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International Association of Pancreatology Revised Guidelines on Acute Pancreatitis 2025: Supported and Endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society

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ABSTRACT

Introduction: The International Association of Pancreatology, alongside the American Pancreatic Association, the European Pancreatic Club, the Indian Pancreas Club, and the Japan Pancreas Society, decided to update its earlier guidelines for the management of acute pancreatitis (AP) given the remarkable advances in our understanding of AP and its management over the last decade.

Methods: These organizations put together a group of international experts to address important issues related to the management of AP. Guideline Development Groups comprising international domain experts framed clinically relevant questions and conducted thorough literature searches and systematic reviews to address the questions. Questions were framed in the PICO (Participant, Intervention, Comparator, and Outcome) format where appropriate. The evidence from the literature was synthesized to develop evidence-based recommendations for each question. The quality of evidence and the strength of the recommendations were graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE). For some questions, we have provided Good Practice Statements if enough direct evidence was unavailable.

Results: The guidelines pertain to 18 domains comprising 96 questions. The recommendations cover almost all aspects of managing AP, including pain control, fluid therapy, patient stabilization, nutritional support, conservative and interventional treatment for infected necrotizing pancreatitis, management of complications, discharge criteria, guidance on follow-up, and strategies for prevention of recurrence. Specific types of AP, such as those associated with pregnancy, trauma, and metabolic factors have been given special attention.

Conclusion: The recommendations presented here should serve as an evidence-based resource for practicing physicians and caregivers to treat patients with AP more effectively. In addition, the guidelines identify areas for future research, mainly targeted therapies for controlling systemic inflammation and mitigating organ dysfunction.

1. Introduction

Acute pancreatitis (AP) is among the most common gastrointestinal reasons for hospitalization. The global annual incidence of AP is 33·74 patients (95 % CI 23·33–48·81) per 100,000 person-years, causing 1·60 deaths (95 % CI 0·85–1·58) per 100,000 person-years [1]. Acute interstitial pancreatitis is seen in approximately 80 % of cases and usually runs a mild course. Acute necrotizing pancreatitis is a severe form of the disease and may lead to significant local and systemic complications [2], significant in-hospital morbidity, and mortality, which can be up to 40 % in those with persistent organ failure [3,4]. The management of patients with AP is complex and requires a multidisciplinary team comprising gastroenterologists, surgeons, intensivists, and radiologists. There are often differences in management between treating centers based on the team's experience, expertise, resources, and individual preferences. Although there is a rapidly expanding evidence base to guide management, a flexible and personalized approach is often

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required in managing the individual patient. The development of evidence-based guidelines provides a consistent framework and a set of recommendations for management that can be used to help standardize management plans across centers. There have been some guidelines for the management of AP over the past 3 decades, but there have also been many inconsistencies. The International Association of Pancreatology (IAP) and the American Pancreatic Association (APA) published evidence-based guidelines for AP in '*Pancreatology*' in 2013, which became one of the most widely cited guidelines [5]. Over the last decade, there have been many remarkable advances in our understanding of AP and its management, often based on level 1 evidence from randomized controlled trials (RCTs). These advances mandate an update of the 2013 guidelines to ensure that the latest evidence and recommendations are provided. The leadership of IAP initiated this update, inviting the participation of the American Pancreatic Association (APA), the European Pancreatic Club (EPC), the Indian Pancreas Club (IPC) and the Japan Pancreas Society (JPS). These organizations put together a group of international experts to cover all important issues relating to the management of AP. They were tasked with formulating relevant questions, conducting thorough literature searches of the best available evidence, and developing guidelines with a set of recommendations. The scope of the 2013 guidelines was expanded to include some new sections.

2. Methods

2.1. Scope and purpose

The 2013 IAP/APA guidelines served as the base document for the 2025 revised guidelines. The objective of the revised guidelines was to provide evidence-based recommendations for managing patients with AP. Clinically relevant questions were framed, and specific recommendations were provided based on available evidence from the literature. In addition, we expanded the scope of the earlier guidelines and included additional clinical questions related to some other previously unaddressed issues. The guidelines were divided into 18 domains, comprising 96 questions. The international domain experts were responsible for literature search and conducting systematic reviews to address each question, which was framed in the PICO format where appropriate. Synthesis of the evidence was used to develop evidence-based recommendations for managing patients with AP. We have not assessed the cost-efficiency and economic burden of various treatment modalities.

2.2. Stages of guideline development

2.2.1. First stage: general framework of the guideline development process

2.2.1.1. Domain experts and formation of committees. Experts in the relevant areas were invited from around the world to join and contribute to developing the revised guidelines. The leadership of the IAP put together core groups of domain experts, a coordination committee, a steering committee, and an apex executive committee of senior pancreatologists. Each core group comprised a chairperson, co-chair, and several domain experts. The core groups of domain experts served as Guideline Development Groups (GDG). Each core group was responsible for systematically reviewing the available literature on each question relevant to each domain. The domain experts from all relevant specialties involved with the care of patients with AP were included. The domain experts were selected based on their publications in the appropriate domain and international standing. The coordination committee periodically interacted with the core groups to coordinate the exercise well and complete it within the agreed timeframe. The coordination committee was responsible for contacting the core group members, assigning them their topics and questions, and following up with them for the section write-ups. The steering committee reviewed the guidelines and provided critical comments and suggestions. The apex committee critically reviewed the recommendations and resolved any conflict(s).

2.2.1.2. Patient's group and contributions. Patients and caregivers with first-hand experience of acute pancreatitis living in a range of countries from across the world were approached to obtain their perspectives on the guidelines. Patients were identified by pancreatic specialists as willing and able to review and provide written comments on the questions and recommendations in the guidelines, which they did after translation into their own language as necessary. Patient contributions were collated from the UK, Spain, Hungary, India, China, Japan and the USA and are presented as their collective viewpoints and suggestions on appropriate management, given at the end of each section (I-XIX).

2.2.1.3. Domains and framing the questions. After reviewing the 2013 guidelines, the coordination committee, in consultation with the GDG and the steering committee, developed 19 sections under which the earlier set of questions were either kept unchanged or edited, or new questions were added for revising and updating the guidelines by the core groups. Overall, 19 main sections and relevant clinical questions were developed. The GDGs were advised to frame the questions and responses in the PICO (participant, intervention, comparator, and outcome) format where applicable.

2.2.1.4. Drafting of the working plan. Each core group was tasked with the following responsibilities:

i. To review the section assigned to them, including the questions and remarks in the 2013 guidelines.
ii. To suggest changes (addition/deletion/modification) in the questions, recommendations, and remarks. The experts were advised to avoid personal biases and exercise caution to develop unbiased guidelines by giving due importance to the published evidence.
iii. To conduct a systematic review of the literature for each question
iv. To frame new questions for the new domains not covered in 2013 guidelines and follow the methodology mentioned above.

2.2.1.5. 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 and meta-analyses, focusing on the specific study questions with a sample size of at least 20 patients [2]; studies published in the English language, and [3] studies available in full text.

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] case series and case reports.

2.2.1.6. Grading of the evidence. All the experts were advised to grade the quality of evidence and the strength of the recommendations according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [6].

Many factors other than evidence may influence the strength of a recommendation as per the GRADE approach. These factors

include the availability and use of resources and expertise across centers, the magnitude of the potential benefits and harms of alternative courses of action, preferences of the individuals affected by the recommendation, health inequities, and accessibility of intervention(s) across the population groups. Thus, the strength of the recommendation may not be commensurate with the quality of the evidence. GRADE allows for making a strong recommendation despite low- or very low-quality evidence and is termed a 'discordant' recommendation. The reasons for discordant recommendations are included in the remarks section where applicable.

2.2.1.7. Outcome reporting. The definitions recommended in the revised Atlanta classification for acute pancreatitis were used [7]. The final outcomes of the systematic reviews were discussed amongst the GDGs and steering committee members. The GDGs provided the following for each section:

i. Clinical question
ii. Statement of recommendation
iii. GRADE strength of recommendation (strong or conditional) and quality of evidence (high, moderate, low or very low).
iv. For some of the questions that were not directly related to an interventional strategy or where it was deemed that the beneficial effects of an intervention outweigh its adverse effects but enough direct evidence was not available and the supportive evidence was indirect, we have provided Good Practice Statements. No formal grading was done for Good Practice Statements as recommended by GRADE guidelines.
v. Remarks: This section provides discussion, limitations, and context for the statement of recommendation. Some caveats related to the recommendations have been mentioned if the evidence was not of high quality.
vi. Summary tables of evidence have been provided for interventions such as analgesics, fluid therapy, nutrition, prophylactic antibiotics, endoscopic retrograde cholangiopancreatography (ERCP), and interventional treatment for drainage and necrosectomy. For each topic, one table with details of studies that were included for the synthesis of evidence and another table of GRADE quality assessment and summary of findings of randomized trials have been given. The tables include the number of included studies, study design, and a standardized critical appraisal of methodology for the summary of outcomes based on the GRADE system [6].

2.2.2. Second stage: development of the first draft

The coordination committee compiled all the write-ups received from each GDG and checked the questions, recommendations, and remarks for language, grammar, and factual errors, removed any duplications, and developed the first draft of the guidelines. The members of the coordination and steering committees reviewed this first draft and provided their comments and suggestions. The first draft of the guidelines was returned to the GDGs with comments and suggestions for revision. The revised version was then sent to the apex executive committee for critical review and resolution of conflicts. The coordinating, steering, and apex executive committees finally reviewed the revised version.

2.2.3. Third stage: decision rules and consensus building for grading the recommendations and evidence

During the development of draft guidelines, informal consensus was developed for the questions, strength of recommendations, and quality of evidence by the GDGs. This informal consensus was reviewed critically by the members of the steering and executive committees. Any further suggested changes were then referred to the GDGs for revision. The questions and recommendations were revised through multiple iterations until a consensus was reached among all the members of all the committees.

2.2.4. Fourth stage: finalization of the manuscript

The coordinators drafted the final version of the guidelines based on all the comments, suggestions, and consensus-building exercises. They shared the final draft with all the members of the steering and apex committees. All the experts approved the final version. Any disagreement was duly noted.

Target Audience and Users: The guidelines have been designed for all clinicians and caregivers involved in managing patients with acute pancreatitis at primary, secondary, and tertiary care levels. The guidelines were not explicitly developed for policymakers.

Future Prospects: The intention is to update these guidelines periodically as and when IAP leadership is convinced that sufficient new evidence has become available that is likely to alter patient management significantly.

3. Results

The 18 domains are presented sequentially, incorporating Recommendations or Good Practice Statements in response to 96 clinical questions. Table 1 provides a summary of the recommendations. The GRADE strength of recommendation and quality (certainty) of evidence are provided after each recommendation. Each recommendation is followed by a Remarks section to explain the reasons for the recommendation and the key references. All the Tables of summary of evidence with GRADE Quality Assessment are provided as Supplementary material. Consensus was reached among all the experts for all the recommendations except two, for which one of the experts had a different opinion, which is mentioned as a footnote at the bottom of the manuscript.

I. Diagnosis and etiology of acute pancreatitis

Q 1 How should a diagnosis of acute pancreatitis be made?

Recommendation: Acute pancreatitis (AP) should be diagnosed based on the fulfillment of two out of three criteria: (i) clinical-acute upper abdominal pain, (ii) biochemical-elevated pancreatic enzymes (serum lipase or amylase concentration >3 times upper limit of normal) and (iii) imaging- features of acute pancreatic inflammation with or without necrosis on abdominal imaging, typically computed tomography or ultrasonography (USG)]. (Strong recommendation; low-quality evidence).

Remarks: Acute inflammatory response to an injurious process leading to (peri)pancreatic inflammation could be defined as acute pancreatitis without evidence of underlying chronic pancreatitis. Though not exhaustive, this definition should help differentiate acute pancreatitis from an acute exacerbation of chronic pancreatitis, which could fulfill the diagnostic criteria of AP. The acute injurious process in AP could be initiated by different etiologies such as gallstones and alcohol. Raised blood levels of pancreatic enzymes are a surrogate for pancreatic cellular injury. However, taking a lipase or amylase threshold greater than 3 times the upper limit of normal (ULN) has limitations. Concentrations <3 times the upper limit of normal does not rule out AP. Further, concentrations >3 times the upper limit of normal may have non-pancreatic causes [8,9]. Since the 2013 guidelines, a Cochrane systematic review was performed to evaluate the diagnostic accuracy of serum amylase and lipase concentrations [10]. Taking radiological features of AP, diagnosis by laparotomy or autopsy pancreatic histology, and consensus conference definition as reference standard for the diagnosis of AP, a cut-off of >3 times serum amylase and lipase had

Table 1
Summary of recommendations for managing acute pancreatitis.

I. Diagnosis and etiology of acute pancreatitis
1. Recommendation: Acute pancreatitis (AP) should be diagnosed based on the fulfillment of two out of three criteria: (i) clinical- acute upper abdominal pain, (ii) biochemical- elevated pancreatic enzymes (serum lipase or amylase concentration >3 times upper limit of normal) and (iii) imaging- features of acute pancreatic inflammation with or without necrosis on abdominal imaging, typically computed tomography (CT) or ultrasonography (USG)]. (Strong recommendation; low-quality evidence) **2. Good Practice Statement**: During hospitalization, the etiology of acute pancreatitis should be determined using a detailed history of previous episode(s) of acute pancreatitis, gallstone disease, alcohol intake, medication intake, known hypertriglyceridemia, trauma, recent invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP), and family history of pancreatic disease(s). Laboratory tests for liver function tests, calcium and triglycerides, and abdominal USG of the gallbladder and biliary system should be performed. **3. Recommendations:** A repeat transabdominal ultrasound should be performed in patients with idiopathic acute pancreatitis after discharge. If this does not confirm an etiology, an endoscopic ultrasonography (EUS) should be performed. If the EUS does not reveal an etiology, a magnetic resonance imaging (MRI) scan with magnetic resonance cholangiopancreatography (MRCP) should be done. (Strong recommendation; moderate quality evidence) Genetic testing should be considered if the etiology remains unidentified, especially after a recurrent episode. (Conditional recommendation; low-quality evidence)
II. Prognostication/prediction of severity
4. Recommendation: Systemic inflammatory response syndrome (SIRS) at admission and persistent SIRS at 48 hours from the onset of abdominal pain, either alone or in combination with a high C-reactive protein (CRP) or Interleukin-6 (IL-6), should be used to predict severe acute pancreatitis. (Strong recommendation; moderate quality evidence). **5. Recommendation**: Persistent (>48 hours) organ failure is the most important clinical determinant of the outcome of acute pancreatitis in terms of mortality and should be used for predicting outcomes. (Strong recommendation; high quality evidence) **6. Good Practice Statement:** If expertise is not available in the local setting, transfer to a high-volume center is recommended for patients with organ failure or infected necrotizing pancreatitis.
III. Imaging in Acute Pancreatitis
7. Recommendation: Initial CT assessment in acute pancreatitis should be done if there is (i) diagnostic uncertainty and (ii) failure to respond to conservative treatment or clinical deterioration. The optimal timing for initial conventional CT to assess severity is at least 72–96 hours after the onset of symptoms. (Strong recommendation; moderate quality evidence) **8. Good Practice Statement**: A follow-up CECT should be done when invasive intervention is considered for local complications or there is clinical deterioration in patients with acute pancreatitis. **9. Good Practice Statement**: To detect local complications, it is recommended to perform a multidetector CT with thin collimation and slice thickness (i.e., 2 mm or less) during the pancreatic and portal venous phases (i.e., 50–70 s delay) after giving 100–150 ml of non-ionic intravenous contrast material at a rate of 3 ml/s. Only a portal venous phase (mono-phasic) CT is generally sufficient to assess fluid collections with or without necrosis during follow-up. If a pseudoaneurysm is suspected, dynamic CT or arterial phase contrast CT should be added. For MRI, the recommendation is to perform axial FS-T2W and FS-T1W scanning; intravenous gadolinium contrast may be required if the MRI is being done instead of a contrast-enhanced CT. If an MRI is done to delineate necrotic and liquefied components of fluid collections, an axial FS-T2W sequence should suffice.
IV. Fluid therapy
10. Recommendation: Lactated Ringer's solution should be used for fluid therapy in patients with acute pancreatitis. (Strong recommendation; moderate quality evidence) **11. Recommendation:** A moderate fluid infusion rate of 1.5 ml/kg/h is recommended. A fluid bolus is recommended if the patient has hypovolemia or hypotension at presentation. Additional fluids may be given depending on hematocrit and clinical signs of hypovolemia. (Strong recommendation; moderate quality evidence) **12. Good Practice Statement**: Both clinical signs and laboratory parameters should be considered when assessing fluid status. A mean arterial pressure between 65 and 85 mm Hg (8.7–11.3 kPa), a urine output $\geq$0.5 ml/kg/h, a blood urea nitrogen (BUN) < 20 mg/dL (or blood urea <40 mg/dL), and a hematocrit <44 % are reasonable targets which may reflect adequate fluid status. Invasive monitoring should be reserved for patients in an intensive care unit setting.
V. Analgesics
13. Good Practice Statement: Abdominal pain in patients with acute pancreatitis should be assessed periodically using a visual analog or numeric rating scale to judge the requirement of analgesics. **14. Recommendation**: Either opioid analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) should be used for pain relief. Opioid analgesics provide better pain relief in patients with severe pain. (Strong recommendation; moderate quality evidence)
VI. Organ failure and Intensive care management
15. Good Practice Statement: Organ failure of grade 2 or more as per the modified Marshall's classification is an indication for the transfer of a patient with acute pancreatitis to an intensive care unit (ICU). Patients with infected necrotizing pancreatitis with sepsis or other complications such as intra-abdominal hemorrhage or colonic fistulization also merit admission to a high-dependency unit or ICU. **16. Good Practice Statement:** Patients with acute pancreatitis and organ failure require organ support, similar to any other critically ill patient in the ICU.
VII. Use of Antibiotics to prevent and control infectious complications
17. Recommendation: Antibiotics should be used if there is proven extrapancreatic infection or strong suspicion of infected necrotizing pancreatitis. (Strong recommendation; moderate quality evidence) **18. Recommendation:** i. Positive microbiologic cultures from body fluids, e.g., blood, sputum, bile, urine, and drain fluid, are definite indications for antibiotic therapy. ii.The presence of gas bubbles within the pancreatic/peri-pancreatic necrotic collection on a CT scan suggests infected necrotizing pancreatitis and is an indication for antibiotic therapy. iii. Elevated levels of C-reactive protein (CRP), white blood cell (WBC) count, or procalcitonin (PCT) alone should not be used as biomarkers to start antibiotic therapy. (Strong recommendation; moderate quality evidence) **19. Recommendation:** The use of antibiotic prophylaxis is not recommended for the prevention of infectious complications associated with acute pancreatitis. (Strong recommendation; high-quality evidence) **20. Recommendation:** Probiotic use is not recommended to prevent infectious complications associated with acute pancreatitis. (Strong recommendation; high quality evidence) **21. Recommendation**: Selective gut decontamination is not recommended to prevent infectious complications associated with acute pancreatitis. (Conditional recommendation; low-quality evidence)

