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Original article

IAP/APA evidence-based guidelines for the management of acute pancreatitis

Working Group IAP/APA Acute Pancreatitis Guidelines[a,b,*,1]

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ABSTRACT

Background: There have been substantial improvements in the management of acute pancreatitis since the publication of the International Association of Pancreatology (IAP) treatment guidelines in 2002. A collaboration of the IAP and the American Pancreatic Association (APA) was undertaken to revise these guidelines using an evidence-based approach.
Methods: Twelve multidisciplinary review groups performed systematic literature reviews to answer 38 predefined clinical questions. Recommendations were graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The review groups presented their recommendations during the 2012 joint IAP/APA meeting. At this one-day, interactive conference, relevant remarks were voiced and overall agreement on each recommendation was quantified using plenary voting.
Results: The 38 recommendations covered 12 topics related to the clinical management of acute pancreatitis: A) diagnosis of acute pancreatitis and etiology, B) prognostication/predicting severity, C) imaging, D) fluid therapy, E) intensive care management, F) preventing infectious complications, G) nutritional support, H) biliary tract management, I) indications for intervention in necrotizing pancreatitis, J) timing of intervention in necrotizing pancreatitis, K) intervention strategies in necrotizing pancreatitis, and L) timing of cholecystectomy. Using the GRADE system, 21 of the 38 (55%) recommendations, were rated as 'strong' and plenary voting revealed 'strong agreement' for 34 (89%) recommendations.
Conclusions: The 2012 IAP/APA guidelines provide recommendations concerning key aspects of medical and surgical management of acute pancreatitis based on the currently available evidence. These recommendations should serve as a reference standard for current management and guide future clinical research on acute pancreatitis.

1. Introduction

Acute pancreatitis is one of the most common gastrointestinal disorders requiring acute hospitalization worldwide, with a reported annual incidence of 13–45 cases per 100,000 persons [1]. In the U.S. alone, acute pancreatitis leads to 270,000 hospital admissions annually and inpatient costs exceed 2.5 billion dollars [2]. It is clear that such a common disease associated with mortality up to 30% in severe cases, requires up-to-date evidence-based treatment guidelines with broad support from the pancreatic community. A recent systematic review has demonstrated the variable quality of the 30 guidelines published since 1988 and has highlighted the need for a high quality update [3]. Eleven years have passed since the "*Guidelines for the surgical management of acute pancreatitis*" by the International Association of Pancreatology (IAP) were published in 2002 [4]. Since then, a large body of new evidence has become available, not infrequently from randomized controlled trials (RCTs) and systematic reviews. This evidence has greatly influenced many important aspects of the medical and surgical management of acute pancreatitis.

The leadership of both the IAP and the American Pancreatic Association (APA) supported an initiative for an international multidisciplinary approach to update the evidence-based guidelines for the management of acute pancreatitis. To this end an

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adapted version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [5] was used. Both the revised Atlanta classification for acute pancreatitis [6] and the outcome of a recent consensus conference on interventions for necrotizing pancreatitis [7] were taken into account. Systematic reviews on 12 main topics answered 38 predefined clinical questions which were presented and discussed during an interactive symposium at the IAP/APA joint meeting in Miami on October 31, 2012.

2. Methods

2.1. Scope and purpose

The overall objective of these guidelines is to provide evidence-based recommendations for the medical and surgical management of patients with acute pancreatitis using clearly specified, clinically relevant questions.

2.2. Stakeholder involvement

Individuals from all relevant professional groups involved with acute pancreatitis were included. Target users of the guidelines are all clinicians involved in the care of patients with acute pancreatitis.

2.3. General outline of the process

2.3.1. First phase: drafting of the working plan

The IAP/APA leadership actively supported an initiative (MGB, HCvS, JW) to develop the current guidelines and invited seven clinicians to form the steering committee and provided secretarial support (EB). Three coordinators (MGB, HCvS, JW) wrote the initial version of the working plan and proposed the 12 main topics and associated clinical questions per topic and suggested the reviewers for each topic. This preliminary working plan was discussed via telephone conferences and e-mails within the full steering committee and the IAP/APA leadership, and then the document including the composition of review groups was finalized. The IAP/APA leadership also invited nine additional senior clinicians to form the executive committee in addition to the members of the steering committee.

Each review group consisted of at least one primary reviewer chosen because of recent publications on a particular topic and several senior reviewers. An attempt was made to have multidisciplinary input in each review group as well as representatives of at least two continents. Each review group was also assigned a time manager from the steering committee, whose primary task was to ensure the completion of the review within the agreed timeframe. The working plan for the review groups provided a structured format for the systematic reviews. It included instructions on how to grade the level of evidence and the strength of the recommendations regarding clarity of risk/benefit, quality of the supporting evidence, and clinical implications according to the GRADE guidelines as adapted for 'UpToDate'.

A group of 'expert referees' (see Collaborator section) was identified based on relevant publications in the field of clinical acute pancreatitis and input during the IAP/APA meeting. This group reviewed the guidelines in the final stages. After a last round of discussion within the executive committee, the working plan was finalized to include 12 main topics and 38 clinical questions concerning key aspects of medical and surgical management of acute pancreatitis.

2.3.2. Second phase: Systematic literature reviews

The suggested reviewers were invited and given their respective topics and clinical questions. All 12 review groups had the opportunity to suggest changes in clinical questions or suggest additional questions to the steering committee. Over a five-month period (June–Oct 2012) the review groups performed systematic reviews according to the guidelines defined in the finalized working plan.

2.4. Systematic review guidelines

A systematic search for relevant articles was performed in the PubMed, Embase, and Cochrane databases.

Inclusion criteria were: (1) randomized or observational cohort studies, including systematic reviews, on patients with acute pancreatitis focusing on the specific study questions with a sample size of at least 20 patients, (2) studies published in English language, and (3) available in full text. If review groups were capable of translating non-English publications they were encouraged to do so.

Exclusion criteria were: (1) non-randomized studies with less than 20 patients because of the likelihood of selection bias, (2) studies on patients with 'acute on chronic pancreatitis', and (3) non-randomized studies prior to 1993 (i.e. publication of the initial Atlanta classification). RCTs prior to 1993 could only be excluded if the reviewers felt that the generalizability to today's practice was not appropriate.

2.5. Grading of the evidence

All reviewers were asked to take a GRADE system tutorial (link on UpToDate®: http://www.uptodate.com/home/grading-tutorial).

2.6. Outcome reporting

The definitions of the revised Atlanta classification for acute pancreatitis were used [6].

The final outcomes of the systematic reviews were discussed amongst the members of the review group. The review groups provided the following for each clinical question:

a. *Recommendation*: the GRADE strength of recommendation (1 = strong, 2 = weak) and quality of evidence (A = high, B = moderate, C = low) are provided along with the strength of agreement during plenary voting (strong/weak) (see Appendix). In the absence of studies specifically addressing the question, this had to be stated and the recommendation was then based on related studies or expert opinion.
b. *Remarks*: these remarks could discuss any relevant aspect regarding the recommendation, such as important exceptions/contra-indications, availability, lack of evidence, risks, and costs.
c. A summary table of relevant studies was produced, including columns on outcome assessed (e.g. mortality, infected necrosis), the total number of patients, the number of included studies per outcome, design of the study (e.g. retrospective cohort, prospective cohort, RCT), and critical appraisal of methodology according to the GRADE system for each study as well as a summary of outcomes

2.6.1. Third phase: IAP/APA joint meeting

The review groups (see Collaborator section) presented their work at the IAP/APA Joint Annual Meeting on October 31st, 2012 in Miami, Florida, USA using standardized PowerPoint templates. Each clinical question was addressed in a similar manner in three slide sections: (1) the question with the recommendation including the GRADE score, (2) the remarks, and (3) a summary of the literature studied. After each presentation, the 171 registered attendees (North

America, $n = 71$; South America, $n = 7$; Europe, $n = 54$; Asia/Oceania, $n = 39$) were invited to comment. The general aim was not to alter the recommendations, because these were based on systematic reviews but rather to obtain clinically relevant comments to be added to the 'remarks' section for that specific clinical question. Occasionally, in case of absence of studies or unclear phrasing of the recommendation, its' wording was amended. In order to assess the level of support from the international pancreatologists objectively, an electronic plenary vote was conducted for each recommendation. The attendees voted on a five point Likert scale ('definitely yes', 'probably yes', 'no specific recommendation', 'probably no', 'definitely no') on the recommendation and their GRADE score. These answers were projected to the audience immediately after each round of voting. Before the meeting, it was defined that 'strong agreement' would require at least 70% of votes to be either 'definitely yes' or 'probably yes'. For optimal transparency the meeting was filmed and these films are accessible via the APA office.

