetes (OR = 3.23, CI = 1.92–4.38, P = 0.04), chronic immunosuppression (OR = 2.41, CI = 0.33–5.25, P = 0.003), previous hernia repair (OR = 1.99, CI = 1.5–2.9, P = 0.002), dirty surgical field (OR = 1.87, CI = 0.35–4.4, P = 0.04), sublay extraperitoneal bio-prosthesis placement (OR = 0.45, CI = 0.27–1.13, P = 0.009), and no anterior fascia closure (OR = 0.33, CI = 0.2–2.3, P = 0.04) were associated with wound complications. After a mean follow-up time of 27.2 months, hernia recurrence occurred in 19 patients (26.76%) [93].

Haskins et al. evaluated the outcomes after emergency ventral hernia repair in 1092 patients from the ACS NSQIP database and did not find any statistical significance in wound-related or additional 30-day patient morbidity or mortality, between mesh and non-mesh emergency ventral hernia repair. The authors concluded that emergency ventral hernia repair with a mesh can be safely performed without an increase in early wound-related or additional 30-day patient morbidity or mortality in CDC wound classes III and IV [56].

The use of biological materials in clinical practice has led to innovative methods of treating abdominal wall defects in contaminated surgical fields, although there is still an insufficient level of high-quality evidence on their value, and there is still a very huge price difference between the synthetic and biological meshes [10]. All literature reviews found in the MEDLINE database supported biologic mesh use in the setting of contaminated fields, but the literature included in these reviews consisted of case series and case reports with low levels of evidence [94]. Despite the lack of a cohesive body of evidence, published studies on biological mesh suggest that cross-linked mesh prosthetics have the lowest failure rate in contaminated and outright infected fields. To better guide surgeons, prospective randomized trials should be undertaken to evaluate the short- and long-term outcomes associated with biological meshes [90, 95].
abdominal pressure may be measured intraoperatively (grade 2C recommendation).

A prospective study published by Beltrán et al. examined 81 consecutively unselected patients presenting with complicated hernias and intestinal obstruction. The researchers used intra-abdominal pressure, measured with the intravesicular pressure method, to assess the clinical severity of strangulated hernias and predict intestinal strangulation [96]. Patients with intestinal strangulation and peritonitis are critically ill cases, commonly shocked and at high risk of septic complications; these patients may experience high intraoperative intra-abdominal pressure. Such hypertension may be the underlying cause of increased pulmonary pressures, reduced cardiac output, splanchnic hypoperfusion, and oliguria, leading to an abdominal compartment syndrome. Increased pressure within the constricting abdominal compartment in conjunction with unchanging or more likely disease-induced reduced abdominal compliance will also greatly reduce visceral perfusion within the abdominal compartment leading to an acute bowel injury [97–99]. This “acute bowel injury” results in release of pro-inflammatory mediators into the peritoneum and systemic circulation, leading to neutrophil priming, increased intestinal wall permeability, extravasation of fluid into the bowel wall and mesentery, translocation of intestinal bacteria, and absorption of bacterial endotoxin [100–103]. Even relatively mild intra-abdominal hypertension (IAH) (e.g. an IAP of 15 mmHg) has been reported to decrease intestinal microcirculatory blood flow, increase bowel wall permeability, and induce irreversible gut histopathological changes, bacterial translocation, and multi-organ dysfunction syndrome [103–105].

Prophylactic treatment to avoid abdominal compartment syndrome involves refraining from abdominal closure when fascial approximation becomes problematic due to excessive tension (“open abdomen”) [106, 108]. In this setting, negative pressure peritoneal therapy may play a role in mitigating the bio-mediator effects that cause distant organ failure and is an additional potential benefit of an open abdomen.

Even in cases where the abdominal wall can be closed after a laparotomy involving the discovery of diffuse contamination, fulfilling the World Society of Emergency Surgery criteria for severe complicated intra-abdominal sepsis [107, 108], there is controversy as to whether the abdominal wall should be closed or left open. It is financially cheaper and would be preferable from a patient's standpoint to have a single operation and to not be submitted to longer critical care unit management if it was possible to primarily close the abdomen [109]. However, there is a growing biologic rationale with early clinical evidence that the open abdomen after severe complicated intra-abdominal sepsis may be preferable due to its ability to allow negative pressure peritoneal therapy which may modulate the course of systemic inflammation with progressive organ dysfunction [110, 111] and to provide a survival signal that needs to be confirmed in larger studies [112, 113].

Following stabilization of the patient, surgeons should attempt early, definitive closure of the abdomen. Primary fascial closure may be possible only when the risk of excessive tension or recurrent IAH is minimal (grade 2C recommendation).

When early definitive fascial closure is not possible, progressive closure can be gradually attempted at every surgical wound revision. Cross-linked biological meshes may be considered as a delayed option for abdominal wall reconstruction (grade 2C recommendation).

After the patient's stabilization, the primary objective is early and definitive closure of the abdomen to minimize complications. For many patients, primary fascial closure may be possible within a few days of the first operation. In other patients, early definitive fascial closure may not be possible. In these cases, surgeons must resort to progressive closure, in which the abdomen is incrementally closed each time the patient undergoes a surgical revision. Many methods of fascial closure have been described in the medical literature [94, 114–117].

In 2012, a retrospective analysis evaluating the use of vacuum-assisted closure and mesh-mediated fascial traction (VACM) as temporary abdominal closure was published. The study compared 50 patients treated with VACM and 54 using non-traction techniques (control group). VACM resulted in a higher fascial closure rate and lower planned hernia rate than methods that did not provide fascial traction [117].

Occasionally, abdominal closure is only partially achieved, resulting in large, debilitating hernias of the abdominal wall that will eventually require complex surgical repair. Bridging meshes will often result in bulging or recurrences [118]. The Italian Biological Prosthesis Working Group (IBPWG) proposed a decisional algorithm in using biological meshes to restore abdominal wall defects [64].

When definitive fascial closure cannot be achieved, a skin-only closure is a viable option and subsequent evacuation can be managed at a later stage with delayed abdominal closure and synthetic mesh repair (grade 1C recommendation).

Damage control surgery has been widely used in trauma patients, and its use is rapidly expanding in the setting of acute care surgery. Damage control surgery can be used in patients with strangulated obstruction and peritonitis caused by bowel perforation.
with enteric spillage due to a complicated abdominal wall hernia. These patients are often considered critically ill due to septic complications. Ordonez et al. described a series of 217 non-trauma patients with severe peritonitis and who were managed with damage control surgery. Definitive fascia closure was achieved in 51% of the patients. Failure of definitive fascia closure occurred in 106 patients; of these, 72 (68%) were managed with skin-only closure. Skin-only closure could be an alternative for patients with failure of definitive fascia closure, reducing the risk of complications of open abdomen and abdominal compartmental syndrome. Patients could be deferred for delayed definitive abdominal closure with synthetic mesh repair [119].

The component separation technique may be a useful and low-cost option for the repair of large midline abdominal wall hernias (grade 1B recommendation).

The component separation technique (CST) for reconstructing abdominal wall defects without the use of prosthetic material was described in 1990 by Ramirez et al. [120]. The technique is based on enlargement of the abdominal wall surface by translation of the muscular layers without damaging the muscle innervation and blood supply [121]. In most series, several modifications to the original technique have been performed, including the use of prosthetic material [122–125]. In a prospective randomized trial comparing CST with bridging the defect with a prosthetic material, CST was found to be superior, although a similar recurrence rate was found after a 24-month follow-up [126]. However, high recurrence rates (up to 38.7%) after component separation have recently been reported [127].

The microvascular tensor fasciae latae (TFL) flap is a feasible option for reconstruction of exceptionally large abdominal wall defects. This technique can also be combined with other methods of reconstruction. Vascularized flaps provide healthy autologous tissue coverage without implantation of foreign material at the closure site. A close collaboration between plastic and abdominal surgeons is important for this reconstruction [128].

Antimicrobial therapy is recommended for patients with peritonitis (CDC wound class IV, grade 2C recommendation).

In aseptic hernia repair, *Staphylococcus aureus* from the exogenous environment or the patient’s skin flora is typically the source of infection. In patients with intestinal strangulation, the surgical field may be contaminated by bacterial translocation [8, 9] from intestinal villi of incarcerated ischemic bowel loops as well as by concomitant bowel resections. In patients with peritonitis, both antimicrobial therapy and surgery are always recommended.

**Anaesthesia**

Local anaesthesia (LA) can be used, providing effective anaesthesia with less postoperative complications for emergency inguinal hernia repair in the absence of bowel gangrene (grade 1C recommendation).

LA is one of the most commonly used anaesthetic methods in inguinal hernia repair [129–131]. However, the role of LA in emergency inguinal hernia repair is still controversial [132–134]. The recent retrospective 5-year experience by Chen et al. reported that LA could provide effective anaesthesia and patient safety in emergency inguinal hernia repair, with less cardiac complications (*P* = 0.044) and respiratory complications (*P* = 0.027), shorter ICU stay (*P* = 0.035) and hospital stay (*P* = 0.001), as well as lower cost (*P* = 0.000) and faster recovery time (*P* = 0.000) than general anaesthesia [135].

However, general anaesthesia should be preferred in the case of suspected bowel gangrene and need of intestinal resection and always in the case of peritonitis.

**Conclusions**

Emergency repair of complicated abdominal hernias remains one of the most common and challenging surgical emergencies and is associated with a significant burden for health care systems worldwide. These comprehensive guidelines on the emergency repair of complicated hernia have been developed by a panel of experts through a Web-based discussion and consensus. This document provides evidence-based recommendations on the timing of intervention, laparoscopic approach, surgical repair according to the CDC wound classification, and antimicrobial prophylaxis on the topic of emergency repair of complicated abdominal wall hernias. One of the novel aspects of the present guidelines is the stratification of the management recommendations according to the CDC wound classification, which is a widely used and standardized classification of the surgical wounds. In addition, this 2017 revision includes a new topic on the role of local anesthesia.
## Appendix

**Table 3** Resume of recommendation guidelines

<table>
<thead>
<tr>
<th>GoR</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing of intervention</strong></td>
<td></td>
</tr>
<tr>
<td>1C</td>
<td>Patients should undergo emergency hernia repair immediately when intestinal strangulation is suspected</td>
</tr>
<tr>
<td>1C</td>
<td>Systemic inflammatory response syndrome (SIRS), contrast-enhanced CT findings, as well as lactate, CPK, and D-dimer levels are predictive of bowel strangulation</td>
</tr>
<tr>
<td><strong>Laparoscopic approach</strong></td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>Diagnostic laparoscopy may be a useful tool with the target of assessing bowel viability after spontaneous reduction of strangulated groin hernias</td>
</tr>
<tr>
<td>2C</td>
<td>Repair of incarcerated hernias—both ventral and groin—may be performed with a laparoscopic approach in the absence of strangulation and suspicion of the need of bowel resection, where an open preperitoneal approach is preferable</td>
</tr>
<tr>
<td><strong>Emergency hernia repair in &quot;clean surgical field&quot; (CDC wound class I)</strong></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>The use of mesh in clean surgical fields (CDC wound class I) is associated with a lower recurrence rate, if compared to tissue repair, without an increase in the wound infection rate. Prosthetic repair with a synthetic mesh is recommended for patients with intestinal incarceration and no signs of intestinal strangulation or concurrent bowel resection (clean surgical field)</td>
</tr>
<tr>
<td><strong>Emergency hernia repair in &quot;clean-contaminated surgical field&quot; (CDC wound class II)</strong></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>For patients having complicated hernia with intestinal strangulation and/or concomitant need of bowel resection without gross enteric spillage (clean-contaminated surgical field, CDC wound class II), emergent prosthetic repair with synthetic mesh can be performed (without any increase in 30-day wound-related morbidity) and is associated with a significant lower risk of recurrence, regardless of the size of hernia defect</td>
</tr>
<tr>
<td><strong>Emergency hernia repair in &quot;contaminated-dirty surgical field&quot; (CDC wound classes III and IV)</strong></td>
<td></td>
</tr>
<tr>
<td>2C</td>
<td>For stable patients with strangulated hernia with bowel necrosis and/or gross enteric spillage during intestinal resection (contaminated, CDC wound class III) or peritonitis from bowel perforation (dirty surgical field, CDC wound class IV), primary repair is recommended when the size of the defect is small (&lt; 3 cm); when direct suture is not feasible, a biological mesh may be used for repair</td>
</tr>
<tr>
<td>2C</td>
<td>The choice between a cross-linked and a non-cross-linked biological mesh should be evaluated depending on the defect size and degree of contamination</td>
</tr>
<tr>
<td>2C</td>
<td>If biological mesh is not available, either polyglactin mesh repair or open wound management with delayed repair may be a viable alternative</td>
</tr>
<tr>
<td>2C</td>
<td>For unstable patients (experiencing severe sepsis or septic shock), open management is recommended to prevent abdominal compartment syndrome; intra-abdominal pressure may be measured intraoperatively</td>
</tr>
<tr>
<td>2C</td>
<td>Following stabilization of the patient, surgeons should attempt early, definitive closure of the abdomen. Primary fascial closure may be possible only when the risk of excessive tension or recurrent intra-abdominal hypertension (IAH) is minimal</td>
</tr>
<tr>
<td>2C</td>
<td>When early definitive fascial closure is not possible, progressive closure can be gradually attempted at every surgical wound revision. Cross-linked biological meshes may be considered as a delayed option for abdominal wall reconstruction</td>
</tr>
<tr>
<td>1C</td>
<td>When definitive fascial closure cannot be achieved, a skin-only closure is a viable option and subsequent evagination can be managed at a later stage with delayed abdominal closure and synthetic mesh repair</td>
</tr>
<tr>
<td>1B</td>
<td>The component separation technique may be a useful and low-cost option for the repair of large midline abdominal wall hernias</td>
</tr>
<tr>
<td><strong>Antimicrobial prophylaxis</strong></td>
<td></td>
</tr>
<tr>
<td>2C</td>
<td>In patients with intestinal incarceration with no evidence of ischaemia and no bowel resection (CDC wound class I), short-term prophylaxis is recommended</td>
</tr>
<tr>
<td>2C</td>
<td>In patients with intestinal strangulation and/or concurrent bowel resection (CDC wound classes II and III), 48-h antimicrobial prophylaxis is recommended</td>
</tr>
<tr>
<td>2C</td>
<td>Antimicrobial therapy is recommended for patients with peritonitis (CDC wound class IV)</td>
</tr>
<tr>
<td><strong>Anaesthesia</strong></td>
<td></td>
</tr>
<tr>
<td>1C</td>
<td>LA can be used, providing effective anaesthesia with less postoperative complications for emergency inguinal hernia repair in the absence of bowel gangrene</td>
</tr>
</tbody>
</table>
Abbreviations

CDC: Centers for Disease Control and Prevention; OR: odds ratio; RCT: randomized controlled trial; WSES: World Society of Emergency Surgery

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2019 update of the WSES guidelines for management of Clostridioides (Clostridium) difficile infection in surgical patients


Abstract

In the last three decades, Clostridium difficile infection (CDI) has increased in incidence and severity in many countries worldwide. The increase in CDI incidence has been particularly apparent among surgical patients. Therefore, prevention of CDI and optimization of management in the surgical patient are paramount. An international multidisciplinary panel of experts from the World Society of Emergency Surgery (WSES) updated its guidelines for management of CDI in surgical patients according to the most recent available literature. The update includes recent changes introduced in the management of this infection.

Keywords: Clostridioides difficile infection, Clostridium difficile infection, Pseudomembranous colitis, Antimicrobial treatment, Fecal microbiota transplantation, Infection control, Antimicrobial stewardship

Introduction

In the last three decades, the dramatic worldwide increase in incidence and severity of Clostridium difficile infection (CDI) [1] has made CDI a global public health challenge [2–14]. Surgery is a known risk factor for development of CDI yet surgery is also a treatment option in severe cases of CDI [15–18]. The World Society of Emergency Surgery (WSES) guidelines for management of CDI in surgical patients were published in 2015 [19]. In 2019, the guidelines have been revised and updated. A multidisciplinary expert panel worldwide prepared the manuscript following an in-depth review of the most recent current literature using MEDLINE, EMBASE, and Cochrane Database and aimed to provide an insight into these complex issues. The expert panel met via email to prepare, discuss, and revise the paper. The manuscript was successively reviewed by all members and ultimately re-formulated as the present manuscript.
These guidelines outline clinical recommendations based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) hierarchy criteria from Guyatt et al. [20, 21] (Table 1).

*Clostridioides difficile* (formerly *Clostridium difficile*) is an anaerobic, spore-forming, Gram-positive bacillus, which may be part of the normal intestinal microbiota in healthy babies [22–25]. The organism is spread via the oral-fecal route and in hospitalized patients may be acquired through the ingestion of spores from other patients, healthcare personnel’s hands, or from environmental surfaces [26, 27]. *C. difficile* is the main pathogen associated with nosocomial infections and is the most common cause of diarrhea in hospitalized patients [28]. CDI can present as a spectrum of symptoms ranging from an asymptomatic carriage to fulminant disease with toxic megacolon. The basis for this range of clinical manifestations is not fully understood but is likely related to host and pathogen interactions.

The rapid evolution of antibiotic resistance in *C. difficile* and the consequent effects on prevention and treatment of CDIs are a matter of concern for public health. Multi-drug resistant (MDR) *C. difficile* strains are increasing (about 60% of the epidemic strains circulating in hospital settings show resistance to three or more antibiotics) [29].

### Pathogenesis

*C. difficile* spores survive the acidic environment of the stomach and germinate in the intestine [30], which act as a reservoir for *C. difficile* and can facilitate spread among patients, as well as contribute to the high recurrence rates observed in CDI. The primary toxins produced by this bacterium are toxins A and B [31]. Toxins A and B act as glucosyltransferases, promoting the activation of Rho GTPases leading to disorganization of the cytoskeleton of the colonocyte, and eventual cell death [32]. Since CDI is a toxin-mediated infection, non-toxigenic *C. difficile* strains are non-pathogenic. The respective roles and importance of toxins A and B have been debated. Toxin A was thought to be the major virulence factor for many years [33–35]. It is now established that both toxins A and B are important for inducing colonocyte death and colitis, and there is increasing evidence pointing toward their role in CDI extra-intestinal effects [36]. In addition to toxins A and B, some strains

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Strong recommendation, high-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>1B</td>
<td>Strong recommendation, moderate-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses or imprecise conclusions) or exceptionally strong evidence from observational studies</td>
</tr>
<tr>
<td>1C</td>
<td>Strong recommendation, low-quality or very low-quality evidence</td>
<td>Benefits clearly outweigh risk and burdens, or vice versa</td>
<td>Observational studies or case series</td>
</tr>
<tr>
<td>2A</td>
<td>Weak recommendation, high-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
</tr>
<tr>
<td>2B</td>
<td>Weak recommendation, moderate-quality evidence</td>
<td>Benefits closely balanced with risks and burden</td>
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</tr>
<tr>
<td>2C</td>
<td>Weak recommendation, low-quality or very low-quality evidence</td>
<td>Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced</td>
<td>Observational studies or case series</td>
</tr>
</tbody>
</table>
produce a third toxin known as binary toxin [37–41]. Binary toxin has an ADP-ribosyltransferase function, which also leads to actin depolymerization [42, 43]. However, its pathogenetic role is still debated [44, 45].

Asymptomatic \textit{C. difficile} colonization occurs when \textit{C. difficile} is detected in the absence of symptoms of infection. Asymptomatic colonized individuals with no clinical signs of CDI can still act as an infection reservoir and transmit \textit{C. difficile} to others [46, 47]. Asymptomatic colonization with \textit{C. difficile} may be a crucial factor in the progression to CDI, as carriers of toxigenic strains may be at a higher risk for the development of an infection compared to non-colonized patients [48]. Other data suggests that carriage of non-toxigenic \textit{C. difficile} may be protective against toxigenic ribotypes [49]. Estimates of prevalence of asymptomatic \textit{C. difficile} colonization vary considerably between different patient groups. Among healthy adults with no prior risk factors for CDI, asymptomatic colonization prevalence varied between 0 and 15% [50–56].

**Risk factors**

Risk factors for CDI may be divided into three general categories: host factors (immune status, comorbidities), exposure to \textit{C. difficile} spores (hospitalizations, community sources, long-term care facilities), and factors that disrupt normal colonic microbiome (antibiotics, other medications, surgery) [57].

**Patient factors**

Risk factors identified to date include age > 65 years, comorbidity or underlying conditions, inflammatory bowel diseases, immunodeficiency (including human immunodeficiency virus infection), malnutrition, obesity, female sex, and low serum albumin level [3, 58]. Patients with comorbidities may have distinct characteristics of their CDI, for example, in type 2 diabetes mellitus, patients with CDI were younger, and sepsis and proton pump inhibitors (PPIs) were important causes, but fever was not a dominant feature [59].

The effects of prior appendectomy on the development of \textit{C. difficile} colitis have been debated [60]. A review by Seretis et al. [61] of five studies conducted retrospectively and published in 2014 reported that an in situ appendix did not impact on the development of CDI. In the retrospective analysis by Clanton et al. [62] on 55 patients who underwent colectomy for CDI between 2001 and 2011, a prior appendectomy was noted in 24 of 55 patients (44%, 99% CI 0.280–0.606). In another retrospective study of 507 patients [63], 13 of 119 patients (10.9%) with a previous appendectomy required colectomy compared to 20 of 388 patients (5.2%) with an intact appendix developing fulminant infection and requiring colectomy and increased disease severity, indicated by increased rates of colectomy, occurred in the group with a history of appendectomy (\(p = 0.03\)). A sub-group analysis of a large population-based study published in 2013 [64] showed that appendectomy was not associated with adverse outcomes in CDI. Patients with appendectomy before CDI showed no differences in risk factors, treatment, or outcomes including treatment failure, development of severe or severe-complicated CDI, or recurrence rates as compared with patients without appendectomy. Larger prospective studies are needed to assess the impact of prior appendectomy on the development and severity of CDI.

**Exposure to \textit{Clostridium difficile} spores**

Factors that increase risk of exposure to \textit{C. difficile} spores, such as increased duration of hospital stay, increase the risk of CDI. A length of stay > 2 weeks has been shown to be a risk factor for CDI [65]. Hospitals with well-implemented infection prevention and control measures are at lower risk of nosocomial CDI [66].

**Normal flora disruption**

The indigenous gut microflora is a complex community of microorganisms that populates the gastrointestinal tract in a healthy person. This micro-ecosystem plays a crucial role in protecting the intestines by providing resistance to colonization and infection by pathogenic organisms [67]. Gut microbiota has also immeasurable effects on homeostasis of the host [68]. Under normal conditions, the human gut microbiota may impede pathogen colonization through general mechanisms such as direct inhibition through bacteriocins, nutrient depletion (consuming growth-limiting nutrients), or stimulation of host immune defenses [57], though the exact mechanism by which the microflora protects against CDI is unknown [69]. Disruption of the normal balance of colonic microflora as a consequence of antibiotic use or other stressors is, however, of major importance [70].