Table 1 (*continued*)

VIII. Nutritional support

22. Recommendation: In patients with predicted mild to moderate pancreatitis, oral feeding can be started as soon as possible when patients have an appetite and there is no vomiting. It is safe to start oral feeding with a regular, low-fat, solid diet. (Strong recommendation; moderate quality evidence)
23. Recommendation: Early enteral tube feeding, preferably within 72 hours of the onset of acute pancreatitis, is recommended if patients cannot tolerate oral feeding. (Strong recommendation; high quality evidence)
24. Recommendation: In the case of insufficient oral intake during the first 72 hours of hospital admission, nasoenteric tube feeding is indicated in patients with predicted severe or established acute necrotizing pancreatitis. (Strong recommendation; high quality evidence)
25. Recommendation: Polymeric enteral nutrition formulations are recommended for enteral tube feeding in patients with acute pancreatitis who do not tolerate oral intake. (Conditional recommendation; moderate quality evidence)
26. Recommendation: Enteral tube feeding can be administered via either the nasogastric or nasojejunal route in patients with acute pancreatitis. (Strong recommendation; high quality evidence)
27. Recommendation: Parenteral nutrition should be administered to patients with acute pancreatitis if enteral nutrition cannot meet nutritional goals during the course of the disease. (Strong recommendation; moderate quality evidence)

IX. Biliary tract management

28. Recommendations:
i. Early Endoscopic Retrograde Cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) within 72 hours is not recommended in the course of predicted mild biliary pancreatitis without acute cholangitis (Strong recommendation; high-quality evidence)
ii. Early ERCP/ES is not recommended in predicted severe acute biliary pancreatitis without acute cholangitis (Strong recommendation; moderate quality evidence)
iii. Early ERCP/ES is recommended in patients with acute biliary pancreatitis and acute cholangitis (Strong recommendation; high-quality evidence)
iv. ERCP/ES may be done to prevent recurrecne of pancreatitis if cholecystectomy cannot be performed during the same hospital admission (Conditional recommendation; low-quality evidence)
29. Recommendation: In patients with acute biliary pancreatitis without cholangitis, elective ERCP/ES is indicated when a common bile duct stone is identified on imaging such as EUS or MRCP. (Strong recommendation; high quality evidence)

X. Management of necrotizing pancreatitis: Conservative Management

30. Recommendation: Conservative management is recommended for sterile acute necrotizing pancreatitis in the early phase. (Strong recommendation; low-quality evidence)
31. Recommendation: A diagnosis of infected necrotizing pancreatitis should be established based on a combination of clinical, serologic, and radiological findings. Routine use of fine needle aspiration (FNA) to confirm infected necrotizing pancreatitis is not recommended. (Strong recommendation; low-quality evidence)
32. Recommendation: The initial management of infected necrotizing pancreatitis should be medical 'conservative first' (non-interventional) treatment, ensuring optimal nutritional supplementation and intravenous administration of broad-spectrum antibiotics. (Strong recommendation; low-quality evidence)
33. Good Practice Statement: Broad-spectrum antibiotic therapy should be administered initially in patients with suspected infected necrotizing pancreatitis.
34. Recommendation: Prophylactic and empirical administration of antifungal agents for infected necrotizing pancreatitis is not recommended. (Conditional recommendation; low-quality evidence)
35. Good Practice Statement: Failure of medical conservative therapy should be defined if, despite the application of broad-spectrum or targeted antibiotic therapy and supportive therapy, the clinical condition of patients with suspected infected necrotizing pancreatitis does not improve (persistent fever and leukocytosis) or worsens with the development of sepsis.

XI. Interventions in acute pancreatitis: Indications, Timing, and Intervention strategies

36. Recommendations: Common indications for intervention (either radiological, endoscopic, or surgical) in acute necrotizing pancreatitis are:
i. Clinical suspicion of, or documented, infected necrotizing pancreatitis with clinical deterioration, preferably when the necrotic collection has become walled off.
ii. Prolonged symptomatic sterile walled-off necrosis, e.g., abdominal pain, gastrointestinal luminal or biliary obstruction, or nutritional failure, even without signs of infection
iii. Less common indications for intervention are pancreatic hemorrhage, and bowel ischemia and fistula. (Strong recommendation; low-quality evidence)
37. Recommendation: Interventional treatment should be delayed in patients with suspected or confirmed infected necrotizing pancreatitis, if possible, to allow for the collection to become 'walled-off' (Walled off necrosis; WON) with better demarcation and liquefaction of the necrosis, which generally takes around 3–4 weeks. (Strong recommendation; low-quality evidence)
38. Recommendation: Early (<4 weeks) intervention such as transluminal or percutaneous drainage may be appropriate for patients with suspected or confirmed infected necrotizing pancreatitis who have failed conservative medical management (including antibiotics), provided they have at least partial encapsulation of the necrotic collections. (Conditional recommendation; low-quality evidence)
39. Recommendation: Abdominal paracentesis drainage (APD) may be done in patients with severe acute pancreatitis with abdominal or pelvic fluid (ascites) in the acute stage. (Conditional recommendation; moderate quality evidence)
40. Recommendation: The step-up approach consisting of initial antibiotics, then percutaneous drainage or endoscopic transluminal drainage followed, if necessary, by minimally invasive necrosectomy via the retroperitoneal route or per-oral endoscopic necrosectomy is recommended for suspected or confirmed infected necrotizing pancreatitis. (Strong recommendation; high quality evidence),
41. Recommendation: Either percutaneous catheter or endoscopic transluminal drainage is recommended for treating patients with suspected or confirmed infected necrotizing pancreatitis, depending on the location of infected necrotic collections and available expertise. (Strong recommendation; high quality evidence)
42. Recommendation: Multiple plastic stents or a lumen-apposing metal stent (LAMS) can be used for endoscopic transluminal drainage of walled-off necrosis in acute pancreatitis. However, LAMS should be preferred in those with infected WON or if the extent of necrosis is >30 % of the WON. (Strong recommendation; high quality evidence)
43. Recommendations: During the step-up approach, necrosectomy is recommended in:
i. Patients who continue to have persistent fever or signs of sepsis despite optimal utilization of sensitive antibiotics and adequate drainage (either percutaneous or endoscopic).
ii. Patients with infected necrotizing pancreatitis who fail to improve clinically despite adequate antibiotic treatment and cannot undergo drainage either percutaneously or endoscopically.
(Strong recommendation; high quality evidence)
44. Recommendations: The following interventional necrosectomy strategy should be chosen for infected pancreatic necrosis:
i. Minimally invasive approaches are preferred to open approaches and recommended for necrosectomy once the (peri) pancreatic necrotic collection is walled-off.
ii. Minimally invasive retroperitoneal pancreatic necrosectomy is recommended through the percutaneous drainage (PCD) tract in patients who have undergone percutaneous drainage using a retroperitoneal route.
iii. Per-oral endoscopic necrosectomy is recommended in patients who have undergone endoscopic transluminal drainage.
iv. Trans-gastric surgical necrosectomy (laparoscopic or open) is also an effective single-stage procedure ensuring wide stoma with durable internal drainage in patients with WON mainly localized to the lesser sac.

(*continued on next page*)

Table 1 (*continued*)

v. Open debridement is rarely indicated and should be reserved for patients with predominantly solid collections and other intraabdominal complications such as bowel fistula. (Strong recommendations; high quality evidence)

XII. Acute non-infectious complications in acute pancreatitis (Intra-abdominal hypertension/Pseudoaneurysm/Venous thrombosis/Bowel fistula)

Intra-abdominal hypertension (including abdominal compartment syndrome): Diagnosis and treatment

45. Good Practice Statement: Intra-abdominal hypertension (IAH) is defined by sustained or repeated elevation in intra-abdominal pressure (IAP) of >12 mmHg. Abdominal compartment syndrome (ACS) is defined as a sustained IAP of >20 mmHg (with or without abdominal arterial perfusion pressure <60 mmHg) that is associated with new onset or progressive organ dysfunction.

46. Good Practice Statement: It is recommended to measure IAP in patients with severe acute pancreatitis. If IAP is >12 mmHg, the IAP should be monitored periodically in patients with severe AP.

47. Recommendation: Patients with IAH should be treated with percutaneous catheter drainage of ascites and fluid collections, adequate pain relief, enteral decompression with nasogastric or rectal tubes, and avoidance of a positive cumulative fluid balance. (Conditional recommendation; low-quality evidence)

48. Recommendation: Surgical decompression may be considered to treat ACS if a patient has worsening organ dysfunctions and non-operative modalities have failed. (Conditional recommendation; very low-quality evidence)

Hemorrhagic Complications:

49. Recommendations: Angioembolization is recommended to treat arterial pseudoaneurysms and other arterial bleeding complications in patients with AP. (Strong recommendation; low-quality evidence)

Percutaneous embolization with thrombin or gelfoam and glue under ultrasound guidance or surgical management can be used when angioembolization is not possible or unsuccessful. (Conditional recommendation; low-quality evidence)

Splanchnic venous thrombosis:

50. Good Practice Statement: Contrast-enhanced computed tomography (CECT) is the most appropriate test to diagnose splanchnic venous thrombosis (SVT) in acute pancreatitis.

51. Recommendation: Anticoagulation is not recommended in patients with isolated splenic vein thrombosis. Anticoagulation may be used in more extensive venous thrombosis involving portal or mesenteric vein. (Conditional recommendation; low-quality evidence)

Bowel fistula

52. Good Practice Statement: Bowel fistula may occur in 10–15 % of patients with acute necrotizing pancreatitis. The most common sites of bowel fistula are the colon and duodenum, followed by the stomach and small intestine.

53. Good Practice Statement: Bowel fistulas should be suspected if there is worsening infection, gastrointestinal bleeding, or percutaneous drain showing intestinal/feculent material. Gas in or around the pancreas may also be due to a bowel perforation or fistula.

54. Recommendations: Upper gastrointestinal fistula generally do not require treatment and may be beneficial by providing internal drainage of pancreatic fluid collections; they usually close spontaneously over time. (Conditional recommendation; low-quality evidence)

For colonic fistula, conservative management with control of infection may suffice, but surgical treatment is required if there are signs of persistent or worsening infection or peritonitis or fecal discharge from a peripancreatic collection. (Conditional recommendation; low-quality evidence)

XIII. Management of special types of acute pancreatitis

Acute Pancreatitis in the Pediatric Population

55. Good Practice Statement: The criteria for diagnosing AP in children are the same as in adults, but these criteria may be less accurate in children.

56. Good Practice Statement: Etiologies of AP are diverse and differ substantially between children and adults. Most cases are idiopathic. Gallstone disease, multi-system illnesses, medications, viral infection, developmental abnormalities, trauma and genetic causes are common etiologies in children.

57. Good Practice Statement: Severe AP in children is defined if there is a presence of persistent organ failure similar to adults but utilizing the International Pediatric Sepsis Consensus definitions of organ failure.

58. Good Practice Statement: Trans-abdominal ultrasonography is the preferred first-line imaging modality in children, while CT and MRI/MRCP should be reserved for patients in whom USG is not diagnostic and ideally delayed at least 96 hours after the onset of symptoms.

59. Recommendation: Therapies for AP, including fluid resuscitation, nutrition support, analgesics, and the use of antibiotics, are similar in children as those for adults. (Strong recommendation; low-quality evidence)

60. Good Practice Statement: The complications of AP in children are similar to those in adults, with similar interventional management approaches.

Acute pancreatitis related to hyperparathyroidism.

61. Good Practice Statement: Acute pancreatitis due to primary hyperparathyroidism (PHPT) should be suspected in patients with elevated calcium levels and those with other clinical features suggestive of hyperparathyroidism.

62. Good Practice Statement: Patients with AP and elevated serum calcium levels should be further evaluated by measuring serum parathyroid hormone (PTH). An inappropriately elevated serum PTH confirms the diagnosis of PHPT.

63. Good Practice Statement: Standard treatment is recommended for PHPT-related AP. In addition, patients with serum calcium levels >14 mg/dL or hypercalcemia accompanied by altered sensorium require emergent measures to reduce serum calcium levels, including volume expansion with isotonic saline (and not lactated Ringer's solution), and avoidance of calcium supplements and Vitamin D.

Hypertriglyceridemia associated Acute Pancreatitis.

64. Recommendation: Besides the standard care for acute pancreatitis, insulin is recommended in diabetics and may be considered in non-diabetic patients as the first-line therapy to reduce serum triglyceride (TG) levels for hypertriglyceridemia-associated acute pancreatitis (HTGP). (Strong recommendation; moderate quality evidence)

Short-term (<3 days) use of low molecular weight heparin (LMWH) may also be considered. (Conditional recommendation; moderate quality evidence)

65. Recommendation: In patients with HTGP, plasmapheresis may be considered in case of persistent organ failure with high TG levels, particularly in patients with acute renal failure. (Conditional recommendation; low-quality evidence)

66. Recommendation: Patients with HTGP should fast for the first 48 hours, followed by an oral low-fat soft diet. If oral intake is not tolerated, enteral nutrition via nasogastric or nasojejunal tube should be initiated. (Strong recommendation; low-quality evidence)

If parenteral nutrition is required, intravenous fat emulsion should not be given in patients with TG $\geq$ 400 mg/dL (Strong recommendation; low-quality evidence)

67. Recommendation: The levels of serum TG should be maintained below 500 mg/dL after discharge to prevent relapse of HTGP. (Conditional recommendation; low-quality evidence)

Prevention of Post ERCP-pancreatitis

68. Recommendation: Moderate intravenous fluids with Lactated Ringer's solution should be given to patients undergoing ERCP during the periprocedural period in addition to rectal NSAIDs to prevent post-ERCP pancreatitis (PEP). (Strong recommendation; moderate quality evidence)

69. Recommendation: Prophylactic rectal indomethacin or diclofenac is recommended for patients undergoing ERCP who are at high risk of post-ERCP pancreatitis. (Strong recommendation; high quality evidence)

Prophylactic rectal indomethacin or diclofenac is recommended for average-risk patients undergoing ERCP. (Strong recommendation; moderate quality evidence)

Table 1 (*continued*)