2.6.2. Fourth phase: drafting of the manuscript

Based on the recommendations with remarks and GRADE rating, the voting results, and the remarks provided during the meeting, the coordinators drafted a first version of the guidelines. Although several relevant ongoing multicenter RCTs were identified in the reviews (i.e. through published study protocols), it was decided to only report published work. This draft was discussed with the steering and executive committees, the review groups, and finally the expert referees. The review groups were specifically asked to judge whether the amended remarks section of their clinical question(s) still reflected the current state of the literature. The final version was approved by the steering and executive committees.

2.7. Future aspects

These guidelines will be updated by an IAP/APA committee when these associations believe there is a need to do so [8], but no longer than 10 years after publication of these guidelines.

3. Results

The 12 main topics (A–L) are presented consecutively, incorporating 38 clinical questions (Q1–Q38) and their answers. See table 1 for a summary of the recommendations. The GRADE strength of recommendation (1 = strong, 2 = weak) and quality of evidence (A = high, B = moderate, C = low) are provided along with the strength of agreement during plenary voting (strong/weak). For each recommendation the remarks from the reviewers and attendees at the meeting are listed.

Table 1
Summary of recommendations

A. Diagnosis of acute pancreatitis and etiology

1. The definition of acute pancreatitis is based on the fulfillment of '2 out of 3' of the following criteria: clinical (upper abdominal pain), laboratory (serum amylase or lipase >3x upper limit of normal) and/or imaging (CT, MRI, ultrasonography) criteria.(GRADE 1B, strong agreement)
2. On admission, the etiology of acute pancreatitis should be determined using detailed personal (i.e. previous acute pancreatitis, known gallstone disease, alcohol intake, medication and drug intake, known hyperlipidemia, trauma, recent invasive procedures such as ERCP) and family history of pancreatic disease, physical examination, laboratory serum tests (i.e. liver enzymes, calcium, triglycerides), and imaging (i.e. right upper quadrant ultrasonography).(GRADE 1B, strong agreement)
3. In patients considered to have idiopathic acute pancreatitis, after negative routine work-up for biliary etiology, endoscopic ultrasonography (EUS) is recommended as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis. If EUS is negative, (secretin-stimulated) MRCP is advised as a second step to identify rare morphologic abnormalities. CT of the abdomen should be performed. If etiology remains unidentified, especially after a second attack of idiopathic pancreatitis, genetic counseling (not necessarily genetic testing) should be considered.(GRADE 2C, weak agreement)

B. Prognostication/prediction of severity

4. Systemic inflammatory response syndrome (SIRS) is advised to predict severe acute pancreatitis at admission and persistent SIRS at 48 hours.(GRADE 2B, weak agreement)
5. During admission, a 3-dimension approach is advised to predict outcome of acute pancreatitis combining host risk factors (e.g. age, co-morbidity, body mass index), clinical risk stratification (e.g. persistent SIRS) and monitoring response to initial therapy (e.g. persistent SIRS, blood urea nitrogen, creatinine).(GRADE 2B, strong agreement)

C. Imaging

6. The indication for initial CT assessment in acute pancreatitis can be: 1) diagnostic uncertainty, 2) confirmation of severity based on clinical predictors of severe acute pancreatitis, or 3) failure to respond to conservative treatment or in the setting of clinical deterioration. Optimal timing for initial CT assessment is at least 72–96 hours after onset of symptoms.(GRADE 1C, strong agreement)
7. Follow up CT or MR in acute pancreatitis is indicated when there is a lack of clinical improvement, clinical deterioration, or especially when invasive intervention is considered.(GRADE 1C, strong agreement)
8. It is recommended to perform multidetector CT with thin collimation and slice thickness (i.e. 5mm or less), 100–150 ml of non-ionic intra-venous contrast material at a rate of 3mL/s, during the pancreatic and/or portal venous phase (i.e. 50–70 seconds delay). During follow up only a portal venous phase (monophasic) is generally sufficient. For MR, the recommendation is to perform axial FS-T2 and FS-T1 scanning before and after intravenous gadolinium contrast administration.(GRADE 1C, strong agreement)

D. Fluid therapy

9. Ringer's lactate is recommended for initial fluid resuscitation in acute pancreatitis.(GRADE 1B, strong agreement)
10a. Goal directed intravenous fluid therapy with 5–10 ml/kg/h should be used initially until resuscitation goals (see Q10b) are reached.(GRADE 1B, weak agreement)
10b. The preferred approach to assessing the response to fluid resuscitation should be based on one or more of the following: 1) non-invasive clinical targets of heart rate < 120/min, mean arterial pressure between 65-85 mmHg (8.7–11.3 kPa), and urinary output > 0.5–1ml/kg/h, 2) invasive clinical targets of stroke volume variation, and intrathoracic blood volume determination, and 3) biochemical targets of hematocrit 35-44%.(GRADE 2B, weak agreement)

E. Intensive care management

11. Patients diagnosed with acute pancreatitis and one or more of the parameters identified at admission as defined by the guidelines of the Society of Critical Care Medicine (SCCM). Furthermore, patients with severe acute pancreatitis as defined by the revised Atlanta Classification (i.e. persistent organ failure) should be treated in an intensive care setting.(GRADE 1C, strong agreement)
12. Management in, or referral to, a specialist center is necessary for patients with severe acute pancreatitis and for those who may need interventional radiologic, endoscopic, or surgical intervention.(GRADE 1C, strong agreement)
13. A specialist center in the management of acute pancreatitis is defined as a high volume center with up-to-date intensive care facilities including options for organ replacement therapy, and with daily (i.e. 7 days per week) access to interventional radiology, interventional endoscopy with EUS and ERCP assistance as well as surgical expertise in managing necrotizing pancreatitis. Patients should be enrolled in prospective audits for quality control issues and into clinical trials whenever possible.(GRADE 2C, weak agreement)
14. Early fluid resuscitation within the first 24 hours of admission for acute pancreatitis is associated with decreased rates of persistent SIRS and organ failure.(GRADE 1C, strong agreement)

(*continued on next page*)

Table 1 (*continued*)

15. Abdominal compartment syndrome (ACS) is defined as a sustained intra-abdominal pressure > 20 mmHg that is associated with new onset organ failure.(GRADE 2B, strong agreement)
16. Medical treatment of ACS should target 1) hollow-viscera volume, 2) intra/extra vascular fluid and 3) abdominal wall expansion. Invasive treatment should only be used after multidisciplinary discussion in patients with a sustained intra-abdominal pressure >25mmHg with new onset organ failure refractory to medical therapy and nasogastric/ rectal decompression. Invasive treatment options include percutaneous catheter drainage of ascites, midline laparostomy, bilateral subcostal laparostomy, or subcutaneous linea alba fasciotomy. In case of surgical decompression, the retroperitoneal cavity and the omental bursa should be left intact to reduce the risk of infecting peripancreatic and pancreatic necrosis.(GRADE 2C, strong agreement)

F. Preventing infectious complications

17. Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis.(GRADE 1B, strong agreement)
18. Selective gut decontamination has shown some benefits in preventing infectious complications in acute pancreatitis, but further studies are needed.(GRADE 2B, weak agreement)
19. Probiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis.(GRADE 1B, strong agreement)

G. Nutritional support

20. Oral feeding in predicted mild pancreatitis can be restarted once abdominal pain is decreasing and inflammatory markers are improving.(GRADE 2B, strong agreement)
21. Enteral tube feeding should be the primary therapy in patients with predicted severe acute pancreatitis who require nutritional support.(GRADE 1B, strong agreement)
22. Either elemental or polymeric enteral nutrition formulations can be used in acute pancreatitis.(GRADE 2B, strong agreement)
23. Enteral nutrition in acute pancreatitis can be administered via either the nasojejunal or nasogastric route.(GRADE 2A, strong agreement)
24. Parenteral nutrition can be administered in acute pancreatitis as second-line therapy if nasojejunal tube feeding is not tolerated and nutritional support is required.(GRADE 2C, strong agreement)

H. Biliary tract management

25. ERCP is not indicated in predicted mild biliary pancreatitis without cholangitis.(GRADE 1A, strong agreement). ERCP is probably not indicated in predicted severe biliary pancreatitis without cholangitis (GRADE 1B, strong agreement). ERCP is probably indicated in biliary pancreatitis with common bile duct obstruction (GRADE 1C, strong agreement) ERCP is indicated in patients with biliary pancreatitis and cholangitis (GRADE 1B, strong agreement)
26. Urgent ERCP (<24 hrs) is required in patients with acute cholangitis. Currently, there is no evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis.(GRADE 2C, strong agreement)
27. MRCP and EUS may prevent a proportion of ERCPs that would otherwise be performed for suspected common bile duct stones in patients with biliary pancreatitis who do not have cholangitis, without influencing the clinical course. EUS is superior to MRCP in excluding the presence of small (<5mm) gallstones. MRCP is less invasive, less operator-dependent and probably more widely available than EUS. Therefore, in clinical practice there is no clear superiority for either MRCP or EUS.(GRADE 2C, strong agreement)