**Antibiotic exposure**

Disruption of the normal gut flora allows \textit{C. difficile} to proliferate and produce toxins. In 1974, Tedesco et al. published a prospective study of clindamycin-associated colitis, which had become endemic in many hospitals [71]. In 200 consecutive patients, administration of clindamycin resulted in diarrhea in 21% and the incidence of endoscopy-diagnosed pseudomembranous colitis was 10%. The study led to a search for an infectious cause of colitis, and it identified \textit{C. difficile} as the main causative agent [72].

The risk of CDI is increased up to sixfold during antibiotic therapy and in the subsequent month afterwards [73]. Although nearly all antibiotics have been associated with CDI, clindamycin, third-generation cephalosporins,
penicillins, and fluoroquinolones have traditionally been considered to pose the greatest risk [74–80]. An association between CDI and antimicrobial treatment > 10 days has also been demonstrated [81, 82]. Antibiotics which have been less commonly associated with CDI include macrolides, sulfonamides, and tetracyclines [83]. Even very limited exposure, such as singledose surgical antibiotic prophylaxis, can increase patients risk for both *C. difficile* colonization or infection [84–86].

**Other medications**

Exposure to gastric acid-suppressive medications, such as histamine-2 blockers and PPIs, may be a potential risk factor for development of CDI. Several studies have suggested the association between use of stomach acid-suppressive medications, primarily PPIs, and CDI [87, 88]. In 2012, a systematic review of incident and recurrent CDI in PPI users was published [89]. Forty-two observational studies (30 case-control, 12 cohort) totaling 313,000 participants were evaluated. Despite the substantial statistical and clinical heterogeneity, the findings indicated a probable association between PPI use and incident and recurrent CDI. This risk was further increased by concomitant use of antibiotics and PPI. Other studies suggested that this association may be the result of confounding with the underlying severity of illness and duration of hospital stay [90]. Another meta-analysis about a plausible link between CDI and PPIs was recently published [91]. Pooled analysis of 50 studies showed a significant association between PPI use and risk of developing CDI (odds ratio [OR] = 1.26, 95% confidence interval (CI), 1.12–1.39) as compared with non-users.

Even when compared to other gastric acid-suppressive medication, a recent meta-analysis showed that the use of PPI increased the risk of hospital-acquired CDI (OR = 1.386, 95% CI 1.152–1.668) when compared to H2-antagonist [92].

Given that PPIs are overprescribed in surgical settings, consideration should be given to stop PPIs, when they are not necessary, especially in patients at high risk of CDI.

**Nasogastric tube**

The risk of poor clinical outcomes of CDI in patients with nasogastric tube (NGT) insertion is still controversial. In order to assess the outcomes of CDI in patients with NGT insertion, a systematic review and meta-analysis was recently published [93].

Eight observational studies were included in the analysis to assess the association between NGT insertion and risk of poor outcome of CDI. The pooled relative risk (RR) of severe or complicated clinical outcomes of CDI in patients with NGT insertion was 1.81 (95% CI 1.17–2.81).

This study demonstrated a statistically significant association between NGT insertion and risk of poor outcomes of CDI. This finding may impact clinical management and primary prevention of CDI. Avoidance of unnecessary NGT uses would improve the clinical outcomes of CDI.

**Surgery**

Reports have linked the development of CDI in surgical patients to the widespread use of broad-spectrum antibiotics, and the increasing number of elderly and immunocompromised patients undergoing surgical interventions [17, 94, 95].

Abdelsattar et al. [18] prospectively identified postoperative patients with laboratory-confirmed CDI following general, vascular, or gynecological surgeries at 52 academic and community hospitals in the state of Michigan, USA between July 2012 and September 2013. The highest rates of CDI occurred after lower-extremity amputation (2.6%), followed by bowel resection or repair (0.9%) and gastric or esophageal surgeries (0.7%). Gynecological and endocrine surgeries had the lowest rates of CDI (0.1% and 0%, respectively). Multivariate analysis identified increasing age, chronic immunosuppression, hypoalbuminemia (≤3.5 g/dL), and preoperative sepsis to be associated with postoperative CDI.

Zerey et al. [15] performed a 5-year retrospective analysis of the Agency for Healthcare Research and Quality’s National Inpatient Sample Database representing a stratified 20% sample of hospitals in the United States, from 1999 to 2003. Emergency surgery was at higher risk of CDI than elective surgery. Colectomy, small-bowel resection, and gastric resection were associated with the highest risk of CDI. Patients undergoing cholecystectomy and appendectomy had the lowest risk.

In 2010, Rodriguez et al. [96] published a retrospective analysis of all general surgery in patients admitted to a large tertiary referral general surgical unit in the UK, between March 2005 and May 2007. Multivariate analysis identified malignancy, gastrointestinal disease, anemia, respiratory disease, cardiovascular disease, diabetes mellitus, gastrointestinal surgery, and age as independently associated with *C. difficile*.

To assess risk factors for CDI on a surgical ward, in 2012 Kim et al. conducted a retrospective chart review of all patients admitted between January 2010 and July 2011 [97]. The rate of CDI was 0.4% (19/4720 patients). Multivariate analysis showed that colectomy and hospital stays > 10 days were the main risk factors for CDI in the surgical ward.

Using the Japanese Diagnosis Procedure Combination inpatient database, Yasunaga et al. [98] analyzed factors associated with CDI incidence and outcomes following digestive tract surgery. Of 143,652 patients undergoing
digestive tract surgery, CDI was identified in 409 (0.28%) patients. High mortality, long hospital stay, and high costs were associated with post-surgical CDI.

Colorectal surgery is a documented risk factor for CDI [99, 100]. Damle et al. [101] published a retrospective analysis of patients who developed CDI following colorectal resection. The authors identified adult patients undergoing colorectal surgery between 2008 and 2012 from the US University Health System Consortium database. A total of 84,648 patients met study inclusion criteria. CDI occurred in 1266 (1.5%) patients. The strongest predictors of CDI were emergency procedure, inflammatory bowel disease, and severity of illness score. CDI was associated with a higher rate of complications, intensive care unit (ICU) admission, longer preoperative inpatient stay, 30-day readmission rate, and death within 30 days compared to non-CDI patients.

Recently, a retrospective colectomy database review of the 2015 American College of Surgeons National Surgical Quality Improvement Project [102] demonstrated that stoma reversal (OR = 2.701, 95% CI 1.966–3.711; \(p < 0.001\)), smoking (OR = 1.520, 95% CI 1.063–2.174; \(p = 0.022\)), steroids (OR = 1.677, 95% CI 1.005–2.779; \(p = 0.048\)), and disseminated cancer (OR = 2.312, 95% CI 1.437–3.719; \(p = 0.001\)) were associated with CDI in the 30-day postoperative period.

In 2008, Lumpkins et al. published a retrospective observational study on the incidence of CDI in the critically injured trauma population [103]. Five hundred eighty-one consecutive critically injured trauma patients were followed prospectively for development of CDI, diagnosed by toxin assay. Among 581 patients, 19 cases of CDI were diagnosed (3.3%). ICU length of stay, duration of mechanical ventilation, and hospital length of stay were associated with CDI. The diagnosis was documented with a median delay of 17 days after admission. Fourteen patients (74%) had received antibiotics for confirmed or suspected infection prior to CDI; 4 patients (21%) received only intraoperative prophylaxis, and 1 patient had no antibiotic exposure.

Obesity and bariatric surgery

Obesity as a risk factor for CDI has been debated. Several reports have recently proposed obesity as a novel risk factor for CDI [104–106]. On the other hand, Punni et al. [107], in a case-control study, showed that obesity is not a risk factor for CDI. Importantly, body mass > 35 index has been shown to be an independent risk factor for CDI [108].

To investigate the impact of the two most common bariatric surgeries on CDI, Roux-en-Y gastric bypass (RYGB), and vertical sleeve gastrectomy (VSG), a retrospective cohort study was recently published [109]. CDI rates were higher after RYGB than VSG in the first 30 days (OR = 2.10; 95% CI 1.05–4.20) with a similar but not significant trend within 31–120 days.

Knowledge about the link between obesity, bariatric surgery, and CDI is still evolving. Further studies are needed to reveal the exact mechanisms underlying this association. At this stage, we suggest high suspicion for CDI when managing patients with obesity and undergoing bariatric surgery.

Inflammatory bowel disease

Patients with inflammatory bowel disease (IBD) retain an increased risk of developing CDI, along with worse outcomes, higher rates of colectomy, and higher rates of recurrence [110–115].

Patients with IBD also appear to have higher rates of asymptomatic carriage of C. difficile [116]. These patients commonly receive various types of immunosuppressive drugs including steroids which have been found to increase the risk of CDI. In addition, they have a different microbiota compared to healthy subjects [117, 118].

A recent retrospective study evaluated the impact of CDI on in-hospital outcomes among adults with IBD hospitalized in the USA [119]. Using the 2007–2013 Nationwide Inpatient Sample, hospitalizations among US adults with Crohn’s disease (CD), ulcerative colitis (UC), and CDI were identified using ICD-9 coding. Hospital charges, hospital length of stay (LOS), and in-hospital mortality was stratified by CD and UC and compared. Predictors of hospital charges, LOS, and in-hospital mortality were evaluated with multivariate regression models and were adjusted for age, sex, race/ethnicity, year, insurance status, hospital characteristics, and CDI. Among 224,500 IBD hospitalizations (174,629 CD and 49,871 UC), overall prevalence of CDI was 1.22% in CD and 3.41% in UC. On multivariate linear regression, CDI was associated with longer LOS among CD (coefficient: 5.30, 95% CI 4.61–6.99; \(p < 0.001\)) and UC (coefficient: 4.08, 95% CI 3.54–4.62; \(p < 0.001\)). Higher hospital charges associated with CDI were seen among CD (coefficient: $35,720, 95% CI $30,041–$41,399; \(p < 0.001\)) and UC (coefficient: $26,009, 95% CI $20,970–$31,046; \(p < 0.001\)). CDI among IBD was associated with almost threefold greater risk of in-hospital mortality.

The clinical presentation of an IBD exacerbation and CDI often is indistinguishable and requires a high index of suspicion for adequate treatment [6]. As the symptoms of CDI and an exacerbation of IBD (diarrhea, abdominal pain, fever, and leukocytosis) overlap, the diagnosis of CDI may be delayed [120]. In addition, in IBD patients with ileostomies, the development of acute enteritis manifested as an increase in ileostomy output,
nausea, fever, and leukocytosis may also indicate CDI. The same is true for pouchitis, which presents as an increase in the number of stools per day [121]. In one study, 10.7% of patients with ileal pouch anal anastomosis, presenting with pouchitis, were found to have CDI [122].

Due to high rates of asymptomatic colonization by *C. difficile* in patients with IBD, only patients with increased diarrhea or new symptoms potentially due to CDI should be tested for *C. difficile* toxin. Typical findings of CDI on colonoscopy are often absent in patients with IBD (0–13% of cases) [123] which may be attributed to a weakened inflammatory response. There is no evidence that one antibiotic regimen is better than another for the treatment of CDI in IBD patients. In a survey of North American gastroenterologists, there was no agreement on combination of antibiotics and immunomodulators in patients with an IBD flare and CDI [124]. The American College of Gastroenterology recommended with low-quality supporting evidence, that ongoing immunosuppression can be maintained in patients with CDI and that escalation of immunosuppression should be avoided [125].

An expert review to synthesize the existing evidence on the management of CDI in patients with underlying inflammatory bowel disease was published in 2017. The review suggested six simple advices of best practice [126].

Physicians should remain alert to the possibility of CDI in a patient with an IBD exacerbation to ensure rapid diagnosis and treatment. Early surgical consultation is also key for improving outcomes of patients with severe disease. Colectomy with preservation of the rectum may need to be considered for severely ill IBD patients with CDI.

**Immunocompromised patients**

The rate of CDI is increased in solid organ transplant recipients due to ongoing immunosuppression and antibiotic use [127].

It has also been reported that cancer patients have a higher risk compared with non-cancer patients [128] due to chemotherapy causing immunosuppression [129, 130].

Patients with HIV/AIDS are also at high risks of being infected with *C. difficile* too. The risk is stronger in those with low absolute CD4 T cell counts or those who meet clinical criteria for AIDS [131].

The increased risk may be partially attributed to frequent hospitalization, exposure to antibiotics, and antibiotic prophylaxis for opportunistic infections, but HIV-related alterations in fecal microbiota, gut mucosal integrity, and humoral and cell-mediated immunity may also likely play a role [132].

**Risk factors for community-acquired* C. difficile* infection**

Although predominantly associated with the inpatient health care population, CDI originating in the community has been increasingly reported. The predominant *C. difficile* ribotypes isolated in the hospital setting correspond with those isolated in the community, suggesting that transmission between these two settings is occurring [133].

In 2011, an estimated 159,000 community-associated CDI (CA-CDI) occurred in the USA, representing 35% of the total CDI burden [134].

Risk factors may include increasing outpatient antibiotic prescriptions, acid-suppression medications, asymptomatic carriers in the community, and food or water contamination [135]. A sub-group analysis of a population-based epidemiological study of CDI in Olmsted County, Minnesota in 1991–2005 [136], identified 157 CA-CDI cases (75% women), with a median age of 50 years. Among them, 40% required hospitalization, 20% had severe, and 4.4% severe-complicated infection, while 20% had treatment failure and 28% had recurrent CDI.

A case-control study from ten US sites from October 2014 to March 2015 analyzed risk factors for CA-CDI [137]. Case patients were defined as persons aged ≥18 years with a positive *C. difficile* specimen collected as an outpatient or within 3 days of hospitalization who had no admission to a health care facility in the prior 12 weeks and no prior CDI diagnosis. Each case patient was matched to one control (persons without CDI). Participants were interviewed about relevant exposures; multivariate conditional logistic regression was performed. More case patients than controls had prior outpatient health care (82.1% vs. 57.9%; *p* < 0.0001) and antibiotic (62.2% vs. 10.3%; *p* < 0.0001) exposures. In multivariate analysis, antibiotic exposure—that is, cephalosporin (adjusted matched odds ratio [AmOR], 19.02; 95% CI 1.13–321.39), clindamycin (AmOR, 35.31; 95% CI 4.01–311.14), fluoroquinolone (AmOR, 30.71; 95% CI 2.77–340.05), and beta-lactam and/or beta-lactamase inhibitor combination (AmOR, 9.87; 95% CI 2.76–340.05)—emergency department visit (AmOR, 17.37; 95% CI 1.99–151.22), white race (AmOR 7.67; 95% CI 2.34–25.20), cardiac disease (AmOR, 4.87; 95% CI 1.20–19.80), chronic kidney disease (AmOR, 12.12; 95% CI 1.24–118.89), and IBD (AmOR, 5.13; 95% CI 1.27–20.79) were associated with CA-CDI.

A systematic review and meta-analysis investigated the association between medications and comorbidities with CA-CDI [138]. Twelve publications (*n* = 56,776 patients) met inclusion criteria. Antimicrobial (OR = 6.18, 95% CI 3.80–10.04) and corticosteroid (OR = 1.81, 95% CI 1.15–2.84) exposure were associated with increased risk of...
CA-CDI. Among the comorbidities, IBD (OR = 3.72, 95% CI 1.52–9.12), renal failure (OR = 2.64; 95% CI 1.23–5.68), hematologic malignancy (OR = 1.75; 95% CI 1.02–5.68), and diabetes mellitus (OR = 1.15; 95% CI 1.05–1.27) were associated with CA-CDI. Antimicrobial exposure was associated with a higher risk of CA-CDI in the USA, whereas PPI exposure was associated with a higher risk in Europe. The risk of CA-CDI associated with antimicrobial exposure greatly increased in adults older than 65 years.

Risk factors for recurrent CDI

Recurrent CDI (RCDI) can be defined as reappearance of symptoms within eight weeks following the completion of a course of therapy with complete resolution of symptoms.

The key to preventing recurrent infection is identifying those patients at the greatest risk [139].

In a meta-analysis, Garey et al. [140] found that continued use of non-C. difficile antibiotics after diagnosis of CDI (OR = 4.23; 95% CI 2.10–8.55; p < 0.0001), concomitant receipt of antacid medications (OR = 2.15; 95% CI 1.13–4.08; p = 0.019), and older age (OR = 1.62; 95% CI 1.11–2.36; p = 0.0012) were associated with increased risk of recurrent CDI. Other factors identified in individual studies include age, hospital exposure, comorbid conditions, severe underlying illness, hypoalbuminemia, impaired humoral immunity, poor quality of life, disease severity, and previous recurrent CDI [141–144].

In order to evaluate current evidence of risk factors for recurrent CDI, a systematic review and meta-analysis [145] analyzed 33 studies (18,530 patients). The most frequent independent risk factors for recurrent CDI were age ≥ 65 years (RR = 1.63, 95% CI 1.24–2.14; p = 0.0005), additional antibiotics during follow-up (RR = 1.76; 95% CI 1.52–2.05; p < 0.001), use of PPIs (RR = 1.58; 95% CI 1.13–2.21; p = 0.008), and renal failure (RR = 1.59; 95% CI 1.14–2.23; p = 0.007). The risk was also increased in patients previously on fluoroquinolones (RR = 1.42; 95% CI 1.28–1.57; p < 0.001).

Clinical manifestations

The spectrum of symptomatic CDI ranges from mild diarrhea to severe disease or fulminant colitis and as many as 30% of patients may develop recurrent CDI [146, 147].

Though diarrhea is the hallmark symptom of CDI, it may not be present initially, possibly due to colonic dysmotility either from previous underlying conditions or possibly from the disease process itself [148].

This is especially important in surgical patients who may have a concomitant ileus. Therefore, in surgical patients, it is important to have a high index of suspicion for the development of CDI.

Mild-moderate CDI

Diarrhea may be accompanied by mild abdominal pain and cramps and if prolonged may result in altered electrolyte balance and dehydration. When this occurs in patients with severe comorbidity, particularly after surgery, non-severe CDI may increase morbidity significantly [149].

Severe CDI

Severe CDI is associated with increased abdominal cramping and pain as well as systemic features such as fever, leukocytosis, and hypoalbuminemia. The absence of diarrhea may signal a progression to fulminant infection [150]. Though a wide variety of severity predictors for severe CDI has been described [151–156], international consensus for the definition of severe CDI is lacking [6, 7].

A systematic review identifying risk factors for adverse outcomes of CDI was published by Abou Chakra et al. in 2012 [154]. Except for leukocytosis, albumin, and age, there was much heterogeneity in the data and most studies were limited by small sample sizes.

To investigate the prognostic value of fever, leukocytosis, and renal failure, in 2012 Bauer et al. [153] analyzed the database of two randomized controlled trials, which contained information on 1105 patients with CDI. They found that both leukocytosis and renal failure were useful predictors of severe CDI. Miller et al. [155] in 2013 subsequently published an analysis of the same two clinical therapeutic trials to validate a categorization system to stratify CDI patients into severe or mild-moderate groups. A combination of five simple and commonly available clinical and laboratory variables (ATLAS) measured at the time of CDI diagnosis were able to accurately predict treatment response to CDI therapy. The ATLAS criteria included age, treatment with systemic antibiotics, leucocyte count, serum albumin, and serum creatinine levels.

Any of the following may be predictors of severe CDI:

- WBC > 15 × 10⁹/L
- Rise in serum creatinine level (≥ 133 μM/L or ≥ 1.5 times premorbid level)
- Temperature > 38.5 °C
- Albumin < 2.5 g/dL

It has been recently demonstrated that human serum albumin is capable to bind C. difficile toxin A and B thus impairing their internalization into host cells; this could partially explain the increased CDI severity experienced by hypoalbuminemic patients [157].

The progression to fulminant C. difficile colitis is relatively infrequent [158] (1–3% of all CDI) though mortality in this group of patients remains high due to the
development of toxic megacolon with colonic perforation, peritonitis, and septic shock and subsequent organ dysfunction. Systemic symptoms may not merely result from toxin-induced inflammatory mediators released locally in the colon but likely to the toxins spread into the bloodstream [36, 159, 160].

Studies have demonstrated a significant rise in the number of cases of fulminant colitis associated with multiple organ failure and increased mortality in recent years associated with the hypervirulent 027 strain of \textit{C. difficile} [161, 162]. Early diagnosis and treatment is therefore important in reducing the mortality associated with fulminant colitis. Patients who present organ failure including increased serum lactate or vasopressor requirements should be assessed immediately with regard to early operative intervention [162].

Recurrent CDI

Recurrence of symptoms after initial therapy for \textit{C. difficile} develops in 10–30% of cases, and presents a clinical challenge [144, 163–167]. For a patient with 1–2 previous episodes, the risk of further recurrences is 40–65%.

Recurrences are associated with an impaired immune response to \textit{C. difficile} toxins and/or alteration of the colonic microbiota.

RCDI may be either a consequence of germinating resident spores remaining in the colon after antibiotic treatment has stopped, or re-infection from an environmental source.

Even though consensus regarding factors associated with CDI recurrence is not universal, algorithms have been developed to predict CDI recurrence with good sensitivity [168].

Ultimately, distinction between recurrence and re-infection can only be achieved if the strain of \textit{C. difficile} is “typed” using molecular epidemiology [169].

Recurrent episodes are less severe compared to initial episodes: in a Canadian study, the authors reported a decline in the proportion of severe cases according to the number of recurrent episodes (47% for initial episodes, 31% for first recurrences, 25% for second, and 17% for third) [170].

Additional significant consequences of CDI

Patients who develop CDI have increased hospital length-of-stay, higher medical care costs, more hospital re-admissions, and higher mortality [171–173]. These consequences are also found in surgical patients with CDI.

In the Zerey et al. analysis [15], CDI was an independent predictor of increased length of stay, which increased by 16.0 days (95% CI 15.6–16.4 days; \(p < 0.0001\)). Total charges increased by $77,483 (95% CI $75,174, $79,793; \(p < 0.0001\)), and there was a 3.4-fold increase in the mortality rate (95% CI 3.02–3.77; \(p < 0.0001\)) compared with patients who without \textit{C. difficile infection}.

In the Abdelsattar et al. study [18], postoperative CDI was independently associated with increased length of stay (mean, 13.7 days vs. 4.5 days), emergency department presentations (18.9 vs. 9.1%), and readmissions (38.9% vs. 7.2%, all \(p < 0.001\)).