70. Recommendation: A prophylactic pancreatic duct stent should be placed in patients with inadvertent multiple pancreatic duct cannulation or injection of contrast into the pancreatic duct during ERCP to prevent PEP. (Conditional recommendation; moderate quality evidence) **71. Recommendation:** A prophylactic pancreatic duct stent should be considered in addition to rectal NSAIDs in high-risk patients for PEP prophylaxis. (Conditional recommendation; moderate quality evidence)
Traumatic Pancreatitis
72. Good Practice Statement: A contrast-enhanced CT is recommended for stable patients with suspected pancreatic trauma. MRI/MRCP should be reserved for situations when there is a persistent clinical suspicion of pancreatic ductal injury and equivocal findings on a CT scan. **73. Recommendation:** ERCP is not recommended for diagnostic purposes in patients with acute pancreatitis due to trauma. ERCP should be reserved only for therapeutic purposes to place a stent in the MPD, if indicated. (Conditional recommendation; low-quality evidence) **74. Recommendation:** A hemodynamically unstable patient with pancreatic trauma should be treated with an exploratory laparotomy with a "damage control" approach. Grade 1 and 2 pancreatic injuries should be managed conservatively. For hemodynamically stable patients, early surgical resection is advised for grade 3 injuries. (Conditional recommendation; low-quality evidence) **75. Recommendation:** ERCP with pancreatic stenting is recommended in stable patients with symptomatic main pancreatic duct disruption following trauma who do not have an indication for surgical treatment. Endoscopic transluminal internal drainage is recommended for patients with symptomatic pseudocyst or walled-off necrosis after recovery from the initial pancreatic injury. (Conditional recommendation; low-quality evidence)
Acute pancreatitis and Pregnancy
76. Good Practice Statement: Acute pancreatitis during pregnancy results in higher rates of preterm delivery and perinatal mortality, including intra-uterine death. Fetal loss rates are higher in patients with severe pancreatitis as compared to those with mild pancreatitis. **77. Recommendation:** Transabdominal USG is recommended as the initial imaging modality of choice to confirm the diagnosis of acute pancreatitis during pregnancy. Magnetic resonance imaging (MRI) may be considered for patients with indeterminate sonographic findings. (Strong recommendation; low-quality evidence) **78. Good Practice Statement:** Generally, pregnant patients with AP should be managed similarly to non-pregnant patients. **79. Recommendation:** Early cholecystectomy is recommended for pregnant patients with mild acute biliary pancreatitis, preferably in the second and early third trimester. (Strong recommendation; moderate quality evidence)
XIV. Targeted Therapy for Acute Pancreatitis:
80. Good Practice Statement: At present, no effective targeted therapy is available, and thus no targeted therapy is recommended for patients with AP. **81. Good Practice Statement:** A few therapeutic agents to mitigate inflammation are currently undergoing trials, which could effectively reduce the severity of AP.
XV. Discharge Criteria for Patients with Acute Pancreatitis
82. Recommendation: Stable patients who tolerate an oral diet, demonstrate improvement of inflammatory markers (C-reactive protein) and/or total leukocyte count, absence of persistent fever, and require no or minimal non-opioid analgesia are suitable candidates for discharge following acute pancreatitis. (Conditional recommendation; low-quality evidence) **83. Recommendation:** No validated specific scoring system is recommended to determine safe discharge in acute pancreatitis, although PASS and SNAPP scores may be used as guidance. (Conditional recommendation; low-quality evidence)
XVI. Prevention of recurrent acute pancreatitis
84. Recommendation: Early cholecystectomy during index admission for mild biliary pancreatitis is safe and is recommended to prevent recurrence of acute pancreatitis. (Strong recommendation; moderate quality evidence) **85. Recommendation:** Cholecystectomy should be delayed in patients with moderate and severe acute pancreatitis, in particular, those with necrotizing pancreatitis and peripancreatic fluid collections, until the collections nearly resolve. (Conditional recommendation; low-quality evidence) **86. Recommendation**: Cholecystectomy is recommended for patients with acute biliary pancreatitis who have undergone ERCP and endoscopic sphincterotomy, and are fit for surgery. (Conditional recommendation; moderate quality evidence)
XVII. Long-term complications and long-term care after acute pancreatitis
87. Recommendation: Patients who recover from an attack of acute pancreatitis should be followed up periodically after discharge to assess short- and long-term complications. (Strong recommendation; moderate quality evidence) **88. Recommendation:** Screening for pre-diabetes and diabetes mellitus after acute pancreatitis is recommended in all patients. Blood glucose and hemoglobin A1c levels should be tested every 12 months, starting 3–6 months after recovery from acute pancreatitis. (Strong recommendation; moderate quality evidence) **89. Recommendation:** Pancreatic exocrine insufficiency (PEI) may occur due to extensive pancreatic necrosis in patients with acute pancreatitis. Patients with clinical symptoms of steatorrhea or severe undernutrition with low fecal elastase (<100 μg/g) may be treated with Pancreatic Enzyme Replacement Therapy (PERT). (Conditional recommendation; moderate quality evidence) **90. Good Practice Statement:** Patients who recover from an attack of acute pancreatitis may have a poor quality of life, especially in those with acute necrotizing pancreatitis. **91. Good Practice Statement**: Elimination of treatable causes of acute pancreatitis, including behavioral therapy for de-addiction, is recommended for preventing recurrent acute pancreatitis and progression to CP.
XVIII. Disconnected Pancreatic Duct Syndrome
92. Good Practice Statement: Patients with acute necrotizing pancreatitis may develop disconnected pancreatic duct syndrome (DPDS). Most patients with DPDS remain asymptomatic. DPDS may present with persistent external pancreatic fistula (EPF), recurrent pseudocyst, and/or recurrent acute or chronic pancreatitis involving the upstream pancreatic parenchyma. **93. Good Practice Statement:** A contrast-enhanced CT scan showing central pancreatic necrosis during the early phase of acute pancreatitis may suggest the development of DPDS. Later in the disease course, MRCP should be used to diagnose DPDS. **94. Good Practice Statement:** There is limited data on the natural history of DPDS following acute pancreatitis, but it remains asymptomatic in most patients. **95. Recommendation:** Indications for interventions for DPDS include persistent high-output external pancreatic fistula and symptomatic recurrent fluid collections and/or recurrent acute pancreatitis confined to the upstream pancreas. (Conditional recommendation; low-quality evidence) **96. Recommendation:** Endoscopic management is the preferred option for symptomatic DPDS in the post-acute setting if conservative treatment is unsuccessful. (Conditional recommendation; low-quality evidence)

a sensitivity of 0.72 (95 % CI 0.59—0.82), and 0.79 (95 % CI 0.54—0.92) and a specificity of 0.93 (95 % CI 0.66—0.99) and 0.89 (95 % CI 0.46—0.99) respectively. At the median prevalence of 22.6 % of AP in the included studies, the false positive rate of serum amylase and lipase was 26 % and 32 %, and a false negative rate of 8 % and 7 % respectively. The concentration of serum pancreatic enzyme levels declines over 3—5 days, although lipase levels may remain elevated longer than amylase. There is no clear correlation between the levels of pancreatic enzymes and the clinical course of the disease and thus the levels should not be monitored serially [11]. Pancreatic inflammation can be diagnosed using cross-sectional imaging. USG has poor sensitivity but is a must for diagnosing biliary etiology. A contrast-enhanced computed tomography (CECT) scan is considered most appropriate for diagnosing (peri)pancreatic inflammation but is generally not required in all cases. Magnetic resonance imaging (MRI) is more useful in the later course of illness for diagnosing complications of AP, such as determining the relative amount of necrotic debris within a collection and duct-related complications.

Q2 **What should be done during hospitalization to determine the etiology of AP?**

Good Practice Statement: During hospitalization, the etiology of AP should be determined using a detailed history of previous episode(s) of acute pancreatitis, gallstone disease, alcohol intake, medication intake, known hypertriglyceridemia, trauma, recent invasive procedures such as endoscopic retrograde cholangiopancreatography (ERCP), and family history of pancreatic disease(s). Laboratory tests for liver function tests, calcium and triglycerides, and abdominal USG of the gallbladder and biliary system should be performed.

Remarks: Gallstone disease is the most common etiology, accounting for up to 42 % of AP cases as per a systematic review and meta-analysis of 46 studies, which included 2,341,007 patients with AP from 36 countries [12]. An alanine aminotransferase (ALT) level >150 U/L within 48 hours after the onset of symptoms has a positive predictive value > 85 % to diagnose gallstone-induced pancreatitis [13—15]. In patients with abnormal liver tests and a normal gallbladder on USG, an endoscopic ultrasound (EUS) is recommended to rule in/out biliary microlithiasis after recovery from AP, if available. Acute alcohol-related pancreatitis accounts for approximately 25—40 % of cases, depending upon the population studied [12,16,17]. In about 20 % of cases, a clear etiology is not identified during hospitalization and is classified as idiopathic [12]. Two systematic reviews have found that tobacco smoking increased the risk of AP [18,19].

Q 3 **What further investigations are indicated in patients after a first or second attack of idiopathic AP?**

Recommendations: A repeat transabdominal ultrasound should be performed in patients with idiopathic AP after discharge. If this does not confirm an etiology, an endoscopic ultrasonography (EUS) should be performed. If the EUS does not reveal an etiology, an MRI with MRCP should be done. (Strong recommendation; moderate quality evidence).

Genetic testing should be considered if the etiology remains unidentified, especially after a recurrent episode. (Conditional recommendation; low-quality evidence).

Remarks: Although EUS and MRI/MRCP may complement each other in evaluating idiopathic AP, one systematic review of 5 studies, including 416 patients with idiopathic AP, reported a 32—88 % diagnostic yield of EUS for the detection of either microlithiasis or features of chronic pancreatitis [20]. This also suggests that a negative EUS does not entirely rule out a biliary cause. In another systematic review, which included 34 studies, the pooled sensitivities of EUS, secretin MRCP, and MRCP were 60 %, 43 %, and 24 %, respectively. In the seven studies, which included 249 patients and specifically compared EUS to MRI/MRCP, the diagnostic yield of EUS was 64 %, and MRCP was 34 % [21]. EUS was superior in diagnosing biliary disease and chronic pancreatitis, while MRI was superior for diagnosing anatomic alterations in the biliopancreatic ductal system [22]. Although an association of biliopancreatic anatomical abnormalities such as pancreas divisum, annular pancreas, and anomalous biliary pancreatic ductal union with AP has been shown, clear causality has not been established. For example, pancreas divisum may be a co-factor rather than a sole factor in the pathogenesis of AP [23,24]. Any patient without an apparent cause of acute pancreatitis and who is over the age of 50 years (and younger if in higher risk categories such as a positive family history) should have cross-sectional imaging (either CECT or MRI) of the abdomen and EUS, if available, to rule out pancreatic malignancy. Referral for genetic counseling to determine the appropriateness of genetic testing should be considered, especially in younger patients. Among presumed idiopathic recurrent AP cases, up to 66 % will have a genetic mutation identified [25]. In patients with recurrent attacks of idiopathic pancreatitis, the probability of underlying hereditary pancreatitis or other genetic mutations associated with pancreatitis is high; therefore, genetic testing should be considered [26].

Patients' viewpoints and suggestions: The patients state that their being informed about their medical management is essential, notably etiology, potential disease course, tests, and treatment, at each step of their journey in the hospital and after discharge. Patients recommend that there should be a discussion with them and/or their caregivers of issues in service provision, such as the availability and/or appropriateness of tests and access to specialist care. The patients view discussion with them of their options in management as important since patients may prefer less invasive approaches, e.g., MRI rather than EUS, to determine etiology unless sound justification can be given for a particular approach. Patients indicate that pancreas divisum may be specifically considered as a potential etiology. If genetic testing is considered, patients state that they need to be informed, counseled, and given a choice whether to have this or not, as this can have a serious impact, leading to the inability to obtain life insurance or a mortgage. If AP has a hereditary basis, patients confirm that the increased risk of pancreas cancer should also be discussed with them, enabling them to join a screening program when appropriate.

II. Prognostication/Prediction of severity

Q 4 What is the most appropriate marker to predict severe acute pancreatitis within 48 hours of onset of AP?

Recommendation: Systemic inflammatory response syndrome (SIRS) at admission and persistent SIRS at 48 hours from the onset of abdominal pain, either alone or in combination with a high C-reactive protein (CRP) or Interleukin-6 (IL-6), should be used to predict severe AP. (Strong recommendation; moderate quality evidence).

Remarks: Currently, there is no reliable way of predicting moderately severe and severe AP at admission with a high positive predictive value. Accurately predicting which patients will develop severe AP is crucial because it guides clinical decisions about a patient's transfer and treatment, and research decisions about recruitment and group allocation. SIRS has a high sensitivity and specificity but a low positive predictive value (PPV). Revised Atlanta classification defines severe AP if there is persistent organ failure of

>48 hours. To predict severe AP within 48 hours from the onset of symptoms is difficult. Laboratory markers often reported to predict the severity of AP include CRP [27–40], blood urea nitrogen (BUN), [29,41–46], hematocrit [27,29,43,46,47], procalcitonin (PCT), [29,30,32,34], IL-6 [38,48–50], triglycerides [51,52], glucose [46,53], calcium [54,55], D-dimer [56,57], and neutrophil-lymphocyte ratio [34,46].

In a recent meta-analysis of 181 studies that evaluated 29 biomarkers at admission for moderately severe and severe AP, IL-6 at a threshold of >50 pg/ml had a sensitivity and specificity of 87 % (95 % CI 69–95 %) and 88 % (95 % CI 80–93 %), compared to 53 % (95 % CI 35–71 %) and 82 % (95 % CI 74–88 %) for CRP >150 mg/l and 72 % (95 % CI 64–79 %) and 76 % (95 % CI 67–84 %) for acute physiology and chronic health evaluation-II (APACHE-II) score of ≥8 [58]. Another study showed that IL-6 of >160 pg/ml improved the PPV of persistent SIRS from 56 % to 85 % to predict severe AP [50].

Among the multifactorial prediction systems, a meta-analysis of 30 studies containing data on 5988 patients compared Ranson's, APACHE II, computed tomography severity index (CTSI), modified CTSI, bedside index for severity in acute pancreatitis (BISAP) score, and CRP. It showed APACHE II had the highest predictive value for mortality (area under the curve (AUC) 0.91, 95 % CI 0.88–0.93), with most of the included studies determining APACHE II within the first 24 hours of admission [59]. A systematic review and meta-analysis (14 studies, 1913 cases) [60] indicated that Harmless Acute Pancreatitis Score (HAPS) (cut-off = 0) could be applied to rule out severe AP with a high PPV (0.97, 95 % CI: 0.95–0.99). In a prospective multicenter study of 1544 cases, HAPS, SIRS, and BISAP had high and comparable negative predictive values (all >98 %) for ruling out multiple organ failure. The Pancreatitis Activity Scoring System (PASS) had a high predictive ability (AUC: 0.827, 95% CI: 0.788-0.865) for severe AP [61].

Based on these data, we recommend using SIRS criteria at admission and at 48 hours to predict the severity of AP, preferably along with CRP or IL-6.

Among the risk factors for the severity of AP, recent systematic reviews and meta-analyses have demonstrated that advanced age (≥65 years old), severe comorbidities (Charlson comorbidity index ≥3) [62], and increased body mass index (>25 kg/m^2) [63], increased visceral fat [64] and hypertriglyceridemia [1] were risk factors for developing severe AP.

Q 5 **What is the best strategy to predict the outcome of** AP **during hospitalization?**

Recommendation: Persistent (>48 hours) organ failure is the most important clinical determinant of the outcome of AP in terms of mortality and should be used for predicting outcomes. (Strong recommendation; high quality evidence).

Remarks: Predicting the outcomes of patients with AP is a dynamic and multi-dimensional process. Persistent organ failure is associated with a high mortality of 39–42 % in large cohorts of patients [65,66]. Revised Atlanta Classification (RAC) [7], is the most widely used and accepted classification of severity. The severity and outcome of AP are determined predominantly by organ failure [67–69]. Persistent organ failure is associated with pancreatic necrosis and infection of necrosis [2,66,70]. Infected necrotizing pancreatitis (INP) increases morbidity, hospital stay, resource utilization, and need for interventional treatment, but by itself, it does not increase mortality unless complicated by organ failure [65,66].

Q6 **What are the indications for the transfer of a patient with** AP **to a high-volume center?**

Good Practice Statement: If expertise is not available in the local setting, transfer of a patient to a high-volume center is recommended for patients with organ failure or infected necrotizing pancreatitis.

Remarks: It is important to have robust criteria for patient transfer. Given the rapid progression of the condition and the risk associated with transfer, decisions should be made cautiously. In principle, the indications for transfer can be categorized as prophylactic or reactive according to the personalized situation. Prophylactic transfer may be considered for patients with predicted severe AP, such as those with persistent SIRS, and at high risk of worsening if adequate facilities or expertise is not available. Utilizing prognostic scoring may be helpful in decision-making. Patients who do not respond to initial treatment should be considered for transfer to an appropriate tertiary-care center where multidisciplinary expertise is available. Data from the Nationwide Inpatient Sample of the US indicated that AP patients treated at high-volume centers (≥118 cases/year) had a 25 % lower relative risk of death compared to those treated at low-volume centers [71]. A national, large-sample study demonstrated that older age, male sex, lower income quartiles, admission to a non-teaching hospital, gallstone pancreatitis, indication for surgical interventions, and severe AP were predictors for transferring from small/medium-sized hospitals to large acute-care hospitals [72]. Reactive transfer should be considered in patients with complications such as organ failure or INP that require expertise not available in local settings, such as invasive interventions for INP [73]. Establishing a dedicated multidisciplinary regional network, including tertiary and secondary centers, may help make appropriate transfer decisions [74].

Patients' viewpoints and suggestions: Patients are concerned that when severe AP with persistent organ failure is predicted or identified, they should be assured that they would be provided the best possible care. Patients are also concerned about being allowed to eat and drink at an early stage in their illness, as some during their experience of AP were not allowed, including longer than necessary in the management of hypertriglyceridemia-associated acute pancreatitis. Transfer to a specialist tertiary high-volume center is a particular concern for patients, who recommend early and repeated liaison between centers, with every effort made to ensure this occurs when appropriate. In many countries, there is insufficient capacity in the system for this to occur entirely reliably, and patients consider this should be addressed as effectively as possible at all necessary levels to ensure adequate service provision.

III. Imaging in acute pancreatitis

Q 7 **What is the indication and timing of the initial CT assessment in AP?**

Recommendation: Initial CT assessment in AP should be done if there is (i) diagnostic uncertainty and (ii) failure to respond to conservative treatment or clinical deterioration. The optimal timing for initial conventional CT to assess severity is at least 72–96 hours after the onset of symptoms. (Strong recommendation; moderate quality evidence).

Remarks: Contrast-enhanced CT provides an accurate diagnosis and prediction of the severity of AP(75). However, routine early CT within 48 hours is not recommended in AP for the following reasons: (i) there is no evidence that early CT improves clinical outcome or that early detection of pancreatic necrosis will influence treatment; (ii) CT scoring systems are not superior to clinical scoring systems in predicting prognosis and severity of disease [76]; and (iii) the complete extent of pancreatic and peripancreatic necrosis may only become evident at least 72–96 hours after the

onset of AP [75]. A CECT scan to assess the severity of pancreatitis using the CT severity index (CTSI) or modified CTSI criteria [77] should be performed only thereafter. Early CT may be helpful to rule out bowel ischemia, acute cholecystitis, trauma-related pancreatic injury, cancer-related pancreatitis, vascular emergencies, or bowel obstruction and perforation in patients presenting with acute abdomen, and the diagnosis of AP is uncertain.