I. Indications for intervention in necrotizing pancreatitis

28. Common indications for intervention (either radiological, endoscopical or surgical) in necrotizing pancreatitis are: 1) Clinical suspicion of, or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off, 2) In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled-off.(GRADE 1C, strong agreement)
29. Routine percutaneous fine needle aspiration of peripancreatic collections to detect bacteria is not indicated, because clinical signs (i.e. persistent fever, increasing inflammatory markers) and imaging signs (i.e. gas in peripancreatic collections) are accurate predictors of infected necrosis in the majority of patients. Although the diagnosis of infection can be confirmed by fine needle aspiration (FNA), there is a risk of false-negative results.(GRADE 1C, strong agreement)
30. Indications for intervention (either radiological, endoscopical or surgical) in sterile necrotizing pancreatitis are: 1) Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect of walled-off necrosis (i.e. arbitrarily >4-8 weeks after onset of acute pancreatitis), 2) Persistent symptoms (e.g. pain, 'persistent unwellness') in patients with walled-off necrosis without signs of infection (i.e. arbitrarily >8 weeks after onset of acute pancreatitis), 3) Disconnected duct syndrome (i.e. full transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic (e.g. pain, obstruction) collection(s) with necrosis without signs of infections (i.e. arbitrarily >8 weeks after onset of acute pancreatitis).(GRADE 2C, strong agreement)

J. Timing of intervention in necrotizing pancreatitis

31. For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention (i.e. percutaneous catheter drainage, endoscopic transluminal drainage/ necrosectomy, minimally invasive or open necrosectomy) should be delayed where possible until at least 4 weeks after initial presentation to allow the collection to become 'walled-off'.(GRADE 1C, strong agreement)
32. The best available evidence suggests that surgical necrosectomy should ideally be delayed until collections have become walled-off, typically 4 weeks after the onset of pancreatitis, in all patients with complications of necrosis. No subgroups have been identified that might benefit from earlier or delayed intervention.(GRADE 1C, strong agreement)

K. Intervention strategies in necrotizing pancreatitis

33. The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy.(GRADE 1A, strong agreement)
34. Percutaneous catheter or endoscopic transmural drainage should be the first step in the treatment of patients with suspected or confirmed (walled-off) infected necrotizing pancreatitis.(GRADE 1A, strong agreement)
35. There are insufficient data to define subgroups of patients with suspected or confirmed infected necrotizing pancreatitis who would benefit from a different treatment strategy.(GRADE 2C, strong agreement)

L. Timing of cholecystectomy (or endoscopic sphincterotomy)

36. Cholecystectomy during index admission for mild biliary pancreatitis appears safe and is recommended. Interval cholecystectomy after mild biliary pancreatitis is associated with a substantial risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis.(GRADE 1C, strong agreement)
37. Cholecystectomy should be delayed in patients with peripancreatic collections until the collections either resolve or if they persist beyond 6 weeks, at which time cholecystectomy can be performed safely.(GRADE 2C, strong agreement)
38. In patients with biliary pancreatitis who have undergone sphincterotomy and are fit for surgery, cholecystectomy is advised, because ERCP and sphincterotomy prevent recurrence of biliary pancreatitis but not gallstone related gallbladder disease, i.e. biliary colic and cholecystitis.(GRADE 2B, strong agreement)

3.1. Diagnosis of acute pancreatitis and etiology

Q1. What is the definition of acute pancreatitis (regardless of etiology)?

The definition of acute pancreatitis is based on the fulfillment of '2 out of 3' of the following criteria: *clinical* (upper abdominal pain), *laboratory* (serum amylase or lipase >3× upper limit of normal) and/or *imaging* (computed tomography, magnetic resonance (MR), ultrasonography) criteria.

(GRADE 1B, strong agreement)

Remarks: imaging studies (e.g. contrast-enhanced abdominal CT abdomen (CT)) may be useful but are usually not required to diagnose acute pancreatitis. Scenarios where cross-sectional imaging may be required to confirm the diagnosis include sedated patients, clinical suspicion of duodenal perforation, or a prolonged period between onset of symptoms and presentation (lipase and amylase may have normalized). Although the urinary trypsinogen-2 dipstick test is a rapid and non-invasive bedside

test with adequate accuracy confirmed in a recent meta-analysis (pooled sensitivity 82% and specificity 94%), it was not included because of its presumed limited availability [9].

Q2. On admission, what should be done to determine the etiology of acute pancreatitis?

On admission, the etiology of acute pancreatitis should be determined using detailed personal (i.e. previous acute pancreatitis, known gallstone disease, alcohol intake, medication and drug intake, known hyperlipidemia, trauma, recent invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP)) and family history of pancreatic disease, physical examination, laboratory serum tests (i.e. liver enzymes, calcium, triglycerides), and imaging (i.e. right upper quadrant ultrasonography).

(GRADE 1B, strong agreement)

Remarks: as treatment and follow-up depend on the etiology of pancreatitis (e.g. cholecystectomy for biliary pancreatitis and dedicated follow-up visits after alcoholic pancreatitis to prevent recurrence [10]) transabdominal ultrasonography should be performed on admission. Although several studies have demonstrated that a single biochemical parameter cannot be recommended for reliable prediction of biliary etiology, it should be noted that an alanine aminotransferase (ALT) level >150 U/L within 48 h after onset of symptoms discriminates biliary pancreatitis with a positive predictive value exceeding 85% [11–13].

Q3. What further investigations are indicated in patients after a first or second attack of idiopathic acute pancreatitis?

In patients considered to have idiopathic acute pancreatitis, after negative routine work-up for biliary etiology (e.g. repeated right upper quadrant ultrasonography), endoscopic ultrasonography (EUS) is recommended as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis. If EUS is negative, (secretin-stimulated) magnetic resonance cholangiopancreatography (MRCP) is advised as a second step to identify rare morphologic abnormalities. CT of the abdomen should be performed (i.e. if not performed before). If etiology remains unidentified, especially after a second attack of idiopathic pancreatitis, genetic counseling (not necessarily genetic testing) should be considered.

(GRADE 2C, weak agreement)

Remarks: a systematic review of 5 studies including 416 patients with idiopathic acute pancreatitis, reported a 32–88% diagnostic yield of EUS, detecting either biliary sludge or signs of chronic pancreatitis [14]. If etiology remains unidentified after EUS, thorough review and, if necessary, repeat (e.g. repeat lipid profile and calcium levels) or further investigations for other more uncommon causes should be performed, depending on the clinical scenario. It is recognized that several diagnostic tests are not widely available and need specific expertise (e.g. secretin-stimulated MRCP, genetic counseling, ERCP with manometry, bile analysis). Their exact role in the diagnostic algorithm has yet to be determined.

3.2. Prognostication/prediction of severity

Q4. What is the best score/marker (including cut-off value) to predict severe acute pancreatitis on admission and at 48 h?

Systemic inflammatory response syndrome (SIRS) is advised to predict severe acute pancreatitis at admission and persistent SIRS at 48 h.

(GRADE 2B, weak agreement)

Remarks: a prediction of the course and outcome of the disease on admission, although difficult, can help with tailoring observations and initial treatment, using evidence from RCTs which typically select patients based on the predicted severity of acute pancreatitis.

SIRS is defined by the presence of two or more of the following four criteria: (1) temperature < 36 °C (96.8 °F) or >38 °C (100.4 °F), (2) heart rate >90/min, (3) respiratory rate >20/min, and (4) white blood cells (<4×10^9/L (<4 K/mm^3), >12×10^9 (>12 K/mm^3) or 10% bands [15].

Persistent (>48 h) SIRS is associated with multi-organ failure and mortality in acute pancreatitis. Persistent (>48 h) organ failure is the key determinant of mortality in acute pancreatitis [16]. Persistent SIRS was associated with a mortality of 25% compared with 8% for transient SIRS [17]. The sensitivity of persistent SIRS for mortality is 77–89% and specificity 79–86% [17–19] and of SIRS at admission respectively 100% and 31% [18].

Arguments to recommend (persistent) SIRS as a marker for predicting severe acute pancreatitis over the other predictive scoring systems were highly pragmatic, taking into account the widespread familiarity, simplicity, and the possibility for repetitive measurements [17,19]. It is recognized that there are many different predictive scoring systems for acute pancreatitis (e.g. APACHEII, Ranson and modified Glasgow score), including single serum markers (C-reactive protein, hematocrit, procalcitonin, blood urea nitrogen), but none of these are clearly superior or inferior to (persistent) SIRS [20].

Q5. What is the best strategy to predict outcome of acute pancreatitis during admission?

During admission, a 3-dimension approach is advised to predict outcome of acute pancreatitis combining

- host risk factors (e.g. age, co-morbidity, body mass index [21])
- clinical risk stratification (e.g. persistent SIRS)
- monitoring response to initial therapy (e.g. persistent SIRS, blood urea nitrogen [22], creatinine)

(GRADE 2B, strong agreement).