Data from Nationwide Inpatient Sample database in 2011 of patients who underwent vascular surgery [174] showed that in patients who had experienced CDI, the median length of stay was 15 days (IQR 9, 25 days) compared to 8.3 days for matched patients without CDI, in-hospital mortality 9.1% (compared to 5.0%), and $13,471 extra cost per hospitalization. The estimated cost associated with CDI in vascular surgery in the USA was about $98 million in 2011. Similarly, data from the National Inpatient Sample in patients undergoing lumbar surgery found that CDI increased length of stay by 8 days, hospital costs by 2-fold, and increased inpatient mortality by 36-fold [175].

Higher mortality was also observed for liver transplant recipients (from 2000 to 2010) at a Detroit hospital [176].

The ACS-NSQIP database from 2005 to 2010 was used by Lee et al. to study emergently performed open colectomies for a primary diagnosis of \textit{C. difficile} colitis in the USA [177]. The overall mortality was 33% (111/335).

A study was performed to quantify additional hospital stay attributable to CDI in four European countries, by analyzing nationwide hospital-episode data [5]. Patients in England had the largest additional hospital stay attributable to CDI at 16.09 days, followed by Germany at 15.47 days, Spain at 13.56 days, and The Netherlands at 12.58 days. Propensity score matching indicated a higher attributable length of stay of 32.42 days in England, 15.31 days in Spain, and 18.64 days in the Netherlands. Outputs from this study consistently demonstrate that in European countries, in patients whose hospitalization is complicated by CDI, the infection causes a statistically significant increase in hospital length of stay.

Recommendations for the management of CDI

Infection prevention and control

An infection control “bundle” strategy should be used to successfully control CDI outbreaks. The “bundle” approach should include multifaceted interventions including antibiotic stewardship, hand hygiene, isolation measures, and environmental disinfection.

1. Proper antibiotic stewardship in both selecting an appropriate antibiotic and optimizing its dose and
duration to prevent and cure an infection may prevent the emergence of *C. difficile* (Recommendation 1 B).

As CDI is thought to follow disruption of normal bacterial flora of the colon, a consequence of antibiotic use [178], it is logical that antibiotic stewardship programs may be useful in preventing CDI [179]. Good antibiotic stewardship involves ensuring appropriate antibiotic choices and optimizing antibiotic doses and duration of treatment to prevent and cure an infection while minimizing toxicity and conditions conducive to the development of CDI.

In order to estimate the effectiveness and safety of interventions to improve antibiotic prescribing practices in hospital inpatients in 2017, a systematic review including 221 studies (58 RCTs, and 163 NRS) was published [180]. The results showed a very low level of evidence regarding the effect of interventions to reduce CDI (median – 48.6%, interquartile range – 80.7% to – 19.2%; seven studies).

Another systematic review and meta-analysis quantified the effect of both persuasive (education and guidance) and restrictive (approval required, removal) antimicrobial stewardship programs for CDI [179]. A significant protective role (overall RR = 0.48, 95% CI 0.38–0.62) was found, with the strongest evidence for restrictive program and those with the longest duration. Cephalosporins and quinolones reduction should be an important target for stewardship programs, with a significant expected impact on the incidence of CDI [181, 182].

2. *C. difficile* carriers should be placed in contact (enteric) precautions (Recommendation 1 B). Even if further studies are warranted to establish the benefit of screening and the efficacy of infection control measures for asymptomatic carriers.

Prompt identification of patients with CDI is essential, so that appropriate isolation precautions can be put into effect [183].

This is particularly important in reducing environmental contamination as spores can survive for months in the environment [184], despite regular use of environmental cleaning agents.

It is important to place patients suspected of having CDI on contact precautions before diagnostic laboratory test confirmation if there is a lag before test results are available [185].

Contact (enteric) precautions in patients with CDI should be maintained until the resolution of diarrhea, which is demonstrated by passage of formed stool for at least 48 h. There are no studies demonstrating that further extension of contact precautions results in reductions in CDI incidence.

*C. difficile* carriers should be placed in a private room [186] with en-suite hand washing and toilet facilities. If a private room is not available, known CDI patients may be cohorted in the same area [187] though the theoretical risk of transfection with different strains exists. This is supported by a retrospective cohort of 2859 patients published by Chang et al. [188]. Non-infected patients who were roommates or neighbors of a patient with CDI were at higher risk of nosocomial acquisition of CDI (RR 3.94; 95% CI 1.27–12.24).

Recently, there has been growing interest in asymptomatic carriage/colonization of *C. difficile* since asymptomatic carriers are considered a reservoir for *C. difficile*. Colonization by toxigenic *C. difficile* strain seems to be associated with increased risk of progressing to CDI. Zacharioudakis et al. [48] showed that carriers of toxigenic strains are at a higher risk for the development of an infection compared to non-colonized patients. On the other hand, patients colonized by non-toxigenic strains may be even protected from developing CDI [189]. Conversion of a non-toxigenic strain to a toxin producer by horizontal gene transfer makes the risk assessment of colonization really challenging [190]. More data are needed to assess the precise role of the microbiota and the conditions allowing progression from asymptomatic colonization to CDI, in particular the recognition of the mechanism which may trigger toxin production. Based on current data, screening for asymptomatic carriers and an eradication of *C. difficile* is not indicated because *C. difficile* colonization is not believed to be a direct independent precursor for CDI. *C. difficile* asymptomatic carriers may also play a role in spore dissemination in the hospital and many cases of CDI are thought to be attributable to cross-contamination from asymptomatic carriers. Curry et al. [191] examined patients for *C. difficile* colonization and found that 29% of CDIs were linked to asymptomatic *C. difficile* carriers. Asymptomatic carriers who are colonized at admission appear to contribute to sustaining *C. difficile* transmission in the ward by the shedding of spores to the environment. The frequency of environmental contamination depends on the *C. difficile* status of the patient—34% of rooms of patients with asymptomatic colonization and 49% of rooms of CDI patients were found to be contaminated with *C. difficile* [192]. Infection control measures for asymptomatic carriers may be effective by limiting contamination of the hospital environment and health care workers’ hands, as well as by preventing direct patient-to-patient transmission. Longtin et al. [185] reported that screening of *C. difficile* colonization at hospital admission and contact precautions were associated with a significant decrease in the HA-CDI incidence rate (6.9 per 10,000 patient-days in the pre-intervention period vs. 3.0 per 10,000 patient-days during the intervention period;
p < 0.001). This study provides the most convincing evidence to date for the significant effect of isolating asymptomatic carriers.

3. Hand hygiene with soap and water is the cornerstone of the prevention of C. difficile infection. Hand hygiene, contact precautions, and good cleaning and disinfection of patient care equipment and the environment should be used by all health-care workers in contact with any patient with known or suspected CDI (Recommendation 1 B).

In a health-care setting, transmission of C. difficile spores occurs primarily via the contaminated hands of health-care workers, but contact with a contaminated environment, contaminated utensils or medical devices has also been implicated. Hand hygiene with soap and water and the use of contact precautions along with good cleaning and disinfection of the environment and patient equipment should be used by all health-care workers in contact with any patient with known or suspected CDI. Hand hygiene is a cornerstone of prevention of nosocomial infections, including infection due to C. difficile. Alcohol-based hand sanitizers are highly effective against non-spore-forming organisms, but they do not kill C. difficile spores or remove C. difficile from the hands [193].

Though disposable glove use during care of a patient with CDI may be effective in preventing the transmission of C. difficile, these must be removed at the point of use and the hands should then be thoroughly decontaminated with soap and water.

For environmental cleaning, disinfection with sodium hypochlorite solutions are usually recommended in patient areas where C. difficile transmission is ongoing [194].

In 2016, a cross-sectional study was conducted in a tertiary care hospital to analyze the impact of location of sinks on hand washing compliance after caring for patients with CDI. Healthcare workers’ hand washing compliance was low, and a poor access to sinks was associated with decreased hand washing compliance [195].

Environmental decontamination of clinical areas, ideally using hypochlorite agents or a sporicidal product, is recommended; however, in practice, compliance with cleaning protocols is often suboptimal.

In 2017, a qualitative systematic review including 46 studies investigated the impact of specific interventions on CDI rates in acute-care hospitals. The most effective interventions, resulting in a 45% to 85% reduction in CDI, included daily to twice daily disinfection of high-touch surfaces (including bed rails) and terminal cleaning of patient rooms with chlorine-based products. Chlorhexidine bathing and intensified hand-hygiene practices were not effective for reducing CDI rates [196].

Newer alternatives for environmental decontamination have been introduced, notably hydrogen peroxide vapor (HPV) and, more recently, UV decontamination [197].

In a study conducted by McCord et al., breakpoint time series analysis indicated a significant reduction (p < 0.001) in the CDI rate at the time when HPV disinfection was implemented, resulting in a reduction in the CDI rate from 1.0 to 0.4 cases per 1000 patient-days in the 24 months before HPV usage compared with the first 24 months of HPV usage [198].

Recently, a systematic literature review and meta-analysis on the impact of no-touch disinfection methods to decrease HAIs was performed [199]. Statistically significant reduction in CDI (RR = 0.64; 95% CI 0.49–0.84) was observed using UV light no-touch disinfection technology. Important to point out that the new no-touch methods for room disinfection supplement, but do not replace, daily cleaning [200].

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) study group for C. difficile (ESGCD) recently published a set of guidelines regarding measures for prevention of C. difficile infection in acute healthcare settings [201]. According to the committee, it is recommended:

- To use personal protective equipment (gloves and gowns/disposable aprons) to decrease transmission of C. difficile or incidence of CDI
- To use contact precautions to decrease the transmission of C. difficile and reduce the incidence of CDI
- To introduce daily environmental sporicidal disinfection and terminal disinfection of rooms of patients with CDI to decrease the transmission of CDI
- To perform surveillance of CDI in combination with timely feedback of infection rates on both the hospital and ward level
- To implement restriction protocols of antibiotic agents/classes (effective in reducing CDI rates)
- To implement protocols to reduce the duration of antibiotic therapy (effective in reducing CDI rates)
- Educate healthcare workers on prevention of CDI to enhance their knowledge and skills on prevention strategies

It is not recommended:

- To screen for C. difficile to identify colonized/carrier patients as a way of altering the risk of developing CDI in either colonized subjects or other patients and thus reducing CDI rates
- To screen health care workers for C. difficile gut colonization as a routine control measure for CDI
Diagnosis

4. The diagnosis of CDI should be based on clinical signs and symptoms in combination with laboratory tests. Stool testing should only be performed on diarrheal stools from at-risk patients with clinically significant diarrhea (≥3 loose stools in 24 h) with no obvious alternative explanation (Recommendation 1 C).

5. For patients with ileus who may be unable to produce stool specimens, polymerase chain reaction testing of perirectal swabs provides an acceptable alternative to stool specimen analysis (Recommendation 2B).

Typing is useful to differentiate \textit{C. difficile} strains and to obtain epidemiological information. Different typing methods for \textit{C. difficile} currently available are: restriction endonuclease analysis (REA), pulsed-field gel electrophoresis (PFGE), multi-locus sequence typing (MLST), repetitive-element PCR typing, toxin-typing, multi-locus variable-number tandem-repeat analysis (MLVA), and PCR-ribotyping [201]. \textit{C. difficile} strains with increased virulence traits (hypervirulent) have been described in the last 15 years. In particular, PCR-ribotype 027, also known as North American pulsed-field gel electrophoresis type 1 (NAP1) or restriction endonuclease analysis group BI, has been associated with increased disease severity, recurrence, and significant mortality [202].

The diagnosis of \textit{C. difficile} infection should be suspected in patients with acute diarrhea (≥3 loose stools in 24 h) with no obvious alternative explanation (such as laxative use), particularly in the setting of relevant risk factors (including recent antibiotic use, hospitalization, and advanced age).

Prompt and precise diagnosis is important for the effective management of CDI. An accurate diagnosis of CDI requires both clinical symptoms and a positive laboratory test.

Early identification of CDI allows early treatment and can potentially improve outcomes. Rapid isolation of infected patients is important in controlling the transmission of \textit{C. difficile} [203].

The diagnosis of CDI is based on the presence of a clinical picture compatible with CDI and microbiological evidence of free toxin and/or the demonstration of toxigenic \textit{C. difficile} in a diarrhea stool sample [203]. Clinical features include diarrhea (defined as by passage of three or more unformed stools in 24 h), abdominal pain and cramps, abdominal distension, ileus (signs of severely disturbed bowel function), and toxic megacolon.

Since \textit{C. difficile} can colonize the intestinal tract of healthy individuals, diagnostic testing for CDI should be performed only on diarrheic stools from symptomatic patients. Testing of formed stool can result in false positive tests, which may result in unnecessary antibiotic therapy.

One limitation of the reliance on stool specimens involves patients with suspected severe CDI complicated by ileus as those patients may be unable to produce specimens for testing. For those patients, testing of perirectal swabs may be an accurate and efficient method to detect toxigenic \textit{C. difficile}. In 2012, Kundrapu et al. [204] described the results of a prospective study of 139 patients being tested for \textit{C. difficile} infection by polymerase chain reaction. The sensitivity, specificity, positive predictive value, and negative predictive value of testing perirectal swabs were 95.7%, 100%, 100%, and 99.1%, respectively. The authors concluded that for selected patients, perirectal swabs provided an acceptable alternative to stool specimen analysis.

Clinical context such as a history of recent antibiotic administration and/or residence in hospital are useful in selecting patients for testing. Other signs such as fever, abdominal pain, leukocytosis, in combination with other laboratory tests (e.g., creatinine and serum lactate) are useful for defining the severity of infection.

6. Nucleic acid amplification tests (NAAT) for \textit{C. difficile} toxin genes appear to be sensitive and specific and may be used as a standard diagnostic test for CDI. NAAT as single-step algorithm can increase detection of asymptomatic colonization, therefore it should be performed in patients with high suspicion for CDI or included in two-step algorithm starting with toxin-EIA (Recommendation 1 B).

7. Glutamate dehydrogenase (GDH) screening tests for \textit{C. difficile} are sensitive but do not differentiate between toxigenic and non-toxigenic strains. They may be used in association with toxin A/B enzyme immunoassays (EIA) testing. Algorithms including screening with an EIA for GDH followed by a toxin assay may be suggested (Recommendation 1 B).

8. EIA for toxin A/B is fast and inexpensive and has high specificity but it is not recommended alone due to its relatively low sensitivity (Recommendation 1 B).

9. \textit{C. difficile} culture is relatively slow but sensitive. It is rarely performed today as a routine diagnostic test. \textit{C. difficile} culture is recommended for subsequent epidemiological typing and characterization of strains (Recommendation 1 C).

10. Repeat testing after a first negative sample during the same diarrheal episode may be useful only in selected cases with ongoing clinical suspicion during an epidemic situation or in cases with high clinical suspicion during endemic situations (Recommendation 1 C).
The best standard laboratory test for diagnosis of CDI has not been clearly established [205].

Currently, there is no single stool test that can be relied upon as the reference standard for the diagnosis of CDI. Several methods are suggested for the diagnosis of CDI, including toxigenic culture (TC), cell cytotoxicity neutralization assay (CCNA), enzyme immunoassays (EIA) for toxins A, B, and/or glutamate dehydrogenase (GDH), and nucleic acid amplification tests (NAATs).

In the past, TC was accepted by many microbiologists as the method of choice for diagnosis of CDI. The procedure includes stool culture for C. difficile on a selective differential medium (cycloserine, cefoxitin, fructose agar, or CCFA) and an assay to test the colonies for the ability to produce toxins. Despite TC is considered the gold standard method, there are significant issues with TC including slow turnaround time and its inability to detect the presence of toxins in stool. This may also lead to false positive results as up to 7% of asymptomatic hospitalized patients may be colonized with toxigenic C. difficile [206].

C. difficile culture is also necessary for subsequent epidemiological typing and characterization of strains.

The EIA for toxin A/B has been adopted by most clinical laboratories because it is fast, convenient, and inexpensive [207]. However, studies have shown that sensitivity can be low. Toxin A + B EIA tests have a described sensitivity of 32–98% and a specificity of 84–100% [208].

GDH is an enzyme produced by C. difficile in relatively large amounts compared with toxins A and B [209, 210]. A positive GDH assay only documents the presence of C. difficile but it does not discriminate between toxigenic and non-toxigenic strains (about 20% of the C. difficile population). Therefore, a second test for toxin production is necessary for confirmation. GDH screening tests for C. difficile used in association to toxin A + B EIA testing gives an accurate test result quickly [207, 208] even if the sensitivity of such strategy is lower than NAATs.

The use of NAATs for the detection of C. difficile from diarrheal stool specimens was documented in the early 1990s. NAATs possess a series of advantages such as excellent sensitivity and specificity, low complexity, simplified reporting, reduced need for repeat testing, and improved turnaround time [209–212].

In particular, some NAATs such as multiplex NAATs can simultaneously detect C. difficile strains and toxin encoding genes from stool samples [213].

There are several commercially available NAATs, including a real-time PCR (RT-PCR) assay and loop-mediated isothermal amplification (LAMP) assay, both of which have an overall high analytical sensitivity (80–100%) and specificity (87–99%).

However, although NAATs have a high sensitivity and specificity, not all laboratories routinely perform this assay [214]. Moreover, some limitations have been associated with NAATs [215].

Although NAAT methods are considered superior to other methods of diagnosing CDI, this testing strategy is unable to accurately distinguish between C. difficile colonization and active disease, which may result in both over diagnosis and overtreatment of CDI, delaying recognition of other causes of diarrheal illness/outbreaks, and resulting in unnecessary exposure to antibiotics used to treat CDI.

A current topic of debate is whether a stool sample that was positive by a molecular assay needs to be tested with a confirmatory toxin assay [216] given it can also identify toxigenic C. difficile in asymptomatic patients. This underscores the importance of only testing patients with symptoms. There is no evidence suggesting that surgical patients should be diagnosed any differently than general medical patients [217]. It has already been highlighted that immunocompromised patients including those on glucocorticoids, or chemotherapy and post-transplant patients are at increased risk for CDI.

The issue of if or when to retest for CDI is inherently linked to the accuracy of the employed routine testing method. Methods with suboptimal sensitivity for C. difficile (e.g., stand-alone toxin EIAs) led to frequent retesting in some settings. In the absence of clear changes to the clinical presentation of suspected CDI (i.e., change in character of diarrhea or new supporting clinical evidence), repeating testing should not be performed.

11. CT imaging is suggested for patients with clinical manifestations of severe-complicated C. difficile colitis; however, its sensitivity is not satisfactory for screening purposes (Recommendation 2 B).

In certain clinical settings, adjunct testing methods such as radiologic diagnostic imaging may be useful for diagnosing CDI. Diagnostic computed tomography (CT) imaging can assist with an early diagnosis and may help determine the severity of the disease in patients with CDI [218].

CT has been studied as an imaging modality for diagnosing C. difficile colitis [219–222]. Typical CT findings of CDI include colonic wall thickening, dilatation, peri-colonic stranding, “accordion sign” (high-attenuation oral contrast in the colonic lumen alternating with low-attenuation inflamed mucosa), “double-halo sign, target sign” (intravenous contrast displaying varying degrees of attenuation caused by submucosal inflammation and hyperemia), and ascites [223]. However, the most common finding, colonic wall thickening, is non-specific and can be found in other forms of colitis, although it may be more pronounced with CDI.
In the study by Kirkpatrick et al. [224], CT diagnosis of CDC had a sensitivity of 52%, a specificity of 93%, and positive and negative predictive valued 88%, and 67% respectively. Sensitivity would have been increased to 70% with no change in specificity if colonic wall thickness of greater than 4 mm had been used as a diagnostic criteria, in conjunction with the presence of the following factors, colon wall nodularity, accordion sign, peri-colonic stranding, or otherwise unexplained ascites.

12. Ultrasound may be useful in critically ill patients suspected to have pseudomembranous colitis who cannot be transported to the CT scan suite (Recommendation 2 C).

Point-of-care ultrasound may be useful in diagnosing and managing critically ill patients who cannot be moved to the radiology department [225]. Ultrasound findings of pseudomembranous colitis in severe cases include a thickened colonic wall with heterogeneous echogeneity as well as narrowing of the colonic lumen [226]. Pseudomembranes can also be visualized as hyperechoic lines covering the mucosa [226–229].

In the early stages of pseudomembranous colitis, the texture of the colonic wall is preserved. The hyperechoic edematous mucosa and muscularis propria may be thickened with the echogenic submucosa sandwiched between them. The presence of submucosal gaps may indicate extension of tissue damage into deeper structures. Intraperitoneal free fluid is seen in more than 70% of cases [224–227].

13. Flexible sigmoidoscopy may be helpful in the diagnosis of C. difficile colitis when there is a high level of clinical suspicion for C. difficile infection (Recommendation 2 B).

Endoscopy should be used sparingly to confirm the diagnosis of CDI since the diagnosis can be usually made by laboratory tests, clinical findings, and imaging. However, colonoscopy may be hazardous in the setting of fulminant colitis where there may be increased risk of perforation [169].

A study by Johal et al. [230] described the use of flexible sigmoidoscopy as a tool for the diagnosis of C. difficile colitis when stool assays were negative suggesting that sigmoidoscopy should be considered in all hospitalized patients with diarrhea in whom the stool tests for C. difficile cytotoxin and enteric pathogens are negative.

Antibiotic therapy

14. Unnecessary antibiotic agent(s) should be discontinued if CDI is suspected (Recommendation 1 B).

15. Unnecessary PPIs should always be discontinued in patients at high risk for CDI (Recommendation 1 C).

16. Empirical therapy for CDI should be avoided unless there is a strong suspicion for CDI. If a patient has a strong suspicion for severe CDI, empirical therapy for CDI should be considered while awaiting test results (Recommendation 1 C).

In cases of suspected severe CDI, antibiotic agent(s) should be discontinued, if possible [231].

A meta-analysis addressing factors associated with prolonged symptoms and severe disease due to C. difficile showed that continued use of antibiotics for infections other than CDI is significantly associated with an increased risk of CDI recurrence [232].

If continued antibiotic therapy is required for treatment of the primary infection, antimicrobial therapy with agents that are less frequently implicated with antibiotic-associated CDI should be used; these include parenteral aminoglycosides, sulfonamides, macrolides, vancomycin, or tetracycline/tigecycline.

Although there is a clinical association between PPI use and CDI [89], no RCTs studies have studied the relationship between discontinuing or avoiding PPI use and risk of CDI. Thus, a strong recommendation to discontinue PPIs in patients at high risk for CDI regardless of need for PPI will require further evidences. However, stewardship activities to discontinue unneeded PPIs are strongly warranted.

Antibiotic therapy is the first choice for CDI, and specific antibiotic therapy guideline recommendations should be based on the severity of the disease.

When antibiotic therapy is indicated for symptomatic cases with a positive C. difficile toxin result, options include metronidazole, oral or intraluminal vancomycin, and oral fidaxomicin [233–239].