Q 8 **What is the indication for follow-up cross-sectional imaging with CT or MRI?**

Good Practice Statement: A follow-up CECT should be done when invasive intervention is considered for local complications or there is clinical deterioration in patients with AP.

Remarks: Although routine follow-up CT (e.g., weekly) in AP has been advocated, evidence for this practice is lacking. Routine CT for initial assessment is not recommended because most complications can be suspected by clinical assessment. A CECT is recommended when either invasive intervention is considered for local complications or if the patient's condition fails to improve despite initial conservative management. One important complication, namely arterial pseudoaneurysm, may not become clinically evident until bleeding occurs, but it is uncommon and hence does not justify a 'routine' follow-up CT. MRI may be required to distinguish between pseudocyst and walled-off necrosis at least 3–4 weeks after the index episode of AP. CT generally cannot detect necrosis in a fluid-predominant collection [78]. MRI is also helpful when there is an allergy to iodine contrast or in the presence of renal failure because T2-weighted images can detect necrosis without the need for gadolinium contrast. Advanced CT techniques, e.g., perfusion CT or dual-energy CT, may predict the development of pancreatic necrosis early. [79]. However, it is unknown whether these imaging techniques can either better predict severity or help change the outcomes of AP.

Q 9 **What is the optimal CT and MR protocol to detect local complications?**

Good Practice Statement: To detect local complications, it is recommended to perform a multidetector CT with thin collimation and slice thickness (i.e., 2 mm or less) during the pancreatic and portal venous phases (i.e., 50–70 s delay) after giving 100–150 ml of non-ionic intravenous contrast material at a rate of 3 ml/s. Only a portal venous phase (mono-phasic) CT is generally sufficient to assess fluid collections with or without necrosis during follow-up. If a pseudoaneurysm is suspected, dynamic CT or arterial phase contrast CT should be added.

For MRI, the recommendation is to perform axial FS-T2W and FS-T1W scanning; intravenous gadolinium contrast may be required if the MRI is being done instead of a contrast-enhanced CT. If an MRI is done to delineate necrotic and liquefied components of fluid collections, an axial FS-T2W sequence should suffice.

Remarks: There is a wide variation in the literature regarding CT and MRI protocols, but no dedicated radiology guidelines exist. Both the pancreatic and portal venous phases are adequate for discriminating viable from non-viable pancreatic tissue for CT. The following indications would require a multiphasic protocol: hemorrhage, arterial pseudoaneurysm, and mesenteric ischemia.

Pancreatic necrosis is considered as >1 cm^2 non-enhancing area on CECT in the pancreas with a value of CT < 30–50 HU or <15 HU increase in the value of CT after contrast injection [80–85]. Contrast-enhanced CT is recommended, although an initial non-contrast CT is an option in patients with acute renal failure.

An MR with T2-weighted images is advised when (i) the differentiation between pseudocysts and collections with necrosis (i.e., acute necrotic collection and walled-off necrosis) and relative quantification of necrosis within the collection is clinically relevant before drainage and (ii) in young patients because of the radiation burden of CT [78].

Patients' viewpoints and suggestions: The patients comment that clarification of the timing of initial CT assessment should be provided, as this may be done on the day of admission specifically for diagnosis but would need to be at least 72–96 hours after onset to assess severity of AP and may be required at a later stage if there is clinical deterioration.

IV. Fluid therapy

Q 10 **What is the preferred fluid type to use for fluid therapy in AP?**

Recommendation: Lactated Ringer's solution should be used for fluid therapy in patients with AP. (Strong recommendation; moderate quality evidence).

Remarks: Six full-published RCTs compared lactated Ringer's solution (LR) versus normal saline (NS) in patients with AP [86–91] (Suppl. Table 1A and 1B). Most were single-center studies with small sample sizes. Several meta-analyses indicate that using LR compared to NS is associated with lower severity, ICU admission, and occurrence of local complications [92,93]. Given that the results of individual studies were somewhat conflicting and that most of them were underpowered to investigate clinically relevant endpoints, large-scale multi-center studies are encouraged to clarify the effect of LR on the clinical course of AP. A recent randomized trial compared a balanced multi-electrolyte solution with normal saline and showed lower chloride levels and less SIRS with the use of the balanced solution [94].

Q 11 **What is the optimal fluid infusion strategy for fluid therapy in AP?**

Recommendation: A moderate fluid infusion rate of 1.5 ml/kg/h is recommended. A fluid bolus is recommended if the patient has hypovolemia or hypotension at presentation. Additional fluids may be given depending on hematocrit and clinical signs of hypovolemia.

(Strong recommendation; moderate quality evidence).

Remarks: There have been 6 RCTs investigating specific infusion rate strategies in different patient populations with AP (Suppl. Table 2A and 2B). Two RCTs compared more aggressive versus more restrictive fluid therapy protocols in severe AP defined according to the 1993 Atlanta classification [95,96]. Both showed worse outcomes with aggressive fluids. An RCT showed no difference between goal-directed (aggressive) and non-aggressive fluid therapy in terms of reduction in SIRS [97]. An open-label RCT compared aggressive fluid therapy (20 mL/kg intravenous bolus followed by 3 mL/kg/h) with non-aggressive fluid therapy (10 mL/kg bolus followed by 1.5 mL/kg/h) in patients with mild AP (n = 60) and showed that aggressive early fluid therapy led to faster clinical improvement [98]. Another RCT did not find any difference in the clinical outcomes between aggressive and non-aggressive fluid therapy when patients were included after 24 hours of onset of AP [99]. A recent international multicenter open-label RCT compared aggressive fluid therapy (20 mL/kg intravenous bolus followed by 3 mL/kg/h) vs. non-aggressive fluid therapy (1.5 mL/kg/h plus 10 mL/kg bolus only in case of hypovolemia) in all comers with AP without baseline criteria for moderately severe to severe AP [100]. The study had to be stopped prematurely (n = 249 patients) due to

an incidence of fluid overload in 21 % of patients in the aggressive fluids arm vs. 6 % in patients receiving moderate fluids ($p < 0.01$). There was no statistically significant difference in the primary efficacy outcome of the development of moderate-severe AP between the treatment arms, but aggressive resuscitation tended towards more adverse course of the disease. Systematic reviews support that aggressive fluid resuscitation is detrimental for patients with AP [86,101–104]. It is important to understand the pathophysiological disturbances and fluid dynamics in the case of mild and severe AP. The capillary circulation is intact, and homeostatic neurohumoral mechanisms are preserved in mild AP, while they are perturbed in severe AP with a potential for capillary leak [105]. Therefore, fluid therapy should be more guarded in patients with predicted severe AP. Based on the data available from RCTs, aggressive fluid therapy by itself is highly unlikely to prevent pancreatic necrosis and/or organ failure. Evidence from RCTs suggests that aggressive fluid resuscitation is associated with worse outcomes. Fluid therapy in acute illnesses must be adapted to the patient's needs and can be summarized in four phases [106,107]: i) Rescue: in case of shock, fluid resuscitation should be based on fluid bolus therapy; ii) Optimization: when the shock has improved, but the patient is still at risk of circulatory dysfunction, any additional fluid therapy should be given cautiously, and titrated to optimize cardiac function to improve tissue perfusion, iii) Stabilization: when the patient is in a steady state so that fluid therapy is now only used for ongoing maintenance and iv) De-escalation: when the patient has fluid overload and a negative balance needs to be promoted.

Q 12 How should response to optimal fluid therapy be measured?

Good Practice Statement: Both clinical signs and laboratory parameters should be considered when assessing fluid status. A mean arterial pressure between 65 and 85 mm Hg (8.7–11.3 kPa), a urine output ≥0.5 ml/kg/h, a blood urea nitrogen (BUN) < 20 mg/dL (or blood urea <40), and a hematocrit <44 % are reasonable targets which may reflect adequate fluid status. Invasive monitoring should be reserved for patients in an intensive care unit setting.

Remarks: Assessment of fluid status in hospitalized patients, particularly in an ICU setting, is difficult, and various parameters have been suggested. Clinically desirable hemodynamic parameters in patients with AP are a heart rate of <100/minute and a mean arterial pressure (MAP) of 65–85 mm Hg, urine output of >0.5 ml/kg/h, a blood urea nitrogen (BUN) < 20 mg/dL (or blood urea <40), and absence of signs and symptoms of dehydration or fluid overload. These goals are similar to those in hospitalized patients with other significant illnesses. It is unlikely that a single parameter will be as reliable as the assessment of multiple parameters [108]. Multicenter observational studies have demonstrated the role of BUN as a predictor of outcome in AP (42). Furthermore, the combination of admission hematocrit of ≥44 % and rise of BUN at 24 hours has outperformed other laboratory parameters in monitoring severe disease [43,109].

Invasive monitoring should be reserved for ICU patients, particularly those with hemodynamic impairment for whom volume expansion represents a significant therapeutic decision but with an uncertain benefit-to-risk balance [110]. Central venous pressure is a poor predictor of fluid status and responsiveness [111]. An arterial line is justified in this setting. The impact of passive leg raising on stroke volume, pulse pressure, and velocity of femoral artery flow seems promising for assessing fluid responsiveness in spontaneously breathing patients [112]. Abdominal hypertension may be associated with false negative results, particularly in ventilated patients [113]. An observational study of patients with severe necrotizing pancreatitis suggested that intrathoracic blood volume index was more accurate than central venous pressure and hematocrit for cardiac index assessment [114]. Inferior vena cava (IVC) diameter and its variation with respiratory cycle, as measured by a bedside point-of-care ultrasound (USG), is a good guide in the ICU setting to assess fluid status and responsiveness, as has been shown in critically ill patients [115]. Lung ultrasound to evaluate fluid overload has become a standard practice in many centers for critically ill patients [116]. Although the use of USG for IVC diameter and lung ultrasonography has not been tested specifically in patients with AP, their use is encouraged in patients with severe AP, as in other critically ill patients. There remains a need for additional studies focusing on monitoring fluid status in patients with AP using newer monitoring tools [117].

Patients' viewpoints and suggestions: Patients ask clinicians to be aware that monitoring can be a burden for patients, e.g., prolonged catheterization for assessment of urine output, and consider whether any invasive form of monitoring could be avoided unless essential.

V. Analgesic

Q 13 How should abdominal pain be assessed in AP?

Good Practice Statement: Abdominal pain should be assessed periodically using a visual analog or numeric rating scale to judge the requirement of analgesics.

Remarks: Pain is the cardinal symptom in patients with AP. Being subjective, it is difficult to quantify pain objectively**.** Visual Analogue Scale (VAS; 0–100 mm or 0–10 cm), Numerical Rating Scale (NRS; 0–10), and self-reported scale have been used to quantify pain intensity in RCTs that studied analgesics for pain relief in AP [118–130]. In postoperative settings, VAS and NRS are highly validated pain assessment scales [131]. The included studies assessed pain intensity at admission for up to 5 days and frequently (e.g., 2 hours to daily). Pain intensity, days with pain, requirement of analgesics (type, regimen, and total dose), and adverse events were the most frequently reported outcomes in meta-analyses [132,133] and may be recorded. The need for analgesics however, has not correlated well with the pain assessment tools.

Q 14 Which analgesic should be used for pain relief in patients with AP?

Recommendation: Either opioid analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) should be used for pain relief. Opioid analgesics provide better pain relief in patients with severe pain. (Strong recommendation; moderate quality evidence).

Remarks: Patients with AP should be treated with adequate analgesia. Pharmacological therapies include nonopioid analgesic paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetics (Suppl Table 3A and 3B). Two meta-analyses have shown that opioids and NSAIDs have similar efficacy and safety profile in mild AP, but opioid analgesics lead to the lesser requirement of rescue analgesics [132,133]. Opioids or NSAIDs should be the initial choice of analgesia. It should be supplemented with short-acting rescue analgesia such as fentanyl on an as-needed basis. Patient-controlled analgesia (PCA) given intravenously through a pump may be an effective strategy for rescue analgesia similar to that used for postoperative pain [131]. Two RCTs have shown that compared to diclofenac, opioid analgesics (either pentazocine or buprenorphine) were more effective and equally safe for pain management in AP, even in the sub-cohort of moderately severe or severe pancreatitis [127,130]. However, opioids should be avoided in patients with respiratory depression,

altered sensorium, and paralytic ileus [134]. A recent observational cohort study showed that opioid use after admission for a longer duration was associated with moderately severe or severe disease (OR 2.07 (95 % CI, 1.29—3.33); p = 0.003), [135]. However, the issue of reverse causation bias was not addressed in that study since more severe pain and longer duration of pain were also associated with moderate-severe AP(135).

Epidural analgesia with local anesthetic (with or without opioids) has been recommended for the management of postoperative pain but is not frequently used in AP(131). An earlier meta-analysis of 9 studies (2 randomized, 4 prospective observational, and 4 retrospective) had shown that epidural anesthesia (n = 726) was safe and effective in reducing pain severity, improving pancreatic perfusion, and decreasing mortality in patients with predicted severe AP or acute necrotizing pancreatitis [136]. However, a recent RCT of 148 patients did not show any benefit of epidural analgesia using ropivacaine and sufentanil either for the primary outcome, i.e., the number of ventilator-free days or secondary outcomes. In fact, epidural analgesia was significantly associated with a longer duration of invasive ventilation [137]. Epidural analgesia may be considered, especially in patients with severe pain and co-morbid cardiovascular or respiratory disease.

Well-designed, adequately powered randomized clinical trials (RCTs) are needed to assess the safety and efficacy of analgesics in patients with AP.

Patients' viewpoints and suggestions: Patients consider that pain scales alone do not adequately describe the impact and severity of pain, and recommend clinicians use pain scales as aids alongside patients' subjective descriptions and views on the nature and severity of pain they experience. Patients request that clinicians enquire as to the side effects of analgesics, as some patients do not question their management and may experience severe side effects from specific opiates, e.g., hallucinations and paranoid delusions.

VI. Organ failure and intensive care management

Q 15 What are the indications for admission to an intensive care unit (ICU) in patients with AP?

Good Practice Statement: Organ failure of grade 2 or more as per the modified Marshall's classification is an indication for the transfer of a patient with AP to an ICU. Patients with infected necrotizing pancreatitis with sepsis or other complications such as intra-abdominal hemorrhage or colonic fistulization also merit admission to a high-dependency unit or ICU.

Remarks: While the revised Atlanta Classification [7] defines severe AP as persistent (>48 hours) organ failure, as per the most recent guidelines by the Society of Critical Care Medicine (SCCM) published in 2016, all AP patients requiring life support for organ failure and intensive monitoring require ICU admission. Every patient considered at high risk of rapid clinical deterioration, such as those with a Charlson comorbidity index of ≥3 [138], the morbidly obese, elderly (>65 years), and those with organ dysfunction who require intensive monitoring and/or therapies should be assessed for admission to a high dependency unit or ICU. The routine use of single markers, such as lactate, CRP, hematocrit, or BUN alone, to triage patients to an ICU is not recommended [139].

Patients with infected necrotizing pancreatitis who have severe infection, particularly due to multidrug-resistant organisms, and develop sepsis or other complications such as intra-abdominal hemorrhage or colonic fistulization should also be managed in a high-dependency unit or ICU.

Q 16 How to provide specific organ support to patients with AP admitted to the ICU?

Good Practice Statement: Patients with organ failure require organ support, similar to any other critically ill patient in the ICU.

Remarks: There is a lack of RCTs addressing various aspects of critical care, specifically in patients with AP; thus, the recommendations are derived mainly from the literature on critical care, particularly sepsis [140]. Respiratory, renal, and cardiovascular support to maintain a MAP of ≥65 mm Hg should be provided, as in patients with other critical illnesses. Intraabdominal pressure should be monitored in patients with moderate-severe AP. Detailed recommendations are provided in the Supplementary material.

Patients' viewpoints and suggestions: Patients reiterate they should be assured that everything that can be done will be done wherever they are managed and that every effort is made to ensure their transfer to a specialist high-volume center when appropriate for their management.

VII. Use of antibiotics to prevent and control infectious complications

Q 17 When should antibiotics be used in AP?

Recommendation: Antibiotics should be used if there is proven extrapancreatic infection or strong suspicion of infected necrotizing pancreatitis. (Strong recommendation; moderate quality evidence).

Remarks: Infection of pancreatic necrotic collections is the major indication for antibiotic therapy, but it is an uncommon complication, accounting for approximately 5 % of all patients with AP [141]. Extra-pancreatic indications such as cholangitis or pneumonia occur in up to 14 %—37.4 % of cases [142,143]. Consequently, the justified rate of antibiotic administration should be between 20 % and 40 % [144]. However, antibiotics are frequently overused, and an international multicenter study involving 9869 patients from 23 countries showed that the highest rates of antibiotic therapy were reported in Asia (China 81.4 %, Taiwan 80.6 %) and Eastern Europe (Albania 78.6 %, Bulgaria 78 %). In contrast, the lowest rates were observed in Western Europe (Spain 31.8 %, United Kingdom 31.2 %). Antibiotic therapy was not associated with decreased mortality and severity [144].

Q 18 What are the clinical indications or biomarkers for initiating antibiotic therapy in AP?