Remarks: this clinical approach links prognosis to patient's characteristics and response to initial treatment (e.g. fluid resuscitation) and places emphasis on reassessment to guide further management [23]. More accurate prognostication could facilitate a more tailored approach to treatment of individual patients.

3.3. Imaging

Q6. What is the indication for and timing of the initial CT assessment in acute pancreatitis?

The indication for initial CT assessment in acute pancreatitis can be: (1) diagnostic uncertainty, (2) confirmation of severity based on clinical predictors of severe acute pancreatitis, or (3) failure to respond to conservative treatment or in the setting of clinical deterioration. Optimal timing for initial CT assessment is at least 72–96 h after onset of symptoms.

(GRADE 1C, strong agreement).

Remarks: in the majority of patients, CT is not required for the diagnosis of acute pancreatitis. Routine early CT in acute pancreatitis is not recommended for the following reasons: (1) there is no evidence that early CT improves clinical outcome or that early detection of necrosis will influence treatment; (2) CT scoring systems are not superior to clinical scoring systems in predicting prognosis and severity of disease [24]; (3) there is evidence to suggest that an early (inappropriate) CT may increase the duration of hospital stay [25], has low yield without direct management implications [26], does not improve clinical outcomes [27], and poses risks of contrast allergy and nephrotoxicity. Because the complete extent of pancreatic and peripancreatic necrosis may only become obvious 72 h after onset of acute pancreatitis, a CT to assess the severity of pancreatitis

using the CT severity index (CTSI) criteria [28], should be performed only thereafter. Early CT may be useful to rule out bowel ischemia or intra-abdominal perforations in patients presenting with both acute pancreatitis and acute abdomen.

Q7. What is the indication for follow-up scanning (CT/MR)?

Follow-up CT or MR in acute pancreatitis is indicated when there is a lack of clinical improvement, clinical deterioration, or especially when invasive intervention is considered.

(GRADE 1C, strong agreement).

Remarks: although routine follow-up CT (e.g. weekly) in acute pancreatitis is advocated in several guidelines, evidence for this practice is lacking. The present guidelines does not recommend routine CT for initial assessment, because the vast majority of complications can be suspected by clinical and biochemical assessment. One important complication, namely arterial pseudoaneurysm formation, may not become clinically evident until bleeding occurs, but this complication of acute pancreatitis is so rare that it does not justify a 'routine' follow-up CT. MR may be required to distinguish between pseudocysts and walled-off necrosis as defined by the revised Atlanta classification at least 4 weeks after the index episode of acute pancreatitis. CT is frequently not able to detect necrosis in a fluid-predominant collection [29].

Q8. What is the optimal CT and MR protocol to detect necrosis?

It is recommended to perform multidetector CT with thin collimation and slice thickness (i.e. 5 mm or less), 100–150 ml of non-ionic intravenous contrast material at a rate of 3 ml/s, during the pancreatic and/or portal venous phase (i.e. 50–70 s delay). During follow-up only a portal venous phase (monophasic) is generally sufficient.

For MR, the recommendation is to perform axial FS-T2 and FS-T1 scanning before and after intravenous gadolinium contrast administration.

(GRADE 1C, strong agreement).

Remarks: there is a wide variation in the literature regarding CT and MR protocols but there are no existing dedicated radiological guidelines. For CT, both the pancreatic and portal venous phase are sufficient for discriminating viable from non-viable pancreatic tissue. The following indications would require a multiphasic protocol: hemorrhage, arterial pseudoaneurysm and mesenteric infarction. An MR with T2-weighted images is advised when the differentiation between pseudocysts and collections with necrosis (i.e. acute necrotic collection and walled-off necrosis) is clinically relevant and in young patients because of the radiation burden of CT. Contrast-enhanced CT is clearly preferable, although in patients with impending renal failure an initial non-contrast CT is an option.

3.4. Fluid therapy

Q9. What is the best fluid to use for initial fluid resuscitation in acute pancreatitis?

Ringer's lactate is recommended for initial fluid resuscitation in acute pancreatitis.

(GRADE 1B, strong agreement).

Remarks: only very few studies have investigated the effect of different fluid types on outcome of acute pancreatitis [29–31]. In a multicenter RCT in 40 patients with acute pancreatitis, resuscitation with Ringer's lactate decreased the incidence of SIRS when compared to resuscitation with normal saline [30]. The use of hydroxyethyl starch (HES) is discouraged since it increased the rates of renal failure and mortality, as compared to Ringer's lactate in a multicenter RCT in patients with severe sepsis in an intensive care [32]. Ringer's lactate is very similar but not identical to Hartmann's solution. While there is emerging evidence that addition of HES to fluid resuscitation in acute pancreatitis may be beneficial [31], its detrimental effects in severe sepsis provide enough caution at this stage that its use cannot be endorsed in the current guidelines.

Q10. What is the optimal fluid infusion rate and response measurement for initial fluid resuscitation?

Q10a. Optimal infusion rate for initial fluid resuscitation: goal directed intravenous fluid therapy with 5–10 ml/kg/h should be used initially until resuscitation goals (see Q10b) are reached.

(GRADE 1B, weak agreement).

Remarks: in most patients, a total infusion of 2500–4000 ml will suffice to reach the resuscitation goals within the first 24 h. There is moderate quality evidence from two RCTs, from the same research group, that overly aggressive fluid therapy increases morbidity and mortality. In the first RCT, patients assigned to a fluid infusion rate of 5–10 ml/kg/h experienced less need for mechanic ventilation, abdominal compartment syndrome, sepsis and mortality as compared to patients assigned to 10–15 ml/kg/h infusion rates [33]. In a second RCT, patients assigned to slow hemodilution, aiming at a hematocrit >35% within 48 h, had decreased rates of sepsis and mortality as compared to patients assigned to rapid hemodilution, aiming at a hematocrit <35% within 48 h [34]. Because age and comorbidities such as heart failure need an individualization of the fluid management, the rate of infusions suggested in these guidelines must be interpreted with caution and needs to be tailored to the condition of the patient.

Q10b. Measuring the response to fluid resuscitation: the preferred approach to assessing the response to fluid resuscitation should be based on one or more of the following: (1) non-invasive clinical targets of heart rate <120/min, mean arterial pressure between 65 and 85 mmHg (8.7–11.3 kPa), and urinary output >0.5–1 ml/kg/h, (2) invasive clinical targets of stroke volume variation, and intrathoracic blood volume determination, and (3) biochemical targets of hematocrit 35–44%.

(GRADE 2B, weak agreement).

Remarks: non-invasive targets are useful on a regular ward, while invasive targets are more appropriate in the intensive care unit. It is unlikely that a single parameter will be as reliable as the assessment of multiple parameters. Recent studies have focused on blood urea nitrogen as a predictor of outcome but not on its value as a response measurement [22]. For biochemical parameters (e.g. hematocrit, blood urea nitrogen) not only the absolute level, but also the trend should be noted. A recent study pointed out that central venous pressure alone may be unreliable as a crude indicator of adequate resuscitation [35].

3.5. Intensive care management

Q11. What are the indications for admission to an intensive care unit in acute pancreatitis?

A patient diagnosed with acute pancreatitis and one or more of the following parameters identified at admission as defined by the guidelines of the Society of Critical Care Medicine (SCCM) [36] should be transferred immediately to an intensive care setting: (1) pulse <40 or >150 beats/min; (2) systolic arterial pressure <80 mmHg (<10.7 kPa) or mean arterial pressure <60 mmHg (<8.0 kPa) or diastolic arterial pressure >120 mmHg (>16 kPa); (3) respiratory rate >35 breaths/min; (4) serum sodium <110 mmol/l or >170 mmol/l; (5) serum potassium <2.0 mmol/l or >7.0 mmol/l; (6) paO_2 <50 mmHg (<6.7 kPa);

(7) pH < 7.1 or >7.7; 8) serum glucose >800 mg/dl (>44.4 mmol/L); (9) serum calcium > 15 mg/dl (>3.75 mmol/L); (10) anuria, or (11) coma. Furthermore, a patient with severe acute pancreatitis as defined by the revised Atlanta Classification (i.e. persistent organ failure) [6] should be treated in an intensive care setting.
(GRADE 1C, strong agreement).
Remarks: every patient considered at high risk of rapid clinical deterioration, such as those with persistent SIRS, the elderly, the obese, patients requiring ongoing volume resuscitation, and patients with moderately severe acute pancreatitis as defined by the revised Atlanta classification [6] should be assessed for admission to a high dependency unit (i.e. intermediate care unit, level 2), if available. The routine use of single markers, such as CRP, hematocrit, BUN or procalcitonin alone to triage patients to an intensive care setting is not recommended.

Q12. What are the indications for referral to a specialist center?

Management in, or referral to, a specialist center is necessary for patients with severe acute pancreatitis and for those who may need interventional radiologic, endoscopic, or surgical intervention.
(GRADE 1C, strong agreement).
Remarks: a recent analysis of the United States Nationwide Inpatient Sample suggested that treatment of patients with acute pancreatitis in high volume centers (upper third, >118 patients per year) resulted in a decreased risk of prolonged hospital stay and mortality (adjusted hazard ratio 0.74) [37].