17. Oral metronidazole should be limited to the treatment of an initial episode of mild-moderate CDI (Recommendation 2A). Oral vancomycin is recommended for treatment of patients with mild-moderate disease who do not respond to metronidazole (Recommendation 1 A). Repeated or prolonged courses of metronidazole should be avoided due to risk of cumulative and potentially irreversible neurotoxicity (Recommendation 1 B).

Although metronidazole may be associated with more frequent side effects, and there has been a significant increase in treatment failures (especially in patients infected with the emergent 027/Bi/NAP1 strain), oral metronidazole 500 mg three times per day for 10 days has been used for treating mild-to-moderate cases of CDI [240]. Repeated or prolonged courses of metronidazole
should be avoided due to risk of cumulative and potentially irreversible neurotoxicity [241].

In recent IDSA guidelines, metronidazole is suggested only for patients with an initial episode of non-severe CDI in settings where access to vancomycin or fidaxomicin is limited [242].

In 2015, a systematic review and meta-analysis comparing the efficacy and safety of metronidazole monotherapy with vancomycin monotherapy and combination therapy in CDI patients was published [243]. No statistically significant difference in the rate of clinical cure was found between metronidazole and vancomycin for mild CDI (OR = 0.67, 95% CI 0.45–1.00; p = 0.05) or between either monotherapy and combination therapy for CDI (OR = 1.07, 95% CI 0.58–1.96; p = 0.83); however, the rate of clinical cure was lower for metronidazole than for vancomycin for severe CDI (OR = 0.46, 95% CI 0.26–0.80; p = 0.006). No significant difference in the rate of CDI recurrence was found between metronidazole and vancomycin for mild CDI (OR = 0.99, 95% CI 0.40–2.45; p = 0.98) or severe CDI (OR = 0.98, 95% CI (0.63, 1.53); p = 0.94) or between either monotherapy or combination therapy for CDI (OR = 0.91, 95% CI (0.66, 1.26); p = 0.56). In addition, there was no difference in the rate of adverse events (AEs) between metronidazole and vancomycin (OR = 1.18, 95% CI 0.80–1.74; p = 0.41). In contrast, the rate of adverse effects was significantly lower for either monotherapy than for combination therapy (OR = 0.30, 95% CI 0.17–0.51; p < 0.0001).

However, recent data have suggested an overall superiority of vancomycin to metronidazole for the treatment of patients with CDI and oral vancomycin 125 mg four times per day for 10 days is recommended as first choice antibiotic also for moderate cases.

In 2017, in an update of a previously published Cochrane review, moderate quality evidence suggested that vancomycin is superior to metronidazole in all cases of CDI [244]. The differences in effectiveness between these antibiotics were not too large and the advantage of metronidazole is its far lower cost even if liquid vancomycin is cheaper and reduces the cost.

Vancomycin orally 125 mg four times daily for 10 days is considered superior to metronidazole in severe C. difficile disease [245–247]. This may reflect the superior pharmacokinetic properties of vancomycin which is concentrated in the gut lumen. Doses of up to 500 mg have been used in some patients with severe or fulminant, as defined as hypotension or shock, ileus or megacolon, CDI [7], although there is little evidence for this in the literature.

Unlike vancomycin delivered enterally, intravenous vancomycin has no effect on CDI since the antibiotic is not excreted into the colon. Vancomycin enema may be an effective therapy for patients who cannot tolerate the oral preparation or patients with ileus who have delayed passage of oral antibiotics from the stomach to the colon [248].

Trans-stoma vancomycin may also be effective in surgical patients with Hartmann resection, ileostomy, or colon diversion. A single-hospital, retrospective chart review on 47 consecutive patients with C. difficile colitis treated with intracolonic vancomycin (ICV) was published by Kim et al. in 2013 [249]. Thirty-three of 47 patients (70%) with severe C. difficile colitis responded to adjunct intracolonic vancomycin with complete resolution without surgery. Multivariate analysis suggested that failures to intracolonic vancomycin enemas occurred in patients who were older and frail with albumin < 2.5 g/dl. Early surgery should be considered for those patients. Early surgery should also be offered to those patients who are failing maximal medical therapy including ICV enemas.

Fidaxomicin orally 200 mg twice daily for 10 days may be a valid alternative to vancomycin in patients with CDI [250, 251]. Fidaxomicin was non-inferior to vancomycin for initial cure of CDI in two prospective trials [235, 236]. In a first double-blind, randomized, non-inferiority trial [237], 629 adults with acute symptoms of C. difficile infection and a positive result on a stool toxin test were enrolled and randomly assigned to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis and the per-protocol analysis. In a second multicenter, double-blind, randomized, non-inferiority trial [238], 535 patients, 16 years or older with acute, toxin-positive CDI were randomly allocated (1:1) to receive oral fidaxomicin (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days.
Non-inferiority was shown for both the modified intention-to-treat analysis (15.4% vs. 25.3%; \( p = 0.005 \)) and the per-protocol analysis (13.3% vs. 24.0%; \( p = 0.004 \)). Patients receiving concomitant antibiotics for other infections had a higher cure rate with fidaxomicin (46 [90.2%] of 51) than with vancomycin (33 [73.3%] of 45; \( p = 0.031 \)).

A randomized, controlled, open-label, superiority study, recruited hospitalized adults aged 60 years and older with confirmed CDI at 86 European hospitals extended-pulsed fidaxomicin demonstrated to be superior to standard-dose vancomycin for sustained cure of CDI [252]. Between Nov 6, 2014, and May 5, 2016, 364 patients were enrolled and randomly assigned to receive extended pulsed fidaxomicin or vancomycin. Then, 362 patients received at least one dose of study medication (181 in each group). Further, 124 (70%) of 177 patients in the modified full analysis set receiving extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after end of treatment, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI, 1.0–20.7]; \( p = 0.030 \); OR 1.62 [95% CI, 1.04–2.54]). Incidence of treatment-emergent adverse events did not differ between extended-pulsed fidaxomicin (121 [67%] of 181) and vancomycin (128 [71%] of 181) treatment arms.

Fidaxomicin may be useful for treating patients who are considered at high risk for recurrence (elderly patients with multiple comorbidities who are receiving concomitant antibiotics). However, it is important to note that no data on the efficacy of fidaxomicin in severe life-threatening disease are available.

The use of other antibiotics such as tigecycline [253, 254], fusidic acid, teicoplanin, rifamixin [238], and nitazoxanide [255] has been described in the literature, but they are not currently recommended for general use.

### Surgical management

Patients with fulminant colitis (FC) who progress to systemic toxicity require surgical intervention.

To determine clinical predictors for the development of fulminant colitis in patients with CDI, a 10-year retrospective review of FC patients who underwent colectomy was performed and compared with randomly selected age- and sex-matched non-fulminant CDI patients at a single institution study by Girotra et al. in 2012 [256]. Predictive clinical and laboratory features included age (> 70 years), prior CDI, profound leukocytosis (> 18,000/mm³), hemodynamic instability, use of anti-peristaltic medications, and a clinical trial of increasing abdominal pain, distension and diarrhea.

Another important clinical feature that should be taken into account in patients who are going to experience fulminant colitis is the occurrence of a change in mental status that could reflect significant toxemia [257].

Patients with severe CDI who progress to systemic toxicity are likely to have serious comorbidities. Delaying surgery in this group leads to increased likelihood of adverse outcomes [258], although some reports show that a short period of medical optimization can improve outcomes before colectomy [259].

There are no reliable clinical and/or laboratory findings that can predict those patients who will respond to medical therapy and those who will need surgery [260].

Data comparing mortality rates between surgical and medical treatment for fulminant *C. difficile* colitis were published in a systematic review by Stewart et al. [261]. Five hundred ten patients with fulminant colitis were identified in 6 studies. Emergency colectomy for patients with FC provided a survival advantage compared with continuing antibiotics. When all 6 studies numbering 510 patients were analyzed, the pooled adjusted odds ratio of mortality comparing surgery with medical therapy, and weighted by the contribution of each study, was 0.70 (0.49–0.99) leading the authors to conclude that emergency colectomy has a therapeutic role in treating complicated CDI.

Patients presenting with organ failure (acute renal failure, mental status changes, or cardiopulmonary compromise) also need prompt intervention since the timing of surgical intervention is the key for survival of patients with FC [262–265].

Seder et al. [266] described 6841 patients with CDI and showed a decreased mortality associated with surgery performed before the need for vasopressor requirement, especially in the patients < 65 years old. Hall et al. [264] reviewed 3237 consecutive cases of CDI and showed an increased mortality rate when surgical exploration was performed after intubation or the development of respiratory failure and the use of vasopressors.

Recently, a risk scoring system (RSS) for daily clinical practice was designed by van der Wilden et al. [267]. Age greater than 70 years was assigned 2 points, white blood cell counts equal to or greater than > 20,000/μL or equal to or less than 2000/μL was assigned 1 point, cardiorespiratory failure was assigned 7 points, and diffuse abdominal tenderness on physical examination was assigned 6 points. A value of 6 points was determined to be the threshold for reliably dividing low-risk (< 6) from high-risk (≥ 6) patients. Only patients with cardiorespiratory failure or diffuse abdominal tenderness were high risk.

Ferrada et al. [268] reviewed the existing literature on the treatment of CDI and published practice management
guidelines (PMG) for the Eastern Association for the Surgery of Trauma (EAST). The authors strongly recommended that adult patients with CDI undergo early surgery before developing shock and requiring vasopressors. Although optimal timing remains controversial, the authors found that it was between 3 and 5 days after diagnosis in patients who are worsening or not clinically improving [268].

Many factors have been described as predictors of mortality in patients who undergo emergency surgery. Sailhamer et al. [269] reviewed the records of 4796 inpatients diagnosed with C. difficile colitis. In 199 patients (4.1%) with fulminant CDI, the in-hospital mortality rate was 34.7%. Independent predictors of mortality included age 70 years or older, severe leukocytosis or leukopenia (white blood cell count, > or = 35,000/μL or < 4000/μL) or bandemia (neutrophil bands, > or = 10%), and cardiorespiratory failure (intubation or vasopressors). Survival rates were higher in patients who were cared for by surgical vs. nonsurgical departments.

The ACS-NSQIP database from 2005 to 2010 was used by Lee et al. to study emergency open colectomies performed for C. difficile colitis in the USA [177]. The overall mortality was 33% (111/335). Age 80 years or older, preoperative dialysis dependence, chronic obstructive pulmonary disease, and wound class III were associated with high patient mortality. Thrombocytopenia (platelet count < 150 x 10^3/mm^3), coagulopathy (international normalized ratio > 2.0), and renal insufficiency (blood urea nitrogen > 40 mg/dL) were also associated with a higher mortality.

A systematic review and meta-analysis of outcomes following emergency surgery for CDI was published by Banghu et al. [270]. Thirty-one studies were included, which presented data for 1433 patients. The authors concluded that the strongest predictors for postoperative death were those relating to preoperative physiological status: preoperative intubation, acute renal failure, multiple organ failure and shock requiring vasopressors.

22. Early diagnosis and treatment is important to reduce the mortality associated with fulminant colitis.

23. Resection of the entire colon should be considered to treat patients with fulminant colitis (Recommendation 1 B). However, diverting loop ileostomy with colonic lavage is a useful alternative to resection of the entire colon (Recommendation 1 B).

24. Patients with fulminant colitis should be treated with high dose vancomycin (500 mg, 6 hourly), oral and/or by enema, in combination with intravenous metronidazole (500 mg, 8 hourly) (Recommendation 1 C).

In the Banghu et al. meta-analysis [270], the most commonly performed operation for treatment of fulminant colitis (FC) was total colectomy with end ileostomy (89%, 1247/1401). When total colectomy with end ileostomy was not performed, reoperation to resect further bowel was needed in 15.9% (20/126). In the recent meta-analysis by Ferrada et al. [268], 17 studies comparing colectomy versus other procedures or no surgery as treatment for CDI were analyzed. The authors recommended that total colectomy (versus partial colectomy or other surgery) is the procedure of choice for patients with C. difficile colitis.

To evaluate the role of emergency colectomy in patients with FC, and to identify subgroups of patients that may benefit from it, Lamontagne et al. [271] published a retrospective observational cohort study of 165 cases of FC requiring ICU admission or prolongation of ICU stay in 2 tertiary care hospitals in Quebec, Canada. Eighty-seven (53%) patients died within 30 days of ICU admission, of whom almost half (38 of 87, 44%) died within 48 h of ICU admission. The independent predictors of 30-day mortality were leukocytosis ≥ 5 x 10^9/L, lactate ≥ 5 mmol/L, age ≥ 75 years, immunosuppression, and shock requiring vasopressors. Patients who underwent an emergency colectomy were less likely to die than those treated medically. Colectomy was more beneficial in patients aged 65 years or more, in immunocompetent patients and in patients with a leukocytosis ≥ 20 x 10^9/L or lactate between 2.2 and 4.9 mmol/L.

Diverting loop ileostomy with antegrade colonic lavage may be a colon-preserving alternative to total colectomy [272, 273]. A prospective, nonrandomized, historical control group study was performed at the University of Pittsburgh Medical Center and the Veterans’ Administration Healthcare System, in Pittsburgh between June 2009 and January 2011 [272]. Forty-two patients with FC were managed by a loop ileostomy, intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy, and postoperative antegrade instillation of vancomycin flushes via the ileostomy. There was no significant difference in age, sex, pharmacologic immunosuppression, and Acute Physiology and Chronic Health Evaluation-II scores between the studied cohort and historical controls. The operation was accomplished laparoscopically in 35 patients (83%). This treatment strategy resulted in reduced mortality compared to their historical controls. Preservation of the colon was achieved in 39 of 42 patients (93%). Of note, vancomycin antegrade enemas were continued via the ileostomy every 6 h for 10 days and this likely augmented the effect of the defunctioning surgery.

A retrospective multicenter study conducted under the sponsorship of the Eastern Association for the Surgery
of Trauma to compare loop ileostomy versus total colectomy as surgical treatment for CDI was published in 2017 [274]. Data from ten centers of patients who presented with CDI requiring surgery between July 1, 2010 and July 30, 2014 were collected. When comparing colectomy and loop ileostomy, there was no statistical difference between these two operative strategies. Univariate pre-procedure predictors of mortality were age, lactate, timing of operation, vasopressor use, and acute renal failure. There was no statistical difference between the APACHE score of patients undergoing either procedure (TC, 22 vs. LI, 16). Adjusted mortality (controlled for pre-procedure confounders) was significantly lower in the loop ileostomy group (17.2% vs. 39.7%; \( p = 0.002 \)).

Supportive care

25. Early detection of shock and aggressive management of underlying organ dysfunction are essential for improved outcomes in patients with fulminant colitis (Recommendation 1 C). Supportive measures, including intravenous fluid resuscitation, albumin supplementation, and electrolyte replacement, should be provided to all patients with severe \textit{C. difficile} infection (Recommendation 1 C).

Early detection and prompt aggressive treatment of the underlying organ dysfunction is an essential component in the management of CDI in critically ill patients.

Severe CDI may present with a fulminant course and may be associated with great morbidity and high mortality. Physiologic support including invasive monitoring in an intensive care unit and aggressive resuscitation are often necessary in fulminant colitis. Diarrhea results in significant volume depletion and electrolyte abnormalities, and fluid and electrolyte imbalance should be promptly corrected.

Although it has been debated, albumin supplementation in patients with severe hypoalbuminemia (<2 g/dl) should be considered as a supportive measure and also to exploit its anti-toxin properties [275].

The expert panel suggests measuring intra-abdominal pressure (IAP) when any known risk factor for intra-abdominal hypertension (IAH)/abdominal compartment syndrome (ACS) is present.

RCDI

Recurrence is diagnosed when CDI recurs <8 weeks after the resolution of a previous episode, provided the symptoms from the previous episode resolved after completion of the initial treatment and other causes have been excluded. Symptomatic recurrent \textit{C. difficile} infection (RCDI) occurs in approximately 20% of patients and is challenging [141]. Therefore, patients with recurrent CDI should therefore be treated by experienced clinicians.

26. Agents that may be used to treat the first recurrence of CDI include vancomycin (particularly if metronidazole was used for the first episode) or fidaxomicin. (Recommendation 1 B).

27. Antibiotic treatment options for patients with >1 recurrence of CDI include oral vancomycin therapy using a tapered and pulsed regimen (Recommendation 1 C).

For recurrent cases of CDI, oral vancomycin 125 mg four times per day for 14 days or oral fidaxomicin 200 mg twice a day for 10 days is recommended for first recurrence.

Metronidazole is not recommended as initial treatment of recurrent CDI as sustained response rates are lower than those with vancomycin. Furthermore, metronidazole should not be used for long-term therapy because of the potential for cumulative neurotoxicity.

Vancomycin and fidaxomicin are equally effective in resolving CDI symptoms but fidaxomicin has been shown to be associated with a lower likelihood of CDI recurrence after a first recurrence [237, 238, 276]. However, there are no prospective randomized controlled trials investigating the efficacy of fidaxomicin in patients with multiple recurrences of CDI. Vancomycin is often administered using a prolonged tapered and/or pulsed regimen which may be more effective than a standard 10 to 14 days course, although no RCTs have been reported in second or subsequent CDI recurrences [146].

Probiotics

28. Limited direct evidence exists to support the use of probiotics in the management of a first episode of CDI as an adjunctive treatment to antibiotics for immunocompetent patients (Recommendation 2 B).

The altered composition of gut microbiota in the setting of \textit{C. difficile} infection has raised interest in the potential role of probiotics [163]. Their use aims to re-colonize and restore the diversity of flora following the disruption due to antibiotic treatment and \textit{C. difficile} overgrowth.

There is limited direct evidence to support the use of probiotics in the primary prevention of CDI.

Data for primary prevention of CDI often arises from prevention of antibiotic-associated diarrhea trials with CDI as a secondary outcome and are often underpowered for CDI. Thus, meta-analyses may be useful to evaluate if specific probiotics are efficacious for CDI, as
this statistical method utilizes the increase in power resulting from pooling different studies together. However, since the recent finding that the efficacy of probiotics are both strain-specific and disease-specific [277], for valid conclusions to be reached, the meta-analysis must assess efficacy within subgroups of identical probiotic strains (or mixture of strains) and for the same type of disease. A meta-analysis of 22 randomized controlled trials using sub-group analysis for 5 different types of probiotics for primary prevention of CDI found 4/5 (Saccharomyces boulardii 1-745, Lactobacillus casei DN114001, a mixture of Lactobacillus acidophilus and Bifidobacterium bifidum, and another mixture of three Lactobacillus strains (L. acidophilus CL1285, L. casei LBC80R, Lactobacillus rhamnosus CLR2)) were effective and one type (L. rhamnosus GG) was not effective [278]. Other systematic reviews and meta-analyses report a protective effect of probiotics [279–284], but reviews exploring the contribution of probiotics in CDI prevention can be limited due to heterogeneity between studies, inadequate study power, or significant levels of missing outcome data. In addition, many reviews still fail to account for strain-specificity and pool different types of probiotics together in their analysis [280, 281, 284]. The short-term use of probiotics appeared to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated. Probiotics should not be administered to patients at risk of bacteremia or fungemia.

29. Prophylactic probiotics may be considered for inpatients receiving antibiotics during high-risk period (such as outbreaks) before the disease develops (Recommendation 2 C). Probiotics should be not used in immunocompromised patients (Recommendation 2 C).

Several types of probiotics have been tested on a facility-level intervention as part of an infection control bundle for CDI. In an effort to reduce hospital-wide CDI rates (especially in hospitals having CDI outbreaks), probiotics were given to newly admitted patients receiving antibiotics and continued during either the duration of the antibiotic or duration of the patient's stay. Although lacking in the rigorous strength from randomized trials, these hospital studies showed a significant reduction of CDI rates for some types of probiotics (L. casei Shirot, Lactobacillus plantarum 299v, and a mixture of three lactobacilli strains, Bio-K+) [278]. This three lactobacilli strain mixture (L. acidophilus CL1285, L. casei LBC80R, and L. rhamnosus CLR2) has been tested in seven other hospitals and found to be effective in reducing CDI rates [285]. However, other types of probiotics need further research, particularly in those at high risk of CDI.

Probiotics are contraindicated for immunocompromised patients due to a rare, but serious risk of bacteremia.

30. Probiotics for prevention of recurrent CDI may be an effective adjunct to standard antibiotic treatment (vancomycin) in patients with at least one prior episode of CDI (Recommendation 2 B).

There have been many case reports and case series reporting fewer recurrences of CDI when some probiotics were used as an adjunctive treatment with vancomycin or metronidazole. However, there are fewer randomized trials for this adjunctive therapy. Two randomized controlled trials found significantly fewer CDI patients developed recurrences when Saccharomyces boulardii 1-745 was combined with standard antibiotic therapy [286, 287]. The first trial demonstrated a lower CDI recurrence rate compared with a placebo control group (26% vs. 45%, respectively) [283] and the second trial found that the combination of S. boulardii (1 g/day) with high dose vancomycin (2 g/day) was more effective than high dose vancomycin and placebo (17% vs. 50% recurrence rate) [284]. The probiotic was not able to reduce CDI recurrences when combined with a lower dose of vancomycin (500 mg/day) or with metronidazole (1 g/day). Other studies with Lactobacillus strains (L. rhamnosus GG or L. plantarum 299v) were stopped prematurely due to enrollment problems [146]. There have no published trials currently combining probiotics with fidaxomicin.

Fecal microbiota transplantation

31. Fecal microbiota transplantation (FMT) may be an effective option for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments (Recommendation 2 C).

FMT has been considered as an alternative therapy to treat RCDI [283–293]. It involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of patients to restore the intestinal microbiota.

The rationale of FMT is that disruption of the normal balance of colonic flora allows C. difficile strains to grow and produce CDI. By reintroducing normal flora via donor feces, the imbalance may be corrected, and normal bowel function re-established [288].

FMT has not been widely adopted as a therapeutic tool probably due to concerns regarding safety and acceptability [258].

A systematic literature review of FMT treatment for RCDI and pseudomembranous colitis was published in 2011 by Gough et al. [289]. In 317 patients treated
across 27 case series and reports, FMT was highly effective, showing disease resolution in 92% of cases. In those studies, 35% of patients received FMT via enema, with a response rate of 95%; 23% patients received FMT via naso-jejunal tube by gastroscope, with a response rate of 76%; and 19% via colonoscopy, with a response rate of 89%. Effectiveness varied by route of instillation, relationship to stool donor, volume of FMT given, and treatment before infusion.