Recommendation:

i. Positive microbiologic cultures from body fluids, e.g., blood, sputum, bile, urine, and drain fluid, are definite indications for antibiotic therapy.
ii. The presence of gas bubbles within the pancreatic/peripancreatic necrotic collection on a CT scan suggests infected pancreatic necrosis and is an indication for antibiotic therapy.
iii. Elevated levels of C-reactive protein (CRP), white blood cell (WBC) count, or procalcitonin (PCT) alone should not be used as biomarkers to start antibiotic therapy.

(Strong recommendation; moderate quality evidence).

Remarks: A positive microbiological culture is a definite indication to start antibiotics. Extraluminal gas in the (peri)pancreatic collections also suggests infected necrotizing pancreatitis. The use of inflammatory parameters in AP is important to assess the disease progression and development of secondary infection, although it can be misleading in the early phase of AP [144]. Several

biomarkers, such as CRP level, WBC count, and procalcitonin level, are used in the decision-making process to start antibiotic treatment for suspected infection. However, it has been shown that CRP (AUC: 0.510) and WBC (AUC: 0.454) have low sensitivity and specificity in diagnosing infected necrosis. The only biomarker with an acceptable predictive value is procalcitonin (AUC: 0.729). A single-center randomized trial of 260 patients with mostly mild AP showed that using procalcitonin reduced the use of antibiotics from 63 % to 45 % [145]. There is a need to find better biomarkers to diagnose pancreatic infection earlier.

Q 19 Is systemic antibiotic prophylaxis effective in preventing infectious complications in AP?

Recommendation: The use of antibiotic prophylaxis is not recommended for the prevention of infectious complications associated with AP. (Strong recommendation; High-quality evidence).

Remarks: Prophylactic antibiotics are not recommended in patients with predicted severe and necrotizing pancreatitis [146] (Suppl. Table 4A and 4B). A meta-analysis of 11 studies involving 864 patients concluded that antibiotic prophylaxis does not reduce the incidence of infected pancreatic necrosis but may affect all-cause mortality in acute necrotizing pancreatitis [147]. There was no difference in mortality when a meta-analysis was restricted only to RCTs [148]. A recent study from Japan also found no benefit with prophylactic antibiotics in severe AP [149].

Q 20 Are probiotics effective in preventing infectious complications?

Recommendation: Probiotic use is not recommended to prevent infectious complications associated with AP. (Strong recommendation; high quality evidence).

Remarks: A recent meta-analysis of 13 RCTs showed no reduction in the rate of infected pancreatic necrosis and total infections with probiotics [150]. An older RCT in patients with predicted severe AP did show increased mortality due to bowel ischemia with the use of probiotics [151].

Q 21 Is selective gut decontamination effective in preventing infectious complications in AP?

Recommendation: Selective gut decontamination is not recommended to prevent infectious complications. (Conditional recommendation; low quality evidence).

Remarks: Evidence on selective decontamination in AP is limited to one RCT [152], which showed that selective gut decontamination reduced the incidence of Gram-negative pancreatic infections, but there was no difference in overall mortality [152].

Patients' viewpoints and suggestions: Patients consider that their symptoms may provide clues as to the presence of infection to prompt consideration that infectious complications have arisen, e.g., anorexia, nausea, vomiting, abdominal pain, and bloating.

VIII. Nutritional support

Q 22 When should oral feeding be started in patients with predicted non-severe pancreatitis, and what feed should be given?

Recommendation: In patients with predicted mild to moderate pancreatitis, oral feeding can be started as soon as possible when patients have an appetite and there is no vomiting. It is safe to start oral feeding with a regular, low-fat solid diet. (Strong recommendation; moderate quality evidence).

Remarks: Five meta-analyses [153–157] and other studies [158–164] have addressed the question of optimal timing of oral refeeding in mild and predicted mild AP (Suppl. Table 5A and 5B). These showed that early oral refeeding did not affect the recurrence of abdominal pain, decreased the complication rate, and significantly reduced the length of hospitalization. Early oral feeding was considered appropriate when patients were hungry and abdominal pain was subsiding [159]. Conventional feeding had a 16 % pain relapse rate [164]. Immediate oral diet combined with opioid analgesia improved treatment efficacy [160]. Early oral feeding also reduced treatment costs [158,164].

Many studies [163,166–169], including three meta-analyses [154,157,165], evaluated the type of oral feeding for patients with predicted mild pancreatitis (Suppl Table 6A and 6B). They showed that early oral refeeding with a soft, low-fat, hypocaloric, or solid diet [170] decreased the length of hospitalization and did not increase pain recurrence after refeeding. This diet appeared to be as safe as a clear liquid diet.

Q 23 When should nutritional support be initiated, and what is the preferred route?

Recommendation: Early enteral tube feeding, preferably within 72 hours of onset of AP, is recommended if patients cannot tolerate oral feeding. (Strong recommendation; high quality evidence).

Remarks: There has been much debate about when nutritional support should be started. Early enteral nutrition is preferred (Suppl. Table 5A and 5B). A meta-analysis of 8 randomized studies (including 165 patients) suggested that starting enteral nutrition within 24 hours of hospital admission was associated with a significantly lower combined endpoint (comprising mortality, infected pancreatic necrosis, and organ failure) than those who started enteral nutrition after 24 hours had elapsed (45 %–19 %: OR 0.44; 95 % CI 0.2–0.96), [171]. Another meta-analysis, comprising mainly RCTs including both enteral and parenteral nutrition, showed that early enteral feeding within 24–48 hours was associated with reduced infection and mortality [162]. In contrast, a prospective multi-center RCT in patients with predicted severe AP did not demonstrate the superiority of early nasoenteric tube feeding compared with an oral diet after 72 hours, in reducing the rate of infection or mortality [172]. In the on-demand group, 72 patients (69 %) tolerated an oral diet and did not require enteral tube feeding. A subsequent RCT showed the feasibility and effectiveness of early enteral tube feeding based on appetite/hunger in patients with moderately severe or severe AP with a reduction in the length of hospitalization [173]. The most recent meta-analysis of 17 studies included a subgroup analysis comparing enteral tube feeding before and after 48 hours from admission [174]. Early enteral tube feeding was associated with a significant decrease in mortality (3.9 fold), sepsis, and hospital stay, and this confirmed findings from an earlier meta-analysis [175]. In a meta-analysis of RCTs of patients with mild AP, immediate enteral tube feeding compared with early refeeding was associated with decreased length of hospital stay and decreased intolerance to feeding [176]. The initiation of enteral tube feeding within 48 hours of admission is associated with a significant reduction in mortality, organ failure, local and systemic infections, and a decrease in the need for surgical intervention [175,177].

There are many reasons why enteral nutrition is preferred to parenteral nutrition in patients with AP, providing there are no contra-indications [177]. Parenteral nutrition is associated with catheter sepsis, metabolic and electrolyte disturbances, hyperglycemia, intestinal atrophy, and bacterial overgrowth. Enteral nutrition maintains intestinal integrity and decreases organ failure, risk of infected pancreatic necrosis, hospital stay, and mortality

compared with parenteral nutrition [177]. These findings are supported by three meta-analyses [178–180] and a Cochrane Systematic Review [181].

Q 24 **What is the indication for nasoenteric tube feeding in predicted severe AP?**

Recommendation: In the case of insufficient oral intake during the first 72 hours of hospital admission, nasoenteric tube feeding is indicated in patients with predicted severe or established acute necrotizing pancreatitis. (Strong recommendation; high quality evidence).

Remarks: Some patients with predicted severe AP can tolerate oral feeding and do not need nasoenteric feeding [179,182]. When oral feeding is not tolerated after 72 hours [172] or complete nutritional requirements are not met, nasoenteric tube feeding is indicated. Only 31 % of patients in that study required nasoenteric tube feeding [172]. However, there is also evidence that initiating enteral tube feeding within 48 hours of admission is associated with a significant reduction in mortality, organ failure, local and systemic infections, and a decrease in the need for surgical intervention [175,177].

Q 25 **What type of enteral nutrition formulation should be used**?

Recommendation: Polymeric enteral nutrition formulations are recommended for enteral tube feeding in patients with AP who do not tolerate oral intake. (Conditional recommendation; moderate quality evidence).

Remarks: There are several categories of enteral nutrition formulations: standard or polymeric, semi-elemental, elemental, and immunonutrition. Three meta-analyses [183–185] concluded that there was no evidence to support the use of elemental and semi-elemental formulations (Suppl. Table 7). Polymeric feeding formulations have a similar risk of feeding intolerance, infectious complications, and mortality as the more expensive semi-elemental and elemental formulations. A recent large retrospective Japanese study examined the comparative effectiveness of enteral formulations and found no clinical advantage of an elemental diet in terms of risk of sepsis, mortality, and cost [185]. The benefits of fiber-enriched formulations remain uncertain [186]. There is no proven role of immunonutrition. Further trials are required before immunonutrition [157] or omega-3 fatty acid supplementation [184,187] can be recommended to modulate the systemic inflammatory response and potentially reduce the risk of organ dysfunction in AP.

Q 26 **Should enteral tube feeding be administered via a nasojejunal or nasogastric route?**

Recommendation: Enteral tube feeding can be administered via either the nasogastric or nasojejunal route in patients with AP. (Strong recommendation; high quality evidence).

Remarks: Six meta-analyses of RCTs [188–193] (Supplementary Tables 8A, 8B, 8C) have shown that nasogastric tube feeding is as safe and effective as nasojejunal tube feeding in patients with AP. No significant difference was found in the risk of infection, organ failure, or mortality. Although nasogastric tube feeding is easier than nasojejunal tube feeding, several patients do not tolerate nasogastric feeding (e.g., due to vomiting and gastric ileus). These patients require nasojejunal tube feeding.

Q 27 **When should parenteral nutrition be used in AP?**

Recommendation: Parenteral nutrition should be administered to patients with AP if enteral nutrition cannot meet nutritional goals during the course of the disease.

(Strong recommendation; moderate quality evidence).

Remarks: Multiple RCTs, three meta-analyses [178–180], and a critical review [194] have shown that enteral nutrition (EN) is superior to parenteral nutrition (PN) across all grades of severity of AP because it reduces infection, organ failure, and mortality rates (Supplementary Table 9A and 9B). Similar results were seen in RCTs that included patients with severe AP who might require parenteral nutrition (Supplementary Table 10A and 10B). Despite some methodological limitations, including varying caloric goals, inclusion criteria, timing of recruitment, and outcomes, the included RCTs consistently showed PN to be less effective than EN. It is recommended that PN should only be started if the nutritional goals cannot be reached with oral and/or enteral tube feeding or if complications of severe AP are a contra-indication to EN, including bowel obstruction, abdominal compartment syndrome, prolonged paralytic ileus and mesenteric ischemia [195]. There is no specific evidence for determining the nutritional goals of patients with AP, although general guidelines for the energy and protein requirements for patients in ICU can be used (Suppl. Table 11) [196]. Given that patients with AP are preferentially encouraged to meet their nutritional requirements by oral intake and/or enteral tube feeding, there is usually no need to start PN within the first week of admission to the hospital [197,198].

Patients' viewpoints and suggestions: Patients consider nutritional support most important and welcome the emphasis on this topic and the six questions, as patients view nutrition as a crucial part of their recovery to rebuild their lives.

IX. Biliary tract management

Q 28 What is the indication for early Endoscopic Retrograde Cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) within 72 hours in the course of acute biliary pancreatitis?

Recommendations:

- Early ERCP with ES within 72 hours is not recommended in the course of predicted mild biliary pancreatitis without acute cholangitis (Strong recommendation; high-quality evidence)
- Early ERCP/ES is not recommended in predicted severe acute biliary pancreatitis without acute cholangitis (Strong recommendation; moderate quality evidence)
- Early ERCP/ES is recommended in patients with acute biliary pancreatitis and acute cholangitis (Strong recommendation; high-quality evidence)
- ERCP/ES may be done to prevent recurrence of pancreatitis if cholecystectomy cannot be performed during the same hospital admission (Conditional recommendation; low-quality evidence)

Remarks: For patients with acute biliary pancreatitis, the therapeutic goals of ERCP are biliary sphincterotomy to extract common bile duct stone(s), decompress the bile duct in the setting of acute cholangitis, and place a common bile duct stent when biliary obstruction is present. Early ERCP is defined as performed within 24–72 hours of clinical presentation. Randomized trials evaluating the role of early ERCP in the management of patients with acute biliary pancreatitis without acute cholangitis have shown no

benefit of early ERCP on mortality, organ failure, or pancreatic necrosis (Suppl Table 12A and 12B), [199]. In the setting of AP with SIRS, diagnosing concomitant acute cholangitis may be challenging. In an RCT, urgent ERCP within 24 hours was not associated with improved outcomes in patients with acute gallstone pancreatitis without cholangitis. However, urgent ERCP/ES was associated with a reduced rate of acute cholangitis (2 %) compared to patients managed by conservative treatment (10 %) [200]. However, 41% of patients randomized to conservative treatment underwent ERCP/ES during the same admission. A EUS-guided strategy to direct urgent ERCP only in patients with bile duct stones also did not show benefit in the absence of cholangitis [201].

Q 29 When should ERCP/ES be performed for a common bile duct stone in the setting of acute biliary pancreatitis without cholangitis?

Recommendation:

- Elective ERCP/ES is indicated when a common bile duct stone is identified on imaging such as EUS or MRCP. (Strong recommendation; high quality evidence)

Remarks: The sensitivity of liver chemistries, transabdominal USG, and computed tomography is poor in confirming the presence of common bile duct stones. In patients with suspected choledocholithiasis, EUS or MRCP should be undertaken [202]. Since patients with acute biliary pancreatitis have at least an intermediate risk of choledocholithiasis, they may require further imaging (MRCP, EUS, or intraoperative cholangiography) before cholecystectomy unless first-tier imaging (CT or transabdominal ultrasound) has already demonstrated the presence of choledocholithiasis unequivocally. It is worth noting that the presence of a common bile duct stone alone does not require the performance of early ERCP, as discussed above.

Patients' viewpoints and suggestions: Patients state that for them there is a need for clarity concerning the timing of an ERCP/ES following acute biliary pancreatitis, if patients are not considered suitable for cholecystectomy. This is because Q 28 addresses the indications for ERCP/ES within the first 72 hours of admission, but when ERCP/ES is advised for patients who are not candidates for cholecystectomy, ERCP/ES is usually more suitable later, preferably during the same admission.

X. Management of acute necrotizing pancreatitis: conservative management

Q 30 What is the management of sterile acute necrotizing pancreatitis in the early phase?

Recommendation: Conservative management is recommended for sterile acute necrotizing pancreatitis in the early phase. (Strong recommendation; low-quality evidence).

Remarks: The treatment of acute necrotizing pancreatitis is primarily supportive even beyond the first week. Necrosis generally remains sterile in most (up to 80 %) patients. Analgesia, nutritional therapy, and ICU supportive therapy for those with organ dysfunction are the mainstay of therapy during this period.

The role of imaging is limited during the early phase because early morphologic changes do not correlate with clinical findings or help predict the subsequent clinical course [203]. The clinical usefulness of antisecretory medications and protease inhibitors (somatostatin, octreotide, and gabexate mesilate) in treating AP has not been confirmed including continuous regional arterial infusion [204,205]. The 2nd to 4th week of illness is the period of watchful observation for the development of complications, predominantly infection of the necrotic collection(s). Patients with acute necrotizing pancreatitis are prone to develop secondary infection because of multiple factors, which include (i) a fertile environment for microbial growth in the necrotic tissue, (ii) increased intestinal permeability, and (iii) a state of relative immunosuppression due to compensatory anti-inflammatory response syndrome. Earlier studies on surgical treatment for sterile necrotizing pancreatitis showed a high mortality [206], and therefore, conservative treatment is recommended for sterile acute necrotizing pancreatitis. The necrotic collections are not well organized and walled-off in the early stage [207] and thus not amenable to effective drainage.

Q 31 How should infected necrotizing pancreatitis be diagnosed?

Recommendation: A diagnosis of infected necrotizing pancreatitis should be established based on a combination of clinical, serologic, and radiological findings. Routine use of fine needle aspiration (FNA) to confirm infected necrotizing pancreatitis is not recommended.

(Strong recommendation; low-quality evidence).

Remarks: Infected necrotizing pancreatitis (INP) should be suspected in patients with (peri)pancreatic necrosis who fail to improve after 7–10 days of symptom onset for reasons such as clinical deterioration, new onset of fever, increasing leukocyte count, raised procalcitonin, or features of sepsis [145,147]. The gold standard for the diagnosis of INP is microbiologic confirmation by FNA and culture under CT or ultrasound guidance. In clinical practice, however, a diagnosis of INP is suspected based on a combination of clinical, serologic, and radiological findings without FNA. Routine FNA to identify microorganisms in the pancreatic necrotic collection is not recommended due to a considerable number of false-negative (20–29 %), some false-positive results (4–10 %) [208,209], and the potential risk of introducing infection [209,210]. FNA can be considered in select situations where there is no clinical response to broad-spectrum antibiotics, such as when a multidrug-resistant bacterial or fungal infection is suspected [210,211]. The presence of gas bubbles in the (peri)pancreatic necrotic collection (either due to loss of integrity of the gastrointestinal tract or through gas-forming bacteria) suggests infection with high specificity but moderate sensitivity [208,212].