Q13. What are the minimal requirements for a specialist center?

A specialist center in the management of acute pancreatitis is defined as a high volume center with up-to-date intensive care facilities including options for organ replacement therapy, and with daily (i.e. 7 days per week) access to interventional radiology, interventional endoscopy with EUS and ERCP assistance as well as surgical expertise in managing necrotizing pancreatitis. Patients should be enrolled in prospective audits for quality control issues and into clinical trials whenever possible.
(GRADE 2C, weak agreement).
Remarks: as there are no studies comparing requirements for specialist centers, this recommendation can only be weak. As optimal treatment of severe acute pancreatitis is achieved by a multidisciplinary team, high volume academic centers usually classify as specialist centers. A minimum of two specialists should be available in all fields of expertise (interventional radiology, interventional endoscopy, surgery, critical care medicine) to allow for minimum coverage.

Q14. Can persistent SIRS/organ failure be prevented?

Early fluid resuscitation within the first 24 h of admission for acute pancreatitis is associated with decreased rates of persistent SIRS and organ failure.
(GRADE 1C, strong agreement).
Remarks: persistent organ failure is the key determinant of mortality in acute pancreatitis. Persistent SIRS resulted in a mortality of 25% compared to 8% with transient SIRS [17,38]. Renal failure predicts mortality in severe acute pancreatitis. Fluid resuscitation cannot prevent necrosis formation, but early fluid resuscitation is associated with reduced SIRS, organ failure and in-hospital mortality [39]. Enteral nutrition, as compared to parenteral nutrition, decreases infectious complications, organ failure and mortality [40,41]. The literature is unclear on the impact of early feeding on early SIRS/organ failure [42].

Q15. What is the definition of abdominal compartment syndrome?

Intra-abdominal pressure is the steady-state pressure within the abdominal cavity. Abdominal compartment syndrome (ACS) is defined as a sustained intra-abdominal pressure > 20 mmHg (with or without abdominal arterial perfusion pressure < 60 mmHg) that is associated with new onset organ failure.
(GRADE 2B, strong agreement).
Remarks: ACS cannot be diagnosed by physical examination and requires objective measurements of intra-abdominal pressure via the bladder with a maximal instillation volume of 25 ml of sterile saline, as described in a 2013 international guideline [43]. Measurement of intra-abdominal pressure should be considered in mechanically ventilated patients with severe acute pancreatitis, especially in case of clinical deterioration.
Intra-abdominal hypertension (IAH) is defined by an ongoing or repeated pathologic increase in intra-abdominal pressure >12 mmHg. IAH is reported to occur in 60–80% of patients with severe acute pancreatitis, but only a subset of these patients develops ACS [44]. IAH is graded as follows: grade I: intra-abdominal pressure 12–15 mmHg; grade II 16–20 mmHg; grade III 21–25 mmHg; and grade IV >25 mmHg. In a small, prospective cohort study, IAH and ACS in patients with severe acute pancreatitis contributed to gut barrier failure with significantly greater endotoxin levels [45].

Q16. How should ACS be treated?

Medical interventions for ACS in acute pancreatitis: interventions to decrease intra-abdominal pressure should target the most important contributors to IAH in acute pancreatitis:

1) Hollow-viscera volume: nasogastric drainage, prokinetics, rectal tubes, if necessary endoscopic decompression.
2) Intra/extra vascular fluid: volume resuscitation on demand, if volume overloaded either ultrafiltration or diuretics can be employed.
3) Abdominal wall expansion: adequate analgesia and sedation to decrease abdominal muscle tone, if necessary neuromuscular blockade.

Invasive treatment for ACS in acute pancreatitis: invasive decompression should only be used after multidisciplinary discussion in patients with a sustained intra-abdominal pressure >25 mmHg with new onset organ failure refractory to medical therapy and nasogastric/rectal decompression. Invasive treatment options include percutaneous catheter drainage of ascites, midline laparostomy, bilateral subcostal laparostomy, or subcutaneous linea alba fasciotomy. In case of surgical decompression, the retroperitoneal cavity and the omental bursa should be left intact to reduce the risk of infecting peripancreatic and pancreatic necrosis.
(GRADE 2C, strong agreement).
Remarks: although the necessity of decompression of ACS is a rare event in severe acute pancreatitis, it may be lifesaving [46]. RCTs comparing surgical decompression of ACS to other treatment strategies are lacking. A 2013 international guideline discusses both the prevalence and etiologic factors for ACS in various conditions, including acute pancreatitis, and provides an evidence-based approach to both diagnosis and clinical management [43]. These guidelines state that because of the obvious disadvantages of laparostomy/open abdomen, percutaneous catheter drainage should be considered in patients with ACS and abundant abdominal fluid on CT. Percutaneous drainage should lead to immediate and sustained improvement, if not, surgical decompression should be performed. To avoid an open abdomen and its negative effects of evisceration of intestines, fluid losses and contamination, a primary closure with Mesh-grafts can be considered after open laparotomy.

3.6. Preventing infectious complications

Q17. Is systemic antibiotic prophylaxis effective in preventing infectious complications in acute pancreatitis?
Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis.
(GRADE 1B, strong agreement).
Remarks: according to a recent meta-analysis of 14 RCTs, there is no evidence to support the routine use of antibiotic prophylaxis in patients with (predicted) severe acute pancreatitis [47]. Effects of antibiotics may vary between subgroups, but more evidence is needed [48]. A recent Cochrane meta-analysis suggested a reduction in pancreatic infection in the subgroup of patients who received imipenem, but the authors concluded that more evidence is needed [49]. Prophylactic continuous regional arterial infusion of antibiotics appears to be somewhat promising but further studies are warranted [50]. Intravenous antibiotics should be given in case of suspected infection of necrotizing pancreatitis and further intervention considered [50].

Q18. Is selective gut decontamination effective in preventing infectious complications?
Selective gut decontamination has shown some benefits in preventing infectious complications in acute pancreatitis, but further studies are needed.
(GRADE 2B, weak agreement).
Remarks: evidence on selective decontamination in acute pancreatitis is limited to one RCT [51]. The results of this trial have to be interpreted with caution, because it also included non-randomized systemic antibiotic treatment.

Q19. Are probiotics effective in preventing infectious complications?
Probiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis.
(GRADE 1B, strong agreement).
Remarks: there are abundant variations in type and dosage of probiotic preparations. In one RCT in patients with predicted severe acute pancreatitis a particular combination of probiotic strains (i.e. Ecologic® 641) did not prevent infectious complications but increased mortality [52].

3.7. Nutritional support

Q20. When should oral feeding be restarted in patients with predicted mild pancreatitis?
Oral feeding in predicted mild pancreatitis can be restarted once abdominal pain is decreasing and inflammatory markers are improving.
(GRADE 2B, strong agreement).
Remark: it is not necessary to wait until pain or laboratory abnormalities completely resolve before restarting oral feeding. One RCT showed that immediate oral refeeding with a normal diet is safe in predicted mild pancreatitis and leads to a shorter hospital stay (4 vs 6 days) [53]. A second RCT demonstrated that feeding can be started with a full solid diet without a need to first start with a liquid or soft diet [54]. A third RCT showed that there is no need to wait for normalization of lipase levels before restarting oral feeding [55].

Q21. What is the indication for enteral tube feeding?
Enteral tube feeding should be the primary therapy in patients with predicted severe acute pancreatitis who require nutritional support.
(GRADE 1B, strong agreement).
Remarks: two meta-analyses demonstrated that enteral nutrition, as compared with parenteral nutrition, decreases systemic infections, multi-organ failure, need for surgical intervention, and mortality [40,41]. The overwhelming majority of studies were performed in patients with predicted severe acute pancreatitis. Patients who can eat do not require additional enteral nutrition via a feeding tube. A recent RCT in 60 patients with 'severe acute pancreatitis' found improved outcomes when enteral nutrition was started within 48 h as compared to after 7 days of fasting [56].

Q22. What type of enteral nutrition should be used?
Either elemental or polymeric enteral nutrition formulations can be used in acute pancreatitis.
(GRADE 2B, strong agreement).
Remarks: a recent meta-analysis including 20 RCTs concluded that there is no specific type of enteral nutrition or immunonutrition that improves outcome in acute pancreatitis [57]. The relatively inexpensive polymeric feeding formulations were associated with similar feeding tolerance and appeared as beneficial as the more expensive (semi)elemental formulations in reducing the risks of infectious complications and mortality.

Q23. Should enteral nutrition be administered via a nasojejunal or nasogastric route?
Enteral nutrition in acute pancreatitis can be administered via either the nasojejunal or nasogastric route.
(GRADE 2A, strong agreement).
Remarks: two relatively small RCTs have suggested that nasogastric tube feeding is feasible and safe [58,59]. Although nasogastric tube feeding is probably easier than nasojejunal tube feeding, a number of patients will not tolerate nasogastric feeding because of delayed gastric emptying.