Another systematic review was published by Cammarota et al. [290]. Twenty full-text case series, 15 case reports, and 1 randomized controlled study were included for the final analysis. Almost all patients treated with donors’ fecal infusion had experienced recurrent episodes of CD-associated diarrhea despite standard antibiotic treatment. Of a total of 536 patients treated, 467 (87%) had resolution of diarrhea. Diarrhea resolution rates varied according to the site of infusion: 81% in the stomach, 86% in the duodenum/jejenum, 93% in the cecum/ascending colon, and 84% in the distal colon. No severe adverse events were reported with the procedure.

Recently, a review to evaluate the efficacy of FMT in treating recurrent and refractory CDI was published [291]. Thirty-seven studies were included; 7 randomized controlled trials and 30 case series. FMT was more effective than vancomycin (RR = 0.23, 95% CI 0.07–0.80) in resolving recurrent and refractory CDI. Clinical resolution across all studies was 92% (95% CI 89–94%). A significant difference was observed between lower gastrointestinal (GI) and upper GI delivery of FMT 95% (95% CI 92–97%) vs. 88% (95% CI 82–94%) respectively (p = 0.02). There was no difference between fresh and frozen FMT 92% (95% CI 89–95%) vs. 93% (95% CI 87–97%) respectively (p = 0.84). Administering consecutive courses of FMT following failure of first FMT resulted in an incremental effect. Donor screening was consistent but variability existed in recipient preparation and volume of FMT. Serious adverse events were uncommon.

Although FMT has high success rates with long-term durability [292], few disadvantages still exist. In particular, the manipulation of feces and the classical enteral administration methods are not only laborious but tend to make the procedure rather unattractive for physicians and patients.

In the context of these disadvantages, few efforts have been made to enhance the feasibility and social acceptance of microbiota transplantation.

FMT may be administered via enemas or as a slurry given via a nasogastric tube.

One systematic review which compared various routes of administration included a total of 182 patients (148 received FMT via colonoscopy and 34 received FMT via nasogastric tube) from 12 published studies [293]. Recurrence of CDI after FMT was similar in both the colonoscopy group (8/148, 5.4%) versus the nasogastric tube group (2/34, 5.9%) (p = 1.000). However, the overall rate of cure after FMT was slightly higher in patients receiving FMT by colonoscopy: 85.3% (29 patients, 29/34) in the nasogastric tube group and 93.2% (138 patients, 138/148) in the colonoscopy group (p = 0.162).

A larger and more recent systematic review of 14 studies including 305 patients and comparing FMT delivery by upper and lower gastrointestinal routes also favored lower gastrointestinal delivery [294]. At 30 and 90 days, the risk of clinical failure was 5.6% and 17.9% in the upper gastrointestinal group compared with 4.9% and 8.5% in the lower GI delivery route group, respectively.

More recently, encapsulated preparations of FMT have been used with success. This strategy has the advantage of being less invasive and simpler, which may also result in improved cost-effectiveness [295–298].

In 2014, Youngster et al. [296] reported their experience with frozen FMT capsules in 20 patients who had RCDI. Fourteen patients (70%) had resolution of diarrhea after a single treatment, and 4 patients responded after a second treatment, with a clinical resolution rate of 90%.

Patients who are immunocompromised are at increased risk of CDI. During the last 2 years, the first data on FMT in immunocompromised patients began to appear in the medical literature [299].

A multicenter retrospective series on the use of FMT in immunocompromised patients with recurrent, refractory, or severe CDI was published in 2014 [300]. Immunosuppression included HIV/AIDS (3), solid organ transplantation (19), oncologic condition (7), immunosuppressive therapy for IBD (36), and other medical conditions/medications (15). This series demonstrated the effective use of FMT for CDI in immunocompromised patients with few serious adverse events.

With the increased awareness of the role of native gut microbiome and its role in the gut brain axis, there have been concerns about the long-term effect of transplanted stool, and how the new gut microbiome can affect brain function and immune responses.

Monoclonal antibodies

32. Coadjuvant treatment with monoclonal antibodies (bezlotoxumab) may prevent recurrences of CDI, particularly in patients with CDI due to the 027 epidemic strain, in immunocompromised patients and in patients with severe CDI (Recommendation 1 A).

Since the expression of clostridial toxins (TcdA and TcdB) is mandatory for the development of CDI, the
development of monoclonal antibodies aimed at preventing the cytotoxic effect of these toxins is a potential strategy for controlling the disease. In 2016, the FDA approved bezlotoxumab to reduce the recurrence of CDI in adult patients receiving antimicrobial therapy for CDI who are at high risk of CDI recurrence. Bezlotoxumab (MK-6072) is a human monoclonal antibody which reduces recurrent CDI by blocking the binding of *C. difficile* toxin B to host cells, thus limiting epithelial damage and facilitating recovery of the microbiome [301]. Besides bezlotoxumab, another human monoclonal antibody, actoxumab (MK-3415), was recently designed to neutralize *C. difficile* toxin.

The data from two double-blind, randomized, placebo-controlled, phase 3 trials, MODIFY I and MODIFY II, involving 2655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection showed that bezlotoxumab achieved a significant benefit over placebo in the treatment of recurrent CDI. Participants received an infusion of bezlotoxumab (10 mg/kg of body weight), actoxumab plus bezlotoxumab (10 mg/kg each), or placebo; actoxumab alone (10 mg/kg) was given in MODIFY I but discontinued after a planned interim analysis. The primary end point was recurrent infection (new episode after initial clinical cure) within 12 weeks after infusion in the modified intention-to-treat population [302]. In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab alone than with placebo (MODIFY I: 17% [67 of 386] vs. 28% [109 of 395]; adjusted difference, −10.1 percentage points; 95% CI, −15.9 to −4.3; *p* < 0.001; MODIFY II: 16% [62 of 395] vs. 26% [97 of 378]; adjusted difference, −9.9 percentage points; 95% CI, −15.5 to −4.3; *p* < 0.001) [303].

A post-hoc analysis of pooled monoclonal antibodies for *C. difficile* therapy (MODIFY) I/II data assessed bezlotoxumab efficacy in participants with risk factors for RCDI including age ≥65 years, history of CDI, compromised immunity, severe CDI and ribotype 027/078/244 [304]. Although the patients with only one of the risk factors may benefit from bezlotoxumab, patients with at least three risk factors appeared to have the greatest risk reduction with bezlotoxumab.

**Intravenous immunoglobulin**

33. Intravenous immunoglobulin (IVIG) should only be used as adjunct therapy in patients with multiple recurrent or fulminant CDI until results from large, randomized controlled trials are available (Recommendation 2 C).

Novel treatment modalities for management of CDI have been developed. IVIG treatment is based on evidence that the level of immune response to *C. difficile* colonization is the major determinant of the magnitude and duration of clinical manifestations. Passive immunization with IVIG has been successful in several small series. A review by Abourgergi et al. [305] of 15 small, mostly retrospective and non-randomized studies, documented success with IVIG in the treatment of protracted, recurrent, or severe CDI. The authors concluded that IVIG should only be used as adjunct therapy until results from large, randomized controlled trials are available. Two small retrospective matched cohort studies were published that compared the clinical efficacy of the addition of IVIG to conventional CDI treatment [306, 307]. Neither of these studies found significant differences between the compared cohorts in the main clinical outcomes, although Shahani et al. [306] noted that in their IVIG cohort, there were significantly older patients with more severe CDI than in the control group. It is reasonable to utilize IVIG therapy in patients diagnosed with hypogammaglobulinemia based on the confirmation of IgG levels below the normal laboratory range.

**Enteral nutrition in CDI**

34. Tube feeding patients should be clinically assessed due to their risk for developing CDI (Recommendation 2 C).

It is widely accepted that enteral nutrition (EN) maintains gut mucosal integrity which leads to decreased intestinal permeability, decreased infections, and an improved immunological status. EN during episodes of diarrhea may be well tolerated and may improve enterocyte healing and maintenance of enzyme activity [308–310]. Enteral nutrition, however, has also been associated with increased risk of CDI [310]. Bliss et al. evaluated 76 tube-fed and non-tube-fed hospital patients for the development of CDI [311]. Patients were controlled for age, severity of illness, and duration of hospitalization. Patients who were tube-fed were statistically more likely to develop CDI (20% vs. 8% *p* = 0.03). One of the reasons may be prolonged use of elemental diets. It is known that critically ill patients tolerate feeding well if the feed is given in elemental form and delivered beyond the stomach into the jejunum because it is totally absorbed within the upper small intestine [312], depriving the colonic microbiota of their source of nutrition, such as dietary fibers, fructose oligosaccharides, and resistant starch [313]. The resultant suppression of colonic fermentation may therefore lead to the disruption of the normal gut flora and the creation of a “permissive” environment for *C. difficile* colonization and subsequent infection. In feeding tube patients, the conversion of elemental diet feeding to a diet containing adequate
indigestible carbohydrate after the first week of critical illness may, in theory, be beneficial.

Puri et al. [314] reported that daily concomitant treatment with 4 g cholestyramine in patients receiving long-term intravenous ceftriaxone (2 to 4 g ceftriaxone daily, for an average of > 10 weeks) was associated with CDI in only 3 out of 46 patients (6.5%) compared with 23.1% of those receiving ceftriaxone alone. Cholestyramine (or colestezyme) is a hydrophilic, water insoluble, non-digestible basic anion-exchange resin which can bind luminal TcdA and TcdB.

**Anti-motility agents**

35. The use of anti-peristaltic agents for the treatment of CDI should be discouraged. If anti-peristaltic agents are used to control persistent symptoms in patients with CDI, they must always be accompanied by medical therapy (Recommendation 2 C).

A review of the literature regarding anti-motility treatment of CDI found 55 patients with CDI who were exposed to anti-motility agents [315]. Nine patients (16%) died, and 27 patients (49%) had unknown outcomes. Seventeen patients (31%) with CDI developed colonic dilation; 5 of these patients with severe CDI died. However, all patients who experienced complications or died were given anti-motility agents alone initially, without an appropriate antibiotic and 23 patients who received metronidazole or vancomycin co-administered with the anti-motility agent experienced no complications. Further study of the role of anti-motility agents in providing symptomatic relief and reducing environmental contamination with infectious stool may be warranted though, until there is clear evidence of benefit, their use in patients with CDI should be avoided.

**Conclusions**

In the last three decades, the worldwide increase in CDI incidence has been particularly apparent among surgical patients, becoming a global public health challenge. Therefore, prompt and precise diagnosis is paramount for the effective management of CDI, allowing both the immediate implementation of infection prevention and control strategies, and the optimization of treatment in surgical patients, considering the most recent changes introduced in the management of this infection.

**Abbreviations**

CDI: *Clostridium difficile* infection; FC: Fulminant colitis; RCDI: Recurrent *Clostridium difficile* infection

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**Availability of data and materials**

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**Authors’ contributions**

MS wrote the first draft of the manuscript. All the authors reviewed the manuscript and approved the final draft.

**Ethics approval and consent to participate**

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**Consent for publication**

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Intraoperative surgical site infection control and prevention: a position paper and future addendum to WSES intra-abdominal infections guidelines


Abstract

Background: Surgical site infections (SSI) represent a considerable burden for healthcare systems. They are largely preventable and multiple interventions have been proposed over past years in an attempt to prevent SSI. We aim to provide a position paper on Operative Room (OR) prevention of SSI in patients presenting with intra-abdominal infection to be considered a future addendum to the well-known World Society of Emergency Surgery (WSES) Guidelines on the management of intra-abdominal infections.

Methods: The literature was searched for focused publications on SSI until March 2019. Critical analysis and grading of the literature has been performed by a working group of experts; the literature review and the statements were evaluated by a Steering Committee of the WSES.

Results: Wound protectors and antibacterial sutures seem to have effective roles to prevent SSI in intra-abdominal infections. The application of negative-pressure wound therapy in preventing SSI can be useful in reducing postoperative wound complications. It is important to pursue normothermia with the available resources in the intraoperative period to decrease SSI rate. The optimal knowledge of the pharmacokinetic/pharmacodynamic characteristics of antibiotics helps to decide when additional intraoperative antibiotic doses should be administered in patients with intra-abdominal infections undergoing emergency surgery to prevent SSI.

Conclusions: The current position paper offers an extensive overview of the available evidence regarding surgical site infection control and prevention in patients having intra-abdominal infections.

Keywords: Emergency, Surgical site infection, Prevention, Intra-abdominal infection, Operating room
Background
Surgical site infections (SSI) are a common type of healthcare-associated infections and frequent complication of hospitalization, responsible for prolonged hospital stay, increased intensive care unit admissions, hospital readmissions after surgery, significantly increased costs (1300–5000 USD per SSI), and delays to adjuvant systemic therapy; they occur in 2 to 5% of patients undergoing surgery in the USA [1–3].

Approximately 160,000 to 300,000 SSI are diagnosed and treated every year and represent a considerable burden for healthcare systems in terms of re-operation, increased post-surgical pain, poor wound healing, prolonged hospital stay, cosmetic appearance, and decreased quality of life [4–7].

SSI has also been shown to be an independent risk factor in the development of incisional hernia [8].

The incidence of all types of SSI following abdominal surgery can reach 14% of all hospital-acquired infections and the most common form is the incisional superficial SSI, which is often the first to appear and is easy to diagnose [9].

While more data are available from Western healthcare settings, SSI was the leading cause of hospital-acquired infection in a systematic review of studies in low- and middle-income countries [10].

They also result in deleterious softer endpoints such as patient psychosocial distress, loss of income, and decreased productivity [1–3].

Multiple interventions have been proposed and employed over the past decades in an attempt to prevent SSI. These include skin cleansing protocols, hair removal, the maintenance of intraoperative normothermia, the pre-operative antimicrobial prophylaxis administration, the use of plastic adhesive skin barriers, the high flow oxygen supplementation, the wound protection, the sterility of instruments, the bowel preparation, the length of the incision, and the delayed primary incision closure [11–15].

The development of SSI is multifactorial, and it may be related to patient’s risk factors such as age, comorbidities, smoking habit, obesity, malnutrition, immunosuppression, malignancies, and the class of contamination of the wound [9, 16].

Emergency surgery is a risk factor for SSI because many strong risk factors for SSI such as contaminated and dirty wounds, prolonged duration of the operation, patient comorbidities, and high American Society of Anesthesiologists (ASA) score are commonly present in this type of surgery. For these reasons, the World Society of Emergency Surgery (WSES) developed a position paper for the prevention of SSI in the operating room (OR).

A panel of international experts discussed statements based on predetermined research questions and the results of related systematic literature reviews. The literature search found few articles focused on SSI and emergency surgery; consequently, most of the reviewed studies considered the incidence of SSI in elective surgery because of the lack of valid data from an emergency setting. This is a consequence of the difficulty to conduct a good-quality study in an emergency environment: the workload is often intermittent and unpredictable, patient case-mix is heterogeneous with a wide variety of concomitant problems and severity of initial diagnosis; moreover, the emergency environment poses many barriers and obstacles to patient recruitment and data collection, and this has implications particularly for the staffing of prospective trials.

Considering all these limitations, we cannot ignore the potential benefit from using some devices and equipment or adopting some simple strategies in emergency surgery to decrease the incidence of SSI.

This position paper aims to provide recommendations on OR prevention of SSI in patients with intra-abdominal infections to be an addendum to the WSES Guidelines on the management of intra-abdominal infections.

Materials and methods
In July 2018, the Scientific Board of the WSES, the President of the Society and the President of the 5th World Congress of the WSES decided to prepare a position paper on OR prevention of SSI in patients with intra-abdominal infections in the emergency setting.

The Presidents and ten members of the Scientific Secretariat (SS) agreed on 11 key topics to develop in the position paper (Table 1); nine international experts, members of the WSES Board, were chosen as Steering Committee (SC).

Each topic was developed by members of the SS: the SC and the Presidents supervised every step of literature search, selection, and the final work.

The SS provided the electronic search in PubMed and EMBASE databases, according to specific keywords for each question as you can see in the Appendix 1 without time or language restrictions.

Each expert followed the PRISMA methodology in the selection of papers to consider for review: meta-analyses of randomized controlled trials, randomized control trials, prospective studies, observational studies, large case series, and systematic reviews were included in this study.

Each SS member developed a focused draft and a variable number of statements. Each statement has been evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [17] summarized in Table 2.

The provisional statements and the supporting literature were reviewed by all SS members and the Presidents, discussed with the SC members by email/call conferences and modified if necessary.

<table>
<thead>
<tr>
<th>Main topics</th>
<th>Statements</th>
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</table>
| 1) How to close a surgical incision?                                      | Statement 1.1: There is no significant difference in terms of SSI incidence and length of hospital stay between patients in which the skin is sutured by continuous versus interrupted stitches (GoR 1B)  
Statement 1.2: Superficial wound dehiscence is lower in subcuticular continuous suture versus interrupted stitches. (GoR 1B)  
Statement 1.3: The use of steri-strips doesn’t reduce the incidence of SSI |
| 2) Coated sutures: are they useful?                                       | Statement 2: Triclosan-coated sutures significantly reduce SSI prevalence compared with the non-coated sutures (GoR1B)  
Statement 3: There are insufficient data to support the role of intraperitoneal or topical wound irrigation with antibiotics in preventing SSI |
| 3) What is the role of intraoperative intraperitoneal irrigation vs topical wound lavage with antibiotic solutions to prevent surgical site infections? | Statement 4: There are insufficient data to determine the role of saline or povidone solution irrigation of incisional wounds before closure to prevent SSI (GoR 2B)  
Statement 5: The use of wound protectors has protective effects in reducing incisional SSI (GoR 1A); The use of dual-ring constructed wound protectors appears to be superior to single-ring devices in preventing SSI (GoR1B).  
Statement 6: There is no evidence that plastic adhesive incise drapes with or without antimicrobial properties are useful to decrease SSI (GoR 2C).  
Statement 7: There are insufficient data to determine the role of the use of subcutaneous drainage of incisional wounds before closure to prevent SSI in high-risk patients (GoR 2B)  
Statement 8: There are insufficient data to determine the role of double gloving to prevent SSI (GoR 2C).  
Statement 9: The mechanical resistance of latex gloves depends on the duration of wear. It may be beneficial for surgical team members and their protection to change gloves at certain intervals during surgery (GoR 2C).  
Statement 10: Optimal knowledge and use of the pharmacokinetic/pharmacodynamic characteristics of antibiotics are important to evaluate when additional antibiotic doses should be administered intraoperatively in patients with intra-abdominal infections undergoing emergency surgery (GoR 1C)  
Statement 11: Perioperative hyperoxygenation does not reduce SSI (GoR 2B) |
| 10) Is intraoperative normothermia useful to prevent surgical site infections? | Statement 10.1: Intraoperative normothermia decreases the rate of SSI (GoR 1A).  
Statement 10.2: The use of active warming devices in operating room is useful to keep normothermia and reduce SSI (GoR 1B)  
Statement 11: Perioperative hyperoxygenation does not reduce SSI (GoR 2B)  
Statement 12: Delayed primary skin closure may reduce the incidence of SSI (GoR 2C)  
Statement 12.2: Delayed primary closure of a surgical incision is an option to take into consideration in contaminated abdominal surgeries, in patients with high risk of SSI (GoR 2C)  
Statement 13: Optimal knowledge and use of the pharmacokinetic/pharmacodynamic  
characteristics of antibiotics are important to evaluate when additional antibiotic doses should be administered intraoperatively in patients with intra-abdominal infections undergoing emergency surgery (GoR 1C) |
Table 2 Grading of Recommendations, Assessment, Development and Evaluation (GRADE). RCTs randomized controlled trials

<table>
<thead>
<tr>
<th>Grade of recommendation</th>
<th>Quality of supporting evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A Strong recommendation, high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1B Strong recommendation, moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect analyses or imprecise conclusions) or exceptionally strong evidence from observational studies</td>
<td>Strong recommendation, applies to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td>1C Strong recommendation low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Strong recommendation but subject to change when higher quality evidence becomes available</td>
</tr>
<tr>
<td>2A Weak recommendation high-quality evidence</td>
<td>RCTs without important limitations or overwhelming evidence from observational studies</td>
<td>Weak recommendation, the best action may differ depending on the patient, treatment circumstances, or social values</td>
</tr>
<tr>
<td>2B Weak recommendation moderate-quality evidence</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise) or exceptionally strong evidence from observational studies</td>
<td>Weak recommendation, the best action may differ depending on the patient, treatment circumstances, or social values</td>
</tr>
<tr>
<td>2C Weak recommendation low-quality or very low-quality evidence</td>
<td>Observational studies or case series</td>
<td>Very weak recommendation; alternative treatments may be equally reasonable and merit consideration</td>
</tr>
</tbody>
</table>

The designated member of SS presented the statements to SC along with the grade of recommendation (GoR) and the literature supporting each statement. Clinicians and surgeons must be aware that the present position paper should be considered as an adjunctive tool for decision and management, but they do not substitute for the clinical judgment for individual patients.

Results

How to close a surgical incision?

Statement 1.1: There is no significant difference in terms of SSI incidence and length of hospital stay between patients in which the skin is sutured by continuous versus interrupted stitches (GoR 1B).

Statement 1.2: Superficial wound dehiscence is lower in subcuticular continuous suture versus interrupted stitches (GoR 1B).

Statement 1.3: The use of steri-strips or tissue adhesives doesn’t reduce the incidence of SSI (GoR 1B).

The method of skin closure may have a role in preventing the development of SSI. Compared with interrupted sutures, continuous sutures can provide a better seal preventing the exogenous bacterial invasion of the surgical wound [16].

However, a continuous tightly pulled suture can strainulate the wound edges [18, 19].

Many published trials have demonstrated the benefit of skin closure by subcuticular interrupted sutures compared with conventional skin stapling in different surgical scenarios [9, 16, 17].

On the other hand, very few papers have been designed to investigate differences in the outcome when the skin is closed by continuous or by interrupted sutures.

In a Cochrane meta-analysis [19] published in 2014 and focused on the impact that different methods of skin closure could have on superficial SSI, superficial wound dehiscence, and length of hospital stay, only five RCTs comparing continuous versus interrupted sutures were identified. The five RCTs included a total of 827 participants undergoing abdominal or groin operations (non-obstetric surgery) [19–23]. Most of the enrolled patients were children or adolescents, and appendectomy was the most performed surgery.

Comparisons were made irrespectively of the material of the sutures. From this meta-analysis, no statistically significant differences were found between the two methods of suture regarding the prevalence of superficial SSI (RR 0.73; 95% CI 0.40 to 1.33) and length of hospital stay. However, a lower rate of superficial wound dehiscence was recorded in the continuous suture group (RR 0.08; 95%, CI 0.02 to 0.35).