Optimal cut-off levels of serologic markers are required for discriminating INP from systemic inflammatory response syndrome (SIRS) without infection. Serum procalcitonin has a sensitivity of 90 % and a specificity of 89 % for detecting infected pancreatic necrosis using a cut-off value of 3.5 ng/mL [145,213–215]. Notably, up to 20 % of patients with AP develop extra-pancreatic infections, i.e., bloodstream infections, pneumonia, catheter sepsis, and urinary tract infections [216–218]. Therefore, extrapancreatic infection should be excluded carefully when interpreting elevated serological inflammatory markers. FNA may be useful in patients with unclear clinical signs and no imaging evidence of INP. In light of the worldwide epidemic of antibiotic resistance and the limited diagnostic accuracy of serological biomarkers, further studies are required to confirm the role of percutaneous FNA and other biomarkers in documenting infection and guiding targeted treatment.

Q 32 What should be the initial optimal treatment for suspected infected necrotizing pancreatitis?

Recommendation: The initial management of infected necrotizing pancreatitis should be medical 'conservative first' (non-interventional) treatment, ensuring optimal nutritional

supplementation and intravenous administration of broad-spectrum antibiotics. (Strong recommendation; low-quality evidence).

Remarks: In general, the initial management of pancreatic necrosis should be conservative, by which strategy the majority of cases should resolve. If the necrotic collection becomes infected, initial management should remain conservative until the collection has become walled-off, at which stage it may require drainage either endoscopically, percutaneously, or surgically. Necrosis usually becomes walled-off >3—4 weeks after onset of AP [5,7]. In the parlance of infected necrotizing pancreatitis, the term 'conservative' often suggests non-surgical treatment and includes minimally invasive intervention in the form of drainage without necrosectomy. A strategy of conservative treatment consisting of intensive care, a combination of antimicrobial agents, and nutritional support, with or without drainage of the infected fluid, may be successful in approximately two-thirds of patients with suspected INPwith low mortality while obviating the need for surgical necrosectomy [219,220]. A recent RCT that compared immediate catheter drainage within 24 hours after diagnosing INP with postponed drainage (>4 weeks) showed both strategies to be similar [221] in terms of the primary endpoint (comprehensive complication index), but significantly more procedures were required in the early drainage group. Necrosectomy was required in 51 % and 22 % of patients in the early and postponed drainage groups. More importantly, in the postponed drainage group, 39 % of patients were successfully treated with antibiotics alone, without the need for drainage or necrosectomy.

Q. 33 What is the role of antibiotic therapy in suspected infected necrotizing pancreatitis?

Good Practice Statement: Broad-spectrum antibiotic therapy should be administered initially in patients with suspected infected necrotizing pancreatitis.

Remarks: Antibiotic therapy should be initiated as soon as possible if INP is suspected based on clinical and/or radiological investigations. Although there is no published study that has looked at the timing of antibiotics in suspected/proven infected necrosis, infection is an ominous development during the course of AP. Therefore, as recommended in the Surviving Sepsis guidelines [222], it is prudent to start antibiotics as soon as possible. Antibiotics such as third- and fourth-generation cephalosporin, carbapenems, ureidopenicillins, and quinolones are effective against gut bacteria, the most likely culprit organisms, and are known to penetrate the pancreas. The choice of antibiotics should be based on local antibiotic sensitivity profiles in consultation with microbiologists [223—225]. If positive blood or other culture results are available, antibiotic (or antifungal) therapy should be selected/changed according to culture sensitivity reports. Whether one or two antibiotics should be given is not clear due to the lack of prospective studies in AP. As per the Surviving Sepsis guidelines, a single broad-spectrum antibiotic is generally preferred unless there is a reason to suspect pseudomonas infection, in which case another suitable antibiotic should be added. Recently, it has been suggested that procalcitonin, as an indicator of the presence or absence of bacterial infection, can reduce antibiotic use without increasing infection or harm in patients with AP [145]. However, before procalcitonin-guided antibiotic therapy can be implemented clinically, further research regarding its applicability is required, particularly in patients with moderate to severe AP.

Q 34 What is the role of antifungal therapy in infected necrotizing pancreatitis?

Recommendation: Prophylactic and empirical administration of antifungal agents for infected necrotizing pancreatitis is not recommended. (Conditional recommendation; low-quality evidence).

Remarks: Patients with acute necrotizing pancreatitis are susceptible to developing invasive fungal infection, which leads to poor outcomes [226]. A meta-analysis of 22 studies comprising 2151 subjects with acute necrotizing pancreatitis showed a mean incidence of fungal infection of 26.6 % with a high risk of in-hospital mortality (OR = 3.95, 95 % CI: 2.6—5.8) [227]. However, a distinction should be made between colonization and active invasive fungal infection. Fungal colonization may occur following prolonged percutaneous drains. A 'Candida Colonization' index has been shown to identify patients at greater risk of significant infection but has not been validated [228]. Thus, the decision to administer antifungal drugs should be taken after considering multiple factors. Antifungal therapy may be considered as an adjunct treatment for critically ill patients with INP in whom antibiotic therapy and interventional treatment, including drainage and necrosectomy, are ineffective, even when fungal cultures are negative. The preferred initial antifungal therapy for suspected candidiasis in patients with necrotizing pancreatitis is an echinocandin. Treatment for patients with proven fungal infection includes source control with drainage and/or necrosectomy. Antifungal therapy should be selected according to drug sensitivity if blood, drain fluid, or necrotic tissue culture results are obtained. The duration of antifungal treatment is not well defined. Anti-fungal agents can be discontinued after control of infection and negative fungal cultures [73,229]. Prophylactic antifungals are not indicated, considering the risk of the emergence of resistant fungal organisms that may increase mortality [230]. The issue of fungal infection in AP needs robust data from prospective studies.

Q 35 How should failure of medical conservative therapy for infected necrotizing pancreatitis be defined?

Good Practice Statement: Failure of medical conservative therapy should be defined if, despite the application of broad-spectrum or targeted antibiotic therapy and supportive therapy, the clinical condition of patients with suspected infected necrotizing pancreatitis does not improve (persistent fever and leukocytosis) or worsens with the development of sepsis.

Remarks: In stable patients with INP, antibiotics should be continued, and interventional therapy should be delayed for at least 4 weeks, if possible. Some patients, however, deteriorate fast and develop sepsis with progressive (multi) organ failure [65]. The mortality in such cases is high despite intervention. To date, there are no radiologic or serological markers to predict the failure of conservative medical treatment within a defined period. Close clinical monitoring of body temperature, leukocyte count, CRP or procalcitonin, and organ dysfunction should be done regularly to assess the failure of conservative therapy for INP. New-onset or persistent fever, tachycardia, rising leukocyte count, increased procalcitonin, and organ dysfunction are indicators of persistent infection [231]. In the event of clinical deterioration despite maximal conservative therapy, the decision for upscaling therapy to interventional treatment such as drainage and necrosectomy should be undertaken keeping in view the clinical status of the patient and radiological (CT scan) assessment for amenability of the infected collections for drainage.

Patients' viewpoints and suggestions: Patients laud the endeavor by which these guidelines have been made to ensure patients are managed as considerately and effectively as possible and appreciate all the work that has gone into their production, welcoming conservative management when this is appropriate.

XI. Interventions in acute pancreatitis: indications, timing, and intervention strategies

Q 36 What are the indications for intervention in acute necrotizing pancreatitis?

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

- Clinical suspicion of, or documented, infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled off.
- Prolonged symptomatic sterile walled-off necrosis e.g., abdominal pain, gastrointestinal luminal or biliary obstruction, or nutritional failure, even without signs of infection
- Less common indications for intervention are pancreatic hemorrhage, and bowel ischemia and fistula.

(Strong recommendation; low quality evidence).

Remarks: The best approach to managing acute necrotizing pancreatitis is multidisciplinary with different modalities, either conservative, endoscopic, percutaneous, or surgery required for an individual patient [73,204,232]. Infected necrotizing pancreatitis not responding to antibiotic treatment is a definite indication for intervention. Symptomatic sterile WON also requires intervention. Symptoms may include pain, abdominal fullness restricting nutrition, vomiting due to gastric outlet obstruction from a large fluid collection, obstructive jaundice due to an enlarged pancreatic head or fluid collection, weight loss, and/or persistent unwellness. Prospective cohort studies suggest that patients with 'persistent unwellness' and necrotizing pancreatitis should probably undergo intervention 6–8 weeks after the onset of the disease [204,208,232–238]. According to one observational study of 639 patients, approximately 1 % of patients with necrotizing pancreatitis had symptoms of obstruction during the initial hospital admission, necessitating intervention. Some uncommon complications may also require intervention, such as hemorrhage and bowel ischemia. Spontaneous fistula formation between the gastrointestinal tract and necrosis may occur without documented bowel ischemia. Finally, rare complications requiring (non-surgical) intervention include pancreato-pleural fistula and pancreatic ascites.

Q 37 What is the optimal timing of intervention for suspected or confirmed infected necrotizing pancreatitis?

Recommendation: Interventional treatment should be delayed in patients with suspected or confirmed infected necrotizing pancreatitis, if possible, to allow for the collection to become 'walled-off' with better demarcation and liquefaction of the necrosis, which generally takes around 4 weeks. (Strong recommendation; low-quality evidence).

Remarks: The current evidence suggests that interventions for necrotic collections should be delayed to allow for wall formation (encapsulation) and liquefaction, i.e., at the stage of walled-off Necrosis (WON) [141]. Walled-off necrosis usually takes 4 weeks to develop, although, in many patients, encapsulation of the necrotic collection might occur even earlier, allowing effective drainage [234]. This delay may not be feasible in some patients who may require earlier intervention (typically catheter drainage) due to worsening clinical conditions.

Q 38 Can subgroups of patients with necrotizing pancreatitis be defined that require early intervention?

Recommendation: Early (<4 weeks) intervention such as transluminal or percutaneous drainage may be appropriate for patients with suspected or confirmed infected necrotizing pancreatitis who have failed conservative medical management (including antibiotics), provided they have at least partial encapsulation of the necrotic collections. (Conditional recommendation; low-quality evidence).

Remarks: Intervention should ideally be delayed until necrotic collections have become walled-off; 43 % of patients may show encapsulation (wall-formation) in the first 3 weeks [237]. In a subset of patients, especially those with persistent or new organ dysfunction due to INP, it may not be feasible to delay intervention until 4 weeks. Infection of the necrotic collections may occur within 2 weeks of onset in a quater of patients [239]. In such cases, early intervention may be required to stabilize patients, and minimally invasive procedures have been shown to be beneficial [234,240]. In patients with an indication for early intervention (<4 weeks), either percutaneous drainage or endoscopic transmural drainage can be performed. But necrosectomy should ideally still be delayed until the patient stabilizes.

Regardless of the presence of necrosis or infection, patients with intra-abdominal catastrophes (hemorrhage, perforated hollow viscus, ischemic bowel) require immediate intervention.

Q 39 What is the role of abdominal paracentesis drainage (APD) in acute necrotizing pancreatitis?

Recommendation: Abdominal paracentesis drainage (APD) may be done in patients with severe AP with abdominal or pelvic fluid (ascites) in the acute stage.

(Conditional recommendation; moderate quality evidence).

Remarks: There is no indication for the routine use of peritoneal drainage, with or without lavage [241]. A relative indication of paracentesis in the acute stage could be in patients with marked pancreatic and peripancreatic inflammation, which leads to extravasations of amylase-rich and protein-rich intravascular fluid (likely inflammatory exudate) into the abdominal cavity, resulting in sterile collections or ascites in the first 2 weeks of illness [238]. Abdominal paracentesis or continuous catheter drainage may benefit such patients by removing toxic mediators and inflammatory substances from the sterile fluid collections and may ameliorate systemic inflammation. A few retrospective cohort studies and a meta-analysis, which included 3 RCTs, have shown beneficial effects of early abdominal paracentesis drainage in patients with moderate to severe AP (Suppl Table 13A and 13B), [242–245].

Q 40 What is the optimal interventional strategy (percutaneous, minimally invasive retroperitoneal, endoscopic, laparoscopic, or open surgery) for suspected or confirmed infected necrotizing pancreatitis?

Recommendation: The step-up approach consisting of initial antibiotics, then percutaneous drainage or endoscopic transluminal drainage followed, if necessary, by minimally invasive necrosectomy via the retroperitoneal route or per-oral endoscopic necrosectomy is recommended for suspected or confirmed infected necrotizing pancreatitis. (Strong recommendation; high quality evidence).

Remarks: The treatment of infected necrotizing pancreatitis has shifted from early surgical necrosectomy to a delayed minimally invasive step-up strategy (Suppl Table 14A and 14B), [233–236]. Initially, conservative treatment with supportive therapy, nutrition, and administration of proper antibiotics is recommended when INP is clinically suspected. The step-up approach (delay, drain, and debride) consists of drainage of the necrotic collection and

debridement (necrosectomy) later, if required. Either percutaneous or endoscopic drainage is sufficient in 40–60 % of patients with infected necrotic collections [204,233,234,239,246–250]. In a Dutch multicenter study that randomized 98 patients with suspected or confirmed infected necrotizing pancreatitis to endoscopic step-up (n = 51) or minimally invasive surgical step-up approach (n = 47), 43 % and 51 % of patients, respectively, in each arm resolved with transluminal endoscopic or percutaneous drainage alone [251]. However, the data are heterogeneous and less conclusive given the lack of standardized reporting on the extent of necrosis and imprecise quantification of solid necrotic debris [252].

Open surgery is reserved for those patients who do not respond to or are not eligible for the less invasive techniques and for other acute indications such as a perforated viscus and/or ischemic bowel [253].

Q 41 Which drainage modality (percutaneous or endoscopic transluminal) should be the first line for suspected or confirmed infected necrotizing pancreatitis?

Recommendation: Either percutaneous catheter or endoscopic transluminal drainage is recommended for treating patients with suspected or confirmed infected necrotizing pancreatitis, depending on the location of infected necrotic collections and available expertise.

(Strong recommendation; high quality evidence).

Remarks: Percutaneous catheter drainage (PCD) or transluminal endoscopic drainage are appropriate first-line, nonsurgical approaches to managing patients with walled-off necrosis. Either percutaneous drainage or endoscopic transluminal drainage may be done depending on the location, wall maturity, number of collections, and available expertise. Both methods have their advantages and disadvantages. The benefits of the endoscopic approach compared to PCD include internal drainage and avoidance of external fistulas. However, the advantages of PCD include widespread availability, access by retroperitoneal route to the left and right sides of the abdomen and pelvis, the ability to insert multiple catheters, and the ability to flush catheters [204]. Endoscopic transmural drainage is typically performed for collections in the lesser sac close to the stomach and duodenum, provided the expertise is available [249]. Percutaneous drainage is necessary for paracolic and pelvic (which are anatomically retrocolic) collections where endoscopic drainage is not possible. The classical step-up approach was based on a percutaneous intervention, but simultaneous development in EUS-guided transluminal drainage using wide diameter lumen apposing metal stents (LAMS) led to endoscopic drainage being an effective and minimally invasive approach to treat INP. Subsequently, two RCTs have shown that the endoscopic step-up approach and minimally invasive surgical step-up approach were similar with regard to success, but the endoscopic approach was better in terms of shorter hospital stay and a lower rate of pancreatic fistula [251,254]. A meta-analysis of three RCTs involving 184 patients confirmed the advantage of the endoscopic step-up approach in decreasing the incidence of new organ failure and pancreatic fistula formation [255]. Thus, the endoscopic approach is preferred for collections amenable to both approaches (Suppl Table 14A and 14B). However, approaches are often complementary in patients with multiple and extensive collections requiring multiple drainage procedures [256–258].

Complex pancreatic necrosis affecting one or both lateral quadrants as well as centrally placed collections require a combination of several drainage and necrosectomy procedures, including endoscopic transgastric drainage, retroperitoneal drainage, and large bore external drains to the left subdiaphragmatic space, right lateral quadrant, and left and right pelvic extensions, as required.

Q 42 What type of stent (multiple plastic or LAMS) should be used for endoscopic transluminal drainage of walled-off necrosis?

Recommendation: Multiple plastic stents or LAMS can be used for endoscopic transluminal drainage of walled-off necrosis. However, LAMS may be preferred in those with infected WON or if the extent of necrosis is >30 % of the WON. (Strong recommendation; high quality evidence).

Remarks: While endoscopic drainage of necrotic collections has typically been performed using multiple double pigtail plastic stents (DPPS) of size 7–10 F, lumen-apposing metal stents (LAMS) have become increasingly popular as they facilitate better drainage of solid necrosis and enable performance of through-the-LAMS direct endoscopic necrosectomy. While a meta-analysis of observational studies suggested that the number of necrosectomy sessions to achieve clinical and radiological resolution was lower when using large-caliber metal stents, such as LAMS, no difference was observed in two randomized trials [259,260]. A recent network meta-analysis of 28 studies with 2974 patients showed that LAMS were superior to multiple DPPS (Suppl. Table 15A and 15B), [261]. LAMS may be preferred in those with infected WON or if the amount of necrotic debris is >30 % of the WON [262].

LAMS may get occluded by necrotic debris, and a coaxial DPPS may be placed through the LAMS. A meta-analysis of 9 studies involving 709 patients showed that coaxial DPPS through the LAMS led to a reduced risk of stent occlusion and infection, but there was no difference in the overall adverse events [263]. Another issue about LAMS is whether or not to place a DPPS after removal of the LAMS. A meta-analysis of 3 RCTs showed that placing a DPPS after removal of the LAMS was associated with a lower recurrence rate compared with the no-DPPS group but without any difference in the need for reintervention [264].

Q 43 What are the indications for necrosectomy in patients who are managed with step-up approach for acute necrotizing pancreatitis?