Q24. What is the role of parenteral nutrition?
Parenteral nutrition can be administered in acute pancreatitis as second-line therapy if nasojejunal tube feeding is not tolerated and nutritional support is required.
(GRADE 2C, strong agreement).
Remarks: parenteral nutrition should only be started if the nutritional goals cannot be reached with oral or enteral feeding [40,60]. A delay up to 5 days in initiation of parenteral nutrition may be appropriate to allow for restarting of oral or enteral feeding.

3.8. Biliary tract management

Q25. What is the indication for ERCP and sphincterotomy early in the course of biliary pancreatitis?

- ERCP is not indicated in predicted mild biliary pancreatitis without cholangitis(GRADE 1A, strong agreement).
- ERCP is probably not indicated in predicted severe biliary pancreatitis without cholangitis (GRADE 1B, strong agreement).
- ERCP is probably indicated in biliary pancreatitis with common bile duct obstruction.
  (GRADE 1C, strong agreement).
- ERCP is indicated in patients with biliary pancreatitis and cholangitis (GRADE 1B, strong agreement).

Remarks: a recent meta-analysis of 7 RCTs including 757 patients found no evidence that early routine ERCP significantly affects mortality or local/systemic complications, regardless of the predicted severity of biliary pancreatitis [61]. The meta-analysis did support ERCP in patients with cholangitis or co-existing biliary obstruction. It should be noted that predicting the presence of CBD stones in the early stages of biliary pancreatitis with laboratory findings, transabdominal ultrasonography or CT is unreliable [62]. The individual trials, and even the pooled data in the meta-analyses, did not include enough patients with 'predicted severe biliary pancreatitis without cholangitis' to study

the hard clinical endpoints such as mortality (possible type-2 statistical error).

Q26. If indicated, what is the optimal timing for ERCP in biliary pancreatitis?

Urgent ERCP (<24 h) is required in patients with acute cholangitis. Currently, there is no evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis.

(GRADE 2C, strong agreement).

Remarks: the recent meta-analysis found no statistically significant effect of the timing of ERCP (<24 vs. <72 h) on mortality [61]. However, no studies were specifically designed to study timing of ERCP in biliary pancreatitis. Because it is unclear what the exact timing of early ERCP should be (24–72 h), it is reasonable to await spontaneous improvement of biliary obstruction for 24–48 h. It is important, that ERCP is performed as soon as possible in patients with cholangitis.

Q27. What is the role of MRCP and EUS in biliary pancreatitis?

MRCP and EUS may prevent a proportion of ERCPs that would otherwise be performed for suspected common bile duct stones in patients with biliary pancreatitis who do not have cholangitis, without influencing the clinical course. EUS is superior to MRCP in excluding the presence of small (<5 mm) gallstones. MRCP is less invasive, less operator-dependent and probably more widely available than EUS. Therefore, in clinical practice there is no clear superiority for either MRCP or EUS.

(GRADE 2C, strong agreement).

Remarks: MRCP, EUS and ERCP are generally not indicated in patients with mild biliary pancreatitis without clinical evidence of persistent common bile duct obstruction, as that can be treated with (early) cholecystectomy with/without intraoperative cholangiography. One RCT found that EUS could safely replace diagnostic ERCP in patients with biliary pancreatitis [63]. It should be noted that access to urgent MRCP and EUS is likely to be limited in most hospitals. A negative MRCP does not exclude the presence of small (<5 mm) common bile duct stones [64]. This is especially relevant because small stones are known to cause biliary pancreatitis [65].

3.9. Indications for intervention in necrotizing pancreatitis

Q28. What are the indications for intervention in necrotizing pancreatitis?

Common indications for intervention (either radiological, endoscopical or surgical) in necrotizing pancreatitis are:

- Clinical suspicion of, or documented, infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off.
- In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled-off.

Less common indications for intervention are:

- Abdominal compartment syndrome
- Ongoing acute bleeding
- Bowel ischemia
- Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect from large walled-off necrosis (arbitrarily >4–8 weeks after onset of pancreatitis)

(GRADE 1C, strong agreement).

Remarks: the vast majority of patients with sterile necrotizing pancreatitis can be managed without intervention (i.e. catheter drainage or necrosectomy). Walled-off necrosis usually occurs >4 weeks after onset of acute pancreatitis [6]. The presence of gas in peripancreatic collections on CT is considered evidence of infected necrotizing pancreatitis, irrespective of the source of the gas (i.e. loss of integrity of the gastrointestinal tract or through gas-forming bacteria). In patients who are operated on because of 'persistent unwellness' (also known as 'failure to thrive') approximately 40% will have infected necrotizing pancreatitis [66]. A small proportion of patients with documented infected necrosis who remain clinically stable can be managed with antibiotics alone, without the need for percutaneous catheter drainage or necrosectomy. Future studies should compare (initial) antibiotic treatment of infected necrosis with other, more invasive, strategies [67–70]. During surgical interventions for ACS, acute bleeding, or bowel ischemia in sterile necrotizing pancreatitis, drainage or necrosectomy is not indicated because these procedures may increase the risk of developing infected necrosis. Spontaneous fistula formation between the gastrointestinal tract and necrosis may occur in the absence of documented bowel ischemia. In cases of clinical suspicion, without evidence on imaging, bowel ischemia can be diagnosed by colonoscopy or, if negative, laparoscopy. Finally, very rare complications requiring (non-surgical) intervention include pancreaticopleural fistula, pancreatic ascites, obstructive jaundice due to the enlargement of the pancreatic head, and ongoing symptoms (i.e. pain, gastric outlet obstruction) from a 'true' pseudocyst (i.e. confirmed absence of necrosis in the collection on MR or ultrasonography).

Q29. What is the role of fine needle aspiration to diagnose infected necrotizing pancreatitis?

Routine percutaneous fine needle aspiration of peripancreatic collections to detect bacteria is not indicated, because clinical signs (i.e. persistent fever, increasing inflammatory markers) and imaging signs (i.e. gas in peripancreatic collections) are accurate predictors of infected necrosis in the majority of patients. Although the diagnosis of infection can be confirmed by fine needle aspiration (FNA), there is a risk of false-negative results [66].

(GRADE 1C, strong agreement).

Remarks: false-negative FNA results in patients with infected necrotizing pancreatitis have been reported in 12–25% of patients [66,71]. FNA is indicated in patients without clinical improvement for several weeks after onset of necrotizing pancreatitis in the absence of clear clinical and imaging signs of infected necrotizing pancreatitis. There is no evidence that the theoretical benefits of FNA, shortening the period to diagnosis of infected necrosis and tailoring antibiotic treatment, improve outcome.

Q30. What are the indications for intervention in sterile necrotizing pancreatitis?

Indications for intervention (*either radiological, endoscopical or surgical*) in sterile necrotizing pancreatitis are:

- Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect of walled-off necrosis (i.e. arbitrarily >4–8 weeks after onset of acute pancreatitis).
- Persistent symptoms (e.g. pain, 'persistent unwellness') in patients with walled-off necrosis without signs of infection (i.e. arbitrarily >8 weeks after onset of acute pancreatitis).
- Disconnected duct syndrome (i.e. full transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic (e.g. pain, obstruction) collection(s) with necrosis without signs of infections (i.e. arbitrarily >8 weeks after onset of acute pancreatitis).

(GRADE 2C, strong agreement).

Remarks: according to one observational study in 639 patients, approximately 1% of patients with necrotizing pancreatitis will have symptoms of obstruction during the initial hospital admission necessitating intervention [67]. A recent study of

197 patients with follow-up after necrotizing pancreatitis found a disconnected duct syndrome in 40% of patients and about half of these patients required an intervention more than 8 weeks after surviving necrotizing pancreatitis [72]. Further data are needed on the indication, timing, and type of intervention in the months after an episode of necrotizing pancreatitis. Rare complications requiring (non-surgical) intervention in the follow-up after sterile necrotizing pancreatitis are pancreaticopleural fistula, pancreatic ascites, and a 'true' (no necrosis found in the collection on MR or ultrasonography) symptomatic pseudocyst. Prospective cohort studies suggest that patients with 'persistent unwellness' and necrotizing pancreatitis should probably undergo intervention 6–8 weeks after onset of the disease [66,73].

3.10. Timing of intervention in necrotizing pancreatitis

Q31. What is the optimal timing of intervention for suspected or confirmed infected necrosis?

For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention (i.e. percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) should be delayed where possible until at least 4 weeks after initial presentation to allow the collection to become 'walled-off'.

(GRADE 1C, strong agreement).

Remarks: open necrosectomy is associated with poor outcomes when performed early [67,73–76]. In a subset of patients it will not be feasible to delay intervention until 4 weeks. Even if initial percutaneous catheter drainage is undertaken early, necrosectomy should ideally still be delayed until the collection has become walled-off. The timing for repeat interventions (e.g. repeat percutaneous drainage, repeat endoscopic necrosectomy, or crossover to surgery) should be based on clinical and imaging criteria, and no strict guidelines can be recommended. Consultation with a specialist center before interventional treatment is advisable.