It should be noted that in these trials the continuous skin suture groups received absorbable subcuticular sutures, while the interrupted skin suture groups received non-absorbable transcutaneous sutures. The non-absorbable sutures were removed 7 to 9 days after surgery, which is generally considered to be a suitable time for removal of sutures. The removal of sutures was not necessary for the absorbable subcuticular continuous suture group. The suture material used in the continuous suture groups was 4-0 poliglecaprone and 4-0 polyglyactin [22, 23].

This kind of sutures retains approximately 50 to 75% of their original tensile strength after 1 week in situ. This extra support for the wound after 1 week may be the main reason for the difference between the continuous suture group and the interrupted suture group regarding the development of superficial wound dehiscence [19].
Conclusions of the meta-analysis were that superficial wound dehiscence may be reduced by using continuous subcuticular sutures and that continuous or interrupted skin closure does not have any impact on the development of superficial SSI and on the length of hospital stay. Due to the quality of the evidence, a high grade of uncertainty remains.

In addition to the abovementioned meta-analysis, only one study compared continuous versus interrupted skin suture for abdominal surgery in a non-intra-abdominal infection setting [24].

This review included 586 patients from a single Japanese institution to compare the incidence of incisional SSI after elective hepato-pancreatobiliary surgery (HPB) by different methods of skin closure. The study showed statistically significant efficacy of the subcuticular continuous sutures to prevent incisional SSI in patients undergoing HPB surgery (1.8% in the subcuticular continuous suture group and 10.0% in the stapling group, \( P < 0.01 \)). However, the retrospective and single-institution design substantially affect the evidence of the results.

Many papers showing the benefits of subcuticular sutures versus stapling in terms of reduction of SSI and wound dehiscence are available from the literature, but unfortunately they were designed to compare interrupted rather than continuous subcuticular sutures versus stapling, or they merge continuous and interrupted techniques in a single group [9, 16, 25].

For these reasons, further well-designed RCTs with a low risk of bias should be conceived to establish which type of skin suturing provides better results.

A common practice in OR is to cover the closed wound with adhesive steri-strips.

Custis et al. [26] carried out a prospective study to assess whether the addition of adhesive strips to a wound closed with buried interrupted subcuticular sutures improves outcomes following wound closure. The study enrolled 45 patients and showed that there was no significant difference in the total patient assessment scale score between the combination closure (14.0 [7.6]) and sutures only (14.7 [7.6]) sides at 3 months (\( P = .39 \)). There was also no significant difference between the two closure methods in terms of mean (SD) scar width (both methods, 1.1 [0.8] mm, \( P = .89 \)) at follow-up. There was one case of wound dehiscence at a site that used adhesive strips and two cases at sites without adhesive strips. Three suture abscesses were documented at sites with adhesive strips and six at sites without adhesive strips. One patient had a spitting suture, which was not classified as an abscess; this event occurred at a site without adhesive strips. There were no documented infections, hematomas, or seromas. None of the adverse effects were statistically significant between study arms. The authors concluded that similar outcomes were observed whether or not adhesive strips were applied in addition to buried dermal sutures when performing cutaneous surgical procedures and that the use of adhesive strips cannot be recommended to improve cosmetic outcomes or reduce scar width.

An updated Cochrane review [27] was carried out to determine the effects of various tissue adhesives compared with conventional skin closure techniques for the closure of surgical wounds included 33 studies with a total of 2793 participants and demonstrated that there was low-quality evidence that sutures were significantly better than tissue adhesives for reducing the risk of wound breakdown (dehiscence; RR 3.35; 95% CI 1.53 to 7.33; 10 trials, 736 participants that contributed data to the meta-analysis). The number needed to treat for an additional harmful outcome was calculated as 43. For all other outcomes—infection, patient and operator satisfaction and cost—there was no evidence of a difference for either sutures or tissue adhesives. No evidence of differences was found between tissue adhesives and tapes for minimizing dehiscence, infection, patients’ assessment of cosmetic appearance, patient satisfaction, or surgeon satisfaction. The authors concluded that sutures are significantly better than tissue adhesives for minimizing dehiscence. In some cases, tissue adhesives may be quicker to apply than sutures.

**Coated sutures: are they useful?**

**Statement 2.:** Triclosan-coated suture significantly reduces SSI prevalence compared with the non-coated sutures (GoR 1B).

Sutures with antimicrobial properties were developed to prevent microbial colonization of the suture material in operative incisions. Early studies showed a reduction of the number of bacteria in vitro and wound infections in animals using triclosan-coated sutures, and this effect was subsequently confirmed in clinical studies [28, 29]. Several novel antimicrobial coatings are now available, but still, no clinical studies have been done that compare the efficacy with non-coated sutures [30].

Wu et al. performed a systematic review to assess whether the use of antimicrobial-coated sutures is more effective in reducing the risk of SSI than the use of non-coated sutures.

Eighteen studies comparing triclosan-coated sutures vs non-coated sutures (13 randomized controlled studies and 5 observational studies) were included in the meta-analysis for a total of 7458 patients; all studies investigated triclosan-coated sutures and focused on adult patients, apart from one done in a pediatric population [31]. The meta-analysis of the data demonstrated that antimicrobial sutures significantly reduced SSI risk (for RCTs: OR 0.72, 95% CI 0.59–0.88, \( P = 0.001 \), I² = 14%; for observational studies: OR 0.58, 95% CI 0.40–0.83, \( P = 0.003 \), I² = 22%). Only Vicryl Plus vs Vicryl revealed consistent results in favor of antimicrobial sutures (for 7
RCTs: OR 0.62, 95% CI 0.44–0.88, \( P = 0.007, \text{I}_2 = 3\% \); for 4 observational studies: OR 0.58, 95% CI 0.37–0.92, \( P = 0.02, \text{I}_2 = 41\% \). Besides, the effect of antimicrobial coating was similar between different suture, wound (clean, clean-contaminated, and mixed), and procedure types (colorectal, cardio-vascular, head and neck, breast surgical procedures). Quality of RCT evidence was judged moderate, and observational studies’ evidence was judged of very low quality and many studies had conflicts of interest. The authors concluded that triclosan-coated sutures may reduce SSI risk.

Uchino et al. [32] have recently analyzed the efficacy of antimicrobial-coated sutures in preventing SSIs in digestive surgery. A total of 5188 patients in 15 studies were included, with 10 randomized controlled trials (RCT) and 5 observational studies (OBS). One study enrolled pediatric patients. The sutured surgical sites in the included studies were the abdominal fascia in 12 studies, the subcutaneous alone in 1 study, and unknown in 2 studies.

Regarding the types of surgeries represented, there were 9 colorectal surgeries, 4 mixed digestive surgeries, 1 gastric surgery, and 1 pancreaticoduodenectomy. The RCTs included 6 studies that performed surgeries limited to class 2 wounds or described the incidence distinct from the wound class. Only one study was performed during emergent surgeries and was limited to the dirty/infected wound classes. The remaining 3 studies were analyses conducted together with mixed wound classes. Regarding the suture materials in the RCTs, monofilament sutures were used in 4 RCTs, and poly-filament sutures were used in 4 RCTs. Two RCTs used mixed suture materials. In OBSs, nearly half of the participants had upper gastrointestinal surgery. The meta-analysis showed that in 10 RCTs, the incidence rates of incisional SSIs were 160/1798 (8.9%) with coated sutures and 205/1690 (12.1%) with non-coated sutures. Overall, antimicrobial-coated sutures were superior for reducing the incidence of incisional SSI (RR 0.67, 95% CI 0.48–0.94, \( P = 0.02 \)) in RCTs for digestive surgery with the mixed wound class and surgeries limited to a clean-contaminated wound (RR 0.66, 95% CI 0.44–0.98, \( P = 0.04 \)). A superior effect of antimicrobial-coated sutures was found in 9 RCTs that involved only colorectal surgeries (RR 0.69, 95% CI 0.49–0.98, \( P = 0.04 \)). The superior effect of antimicrobial-coated sutures was also found in OBSs (OR 0.4, 95% CI 0.3 to 0.54, \( P < 0.001 \)). The mean hospital stay length was similar to coated or uncoated sutures in 5 RCTs involving colorectal surgery (mean difference (MD) –5.00, 95% CI 16.68–6.69, \( P = 0.4 \)) [32].

Guo et al. demonstrated that triclosan-coated sutures were associated with a lower risk of SSI than uncoated sutures across all surgeries (risk ratio [RR] 0.76, 95% confidence interval [CI] 0.65–0.88, \( P < 0.001 \)). Similar proportions of patients experienced wound dehiscence with either type of suture (RR 0.97, 95% CI 0.49–1.89, \( P = 0.92 \)). Subgroup analysis showed lower risk of SSI with triclosan-coated sutures in abdominal surgeries (RR 0.70, 95% CI 0.50–0.99, \( P = 0.04 \)) and group with prophylactic antibiotic (RR 0.79, 95% CI 0.63–0.99, \( P = 0.04 \)). However, such risk reduction was not observed in cardiac surgeries, breast surgeries, or the group without prophylactic antibiotics [33].

Henriksen et al. [34] in an overall comparison including both triclosan-coated Vicryl and PDS sutures for fascial closure, reported that triclosan-coated sutures were superior in reducing the rate of SSI (OR 0.67; CI 0.46–0.98). The majority of the studies included only elective surgery procedures. Four of these included only colorectal procedures, whereas Diener et al. [35] included all types of elective procedures through a midline laparotomy. Justinger et al. [36] included both elective and emergency laparotomies, whereas Ruiz-Tovar et al. [37] included only cases with fecal peritonitis and Minglehairak et al. [38] studied patients undergoing open appendectomies. When evaluating PDS sutures separately, there was no effect of triclosan coating on the rate of SSI (OR 0.85; CI 0.61–1.17). After trial sequential analysis, authors concluded that triclosan-coated Vicryl sutures for abdominal fascial closure significantly decrease the risk of SSI and performing further RCTs will not change this outcome, but there was no effect on SSI rate with the use of triclosan-coated PDS sutures for abdominal fascial closure [34]. That means that PDS commonly used in abdominal surgery was not different.

Konstantelias et al. [39] analyzed 30 studies (19 randomized, 11 non-randomized; 15,385 procedures) giving evidence that triclosan-coated sutures were associated with a lower risk of SSIs (risk ratio [RR] = 0.68; 95% confidence interval [CI] 0.57–0.81). Triclosan-coated sutures were associated with a lower risk for SSIs in high-quality randomized studies (Jadad score 4 or 5). A lower risk for the development of SSIs based on wound classification was observed in clean, clean-contaminated, and contaminated but not for dirty procedures. No benefit was observed in specific types of surgery: colorectal, cardiac, lower limb vascular, or breast surgery.

A specific study on emergency surgery was also carried out confirming these findings [40].

What is the role of intraoperative intraperitoneal irrigation vs topic wound lavage with antibiotic solutions to prevent surgical site infections?

Statement 3: There are insufficient data to support the role of intraperitoneal or topic wound irrigation with antibiotics in preventing SSI (GoR 2B).

Although intraoperative irrigation with antibiotic solutions has been suggested to be beneficial in the prevention of infections, no evidence-based results have been made available. The effectiveness of intra-abdominal
lavage with antibiotic solutions on the prevention of postoperative SSI is controversial. Furthermore, issues about its safety need to be examined as well as local adverse effects (increased adhesion formation, postoperative pain), selection of resistant bacteria, and tissue toxicity.

The safety of the intraperitoneal administration of antibacterial agents during or after surgery as prophylaxis or treatment of infection has been investigated in a systematic review that included 29 RCTs and 50 observational studies [41].

The objective of this systematic review was to analyze perioperative intraperitoneal administration of antibacterial agents, to characterize the drugs used, and their safety profile. Administration of topical intraperitoneal antibiotics both during and after surgery was studied. Aminoglycosides, first- and second-generation cephalosporins, tetracyclines, and penicillins were most commonly administered intraperitoneally during or after surgery. The antibacterial agent was usually administered intraperitoneally as monotherapy. However, some studies administered combination regimens with heparin or with another antibacterial agent. The most frequent combination was aminoglycosides and lincosamides. Only a few and mild adverse events were reported and the authors concluded that antibacterial agents can safely be administered intraperitoneally. However, they acknowledged that in 43% of the included articles the adverse events were not reported while 41% of the studies specified that there were no adverse events related to the intraperitoneal administration of drugs. The most frequently reported adverse event was discomfort or pain during administration, especially with the use of oxytetracycline [41].

Animal data about the relationship between intraperitoneal antibiotics and adhesion development are conflicting [42–46].

In the experimental study conducted by Sortini et al. [43], the peritoneal lavage solution showing low adhesion formation and high survival rates was saline solution at 37 °C. In this study, lavage with antiseptics was associated with higher mortality (55–80% versus 0% for chlorhexidine–iodine solutions and saline solution, respectively, \( P < 0.001 \)) but less adhesion formation (\( P < 0.001 \)) as compared to saline solution. The use of antibiotic solutions was associated with 3% mortality in the treatment of peritonitis but with higher Zühlke scores and adhesion formation as compared to saline solution (\( P < 0.001 \)).

According to these data, antiseptic solutions should not be recommended for peritoneal lavage.

Another experimental study was carried out to test the effectiveness of the intraperitoneal application of alternate antibiotics (Imipenem, ceftriaxone, and cefazolin) in an abdominal sepsis model. These data suggest that cephalosporins may be effective in preventing adhesion formation in septic abdomens compared to metronidazole [46].

Tetikcok et al. [47] have recently demonstrated that in rats, peritoneal lavage with prednisolone improved survival rates with increasing doses in abdominal sepsis. Abdominal lavage in rats was made using saline in group 1, equal volumes of cefazolin sodium in group 2, low-dose methylprednisolone (1 mg/kg) in group 3, and high-dose methylprednisolone (2 mg/kg) in group 4. The study showed that the mortality rate of the rats in group 2 was significantly higher than that in group 4, which had no mortality (\( P = 0.032 \)). Although insignificant, the lowest mean value of IL-1β, IL-2, and TNF-α was in group 1, and the highest was in group 2. The lowest IL-4 level was in group 3, and the highest level was in group 2 (\( P = 0.41 \)). Interleukin-10 levels were significantly lower in group 4 and higher in group 2 (\( P = 0.014 \)). The administration of prednisolone in this abdominal sepsis model does not reflect a real-world situation; however, the administration of prednisolone alone helped to understand the effect of corticosteroids without masking the effects with antibiotics.

A 2017 Cochrane review included 36 studies (6163 participants) comparing the use of antibacterial irrigation with non-antibacterial irrigation [48]; authors reported a lower incidence of SSI in patients treated with antibacterial irrigation compared with non-antibacterial irrigation (RR 0.57, 95% CI 0.44 to 0.75; \( I^2 = 53% \); 30 studies, 5141 participants). This was low-certainty evidence downgraded once because 54% of the analysis weight was contributed by studies at high risk of bias in one or more domains, and once because publication bias was considered likely to have affected the result. Besides, the review pools together studies about intra-cavitary and wound irrigation, antibiotics, and antiseptics as antibacterial agents.

The possible benefit was present in each of the surgical contamination subgroups (clean versus clean-contaminated versus contaminated or dirty). The difference in adverse events, mortality, and abscess formation did not reach statistical significance. The hospital stay was reduced in the antibacterial irrigation group.

Concerning intraoperative wound irrigation, Mueller et al. in a meta-analysis of RCTs investigating the incidence of postoperative SSI after intraoperative irrigation of the surgical incision (after the closure of the fascia or peritoneum and before skin closure) performed a subgroup analysis comparing intraoperative wound irrigation with topical antibiotics vs saline solution irrigation. The study showed a significant reduction of postoperative SSI when antibiotic solution irrigation was used compared to both saline solution only irrigation and no irrigation.
The reported length of follow-up in the included trials was 30 days or more in only 21 out of 41 trials. The remaining trials reported follow-up times of as short as 5–10 days or did not specify the follow-up time at all. Besides, the number and frequency of follow-up visits varied largely, as did the type and blinding status of the primary outcome assessor [49].

However, the considerable risk for bias of all the included trials, their large heterogeneity, and the need to balance those findings against the risk of impaired wound healing and the potential increase of the bacterial resistance suggest caution in the clinical application of these results.

Could wound irrigation with saline and/or povidone iodine solution be useful to prevent surgical site infection?

**Statement 4: There are insufficient data to determine the role of saline or povidone irrigation of incisional wounds before closure to prevent SSI (GoR 2B)**

Intraoperative wound irrigation refers to the flow of a solution across the surface of an open wound. It is a widely practiced procedure and considered to help prevent SSI.

Among other benefits, wound irrigation is intended to physically remove foreign material, cellular debris, surface bacteria, and body fluids, to dilute possible contamination and to function as a local antibacterial agent when an antiseptic or antibiotic agent is used.

Wound irrigation must be vigorous enough to perform the above goals but gentle enough to avoid further tissue trauma or passage of bacteria and foreign material deeper into the wound. Practices vary depending on the patient population, the surface of the application, and the solution used.

On the other hand, vigorous irrigation may remove protective immunologic cells that are enable healing to progress through a natural series of processes, including inflammation and granulation, to final re-epithelialization and remodeling. Exposed subcutaneous tissue provides a favorable substratum for a wide variety of microorganisms to contaminate and colonize, and if the involved tissue is devitalized (e.g., ischemic, hypoxic, or necrotic) and the host immune response is compromised, the conditions become optimal for microbial growth [50]. A systematic review was carried out to investigate whether intraoperative wound irrigation (with or without active agents or pressured application) affects the incidence of SSI. Studies investigating the topical application of antibiotics or anti-septics (e.g., powder, gels, sponges) were not included.

Twenty-one RCTs were identified comparing wound irrigation with no wound irrigation in patients undergoing various surgical procedures, and the results were substantially heterogeneous [51].

Saline irrigation was not effective in reducing SSIs [52]. However, when the saline was applied with a syringe to generate some pressure [53], a reduction in the risk of SSI compared with no irrigation was shown in one study (OR 0.35; 95% CI 0.19–0.65; \( P = 0.0009 \)). This benefit also was demonstrated when pulse pressure irrigation with saline was compared with normal saline irrigation in a meta-analysis of two RCTs [54, 55] (OR 0.30; 95% CI 0.08–0.86; \( P = 0.0003 \)).

In the same meta-analysis, a low quality of evidence demonstrated a statistically significant benefit for incisional wound irrigation with an aqueous povidone iodine solution in clean and clean-contaminated wounds (OR 0.31; 95% CI 0.13–0.73; \( P = 0.007 \)); 50 fewer SSI per 1000 procedures (from 19 fewer to 64 fewer) [51].

The 2017 Cochrane review comparing antibacterial irrigation with non-antibacterial irrigation (36 studies, 6163 participants), the largest meta-analysis published, reported a lower incidence of SSI in participants treated with antibacterial irrigation compared with non-antibacterial irrigation (RR 0.57, 95% CI 0.44 to 0.75; \( I^2 = 53\% \); 30 studies, 5141 participants) but evidence are of low certainty [48].

Therefore, where a possible difference in the incidence of SSI was identified (in comparisons of antibacterial and non-antibacterial interventions, and pulsatile versus standard methods), these should be considered in the context of uncertainty, particularly given the possibility of publication bias for the comparison of antibacterial and non-antibacterial interventions.

Clinicians should also consider whether the evidence is relevant to the surgical populations (wound classification and setting) under consideration.

Are wound protector devices useful? (Table 3)

**Statement 5.1: The use of wound protectors has protective effects in reducing incisional SSI (GoR 1A);**

**Statement 5.2: The use of dual-ring constructed wound protectors appears to be superior to single-ring devices in preventing SSI (GoR 1B).**

Wound protector devices (alternatively called “wound guards” or “wound retractors”) have been increasingly used in the effort to reduce SSI rates. These devices form a physical barrier between the wound edges and the contaminated surgical field. More specifically, the impervious plastic barrier prevents both endogenous and exogenous pathogens from imbedding themselves within the wound (skin, fat, fascia, peritoneum). This mechanism, in conjunction with maintaining wound humidity and reducing direct physical trauma from fixed retractors, is believed to reduce the risk of incisional SSI. It must be noted however that some bacterial invasion could occur immediately before the insertion,
or more likely after the removal of the wound protector itself. There are two widely available forms: a single ring that lies within the abdominal cavity connected to a protective drape that extends outward, or two rings that are connected cylindrically by impenetrable plastic with one ring inside the wound and the other secured on the outside [64].

The ROSSINI trial [56] is a multicenter observer-blinded RCT carried out to determine the clinical effectiveness of wound edge protection device (the device used was the 3 M Steri-Drape Wound Edge Protector) in reducing surgical site infection after abdominal surgery, enrolling 760 patients with 382 patients assigned to the device group and 378 to the control group, reported that a total of 184 patients experienced surgical site infection within 30 days of surgery, 91/369 (24.7%) in the device group and 93/366 (25.4%) in the control group (odds ratio 0.97, 95% confidence interval 0.69 to 1.36; \(P = 0.85\)). In the secondary analyses, no subgroup could be identified in which there was evidence of clinical benefit associated with the use of the device. The authors concluded that wound edge protection devices cannot be recommended to reduce the rate of SSI in patients undergoing laparotomy.

Gheorghe et al. cost-effectiveness analysis suggests that the use of wound protector devices for SSI reduction cannot be justified and should be discontinued [64].

Previously, in 2012, Gheorghe et al. [57] reviewed 12 studies (2 prospective controlled studies +10 RCTs) reporting primary data from 1933 patients. The quality assessment found all of them to be at considerable risk of bias. An exploratory meta-analysis was performed to provide a quantitative indication of the wound edge protector device effect. The pooled risk ratio under a random-effects model was 0.60 (95% confidence interval, 0.41–0.86), indicating a potentially significant benefit from the use of the dispositive. No indications of significant between-study heterogeneity or publication bias, respectively, were identified.

In 2012, Edwards et al. [58] analyzed 6 RCTs for a total of 1008 patients were included. They reported that the use of a wound protector was associated with a significant decrease in SSI (RR = 0.55, 95% CI 0.31–0.98, \(P = 0.04\)). Data showed also a nonsignificant trend toward greater protective effect in studies using a dual-ring protector (RR = 0.31, 95% CI 0.14–0.67, \(P = 0.003\)), rather than a single-ring protector (RR = 0.83, 95% CI 0.38–1.83, \(P = 0.64\)).

To assess these controversial results, several meta-analyses have been published looking at the effectiveness of wound protectors in preventing SSIs in abdominal surgeries.