Recommendations: During the step-up approach, necrosectomy is recommended in:

1. Patients who continue to have persistent fever or signs of sepsis despite optimal utilization of sensitive antibiotics and adequate drainage (either percutaneous or endoscopic).
2. Patients with infected necrotizing pancreatitis who fail to improve clinically despite adequate antibiotic treatment and cannot undergo drainage either percutaneously or endoscopically.

(Strong recommendation; high quality evidence).

Remarks: If a patient with infected necrosis does not improve with antibiotics and adequate drainage, the next step is necrosectomy. The success of catheter drainage is less likely in more extensive collections with greater than 50 % pancreatic parenchymal necrosis and containing relatively large amounts of necrotic debris [265–268]. Patients who fail to show control of the infection after adequate percutaneous catheter or endoscopic drainage and lavage require minimally invasive pancreatic necrosectomy [253]. Proactive drain management requires upsizing, additional catheters for undrained collections and instituting irrigation with strict measurement of input and output. Recent studies have shown that the success of PCD is significantly higher when managed proactively compared to simple drainage [269,270]. Criteria for infection control include resolution of fever, decrease of procalcitonin, C-reactive protein (CRP), and leukocyte count, and reversal of organ

failure in those with sepsis [265,266,271,272]. Worsening or new organ failure in patients on PCD has been used as a criterion to scale up intervention in various studies. Given that a significant proportion of patients can be managed with a proactive PCD strategy, it can become difficult at times to decide whether a given patient can be managed without necrosectomy. This scenario may be more relevant in patients who show an initial response in infection control with improvement in organ dysfunction after PCD insertion but then continue with persistent fever and are nutritionally compromised. Therefore, it is important to keep in mind patients' clinical and nutritional status and ability to tolerate the step-up intervention for successful outcomes.

Various studies, including a meta-analysis [273], have shown merit in postponing necrosectomy beyond 4 weeks of onset of AP as necrosis is walled off and more liquified with a clear demarcation between viable and non-viable pancreatic parenchyma, which makes debridement easy with fewer bleeding complications [221,265,273].

Q 44 What interventional necrosectomy strategy should be chosen for infected necrotizing pancreatitis?

Recommendations: The following interventional necrosectomy strategy should be chosen for infected necrotizing pancreatitis:

1. Minimally invasive approaches are preferred to open approaches and recommended for necrosectomy once the (peri) pancreatic necrotic collection is walled-off.
2. Minimally invasive retroperitoneal pancreatic necrosectomy is recommended through the PCD tract in patients who have undergone percutaneous drainage using a retroperitoneal route.
3. Per-oral endoscopic necrosectomy is recommended in patients who have undergone endoscopic transluminal drainage.
4. Trans-gastric surgical necrosectomy (laparoscopic or open) is also an effective single-stage procedure ensuring wide stoma with durable internal drainage in patients with WON mainly localized to the lesser sac.
5. Open debridement is rarely indicated and should be reserved for patients with predominantly solid collections and other intra-abdominal complications such as bowel fistula.

(Strong recommendations; high quality evidence).

Remarks: Open necrosectomy is associated with poor outcomes, particularly when performed early [214,274,275]. Minimally invasive necrosectomy reduces pro-inflammatory response and is associated with a lower rate of new-onset organ failure, lesser need for intensive care, and lower mortality compared to open necrosectomy in patients with infected walled-off necrosis who are managed with the step-up approach [265,269,272,276]. Minimally-invasive surgical techniques include retroperitoneal pancreatic necrosectomy, videoscope-assisted retroperitoneal debridement (VARD), laparoscopic or open transgastric debridement, percutaneous endoscopic necrosectomy (PEN) and minimal incision necrosectomy. The selection of approach is best determined by the type, number, and location of collection(s), the patient's general condition, the multidisciplinary team's experience and expertise, and available resources. In patients managed initially with a percutaneous catheter through the left anterior renal approach, the subsequent step-up should be retroperitoneal pancreatic necrosectomy or VARD if it is technically feasible and expertise and resources are available [253]. Both techniques are commonly employed using the previously placed percutaneous catheter. The goal of surgery is to remove as much loosely adherent necrosis as possible and not to remove adherent necrosis to reduce the risk of bleeding, while the residual necrosis is expected to be liquified and drained/resorbed [272]. Both techniques are usually a single-stage procedure. Postoperative continuous drainage is a part of these techniques. In patients with pancreatic necrosis involving the head of the pancreas or tracking to the right paracolic area or along mesenteric vessels, the initial step of intervention can still be a percutaneous catheter on the right side. Further, step-up by retroperitoneal pancreatic necrosectomy [277] can be conducted by dilating the tract using dilators to 30 Fr and then using an endoscope/nephroscope to undertake the necrosectomy under guidance [278]. Percutaneous endoscopic necrosectomy (PEN) using a flexible endoscope is another option for necrosectomy using the sinus tract created by the PCD catheter [279]. As with retroperitoneal pancreatic necrosectomy, PEN can be done under sedation and local anesthesia and has the advantage of being minimally invasive without the need for incision, which is required for VARD. Overall, VARD seems to have a higher mortality rate than other less invasive techniques [253].

In patients who have undergone per-oral EUS-guided endoscopic transmural internal drainage, direct endoscopic necrosectomy can be done. Necrosectomy is generally performed when the patient is stable. If required, minimally invasive pancreatic necrosectomy should be delayed where clinically possible until ideally 4–6 weeks after initial presentation. This is true for minimally invasive endoscopic and minimally invasive surgical necrosectomy.

Upfront necrosectomy may be considered in stable patients with well-encapsulated collections. In a recent randomized trial of 70 clinically stable patients with confirmed or suspected infected necrotizing pancreatitis who underwent either upfront endoscopic necrosectomy ($n = 37$) or step-up endoscopic treatment ($n = 33$), the median number of reinterventions to achieve treatment success was significantly lower for upfront necrosectomy than for the step-up approach [280]. Endoscopic necrosectomy should not be undertaken in clinically unstable patients or when the collections are poorly demarcated.

In general, the endoscopic approach seems to be the method of choice, followed by the retroperitoneal approach.

The decision and 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.

Transgastric surgical necrosectomy (open or laparoscopic) in WON localized to the retrogastric area with a bulge in the posterior gastric wall ensures durable internal drainage [281,282]. This procedure is typically successful in removing nearly all pancreatic necrosis, providing ongoing drainage from a disconnected left pancreatic remnant, and essentially converting a traditionally multi-procedure approach into a single operative intervention. In cases where necrosis within the lesser sac extends down either the paracolic area and/or the superior mesenteric artery or superior mesenteric vein leash and the connecting fistulous tract to the lesser sac remains patent, the vast majority of necrosis can still be removed through the cystogastrostomy [283–285]. At the same time, removal of the gallbladder is also possible, if considered safe, to prevent recurrence in patients with gallbladder stones. 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. In addition, 57 % of patients with biliary pancreatitis also underwent concurrent cholecystectomy [281]. In an RCT comparing laparoscopic with endoscopic cystogastrostomy in patients with pancreatic fluid collections (PFCs) with <30 % necrotic debris, both approaches had similar success, but the laparoscopic approach was associated with fewer incidences of secondary infection compared to the endoscopic approach [268]. Another recent RCT showed that

the outcomes in the laparoscopic and endoscopic drainage were similar if the type of stent (plastic or LAMS) in the endoscopic drainage group was chosen based on the amount of necrotic debris [262]. The laparoscopic approach is preferable in patients with WON containing significant necrotic collections and biliary etiology [282].

Open necrosectomy is also a viable choice in selected patients with complicated pancreatic necrosis, like bleeding and an external fistula from the small or large bowel. Patients with walled-off necrosis who are treated with open necrosectomy after 28 days from disease onset have around 10 % mortality. Mortality could be more than 50 % when multiple risk factors for open necrosectomy are present. Without these multiple risk factors, an open necrosectomy can be done with much lower mortality [275]. Open necrosectomy is also required when an acute emergency like massive bleeding or intestinal perforation with peritonitis develops.

Patients' viewpoints and suggestions: Patients state that it is vital to explain to them, their family and friends, why they are being left with no treatment for pancreatic necrosis for 4 weeks. Their experience is that this causes a huge amount of anxiety when someone is so ill and is left without treatment, with no explanation as to why this is happening. With no explanation, family and friends may think the patient is not being properly cared for.

XII. Acute non-infectious complications of acute pancreatitis

(Intra-abdominal hypertension/Hemorrhagic complications/ Venous thrombosis/Bowel fistula)

Intra-abdominal hypertension: Diagnosis and treatment.

Q 45 **How to define intra-abdominal hypertension and abdominal compartment syndrome?**

Good Practice Statement: Intra-abdominal hypertension (IAH) is defined by sustained or repeated elevation in Intra-abdominal pressure (IAP) of ≥12 mmHg. Abdominal compartment syndrome (ACS) is defined as a sustained IAP of >20 mmHg (with or without abdominal arterial perfusion pressure <60 mmHg) that is associated with new onset or progressive organ dysfunction.

Remarks: High intra-abdominal pressure decreases perfusion of organs in the abdominal compartment, which may contribute to intestinal ischemia and increased bacterial translocation [286,287]. Sustained high IAP increases lung injury and decreases renal and cardiovascular functions in experimental severe AP [288].

Q 46 **Should IAP be measured routinely in AP?**

Good Practice Statement: It is recommended to measure IAP in patients with severe AP. If IAP is >12 mmHg, the IAP should be monitored periodically in patients with severe AP.

Remarks: IAH develops in 17 % of patients with AP but even higher in patients with severe disease [289,290]. IAH develops early in the disease and correlates with the development of organ dysfunction and death. Diagnosing IAH and ACS requires objective measurement of IAP via the urinary bladder with a maximal instillation volume of 25 ml of sterile saline, as described in the World Society of Abdominal Compartment Syndrome (WSACS) guidelines [291]. However, there is no definite evidence to show that measuring intra-abdominal pressure affects mortality outcomes.

Q 47 **How should patients with AP and IAH be treated?**

Recommendation: Patients with IAH should be treated with percutaneous catheter drainage of ascites and fluid collections, adequate pain relief, enteral decompression with nasogastric or rectal tubes, and avoidance of a positive cumulative fluid balance. (Conditional recommendation; low-quality evidence).

Remarks: These measures have been suggested by WSACS in consensus management guidelines [291]. Percutaneous catheter drainage of ascites can result in a modest (2 mmHg) decrease of IAP in the early stage of AP [292], but the effect of drainage may be more profound in patients with ACS and a significant amount of ascites [293]. However, a substantial amount of ascites for drainage is present in less than half of patients with AP and IAH [294]. After initial fluid resuscitation, a positive cumulative fluid balance should be avoided. Early continuous veno-venous hemofiltration may be effective in decreasing IAP in severe AP with ACS [295]. Evidence from randomized trials to show a clinical benefit is lacking.

Q 48 **Should surgical decompression be used for the treatment of ACS?**

Recommendation: Surgical decompression may be considered to treat ACS if a patient has worsening organ dysfunctions and non-operative modalities have failed. (Conditional recommendation; very low-quality evidence).

Remarks: According to clinical and experimental studies [286–288], prompt treatment of ACS is necessary to avoid ischemic complications and death. Although initial therapy of IAH should be non-operative, surgical decompression may be considered in ACS if non-operative management is ineffective in decreasing IAP and organ dysfunction progresses. According to retrospective studies, AP with ACS was associated with a high mortality of 49 % [296], but in patients who had early surgical decompression for ACS, the mortality was 18 % [297]. Laparotomy is the only definite way to rule out intestinal ischemia in a deteriorating patient with ACS. An open abdomen is associated with a risk of entero-atmospheric fistula, and the inability to close the abdomen results in a giant hernia. An open abdomen should be managed with temporary abdominal closure. For the treatment of an open abdomen, the highest rate of delayed fascial closure can be achieved by using negative pressure wound therapy with continuous fascial traction, which also has the lowest fistula rate [298]. However, laparostomy in patients with ACS and no other specific pancreatic or peripancreatic complication may be detrimental.

Hemorrhagic complications

Q 49 **What is the best way to treat bleeding complications associated with AP?**

Recommendations: Angioembolization is recommended to treat arterial pseudoaneurysms and other arterial bleeding complications in patients with AP.

(Strong recommendation; low-quality evidence).

Percutaneous embolization with thrombin or gelfoam and glue under ultrasound guidance or surgical management can be used when angioembolization is not possible or unsuccessful.

(Conditional recommendation; low-quality evidence).

Remarks: The incidence of bleeding complications associated with AP is about 0.5–1.2 % [299–302]. In a prospective study of 363 patients with AP, 9 % developed pancreatic hemorrhage after a median of 59 [45–68] days from onset of AP. Persistent organ failure [HR 2.3 (1.1–5.1), p = 0.03], use of large bore (>20 Fr) catheter for initial drainage [HR 3.9 (1.7–9.1), p = 0.001], and extensive (>50 %) necrosis [HR 3.1(1.4–6.9), p = 0.005] were significant risk factors for hemorrhage [303]. The incidence of hemorrhage in patients with PCD has been reported to be between 4 and 16 % [246,304]. Overall, about 60 % of arterial hemorrhagic

complications associated with pancreatitis are caused by pseudoaneurysms, 20 % by hemorrhage into pseudocysts without pseudoaneurysms, and 20 % due to small vessel bleeding [305].

The most common site for a pseudoaneurysm associated with pancreatitis is the splenic artery (35–50 %), followed by gastroduodenal and pancreaticoduodenal vessels accounting for 20–25 % each [305]. Contrast-enhanced triple-phase CT is the imaging method of choice to diagnose arterial bleeding complications in AP, but digital subtraction angiography can also be used [299,300,302,305].

Angioembolization is the method of choice to treat arterial pseudoaneurysms and other arterial bleeding complications in AP. Angioembolization using microcoils is successful in 88–100 % of cases, and the need for re-embolization is rare [299,302,305,306]. Direct percutaneous embolization with thrombin or gelfoam and glue under ultrasound guidance is an option especially for non-catheterizable pseudoaneurysms [307,308]. EUS-guided embolization using thrombin or gelfoam and glue has also been reported to be successful [309]. If non-surgical methods to stop the bleeding fail, early surgery is recommended, especially in patients with bleeding associated with acute necrotizing pancreatitis [299,305,310,311]. However, no pseudoaneurysm is found in many patients, and the hemorrhage is suspected to be due to erosion of a vessel in the wall of the necrotic collection.

Direct ligation, proximal or distal resection with splenectomy, and necrosectomy with or without packing are the most commonly used procedures depending on the location of the pseudoaneurysm, extent of necrosis, and the condition of the patient [299,310,311]. Around 1/3rd of patients require open necrosectomy with ligation of bleeding vessel and gauze packing for diffuse venous ooze in hemodynamically unstable patients [312–314]. Venous hemorrhage is best managed by compression, which can be achieved in some patients by clamping the external percutaneous drains. If indicated, endoscopic transmural drainage of associated fluid collections can be undertaken after angioembolization of the bleeding pseudoaneurysms [315–317].

The mortality rate associated with acute arterial bleeding complications in AP is 11–38 %. Shock as a primary indicator of hemorrhage, need for operative intervention, and the presence of necrotizing pancreatitis are risk factors for mortality [299,310,311]. Rebleeding, and end-organ infarction, e.g., splenic infarction and abscess are common complications after embolization [302].

Splanchnic venous thrombosis

Q 50 **How can splanchnic venous (SVT) thrombosis in AP be diagnosed?**

Good Practice Statement: Contrast-enhanced computed tomography (CECT) is the most appropriate test to diagnose splanchnic venous thrombosis in AP.

Remarks: The diagnosis and extent of SVT mainly rely on a CECT scan [318]. There is no prospective study comparing the accuracy of various imaging modalities (Doppler USG, CT, and MRI) in diagnosing SVT in patients with AP.

The reported incidence of pancreatitis-induced splanchnic venous thrombosis (SVT) varies from 1 % to 24 % [319–322]. In a recent post-hoc analysis of a prospective cohort, 97 (22 %) of 432 patients with AP developed SVT [323].

Risk factors for SVT include extensive necrosis, infected necrotizing pancreatitis, recurrent acute pancreatitis, smoking, and hypertriglyceridemia [324–326].

SVT is often an incidental finding on radiological imaging. In some patients, SVT may have severe clinical consequences such as hepatic failure due to portal vein occlusion, small bowel ischemia due to superior mesenteric vein occlusion, hypersplenism, and formation of gastric varices which may lead to upper gastrointestinal variceal bleeding [323,326]. There are no prospective trials on prophylactic anticoagulation to prevent the occurrence of SVT.

Q 51 **What is the best way to treat splanchnic venous thrombosis associated with AP?**

Recommendation: Anticoagulation is not recommended in patients with isolated splenic vein thrombosis. Anticoagulation may be used in more extensive venous thrombosis involving portal or mesenteric vein. (Conditional recommendation; low-quality evidence).

Remarks: There is no definitive evidence to support prophylactic or therapeutic anticoagulation use in patients with SVT associated with AP [327]. One study proposed that anticoagulation would be appropriate for all patients with SVT if detected early and there is no evidence of collaterals [326]. However, anticoagulation is not required, especially in cases of isolated splenic vein thrombosis, as they show higher recanalization rates even without anticoagulation following the resolution of AP and/or the drainage of adjacent collections [322]. A recent systemic review and meta-analysis of 16 studies, including 698 patients with acute pancreatitis-associated SVT, showed that the recanalization rate of SVT with anticoagulation was 44.3 % but marginally increased the risk of bleeding. There was no difference in survival or other outcomes [328].