Q32. Can subgroups of patients with necrotizing pancreatitis be defined that require early or late intervention?

The best available evidence suggests that surgical necrosectomy should ideally be delayed until collections have become walled-off, typically 4 weeks after the onset of pancreatitis, in all patients with complications of necrosis. No subgroups have been identified that might benefit from earlier or delayed intervention.

(GRADE 1C, strong agreement).

Remarks: regardless of the presence of necrosis, patients with intra-abdominal catastrophes (hemorrhage, perforation, abdominal compartment syndrome) require immediate intervention. Minimally invasive methods to address these problems such as angioembolization/-stenting or percutaneous catheter drainage of ascites should be considered in a multidisciplinary team including at least interventional radiologists, endoscopists, and surgeons. Loop ileostomy may be considered for patients with a colonic fistula secondary to (infected) necrotizing pancreatitis, in the absence of bowel ischemia.

3.11. Intervention strategies in necrotizing pancreatitis

Q33. What is the optimal interventional strategy (percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) for suspected or confirmed infected necrotizing pancreatitis?

The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy.

(GRADE 1A, strong agreement).

Remarks: a multicenter RCT in 88 patients with (suspected) infected necrotizing pancreatitis showed that a step-up approach of percutaneous (retroperitoneal) catheter drainage, followed, if needed, by minimally invasive necrosectomy decreased major short-term complications such as new onset multi-organ failure and long-term complications such as endocrine insufficiency, and decreased costs as compared to primary open necrosectomy [77]. Left retroperitoneal catheter drainage can facilitate minimally invasive retroperitoneal necrosectomy. If catheter drainage fails [78], the optimal method of necrosectomy (i.e. minimally invasive or open surgery or endoscopic transluminal) is unclear. Minimally invasive necrosectomy may be associated with a decreased risk of complications and death as compared to open necrosectomy [79]. Several series from centers both in Europe and in the US have confirmed the efficacy of endoscopic transluminal necrosectomy [80,81]. A pilot multicenter RCT in 22 patients suggested that endoscopic transluminal necrosectomy may be superior to surgical necrosectomy in terms of risk of new onset multiple organ failure and overall complications [82]. There is however a large variance in expertise with the various techniques between centers which has to be taken into account.

Q34. Should catheter drainage (percutaneous or endoscopic transluminal) always be the first step for suspected or confirmed infected necrotizing pancreatitis?

Percutaneous catheter or endoscopic transmural drainage should be the first step in the treatment of patients with suspected or confirmed (walled-off) infected necrotizing pancreatitis.

(GRADE 1A, strong agreement).

Remarks: percutaneous catheter drainage alone will prevent 23–50% of necrosectomies in patients with infected necrotizing pancreatitis [75,77,78,83,84]. Percutaneous catheter drainage is technically feasible in >95% of patients with infected necrosis [77]. One prospective, observational multicenter study of 40 patients found that a decrease in the size of the collection of at least 75% after the first 10–14 days of percutaneous drainage ($n = 9$, 23%) correctly predicts successful percutaneous treatment [75] but more data are needed to confirm this finding. After catheter drainage, it is imperative that the patient is followed by an experienced clinician, who in the absence of clinical improvement can direct the next appropriate therapeutic step (i.e. surgical or endoscopic necrosectomy). Although the use of larger bore drains are sometimes claimed to yield better results, data are lacking. Overall, there is currently less experience with endoscopic transluminal drainage than with percutaneous drainage.

Q35. Can subgroups of patients with infected necrotizing pancreatitis be defined who require different strategies (including conservative treatment)?

There are insufficient data to define subgroups of patients with suspected or confirmed infected necrotizing pancreatitis who would benefit from a different treatment strategy.

(GRADE 2C, strong agreement).

Remarks: in a predefined subgroup analysis on severity in a multicenter RCT, the effect of the step-up approach was beneficial in patients with and without multiple organ failure [77]. No other prospective studies were specifically designed to assess the efficacy of certain treatment strategies in specific subgroups. Although several small cohort studies have reported success of conservative treatment (i.e. antibiotics

alone) for infected necrosis the exact subgroup in which this strategy may be successful has not accurately been defined.

3.12. Timing of cholecystectomy (or endoscopic sphincterotomy)

Q36. What is the optimal timing of cholecystectomy after mild biliary pancreatitis?

Cholecystectomy during index admission for mild biliary pancreatitis appears safe and is recommended. Interval cholecystectomy after mild biliary pancreatitis is associated with a substantial risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis.

(GRADE 1C, strong agreement).

Remarks: a systematic review of nine studies including 998 patients found an 18% readmission rate for recurrent biliary events a median of 6 weeks after index admission for mild biliary pancreatitis [85]. Although cholecystectomy during index admission appeared safe, selection bias could not be excluded [85]. ERCP with sphincterotomy before cholecystectomy decreased the rate of recurrent biliary pancreatitis but not of other biliary events [86]. It should be noted that ERCP is rarely indicated in mild biliary pancreatitis, except in the case of cholangitis (see Q25). Alternatively, preoperative MRCP or EUS, or intraoperative cholangiography can be performed during cholecystectomy to select out those patients with common bile duct stones who should be treated either by operative bile duct exploration or endoscopic sphincterotomy. In unfit elderly (i.e. arbitrarily >80 yrs) patients one could refrain from cholecystectomy, especially if sphincterotomy was already performed, although a subset of these patients will develop recurrent biliary colics [87].

Q37. What is the optimal timing of cholecystectomy after severe biliary pancreatitis?

Cholecystectomy should be delayed in patients with peripancreatic collections until the collections either resolve or if they persist beyond 6 weeks, at which time cholecystectomy can be performed safely.

(GRADE 2C, strong agreement).

Remarks: one retrospective study of 151 patients found an increased incidence of infected collections in patients who underwent early cholecystectomy after severe pancreatitis [88]. A second retrospective study of 30 patients reported no episodes of recurrent biliary pancreatitis during the waiting period for interval cholecystectomy after routine ERCP and sphincterotomy [89].

Q38. What is the role of cholecystectomy after endoscopic sphincterotomy in biliary pancreatitis?

In patients with biliary pancreatitis who have undergone sphincterotomy and are fit for surgery, cholecystectomy is advised, because ERCP and sphincterotomy prevent recurrence of biliary pancreatitis but not gallstone related gallbladder disease, i.e. biliary colic and cholecystitis.

(GRADE 2B, strong agreement).

Remarks: one meta-analysis reported a 10% readmission rate after ERCP for mild biliary pancreatitis because of biliary colic and acute cholecystitis [85]. Studies on this topic in severe biliary pancreatitis are lacking. In severe biliary pancreatitis, cholecystectomy should be postponed for 6 weeks.

4. Conclusion

The IAP/APA guidelines on the management of acute pancreatitis are the result of an international, multidisciplinary, evidence-based approach. These guidelines provide recommendations to key aspects of medical and surgical management of acute pancreatitis combined with remarks based on the available literature and the opinion of leading pancreatologists worldwide.

Focus should now shift to optimal dissemination and implementation of these guidelines [90]. Several studies have indicated that guideline implementation in acute pancreatitis is frequently suboptimal [91–94] and hence a structured, ongoing effort is required. Dissemination will be facilitated by free online access to these guidelines. Although there is no optimal strategy to ensure good implementation of a guideline [95], there is clearly a role for pancreatologists in this process. By informing specialist and non-specialist colleagues and encouraging them to use these guidelines, by presenting the guidelines in local or national meetings and by writing about and referring to these guidelines in (inter-)national journals, pancreatologists can optimize implementation of these guidelines. Some evidence also suggests that auditing could increase awareness and improve guideline implementation [96].

These guidelines will also be useful when designing future studies as they reflect the current 'benchmark' of treating acute pancreatitis. The existence of evidence-based guidelines obviously does not relieve clinicians from the professional obligation to keep up-to-date with new developments in acute pancreatitis. Especially, the results of currently ongoing randomized controlled trials (http://apps.who.int/trialsearch/) should be taking into account. How than to decide when to update these guidelines? Some have argued that a clinical guideline should be updated continuously. Although appealing this is clearly impractical. The Working group will use a published framework on how to decide when to update these guidelines [8].

These guidelines on the management of acute pancreatitis should result in reduced variation in practice and an improvement in patient outcome. The challenge now is to ensure high compliance in clinical practice and trial design.

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Collaborators

The 'Working group IAP/APA acute pancreatitis guidelines' consisted of a Steering committee, Executive Committee, the 2012 IAP and APA presidents, Review groups and Expert referees, all of whom are listed below.