In 2015, Mihaljevic et al. [59] analyzed 16 RCTs including 3695 patients investigating wound edge protectors published between 1972 and 2014. Data reported that wound edge protectors significantly reduced the rate of surgical site infections (risk ratio 0.65; 95%CI, 0.51–0.83; \(P = 0.0007; \stackrel{\cdot}{I}^2 = 52\%\)). A similar effect size was found in the subgroup of patients undergoing colorectal surgery (risk ratio 0.65; 95%CI, 0.44–0.97; \(P = 0.04; \stackrel{\cdot}{I}^2 = 56\%\)). Of the two common types of wound

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Number of patients</th>
<th>Outcomes</th>
<th>GoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter RCT</td>
<td>760</td>
<td>Wound edge protection devices do not reduce the rate of surgical site infection in patients undergoing laparotomy, and therefore their routine use for this role cannot be recommended.</td>
<td>1A</td>
</tr>
<tr>
<td>Systematic review and meta-analysis of 2 PCT + 10 RCT</td>
<td>1933</td>
<td>Wound edge protectors may be efficient in reducing SSI rates in patients undergoing open abdominal surgery</td>
<td>1B</td>
</tr>
<tr>
<td>Meta-analysis of 6 RCT</td>
<td>1008</td>
<td>Wound protectors reduce rates of SSI after gastrointestinal and biliary surgery</td>
<td>1A</td>
</tr>
<tr>
<td>Systematic review and meta-analysis of 16 RCT</td>
<td>3695</td>
<td>Wound edge protectors significantly reduce the rate of surgical site infections in open abdominal surgery</td>
<td>1B</td>
</tr>
<tr>
<td>Systematic review and meta-analysis of 11 RCT</td>
<td>2344</td>
<td>Wound edge protector reduces the incidence of SSI in patients receiving laparotomies, especially in the circumstances of dual-ring type and in contaminated incisions. In order to fully assess the effectiveness of WEP, large-scale and well-designed RCTs are still needed in the future</td>
<td>1B</td>
</tr>
<tr>
<td>Systematic review and meta-analysis of 14 RCT</td>
<td>2684</td>
<td>Potentially significant benefit from impervious plastic wound protector use, greater protective effect in using dual-ring protector than a single ring</td>
<td>1A</td>
</tr>
<tr>
<td>Systematic review and meta-analysis of 18 RCT</td>
<td>3808</td>
<td>Wound edge protector is associated with reduced incidence of overall SSI in clean-contaminated and contaminated wounds</td>
<td>1B</td>
</tr>
<tr>
<td>RCT</td>
<td>107</td>
<td>Among adult patients with intrabiliary stents, the use of a dual-ring wound protector during pancreaticoduodenectomy significantly reduces the risk of incisional SSI</td>
<td>1A</td>
</tr>
</tbody>
</table>
producers, double-ring devices were found to exhibit a greater protective effect (risk ratio 0.29; 95% CI, 0.15–0.55) than singlering devices (risk ratio 0.71; 95% CI, 0.54–0.92), but this might largely be due to the lower quality of available data for double-ring devices. Exploratory subgroup analyses for the degree of contamination showed a larger protective effect in contaminated cases (0.44; 95% CI, 0.28–0.67; \( P = 0.0002 \), \( I^2 = 23% \)) than in clean-contaminated surgeries (0.72, 95% CI, 0.57–0.91; \( P = 0.005 \), \( I^2 = 46% \)) and a strong effect on the reduction of superficial surgical site infections (risk ratio 0.45; 95% CI, 0.24–0.82; \( P = 0.001 \), \( I^2 = 72% \)) [59].

Zhang et al. reviewed 11 RCTs including 2344 patients. In particular, 6 trials (1589 patients) testing the single-ring design wound edge protector did not show a statistically significant reduction in SSI of laparotomy (RR 0.76, 95% CI 0.51–1.12). Pooled analysis of the five trials (755 patients) that tested the effect of dual-ring wound protector on SSI showed a significant reduction (RR 0.29, 95% CI 0.15–0.55). The combined data of the 11 trials favored the wound edge protector effect (RR 0.58, 95% CI 0.39–0.87). Analysis adjusted by the degree of contamination revealed that wound protector device is effective in reducing the incidence of SSI after laparotomy incision contamination (RR 0.43, 0.26–0.72) but failed to demonstrate such effect in clean/contaminated and dirty incisions (RR 0.72, 95% CI 0.43–1.21; RR 0.82, 95% CI 0.43–1.55, respectively) [60].

More specifically, two extremely recent systematic reviews that evaluated 2684-patient and 3808-patient RCTs respectively once again confirm this observation. The first from Kang et al. [61] identified and analyzed 14 randomized controlled trials with a total of 2684 patients. The pooled risk ratio under a random-effects model was 0.70 (95% confidence interval, 0.51–0.96; I2, 56.8%), indicating a potentially significant benefit from impervious plastic wound protector use. There was a significant trend toward greater protective effect in studies using a dual-ring protector (relative risk = 0.31; 95% confidence interval, 0.15–0.58), rather than a single-ring protector (relative risk = 0.84; 95% confidence interval, 0.71–1.00). There was no significant between-study heterogeneity or publication bias.

The second from Said et al. [62] analyzed 18 RCTs and demonstrated that wound edge protector is associated with the reduced incidence of overall SSI (OR 0.59; 95% CI 0.43–0.81; \( z = 3.30 \); \( P < 0.001 \)) and superficial SSI (OR 0.42; 95% CI 0.18–0.95; \( z = 2.09 \); \( P < 0.04 \)). In addition, it also successfully reduced the risk of SSI in clean-contaminated wounds (OR 0.67; 95% CI 0.46–0.98; \( z = 2.06 \); \( P < 0.04 \)) as well as in contaminated wounds (OR 0.24; 95% CI 0.12–0.49; \( z = 3.96 \); \( P < 0.0001 \)). The reported overall reduction in SSI was substantial in both reviews (OR = 0.70 and 0.59 respectively).

When superficial (wound) SSI is the focus of the analysis, there is a further reduction in the postoperative rate (OR = 0.42). Furthermore, these trends appear to extend to both clean-contaminated and contaminated wounds (OR = 0.67 and 0.24 respectively). While these comprehensive reviews and statistical analyses are compelling, they omit a single large recent RCT that evaluated the role of wound protectors in high-risk non-colorectal scenarios (i.e., pancreaticoduodenectomies (PD) following preoperative insertion of biliary stents for obstruction). This study including a total of 107 patients reported a significant reduction in the incidence of incisional SSI in the wound protector group (21.1% vs 44.0%; relative risk reduction 52%; \( P = 0.010 \)).

While the utility of wound protectors is clear, the superior mechanical configuration of these devices remains debated. More specifically, both single-ring (with or without large adhesive drape components) and dual-ring modalities (internal and external ring connected by impervious plastic) are currently available. Two high-quality analyses [61, 62] have both noted a strong trend toward a greater protective effect with dual-ring variants when compared to devices constructed with a single external ring and associated semi-adhesive drape. It is also interesting to note that among this level 1 RCT data, there is a clear modifying effect of the publication year. In other words, as time has progressed in the study of wound protectors and therefore the evaluation of more diverse surgical subgroups, their protective effect has become increasingly evident.

In clinical practice, the only possible barrier to the routine use of these types of devices is cost and availability. A possible solution to decrease cost is to reserve wound protectors for high-risk patients or dirty surgical incisions to reduce SSI and equate costs related to wound protectors and hospitalization(s).

**Are adhesive sterile surgical incise drapes useful?**

**Statement 6.1:** There is no evidence that plastic adhesive drapes with or without antimicrobial properties are useful to decrease SSI (GoR 2C).

Adhesive plastic incise drapes are used on a patient’s skin after surgical site preparation, with or without antimicrobial impregnation, and the surgeon performs the incision of the drape and the skin simultaneously. There are conflicting recommendations on the use of plastic adhesive drapes, mainly discouraging their use.
In 2015, the fourth update of the Cochrane review carried out to investigate the advantages about using plastic adhesive drapes to protect the wound from organisms that may be present on the surrounding skin during surgery, analyzed 5 studies with a total 3082 participants comparing plastic adhesive drapes with no drapes and 2 studies involving 1113 participants comparing iodine-impregnated adhesive drapes with no drapes. A significantly higher proportion of patients in the adhesive drape group developed a surgical site infection when compared with no drapes (risk ratio (RR) 1.23, 95% confidence interval (CI) 1.02 to 1.48, \( P = 0.03 \)). Iodine-impregnated adhesive drapes did not affect the surgical site infection rate (RR 1.03, 95% CI 0.06 to 1.66, \( P = 0.89 \)). The length of hospital stay was similar in the adhesive drape and non-adhesive drape groups. There was no evidence from the 7 trials that plastic adhesive drapes reduce surgical site infection rates and some evidence that they increase infection rates [65].

In 2016, Allegranzi et al. analyzed 4 studies (one RCT, one quasi-RCT, and two observational studies) comparing adhesive iodine-impregnated incise drapes with no drapes and showed no difference in the SSI risk (RCTs: OR 2.62; 0.68–10.04; observational studies: OR 0.49; 0.16–1.49). Similarly, a meta-analysis of two RCTs comparing non-impregnated adhesive incise drapes to no drapes showed no difference in the SSI risk (OR 1.10; 0.68–1.78) [66].

Recently, Rezapoor et al. carried out a prospective, randomized clinical trial to evaluate the efficacy of iodophor-impregnated adhesive drapes for reducing bacterial contamination and counts at the incision site during hip surgery. The study enrolled 101 patients undergoing open joint preservation procedure of the hip. Half the patients had the adhesive drape applied to the skin before incision, while the remainder underwent the same surgery without a drape. Culture swabs were taken from the surgical site at 5 points (pre skin preparation, after skin preparation, post-incision, before subcutaneous closure, before dressing application) and sent for culture and colony counts. After surgery, 12.0% of incisions with adhesive drapes and 27.4% without adhesive drapes were positive for bacterial colonization. It appears that the iodophor-impregnated adhesive draping significantly reduces bacterial colonization of the incision [67].

Recently, Zarei et al. have conducted a quasi-experimental study with non-equivalent control group design enrolling 88 patients who were the candidate for lumbar spine surgery in the elective operating room to investigate the effect of the incise drape on the rate of bacterial contamination of surgical wound, and they concluded that the use of ID is unable to reduce surgical wound bacterial contamination in clean lumbar spine surgery [68].

To drain or not to drain in closing surgical incision?

Statement 7.1: There are insufficient data to determine the role of subcutaneous drainage of incisional wounds before closure to prevent SSI in high-risk patients (GoR 2B).

Evidence regarding the utility of subcutaneous drains in preventing incisional SSI are controversial.

The presence of fluid collection between the skin surfaces and underlying fascia is thought to increase the risk for SSIs, as it can provide a medium for bacterial growth. The concept of subcutaneous drainage is to remove these fluids before they become infected, resulting in a reduction of SSI.

Recently, several studies have examined suctioning/active drainage systems as a means to prevent SSI in digestive surgery, but the utility of these systems is still controversial [69, 70].

Fuji et al. assessed the efficiency of subcutaneous drains for high-risk patients undergoing colorectal surgery, including patients with thick subcutaneous fat tissue and those undergoing emergency operations. They enrolled in their 79 high-risk patients for SSI. The overall incidence of incisional SSI was 27.8%. The incidences of incisional SSI in these cases with or without a subcutaneous drain were 14.3% and 38.6%, respectively. The authors concluded that subcutaneous drains are effective for preventing incisional SSI in patients with thick subcutaneous fat in colorectal surgery [71].

In 2013, Kosins et al. [72] reviewed and analyzed 52 randomized controlled trials with a total of 6930 operations aimed to determine the evidenced-based value of prophylactic drainage of subcutaneous wounds in surgery. Subgroups were determined by specific surgical procedures or characteristics (cesarean delivery, abdominal wound, breast reduction, breast biopsy, femoral wound, axillary lymph node dissection, hip and knee arthroplasty, obesity, and clean-contaminated wound). There were 3495 operations in the drain group and 3435 in the no-drain group. Prophylactic subcutaneous drainage offered a statistically significant advantage only for the prevention of hematomas in breast biopsy procedures and the prevention of seromas in axillary node dissections. In all other procedures studied, drainage did not offer an advantage.

The authors concluded that drain placement following a surgical procedure is the surgeon’s choice and can be based on multiple factors beyond the type of procedure being performed or the patient’s body habitus [72].

All the previous studies assessed the usefulness of active-suctioning subcutaneous drain in a closed surgical wound. Numata et al. [73] decided to evaluate the efficacy of a passive drainage system for preventing surgical site infections during major colorectal surgery, enrolling 246 (124 underwent passive drainage, and 122 underwent no
When is double gloving recommended? When is changing gloves recommended during an operation?

**Statement 8.1:** There are insufficient data to determine the role of double gloving to prevent SSI (GoR 2B).

**Statement 8.2:** The mechanical resistance of latex gloves depends on the duration of wear. It may be beneficial for surgical team members and their protection to change gloves at certain intervals during surgery (GoR 2C).

Surgical gloves are an important physical barrier between the surgical staff and the patient. They enable the prevention of transmission of microorganisms in both directions, from the surgeons' hands to the patient.

The integrity of gloves depends on the duration of wearing, the role within the surgical team, and the type of surgery performed.

Their use since the beginning was a barrier against infections. With the recognition of HIV infection and the associated concerns about transmission of HBV and hepatitis C virus in the operating room during the 1980s and early 1990s, considerable interest emerged in the provision of better protection of the hands for surgical personnel [78].

The intact surgical glove is the most important barrier to the bi-directional migration of microorganisms between the hands of the members of a surgical team and the patient. Several studies have shown that undetected perforations of surgical gloves are common and that the frequency of such defects increases with the duration of glove wear. The risk of glove defects is related to the type of surgery being done, ranging from 7% in urologic surgery to 65% in cardiothoracic surgery [78, 79].

Various measures have been developed to reduce the risk of surgical site contamination with microorganisms originating from the surgeon’s hands.

Standard practice for decreasing the microbial bio-burden on the hands of surgeons and other surgical team members is preoperative surgical hand disinfection with an antimicrobial soap (surgical scrub) or an alcohol-based hand disinfectant (surgical rub). Preoperative surgical hand disinfection can reduce, but not eradicate, the resident flora on the surgeon’s hands. Because of the re-growth of skin flora during a surgical procedure, original levels of skin flora on a surgeon’s hands can be re-established within 3–6 h, depending on the formulation of the product used to disinfect the hands [78].

A novel sterile antimicrobial surgical glove, featuring a proprietary complex coating with 14 ingredients and chlorhexidine as an active antimicrobial ingredient on its inner surface, has been developed to reduce the risk of contamination of the surgical site in the event of a glove breach. Further clinical studies are needed to confirm this concept [79].

Drainage (passive or subcutaneous) patients who underwent major colorectal surgery. Patients were randomly assigned to receive subcutaneous passive drainage or no drainage. The primary outcome measured was the incidence of superficial SSI. The secondary outcomes measured were the development of hematomas, seromas, and wound dehiscence.

They reported a significant difference in the incidence of superficial SSIs between patients assigned to the passive drainage and no drainage groups (3.2% vs 9.8%, respectively, \( P = 0.041 \)). There were no cases that developed a hematoma, seroma, or wound dehiscence in either group. The authors concluded that subcutaneous passive drainage provides benefits over no drainage in patients undergoing major colorectal surgery.

The benefit of subcutaneous drainage was studied also in ileostomy closure that is in a dirty surgical field; after having conducted an RCT, Lauscher et al. [74] were able to affirm that the omission of subcutaneous suction drains is not inferior to the use of subcutaneous suction drains after ileostomy reversal in terms of length of hospital stay, surgical site infections, and hematomas/seromas.

In another RCT, the rate of SSI appeared to be reduced with subcutaneous suction drains in open abdominal surgery, but the authors concluded that prospective randomized larger-scale studies should be performed to confirm data [75].

Recently, Watanabe et al. [76] decided to evaluate the effects of subcutaneous closed-suction Blake drain for preventing SSIs after colorectal surgery performing an RCT, enrolling 240 patients. The incidence of incisional SSI was 8.7% in the overall patients. The incidence of incisional SSI was 12.8% in the control arm and 4.5% in the subcutaneous drainage arm. They reported a significant reduction of the incidence of SSI in the subcutaneous drainage arm than in the control arm (\( P = 0.025 \)). Logistic regression analysis demonstrated that thickness of subcutaneous fat > 3.0 cm, forced expiratory volume in 1 s as percent of forced vital capacity (FEV1.0%) > 70%, and subcutaneous drain were independent predictors of postoperative incisional SSIs (\( P = 0.008 \), \( P = 0.004 \), and \( P = 0.017 \), respectively). The authors affirmed that a subcutaneous Blake drain is beneficial for preventing incisional SSIs in patients undergoing colorectal surgery [76].

Manzoor et al. [77] after reviewing the literature to assess the evidence on the efficacy of subcutaneous wound drainage in reducing SSI concluded that not all patients will benefit from subcutaneous drainage. Subcutaneous wound drainage seems to be useful in patients with high risk to develop an SSI including patients who are obese and/or have contaminated wounds but in clean and clean-contaminated surgical wounds, it remains a surgeon’s choice [77].
Double gloving has been demonstrated to reduce blood contact with the hands of the operating team. Quebbeman and colleagues noted a nearly 90% reduction in hand exposure to blood with double gloving in a prospective, randomized trial [80]. Wearing two pairs of latex gloves significantly reduces the number of perforations to the innermost glove. This evidence comes from trials undertaken in “low-risk” surgical specialties. Wearing two pairs of latex gloves does not cause the glove wearer to sustain more perforations to their outermost glove. Wearing double latex indicator gloves enables the glove wearer to detect perforations to the outermost glove more easily than when wearing double latex gloves. However wearing a double latex indicator system will not assist with the detection of perforations to the innermost glove, nor reduce the number of perforations to either the outermost or the innermost glove. There is no direct evidence that additional glove protection worn by the surgical team reduces surgical site infections in patients; however, the most important published review has insufficient power for this outcome [81].

The adequate protection, however, requires that the glove material remain intact. The electrical conductivity, insulation, and mechanical resistance of glove latex depend on the duration of wear. Latex is subject to hydration; 30 min of surgical use was associated with measurable hydration of glove latex and a statistically significant loss of electrical and mechanical resistance, with rupture load decreasing by 24% [82].

Parteke et al. prospectively collected 898 consecutive pairs of used surgical gloves over 9 months in a single institution and reported that wearing gloves for 90 min or less resulted in microperforations in 46 (15.4%) of 299 pairs of gloves, whereas wearing gloves for 91–150 min resulted in perforation of 54 (18.1%) of 299 pairs, and 71 of (23.7%) of 300 pairs were perforated when the duration of wear was longer than 150 min (P = .05). Because of the increase in the rate of microperforation over time, authors recommended that surgeons, first assistants, and surgical nurses directly assisting in the operating field change gloves after 90 min of surgery [83].

Several studies demonstrated that the occurrence of microperforations in surgical gloves increases over time.

Even in orthopedic surgery, surgical gloves should be changed when they are excessively contaminated with surgical fluids and the surgeon and first assistant should also change their outer gloves at an average of every 90 min [84].

Glove perforation rates are high in open abdominal surgery; considering data available, it may be beneficial for surgical team members to change gloves at certain intervals during surgery or use indicator glove systems [84].

Is negative-pressure wound dressing useful to prevent surgical site infections? (Table 4)

Statement 9: The application of negative-pressure wound therapy in preventing SSI may be effective in reducing postoperative wound complications and it may be an option, especially in patients with a high risk of SSI. (GoR 2C).

Gomoll et al. [93] first reported the application of negative-pressure wound therapy in closed incisions (cINPT), and their outcomes showed that its use for treating closed incisions in orthopedic surgery can reduce the incidence of SSI.

A subsequent series of reports [85–87] confirmed the effectiveness of cINPT in reducing SSI.

In 2015, Sandy-Hodgetts et al. [88] decided to conduct a systematic review and meta-analysis of all papers available from 1990 to 2013 evaluating the effectiveness of cINPT in preventing postoperative surgical wound complications. Eight studies were included in the review. Meta-analyses revealed a statistically significant difference in favor of the use of cINPT as compared with standard surgical dressings in managing SSI, but conflicting results were found for wound dehiscence and seroma. Considering the small number of studies included and that most of them were retrospective comparative cohort in design, authors could not recommend cINPT to prevent SSI even if the study demonstrated an association between the use of cINPT and reduction of SSI.

A more recent meta-analysis by Strugala et al. [89] investigated the effectiveness of prophylactic use of a specific design of cINPT device on surgical site complications. The authors considered all articles comparing the specific single-use cINPT device (PICO) with standard care for SSI in closed surgical wounds. Ten randomized and 6 observational studies were selected with a total of 1863 patients (2202 incisions) included. The randomized studies reported a significant reduction in SSI rate of 51% from 9.7 to 4.8% with cINPT intervention (RR 0.49 [95% CI 0.34–0.69] P < 0.0001). The observational studies assessed a reduction in SSI rate of 67% from 22.5 to 7.4% with cINPT (RR 0.32 [95% CI 0.18–0.55] P < 0.0001). Pooling all the data, there was a significant reduction in SSI of 58% from 12.5 to 5.2% with cINPT (RR 0.43 [95% CI 0.32–0.57] P < 0.0001) regardless of the type of surgery (orthopedic, abdominal, colorectal, or cesarean section), although the numbers needed to treat were lower in operations with higher frequencies of complications. Furthermore, meta-analysis showed a significant reduction in dehiscence from 17.4 to 12.8% with cINPT (RR 0.71 [95% CI 0.54–0.92] P < 0.01) and in-hospital length of stay by cINPT (– 0.47 days [95% CI – 0.71 to – 0.23] P < 0.0001).

Another meta-analysis carried out by Sahebally et al. [90] in 2018 evaluated the association of prophylactic
clNPT with SSI rates in general and colorectal surgery in elective and emergency settings.

Three randomized trials and 2 prospective and 4 retrospective studies were selected for the meta-analysis, involving 1187 patients with 1189 incisions. The authors found significant clinical and methodologic heterogeneity among the studies. On random-effects analysis, clNPT was associated with a significantly lower rate of SSI compared with standard dressings (pooled odds ratio [OR], 0.25; 95% CI, 0.12–0.52; *P* < .001) but no difference in rates of seroma (pooled OR, 0.38; 95% CI, 0.12–1.23; *P* = .11) or wound dehiscence (pooled OR, 2.03; 95% CI, 0.61–6.78; *P* = .25). On sensitivity analysis, focusing solely on colorectal procedures, clNPT significantly reduced SSI rates (pooled OR, 0.16; 95% CI, 0.07–0.36; *P* < .001). Thus, this study demonstrated that the application of clNPT on closed laparotomy wounds in general and in colorectal surgery is associated with reduced SSI rates but no different significant rates of seroma and wound dehiscence compared with traditional dressings.

Readership expressed some criticisms about the clinical value of these outcomes considering the high level of statistical heterogeneity associated with the included studies in the discussion and the necessity for randomized controlled trials before recommending the application of clNPT in clinical practice.

Uncertainty in the indications for the use of clNPT had been reported in 2012 [91] and then confirmed in 2014 [92] and the updated 2019 [94] version of the Cochrane systematic review. In the last systematic review, despite the addition of 25 trials, the authors judged the evidence to be low or very low certainty for all outcomes.

The study involved 2957 participants (30 intervention trials and two economic studies nested in trials). Surgeries included abdominal and colorectal (n = 5); cesarean sections (n = 5); knee or hip arthroplasties (n = 5); groin

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### Table 4 Negative wound dressing in preventing SSI: characteristics of the studies included in the review [85–96]. SSI surgical site infection, RCT randomized controlled trial, GoR grade of recommendation, NPWT negative-pressure wound therapy, LOS length of hospital stay

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Outcomes</th>
<th>GoR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandy-Hodgetts K et al. (2015) [88]</td>
<td>Systematic review and meta-analysis of 8 RCT, pseudo-randomized trials, quasi-experimental studies, prospective and retrospective cohort studies, case control studies, and analytical cross sectional studies</td>
<td>1277</td>
<td>NPWT in preference to standard postoperative dressings may be considered for closed surgical incisions in adults assessed as high-risk for SSI; further research is needed (level 1 studies—RCT) on patients identified as “at risk” in the preoperative period.</td>
<td>2C</td>
</tr>
<tr>
<td>Strugala V et al. 2017 [89]</td>
<td>Meta-analysis of 10 RCT + 6 prospective observational trials</td>
<td>1863</td>
<td>The significant reduction in SSI, wound dehiscence, and LOS on the basis of pooled data shows a benefit of the PICO single-use NPWT system compared with standard care in closed surgical incisions.</td>
<td>1A</td>
</tr>
<tr>
<td>Sahebally SM et al. 2018 [90]</td>
<td>Systematic review and meta-analysis of 9 studies (3 RCT and 2 prospective and 4 retrospective studies)</td>
<td>1266</td>
<td>Application of NPWT on closed laparotomy wounds in general and colorectal surgery is associated with reduced SSI rates but similar rates of seroma and wound dehiscence compared with conventional nonpressure dressings.</td>
<td>2C</td>
</tr>
<tr>
<td>Webster J et al. 2019 [94]</td>
<td>Cochrain systematic review (30 interventional studies)</td>
<td>2957</td>
<td>uncertainty remains about whether NPWT compared with a standard dressing reduces or increases the incidence of important outcomes such as mortality, dehiscence, seroma, or if it increases costs. Given the cost and widespread use of NPWT for SSI prophylaxis, there is an urgent need for larger, well-designed and well-conducted trials to evaluate the effects of newer NPWT products designed for use on clean, closed surgical incisions. Such trials should initially focus on wounds that may be difficult to heal, such as sternal wounds or incisions on obese patients.</td>
<td>2C</td>
</tr>
<tr>
<td>Katsuki Danno et al. 2018 [95]</td>
<td>Prospective study</td>
<td>28</td>
<td>The use of NPWT is an effective measure for preventing SSI in patients undergoing abdominal surgery for peritonitis caused by lower-gastrointestinal perforation.</td>
<td>2C</td>
</tr>
<tr>
<td>Lozano-Balderas G et al. 2017 [96]</td>
<td>Prospective randomized study</td>
<td>81</td>
<td>Statistical significance was found between infection rates of the vacuum-assisted group and the other two groups (primary closure and delayed primary closure). The infection rate in contaminated/dirty-infected laparotomy wounds decreases from 37 and 17% with primary and delayed primary closures, respectively, to 0% with vacuum-assisted systems.</td>
<td>1C</td>
</tr>
</tbody>
</table>
surgery \((n = 5)\); fractures \((n = 5)\); laparotomy \((n = 1)\); vascular surgery \((n = 1)\); sternotomy \((n = 1)\); breast reduction mammoplasty \((n = 1)\); and mixed \((n = 1)\). Webster et al. showed uncertainty about whether cINPT compared with a standard dressing reduces or increases the incidence of important outcomes such as mortality, dehiscence, and seroma or if it increases costs. Given the cost and widespread use of cINPT for SSI prophylaxis, authors claimed an urgent need for larger, well-designed and well-conducted trials to evaluate the effects of newer cINPT products designed for use on clean, closed surgical incisions.

Several studies investigated the role of cINPT in contaminated and dirty surgical wounds.

Danno et al. [95] prospectively included in their study 28 patients undergoing abdominal surgery for peritonitis caused by a lower-gastrointestinal perforation. They compared data from this group with a 19 patients historical control group who had undergone primary suturing for managing peritonitis incisions for a lower-gastrointestinal perforation. Authors reported a significant association between the SSI incidence and the type of incision management \((10.7\% \text{ with cINPT and delayed closure vs. } 63.2\% \text{ with primary suturing}; P < 0.001)\); no significant difference between the groups in the length of the hospital stay \((22 \text{ days for cINPT and delayed closure vs. } 27 \text{ days for primary suturing}; P = 0.45)\) was found.

Therefore, the association of cINPT and delayed closure of the abdominal wall is an effective method to prevent SSI.

A Spanish group [96] decided to compare outcomes about three techniques used for wound management after laparotomy in contaminated and dirty/infected wounds: the primary, delayed primary, and vacuum-assisted closures in terms of SSI. Eighty-one patients undergone laparotomy with Class III or IV surgical wounds were enrolled in a three-arm randomized prospective study. Twenty-seven patients received primary closure, 29 delayed primary closure, and 25 vacuum-assisted closure, with no exclusions for analysis. Surgical site infection was present in 10 \((37\%)\) patients treated with primary closure, 5 \((17\%)\) with primary delayed closure, and 0 \((0\%)\) patients receiving vacuum-assisted closure. Statistical significance was found between infection rates of the vacuum-assisted group and the other two groups. No significant difference was found between the primary and primary delayed closure groups. The infection rate in contaminated/infected laparotomy wounds decreases from \(37\% \text{ and } 17\% \text{ with primary and delayed closures, respectively, to } 0\% \text{ with vacuum-assisted systems [96].} \) We have to consider that in this study the number of patients is very small for each group.

Several studies evaluated the cost-utility of cINPT in preventing SSIs compared to standard dressings and demonstrated that the use of closed-incision negative-pressure therapy is cost-saving following the closure of abdominal incisions in high-risk patients [97–99].

Furthermore, to obviate the high costs related to current equipment for cINPT, more cost-effective alternatives were developed using standard gauze sealed with an occlusive dressing and wall suction. Several studies comparing both methods of treatment appear to be similarly effective for reducing wound surface area and volume [94, 100, 101].

Is intraoperative normothermia useful to prevent surgical site infections?

**Statement 10.1: Intraoperative normothermia decreases the rate of SSI (GoR 1A).**

**Statement 10.2: The use of active warming devices in operating room is useful to keep normothermia and reduce SSI (GoR 1B).**

Core body temperature is kept in a narrow range by several mechanisms, namely heat genesis and thermal insulation (mainly vasoconstriction or dilatation). This balance is greatly challenged during major surgery. On the one hand, surgery may imply exposure of large surface areas with consequent loss of heat and fluids. On the other hand, anesthesia disrupts the temperature setpoint (i.e., a lower than usual temperature triggers an adaptive reflex as shivering or metabolic thermogenesis) and can increase heat loss by vasodilatation [102]. Animal studies have shown that hypothermia increases complications such as infection, myocardial infarction, and coagulation derangements. Perioperative hypothermia can increase SSI due to its reflex vasoconstriction and mediated local immunosuppression. Vasoconstriction reduces partial oxygen pressure which lowers resistance to infections in animal models [103].

Perioperative normothermia has been addressed by several studies, papers, and meta-analysis. Considering only RCTs, the subsequent comparisons, but not limited to them, have been evaluated: head-to-head RCTs of one active warming device vs another, different extension of the active warming period through the perioperative one, active warming device vs no warming, warming of fluids and or insufflation gases during laparoscopic vs no active warming. We decided to focus on RCTs comparing interventions aimed at preventing hypothermia vs a control group where no such an intervention was implemented (a placebo group), the outcome was the incidence of SSI. Four relevant papers were analyzed [104, 105]. All of them dealt with an active body warming device against the placebo.

Kurz et al. [105] in 1996 randomized 200 patients scheduled for major abdominal contaminated surgery to receive active body surface warming by a forced-air warmer device.
The incidence of SSI was 6/104 in the intervention group and 18/96 in the control one ($P = 0.009$).

Melling et al. [106] in 2001 randomized 421 patients scheduled for clean surgery into three arms placebo, local warming (non-contact, radiant heat dressing), and systemic warming (forced-air warming device). Pooling the data of the two intervention groups, the incidence of SSI was 19/139 in the placebo group vs 13/277 in the intervention group ($P = 0.001$).

Pu et al. [107] in 2014 randomized 110 patients scheduled for laparoscopic gastrointestinal procedure into placebo group vs systemic warming (disposable under-body warming blanket with reusable forced-air warming system). The incidence of SSI was 0 in both the intervention and control groups.

Yi et al. [104] in 2018 randomized, in an open-label, pilot study 62 patients scheduled for open thoracic or hip replacement surgery to systemic warming (forced-air warming device) vs control (quilt). The incidence of SSI was 0/32 in the control group and 3/30 in the warming group ($P = 0.238$).

The effectiveness of temperature measurement in preventing SSIs has been assessed in a large cohort 2013 study in the colonic surgery population [108]. Several meta-analyses have been published on the topic. A recent Cochrane review from Madrid et al. [106] reviewed the literature and found a significant decrease in SSI after the implementation of an active warming intervention (risk ratio (RR) 0.36, 95% confidence interval (CI) 0.20 to 0.66; $P = 0.0008$; $I^2 = 0%$); the studies were rated of fair quality. Another meta-analysis reached the same conclusions [106]. There exists little debate around the effectiveness of reducing SSI by keeping the patients normothermic throughout the perioperative period. Four RCTs [100–103] and at least two meta-analyses [109, 110] confirm this risk reduction. It seems unlikely that other RCTs comparing a device to keep normothermia will be compared with a placebo group as this recommendation has been implemented in several national and international guidelines [111–114]. The last two RCTs [104, 107] with a real placebo group have been carried out in a nation where it is not common practice to warm patients during surgery. Those studies [100, 103] were meant to be pilot studies to assess the feasibility of forced-air warming in that context.

The two open questions are which device and/or strategy should be used and when (only intraoperative or intraoperative and pre- and/or postoperative?). There are three main devices to warm the patients: forced-air warming (so far the most studied and used worldwide), resistive polymer fabric warming, and circulatory warming systems using a closed fluid circuit. The use of radiant heating systems is considered feasible only during pediatric procedures. On the other side, other strategies have been implemented to reduce heat loss and prevent hypothermia (e.g., warm iv infusion, warm irrigation fluids or gases for pneumoperitoneum during laparoscopic, preoperative infusion of nutrients to increase metabolic rate and protein turn-over, reflective blankets). A thorough evaluation of those questions is outside the statement. The majority of those studies has as main outcome the achievement of normothermia and were not powered enough to detect a difference in SSI.

To date, Madrid et al. [109] evaluated in their meta-analysis the studies comparing head-to-head the different modality to warm up the patients and found no differences in SSI incidence. The main concern is the use of forced-air warming devices in surgery where air-borne pathogens are a major threat to orthopedic prosthesis surgery. In this particular scenario, the surgery takes place under the condition of ultra clean ventilation, at least in affluent countries, and it is known that forced-air disrupt the laminar flow and increases a load of bacteria at the operation site (in lab models). The bacterial load is the main risk factor for prosthesis colonization [115]. A systematic review is available but results are inconclusive [116]. Anyway, this hypothesis has not been formally tested in an adequately powered RCT.

The timing of warming has been evaluated in several papers. Pre-emptive warming plus intraoperative warming has shown better results in providing normothermia than intraoperative warming alone in small RCTs [117–119] and in a systematic meta-analysis [120]. Heterogeneity between the studies is high as well as the results from the single trials and the meta-analysis was not conclusive.

Several guidelines from national and international institutions stated in favor of achieving normothermia in the perioperative period to reduce the incidence of SSI [111–114].

**Is perioperative supplemental oxygen effective to reduce SSI?**

**Statement 11: Perioperative hyperoxegenation does not reduce SSI (GoR 2B).**

The most important defense against SSI is oxidative killing by neutrophils, and molecular oxygen is the substrate of the process. The easiest way to increase tissue oxygenation is to increase inspired oxygen. For example, intraoperative tissue oxygen partial pressure is typically about 6.6 kPa in patients given 30% inspired oxygen and about 13.3 kPa in those given 80% inspired oxygen [121].

Despite some early evidence [121], there have since been conflicting results from numerous randomized clinical trials.

Two well-conducted randomized trials ($n = 500$ and $n = 300$) [121, 122], a smaller trial [123] and a registry
analysis [124], suggested that supplemental oxygen (80% vs 30%) halved infection risk, supporting the role of supplemental oxygen in reducing the risk of SSI. However, other studies have not been able to confirm this.

The PROXI trial [125], that is a large, multicenter, randomized trial involving 1400 patients undergoing abdominal surgery, found no evidence of any beneficial effect of supplemental oxygen; in fact, SSI occurred in 131 of 685 patients (19%) receiving 80% oxygen and in 141 of 701 (20%) receiving 30% oxygen [odds ratio 0.94 (95% confidence interval 0.72–1.22), \( P = 0.64 \)]. Indeed, a long-term follow-up study (median 2.3 years after surgery) found poorer survival in the supplemental oxygen group [126].

Another recently published randomized, blinded trial including 400 patients [127] tested the hypothesis that extending intraoperative supplemental oxygen 12 to 16 h into the postoperative period reduces the risk of SSI and healing-related complications in the morbidly obese patients and reported no benefit of supplemental oxygen.

In 2018, Cohen et al. [128] published a meta-analysis including 26 trials with a total of 14,710 patients, to investigate the effect. The RR [95% CI] for wound infection was 0.81 [0.70, 0.94] in the high vs. low inspired oxygen groups. The effect remained significant in colorectal patients (10,469 patients), 0.79 [0.66, 0.96], but not in other patients (4,241 patients), 0.86 [0.69, 1.09]. When restricting the analysis to studies with low risk of bias, either by strict inclusion criteria (5047 patients) or by researchers’ judgment (12,547 patients), no significant benefit remained: 0.84 [0.67, 1.06] and 0.89 [0.76, 1.05], respectively. The authors concluded that meta-analysis of the most reliable studies does not suggest that supplemental oxygen substantively reduces wound infection risk when considering all available data, but more research is needed to fully answer this question.

Whether supplemental oxygen, which is inexpensive and easy to provide, reduces infection risk, thus remains in dispute.

Leaving the skin open for delayed primary closure can reduce SSI?

Statement 12.1: Delayed primary skin closure may reduce the incidence of SSI (GoR2C).

Statement 12.2: Delayed primary closure of a surgical incision is an option to take into consideration in contaminated abdominal surgeries in high-risk patients (GoR 2C).

Delayed primary closure of dirty wounds has been widely practiced in war surgery; it is a procedure which aims to reduce the rate of SSI by suturing a wound later after proper dressing, considering the fundamental principles of decreasing bacterial inoculums and potentiating local wound resistance from increasing wound oxygenation and blood supply from developing granulation tissue. It was first applied to traumatic wounds and later was more widely applied to various types of operations with the demonstration of good efficacy [129–131].

These results were mainly from observational studies that may be prone to selection and confounding biases.

Besides, the delayed primary closure also has its disadvantages including pain from routine dressing, the necessity for later wound suturing, and increase the cost of treatments [129–132].

In 2013, Bhangu et al. [132] decided to determine using meta-analysis whether delayed primary skin closure of contaminated and dirty abdominal incisions reduces the rate of SSI compared with primary skin closure.

The authors included in the final analysis 8 studies randomizing 623 patients with contaminated or dirty abdominal wounds to either delayed primary skin closure or primary closure. The most common diagnosis was appendicitis (77.4%), followed by perforated abdominal viscus (11.5%), ileostomy closure (6.5%), trauma (2.7%), and intra-abdominal abscess/other peritonitis (1.9%). The time to the first review for delayed primary skin closure was provided at between 2 and 5 days postoperatively. All studies were found to be at high risk of bias, with marked deficiencies in study design and outcome assessment. When SSI was assessed across all studies using a fixed-effect model, delayed primary skin closure significantly reduced the chance of SSI (odds ratio, 0.65; 95% CI, 0.40–0.93; \( P = .02 \)). However, heterogeneity was high (72%), and using a random-effects model, the effect was no longer significant (odds ratio, 0.65; 95% CI, 0.25–1.64; \( P = .36 \)).

The authors concluded that delayed primary skin closure may reduce the rate of SSI, but current trials fail to provide definitive evidence.

In 2014, Siribumrungrungwong et al. [133] decided to investigate the same topic carrying out a systematic review and meta-analysis to compare SSI between delayed primary and primary wound closure in complicated appendicitis and other contaminated abdominal wounds. Eight studies were considered for meta-analysis: 5 studies were done in complicated appendicitis, 2 with mixed complicated appendicitis and other types of abdominal operation, and 1 with ileostomy closure. Most studies (75%) had a high risk of bias in sequence generation and allocation concealment. Among 6 RCTs of complicated appendicitis that underwent open appendectomy, the SSI between primary closure and delayed primary closure were not significantly different with a risk ratio of 0.89 (95% CI, 0.46, 1.73). Delayed primary closure had significantly
of infection, and particularly in resource-constrained environments, even if more high-quality studies are needed to provide clear evidence.

When should additional antibiotic doses be administered intraoperatively?

**Statement 13: Optimal knowledge and use of the pharmacokinetic/pharmacodynamic characteristics of antibiotics is important to evaluate when additional antibiotic doses should be administered intraoperatively in patients with intra-abdominal infections undergoing emergency surgery (GoR 1C).**

Optimal use of the pharmacokinetic/pharmacodynamic characteristics of antibiotics is helpful to evaluate when additional antibiotic doses should be administered intraoperatively in patients with intra-abdominal infections undergoing emergency surgery.

Antibiotics should be used after a treatable intra-abdominal infection (IAI) has been recognized or there is a high degree of suspicion of infection. Initial antimicrobial therapy for patients with IAI should be prompt because especially critically ill patients need immediate treatment. It may be interesting to evaluate when additional antibiotic doses should be administered intraoperatively in patients with intra-abdominal infections undergoing emergency surgery.

To define how to administrate antibiotics in patients with IAI, it is necessary to know the pharmacokinetic/pharmacodynamic relationship of antibiotics. Knowledge of the pharmacokinetic and pharmacodynamic antibiotic properties may provide a more rational determination of optimal dosing regimens in terms of the dose and the dosing interval [136].

Antibiotic pharmacodynamics integrates the complex relationship between organism susceptibility and patient pharmacokinetics. Pharmacokinetics describes the fundamental processes of absorption, distribution, metabolism, and elimination and the resulting concentration-versus-time profile of an agent administered in vivo. The achievement of appropriate target site concentrations of antibiotics is essential to eradicate the pathogens [136]. Suboptimal target site concentrations may have important clinical implications and may explain therapeutic failures, in particular, for bacteria for which in vitro MICs are high. During the operation, target site concentrations should remain steadily optimal.

Dosing frequency is related to the concept of time-dependent versus concentration-dependent killing. Beta-lactam agents exhibit time-dependent activity and exert optimal bactericidal activity when drug concentrations are maintained above the MIC [137]. Therefore, the serum concentration must exceed the MIC for the appropriate duration of the dosing
interval. Higher-frequency dosing, prolonged infusions, and continuous infusions have been utilized to achieve this effect. It is well known that for beta-lactams, prolonged or continuous infusions have been advocated to maximize the time that the drug concentration exceeds the MIC, whereas high peak concentrations are not beneficial. This concept should be extended also to patients undergoing an emergency operation and higher-frequency dosing, prolonged infusions, and continuous infusions should be suggested also in the operatory room.

In contrast, antibiotics such as aminoglycosides exhibit concentration-dependent activity and should be administered in a once-daily manner (or with the least possible number of daily administrations) to achieve high peak plasma concentrations [137].

With these agents, the peak serum concentration, and not the time the concentration remains above the MIC, is more closely associated with efficacy. In these patients, additional doses are not necessary during operation.

Conclusions
We conceived this position paper to offer an extensive overview of available evidence regarding OR prevention of surgical site infection in emergency surgery as a potential addendum to WSES guidelines on the management of intra-abdominal infections.

The use of triclosan-coated suture significantly reduces SSI prevalence compared with the non-coated sutures.

The use of wound protectors has protective effects in reducing incisional SSI, in particular, the use of dual-ring constructed wound protectors appears to be superior to single-ring devices in preventing SSI.

The application of negative-pressure wound therapy in preventing SSI may be effective in reducing postoperative wound complications and it may be an option to take into consideration especially in patients with a high risk of infection.

Intraoperative normothermia decreases the rate of SSI, and the use of active warming devices in the operating room is useful to keep normothermia.

Perioperative supplemental oxygenation does not reduce SSI.

There is no strong evidence that delayed primary skin closure may reduce the incidence of SSI but it may be a valid option to primary skin closure in highly contaminated or “dirty” abdominal operations, especially in patients at high risk of infection.

The optimal knowledge and use of the pharmacokinetic/pharmacodynamic characteristics of antibiotics are important to evaluate when additional antibiotic doses should be administered intraoperatively in patients with intra-abdominal infections undergoing emergency surgery.

Appendix 1
Key words’ list for literature searching:
- “surgical incision” and “closure” and “suture” and “surgical site infection”
- “irrigation” and “incisional wound”;
- “wound protector” and “surgical site infection”;
- “dual ring” and “wound protector” and “wound infection”;
- “incisional drape” and “wound infection”;
- “drainage” and “subcutaneous” and “surgical incision”;
- “gloves” and “surgical site infection”;
- “negative pressure wound therapy” and wound infection” and surgical incision”;
- “normothermia” and “surgical site infection” and warming device”;
- “antibiotics” and “surgical wound infection” and “prevention”;
- “hyperoxia/hyperoxigenation” and “surgical site infection”;
- “timing skin closure” and “early” and “delayed” and “wound infection” and “dirty surgical incision”.

Abbreviations
cINPT: Closed-incision negative-pressure therapy; NPWT: Negative-pressure wound therapy; OBS: Observational trial(s); OR: Operating room; RCT: Randomized controlled trial(s); SC: Steering committee; SS: Scientific secretary; SSI: Surgical site infection(s)

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FC and MS conceived the study; all the experts nominated contributed writing a summary of evidence; BDS collected summaries, updated the literature, and wrote the manuscript; all the authors read and revised the manuscript; BDS revised the final manuscript; MK checked the English language. All authors read and approved the final manuscript.

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