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Julia Mayerle, Ernst-Moritz-Arndt-University, Greifswald
Santhi Swaroop Vege, Mayo Clinic, Rochester
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Marc Besselink, Hjalmar van Santvoort, Jens Werner: coordinators, writing of working plan and current guidelines, preparations for IAP/APA meeting, time managers; Marc Besselink wrote the first versions of the working plan and these guidelines, integrated comments from reviewers and referees in both the working plan and in these guidelines. Martin Freeman, Timothy Gardner, Julia Mayerle, Santhi Swaroop Vege: discussions on working plan, guidelines and meeting, critical review and co-authors of working plan and guidelines, time managers.

Executive committee

Peter Banks, Brigham & Womens Hospital, Boston
Colin McKay, Glasgow Royal Infirmary, Glasgow
Carlos Fernandez-del Castillo, Massachussets General Hospital, Boston
Jeremy French, Freeman Hospital, Newcastle upon Tyne
Hein Gooszen, University Medical Centre St Radboud, Nijmegen
Colin Johnson, Southampton General Hospital, Southampton
Mike Sarr, Mayo Clinic, Rochester
Tadahiro Takada, Teikyo University School of Medicine, Tokyo
John Windsor, The University of Auckland, Auckland
and the members of the Steering committee.

IAP/APA presidents 2012:

Ashok Saluja, IAP president.
Rodger Liddle, APA president.
Ashok Saluja provided secretarial support and provided, with Roger Liddle, facilities for the one-day interactive meeting at the IAP/APA 2012 meeting in Miami. Both were involved in the development of the working plan and guidelines.

Reviewers and time managers

A. Diagnosis of acute pancreatitis and etiology (Q1–3)
   Reviewers: Georgios Papachristou, Pittsburgh; Vijay Singh, Pittsburgh (presenter); Michael Rünzi, Essen.
   Time manager: Julia Mayerle, Greifswald
B. Prognostication/predicting severity (Q4–5)
   Reviewers: Bechien Wu, Los Angeles (presenter); Vikesh Singh, Baltimore; John Windsor, Auckland; Peter Banks, Boston; Georgios Papachristou, Pittsburgh.
   Time manager: Santhi Swaroop Vege, Rochester
C. Imaging (Q6–8)
   Reviewers: Thomas Bollen, Nieuwegein (presenter); Desiree Morgan, Birmingham; Koenraad Mortele, Boston.
   Time manager: Santhi Swaroop Vege, Rochester
D. Fluid therapy (Q9–10)
   Reviewers: Anubhav Mittal, Auckland (presenter); John Windsor, Auckland; Mao En-qiang, Shanghai, Timothy Gardner, Lebanon; Julia Mayerle, Greifswald.
   Time manager: Santhi Swaroop Vege, Rochester
E. Intensive care management (Q11–16)
   Reviewers: Julia Mayerle, Greifswald (presenter); Colin Johnson, Southampton; Jan de Waele, Gent.
   Time manager: Hjalmar van Santvoort, Utrecht
F. Preventing infectious complications (Q17–19)
   Reviewers: Maxim Petrov, Auckland; Patchen Dellinger, Seattle; Marc Besselink; Amsterdam; Markus M. Lerch, Greifswald (presenter).
   Time manager: Timothy Gardner, Lebanon
G. Nutritional support (Q20–24)
   Reviewers: Maxim Petrov, Auckland; Roland Anderson, Lund; Stephen McClave, Louisville.
   Time manager: Timothy Gardner, Lebanon (presenter)
H. Biliary tract management (Q25–27)
   Reviewers: Werner Hartwig, Heidelberg; Hjalmar van Santvoort, Utrecht (presenter); Martin Freeman, Minneapolis; Marco Bruno, Rotterdam; Alejandro Oria, Buenos Aires; Peter Banks, Boston.
   Time manager: Julia Mayerle, Greifswald
I. Indication for intervention in necrotizing pancreatitis (Q28–30)
   Reviewers: Marc Besselink, Amsterdam (presenter); Timothy Gardner, Lebanon; Hein Gooszen, Nijmegen; Todd Baron, Rochester; Carlos Fernandez-del Castillo, Boston;
   Time manager: Jens Werner, Heidelberg
J. Timing of intervention in necrotizing pancreatitis (Q31–32)
   Reviewers: Peter Fagenholz, Boston (presenter); Santhi Swaroop Vege, Rochester; Marc Besselink, Amsterdam; Jens Werner, Heidelberg; Carlos Fernandez-del Castillo, Boston.
   Time manager: Hjalmar van Santvoort, Utrecht
K. Intervention strategy in necrotizing pancreatitis (Q33–35)
   Reviewers: Hjalmar van Santvoort, Utrecht (presenter); Carlos Fernandez-del Castillo, Boston; Todd Baron, Rochester; Karen Horvath, Seattle; Thomas Bollen, Nieuwegein; Koenraad Mortele, Boston; Jens Werner, Heidelberg.
   Time manager: Martin Freeman, Minneapolis
L. Timing of cholecystectomy (or endoscopic sphincerotomy) (Q36–38)
   Reviewers: Mark van Baal, Nijmegen; William Nealon, Nashville; Timothy Gardner, Lebanon; Julia Mayerle, Greifswald (presenter).
   Time manager: Santhi Swaroop Vege, Rochester.

Expert referees (alphabetical order)

Ake Andren-Sandberg, Stockholm.
Olaf Bakker, Utrecht.
Claudio Bassi, Verona.
Markus Buchler, Heidelberg.
Marja Boermeester, Amsterdam.
Ed Bradley, Tallahassee.
Suresh Chari, Rochester.
Richard Charnley, Newcastle upon Tyne.
Saxon Connor, Christchurch.
Christos Dervenis, Athens.
Jacques Deviere, Brussels.
Vikas Dudeja, Minneapolis.
Paul Fockens, Amsterdam.
Chris Forsmark, Gainesville.
Helmut Friess, Munich.
Shuji Isaji, Mie
Rainer Isenmann, Ellwangen
Ernst Klar, Rostock.
Philippe Lévy, Clichy.
Keith Lillemoe, Boston.
Xubao Liu, Chengdu Matthias Löhr, Stockholm.
Toshihiko Mayumi, KitaKyushu.
Joachim Mossner, Leipzig.
John Neoptolemos, Liverpool.
Isto Nordback, Tampere.
Attila Olah, Gyor.
Roy Padbury, Adelaide.
Rowan Parks, Edinburgh.

Dejan Radenkovic, Belgrade.
Bettina Rau, Rostock.
Vinciane Rebours, Clichy.
Stefan Seewald, Hamburg.
Hans Seifert, Oldenburg.
Tooru Shimosegawa, Sendai.
Ajith Siriwardena, Manchester.
William Steinberg, Rockville
Robert Sutton, Liverpool.
Masao Tanaka, Fukuoka.
Kazunori Takeda, Sendai.
Francis Tse, Hamilton.
Harry van Goor, Nijmegen.
Andrew Warshaw, Boston.
Chunyou Wang, Wuhan.
David Whitcomb, Pittsburgh.
Yupei Zhao, Beijing.
Nicholas Zyromski, Indianapolis.
The expert referees reviewed the final version of these guidelines.

Appendix. GRADE system

http://www.uptodate.com/home/about/tutorial/index.html (30 min tutorial).
http://www.uptodate.com/home/about/policies/grade.html.

GRADE system: step 1, grade the evidence.

A = high quality evidence.
B = moderate quality evidence.
C = low quality evidence.

If RCTs, start by assuming high quality (grade A), but then grade down for:

- Serious methodologic limitations.
- Indirectness in population, intervention, or outcome.
- Inconsistent results.
- Imprecision in estimates.
- High likelihood of publication bias.

If no RCTs, start by assuming low quality (grade C), but then grade up for:

- Large or very large treatment effects.
- All plausible biases would diminish the effect of the intervention.
- Dose–response gradient.

GRADE system, step 2, grade the recommendation.

1 = strong recommendation
2 = weak recommendation

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation. High quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Strong recommendation, can apply to most patients in most circumstances without reservation
1B Strong recommendation. Moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.	Strong recommendation, likely to apply to most patients
1C Strong recommendation. Low quality evidence	Benefits appear to outweigh risk and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Relatively strong recommendation; might change when higher quality evidence becomes available
2A Weak recommendation. High quality evidence	Benefits closely balanced with risks and burdens	Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B Weak recommendation. Moderate quality evidence	Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances
2C Weak recommendation. Low quality evidence	Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.	Very weak recommendation; other alternatives may be equally reasonable.

Please note: the abovementioned guideline for grading evidence is specifically for therapeutic studies. For studies on diagnostic accuracy, the GRADE system suggests different criteria. Valid diagnostic accuracy studies – cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard – provide high quality evidence. However, they often are downgraded to lower quality evidence based on an assessment of limitations, particularly indirectness of outcomes, i.e. uncertainty about the link between the test accuracy and outcomes that are important to patients, inconsistency, imprecision and publication bias. For background and specific instructions on the GRADE system in evaluating diagnostic question see Ref. [5].

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