Bowel fistula

Q 52 **What are the incidence and most common sites of bowel fistulas in AP?**

Good Practice Statement: Bowel fistula may occur in 10–15 % of patients with acute necrotizing pancreatitis. The most common sites of bowel fistula are the colon and duodenum, followed by the stomach and small intestine.

Remarks: The incidence and forms of bowel fistulas in AP vary among studies. One retrospective study of 344 patients found bowel fistula in 52 (15.1 %) patients [329]. Another cohort of 928 patients found bowel fistula in 119 (12.8 %) patients, with colonic fistula being the most common in 60.5 % of all bowel fistulas [330].

In a prospective cohort of 896 patients, perforation or fistula of the GI tract developed in 16 % of patients, with the location being stomach in 14 %, duodenum in 35 %, small intestine in 11 %, and colon in 40 % [331]. The risk factors for gastrointestinal fistula include extensive necrosis, infected necrotizing pancreatitis, vascular thrombosis, and percutaneous catheter-related iatrogenic injury [329].

Q 53 **When should bowel fistulas be suspected in AP?**

Good Practice Statement: Bowel fistulas should be suspected if there is worsening infection, gastrointestinal bleeding, or percutaneous drain showing intestinal/feculent material. Gas in or around the pancreas may also be due to a bowel perforation or fistula.

Remarks: Bowel fistula may be asymptomatic and detected incidentally. In symptomatic patients, diagnosis and symptoms of bowel fistulas commonly occur late. In a pooled analysis of 97 patients, the median interval between the onset of symptoms and detection of the colonic fistula was 25 days (1–55 days), [332]. Patients with large WON may be more susceptible to develop bowel fistula. Bowel fistulas may lead to worsening infection,

gastrointestinal bleeding, and new onset organ failure. Colonic fistula, in particular, leads to infection of the PFCs and may present with features of new onset or worsening sepsis [331].

The diagnosis of gastrointestinal fistula can be suspected by the presence of gas bubbles in the fluid collections on a CT scan or feculent discharge through a percutaneous drain. Upper GI fistula can be diagnosed on endoscopy. Lower GI fistula can be diagnosed on a CT scan or a contrast study through the percutaneous catheter.

Q 54 What is the optimal strategy for treating bowel fistulas associated with AP?

Recommendations: Upper gastrointestinal fistula do not require treatment and may be beneficial by providing internal drainage of PFCs; they usually close spontaneously over time.

(Conditional recommendation; low-quality evidence).

For colonic fistula, conservative management with control of infection may suffice, but surgical treatment is required if there are signs of persistent or worsening infection or peritonitis or fecal discharge from a peripancreatic collection.

(Conditional recommendation; low-quality evidence).

Remarks: Most upper gastrointestinal fistulas, like gastric and duodenal fistula, usually resolve spontaneously during the disease course. In a cohort of 121 patients with infected pancreatic necrosis, 10 developed duodenal fistula, of whom 9 resolved spontaneously with infection control [333].

For the management of colonic fistula, conservative treatment with adequate drainage and nutritional support [334] should be the primary choice, and surgery could serve as a backup. In a pooled analysis of 97 patients, 36 developed colonic fistula, of whom only 9 patients underwent surgery due to colonic fistula [332]. In another study of 72 patients with colonic fistula and infected pancreatic necrosis, 47 (65 %) were managed with ileostomy or colostomy, and the other 25 (35 %) were treated conservatively [330]. Another study showed that 59 % of patients with colonic fistula required surgery [331].

Patients' viewpoints and suggestions: Patients emphasize the requirement for them, their families and friends to be properly informed about their complications and management, as rarer complications may prompt clinicians to focus on arranging and/or undertaking what is considered necessary and/or lifesaving, whilst forgetting to explain fully what is proposed to be done.

XIII. Management of special types of acute pancreatitis

Acute pancreatitis in the pediatric population

Q 55 Do the criteria for the diagnosis of AP in children differ from those for adults?

Good Practice Statement: The criteria for diagnosing AP in children are the same as in adults, but these criteria may be less accurate in children.

Remarks: The diagnosis of AP in children requires two out of the same three criteria as in adults. However, there are several caveats [335]. In many children, abdominal pain may be less common as a predominant symptom ranging from 29 % to 100 % [336]. Some of the variations likely reflect the pediatric age span. In a study of children under 3 years of age, only 29 % presented with abdominal pain [337]. Even if irritability was included as a surrogate for pain, the percentage of patients with abdominal pain was just 46 %. Another study in this age group found that 43 % presented with abdominal pain [338]. Fever was the presenting complaint in 40 % of young children. Additionally, both lipase and amylase have a developmental pattern of expression, leading to low levels of both in infancy [339]. The implications of this pattern on the diagnosis of AP in infants are unclear. Taken together, these studies suggest that diagnosing AP in children may be less accurate when utilizing standard diagnostic criteria.

Q 56 Does the etiology of AP differ between children and adults?

Good Practice Statement: Etiologies of AP are diverse and differ substantially between children and adults. Most cases are idiopathic. Gallstone disease, multi-system illnesses, medications, viral infection, developmental abnormalities, trauma and genetic causes are common etiologies in children.

Remarks: A significant difference in the etiology of AP between children and adults is that alcohol-associated pancreatitis is rare in children [336,340]. Gallstone disease, however, is found more commonly than previously thought and may account for 30 % of pediatric cases [341]. Systemic or multi-system illness may account for up to 40 % of cases in children with AP, and almost 20 % have genetic risk factors for AP [340]. Structural anomalies that can cause recurrent acute pancreatitis or chronic pancreatitis are first identified during childhood, including pancreas divisum, anomalous pancreaticobiliary junction, annular pancreas, choledochal cysts, and intestinal duplication. However, direct causality due to congenital structural abnormalities is not certain. Trauma once thought to be the most common reason for pancreatitis in children, accounts for 10 % or less of cases in recent series [339]. Drug-induced pancreatitis is another significant contributor, frequently involving medications such as L-asparaginase, which are less commonly used in adults [342]. Genetic evaluation is usually reserved for patients with more than one episode of pancreatitis or signs of chronic pancreatitis before the age of 18 years.

Q 57 How should severity be assessed in children with AP?

Good Practice Statement: Severe AP in children is defined if there is a presence of persistent organ failure similar to adults but utilizing the International Pediatric Sepsis Consensus definitions of organ failure.

Remarks: The Pancreas Committee of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) [343] defined pediatric AP severity using the revised Atlanta Classification of mild, moderately severe, and severe AP [7]. The notable difference was that organ failure was graded according to the International Pediatric Sepsis Consensus rather than the modified Marshal scoring system. SIRS increases the risk of organ failure and should be assessed in pediatric patients with AP. The NASPGHAN clinical report recommends using pediatric SIRS criteria, which incorporate age-based cut-offs for the leukocyte count, heart rate, and respiratory rate [343]. Overall, severe AP is less common in children than in adults. Similar to adults, however, overall mortality in AP in children is less than 5 % [336]. The exceptions include special cases of pancreatitis, such as drug-induced pancreatitis due to L-asparaginase, which is used for treating acute lymphoblastic leukemia (ALL). In most series [344], including a recent pooled analysis of raw data from 26 ALL trials [345], one-quarter to two-thirds of patients, mostly children, with asparaginase-associated pancreatitis had at least moderately severe AP.

Q 58 **What is the optimal imaging modality to diagnose AP in children?**

Good Practice Statement: Trans-abdominal ultrasonography (USG) is the preferred first-line imaging modality in children, while CT and MRI/MRCP should be reserved for patients in whom USG is not diagnostic and ideally delayed at least 96 hours after the onset of symptoms.

Remarks: The indications for imaging in children are to diagnose pancreatitis and exclude other causes of abdominal pain, to identify risk factors for pancreatitis, or to assess for complications of pancreatitis [346]. Transabdominal USG avoids cumulative exposure to ionizing radiation and is more feasible in children because most children have a thinner abdominal wall than adults. A CT or MRI scan should be done if the diagnosis of AP is not sure and when an intervention is planned.

In patients with unexplained AP, evaluation for structural anomalies, including pancreas divisum, anomalous pancreaticobiliary junction, annular pancreas, or choledochal cyst, is not indicated after a single episode of AP. However, MRCP may be advised if there is a recurrence of AP [347].

Q 59 **Does the optimal therapy for AP in children differ from that in adults?**

Recommendation: Therapies for AP, including fluid resuscitation, nutrition support, analgesics, and the use of antibiotics, are similar in children as those for adults (Strong recommendation; low-quality evidence).

Remarks: Overall, there is a paucity of therapeutic trials in pediatric pancreatitis. Fluid resuscitation (1.5–2 times the maintenance intravenous fluid requirements) may reduce ICU admission and shorten hospital stay [348]. Dextrose-containing crystalloid has been recommended as the initial choice for fluid replacement [349]. Most trials of fluid therapy in AP have not included the pediatric population; therefore, there is a need for such trials to provide robust evidence in the pediatric population. A recent multicenter randomized trial has shown that Lactated Ringer's solution given within 48 hours after diagnosis was associated with a shorter hospital stay in pediatric patients with AP [350]. Early enteral feeding should be initiated as soon as it can be tolerated. Children fed enterally within 24–48 hours are more likely to have a milder disease course [351]. If unable to eat within 72 hours, enteral tube feeding (nasogastric or nasojejunal) is recommended [352]. Pain should be managed adequately, starting with non-narcotic analgesia and utilizing opioids as necessary. Antibiotics are not indicated unless systemic infection, cholangitis, or infected pancreatic necrosis are suspected [349].

Q 60 **What are the complications of AP that occur in children?**

Good Practice Statement: The complications of AP in children are similar to those in adults, with similar interventional management approaches.

Remarks: As per the NASPGHAN classification, complications may be associated with moderately severe or severe forms of AP [343]. Early ERCP is indicated for children with biliary pancreatitis if they develop cholangitis or if choledocholithiasis is present with ongoing jaundice when they are stable [349]. Cholecystectomy is recommended for uncomplicated gallstone pancreatitis during the index admission [353–355] and after complications have been addressed in severe cases. Many cases of PFCs will resolve spontaneously without intervention [356]. If a PFC is symptomatic or fails to resolve, it is preferable to drain it internally under endoscopic ultrasound (EUS)-guidance [357].

Acute pancreatitis related to hyperparathyroidism

Q 61 **When should AP due to hyperparathyroidism be suspected?**

Good Practice Statement: Acute pancreatitis due to hyperparathyroidism should be suspected in patients with elevated calcium levels and those with other clinical features suggestive of hyperparathyroidism.

Remarks: A high index of clinical suspicion is needed to diagnose primary hyperparathyroidism (PHPT) as an etiology of AP. Although uncommon, a history of renal stones, renal dysfunction, and bone diseases, including osteoporosis or pathological fractures, may provide a clinical clue to PHPT as the cause of AP. However, a careful interpretation of biochemical laboratory results is required for the diagnosis. Elevated serum calcium levels in AP should raise the suspicion of PHPT. Hypercalcemia from any cause can trigger AP by multiple proposed mechanisms [358,359]. During AP, calcium levels may be normal, especially in patients with severe pancreatitis, and repeat evaluation is indicated after resolution in patients where a high index of suspicion persists [360,361]. It is important to consider albumin-adjusted total calcium or ionized calcium to confirm hypercalcemia.

Although PHPT is the most common cause of hypercalcemia, it is a rare cause of AP, with <1 % of patients having underlying PHPT [358,359]. A population-based study reported that the incidence of AP was not increased in community patients with PHPT. Therefore, there may not be a causal relationship between PHPT and AP [362].

Q 62 **What is the optimal testing approach to document AP due to hyperparathyroidism?**

Good Practice Statement: Patients with AP and elevated serum calcium levels should be further evaluated by measuring serum parathyroid hormone (PTH). An inappropriately elevated serum PTH confirms the diagnosis of PHPT.

Remarks: Classic PHPT is diagnosed in the presence of hypercalcemia with inappropriately elevated serum PTH [363,364]. Serum PTH levels can be measured using a second-generation PTH assay (also known as the intact PTH assay that recognizes intact PTH (amino acids 1–84) or a third-generation ("whole" PTH) assay that prevents cross-reactivity [363]. The second- and third-generation PTH assays perform similarly in the diagnostic evaluation of PHPT. Serum PTH levels are elevated in Vitamin D deficiency, and therefore, it is recommended that 25(OH)D be measured in all subjects with suspected PHPT [364]. Normal PTH levels when serum calcium is elevated are considered "inappropriately" high and warrant further evaluation by an appropriate specialist [365].

Q 63 **What is the optimal strategy for treating patients with PHPT-related AP?**

Good Practice Statement: Standard treatment is recommended for PHPT-related AP. In addition, patients with serum calcium levels >14 mg/dL or hypercalcemia accompanied by altered sensorium require emergent measures to reduce serum calcium levels, including volume expansion with isotonic saline (and not lactated Ringer's solution), and avoidance of calcium supplements and Vitamin D.

Remarks: The standard treatment of AP is applicable in the setting of PHPT. Medical management of life-threatening hypercalcemia in PHPT pancreatitis requires close coordination between

gastroenterologists, critical care specialists, and endocrinologists. It includes volume expansion with isotonic saline (and not lactated Ringer's solution), and avoidance of calcium supplements and Vitamin D. Most patients with AP due to PHPT do not have acute symptoms attributable to elevated serum calcium levels and thus do not require immediate treatment to lower serum calcium levels [359,360]. After the resolution of pancreatitis, these patients typically need definitive therapy for PHPT to prevent further attacks, as well as to prevent the long-term adverse consequences of prolonged hypercalcemia. Parathyroidectomy leads to the normalization of serum calcium and PTH levels and prevents further attacks of AP ([361,363]).

Hypertriglyceridemia associated acute pancreatitis

Q 64 What is the optimal medical therapy to reduce triglyceride levels in hypertriglyceridemia-associated AP?

Recommendation: Besides the standard care for AP, Insulin is recommended in diabetics and may be considered in non-diabetic patients as the first-line therapy to reduce serum triglyceride (TG) levels for hypertriglyceridemia-associated acute pancreatitis (HTGP). (Strong recommendation; moderate quality evidence).

Short-term (<3 days) use of low molecular weight heparin (LMWH) may also be considered.

(Conditional recommendation; moderate quality evidence).

Remarks: HTGP is a well-established etiological factor for AP, accounting for up to 10 % of cases with AP [366]. It is the second leading cause of AP in China [367,368]. HTGP may be more severe with an increased incidence of SIRS, persistent organ failure, local complications, and mortality compared to other etiologies [51,369,370].

The pathogenesis of HTGP is incompletely understood, and the proposed mechanisms could be: (i) Elevated levels of chylomicrons in pancreatic capillary circulation lead to ischemia and acidosis [371], and (ii) Excessive free fatty acids released by lipolysis cause acinar cell injury [372–375].

The initial management of HTGP is similar to that of other causes of AP. Fasting and intravenous fluids may be effective in lowering TG concentrations [376]. In terms of specific therapy for HTGP, few large RCTs are available. Systematic review and meta-analysis have suggested that insulin and/or heparin are the most effective and specific therapy for HTGP [366,377]. Insulin can stimulate lipoprotein lipase (LPL) activity, accelerate the degradation of TG into free fatty acids (FFAs) and glycerol, and promote tissue uptake and metabolism [378,379]. Insulin treatment may be safe even in the absence of diabetes, as shown in case reports [380,381]. One comparative study, however, reported similar reductions in triglyceride levels with insulin and conservative treatment [376]. The synergistic effect of a combination of insulin with heparin has been reported from case series and can be used as first-line therapy for severe HTGP [366]. Long-term use of heparin alone can lead to LPL depletion and rebound increase in triglycerides [382]. One RCT demonstrated a lower incidence of organ failure in those treated with insulin/LMWH compared with plasmapheresis, and no significant TG rebound was observed [383]. Heparin or LMWH is not recommended when contraindications are present, such as bleeding disorders and renal failure.

Q 65 Should plasmapheresis be used for HTGP?

Recommendation: In patients with HTGP, plasmapheresis may be considered in case of persistent organ failure with high TG levels, particularly in patients with acute renal failure.

(Conditional recommendation; low-quality evidence).

Remarks: Patients with severe HTGP who develop renal failure most likely benefit from plasmapheresis, and plasmapheresis and hemofiltration can be combined. Sodium citrate should be used instead of heparin or LMWH for anticoagulation to reduce the risk of bleeding during plasmapheresis. A case-control study found that double filtration plasmapheresis (DFPP) shortened hospitalization duration in patients with serum triglyceride >5000 mg/dL [384].

Although case series have shown that plasmapheresis can effectively reduce serum TG concentrations [385], a systematic review [386] found no clear evidence that plasmapheresis leads to more favorable clinical outcomes. A multicenter, prospective cohort study found that plasmapheresis did not reduce the incidence and duration of organ failure but increased ICU stay [387]. A prospective trial suggested that short-term high-volume hemofiltration (HVHF) might reduce local and systemic complications and mortality in patients with severe HTGP [388]. Due to its high cost, invasive approach, unclear benefits, and risk of adverse events, plasmapheresis should be used selectively in HTGP patients.

Q 66 What is the optimal nutritional approach for patients with hypertriglyceridemia-associated AP?

Recommendation: Patients with HTGP should fast for the first 48 hours, followed by an oral low-fat soft diet. If oral intake is not tolerated, enteral nutrition (EN) via nasogastric or nasojejunal tube should be initiated. (Strong recommendation; low-quality evidence).

If parenteral nutrition is required, intravenous fat emulsion should not be given in patients with TG $\geq$ 400 mg/dL (Strong recommendation; low-quality evidence).

Remarks: Patients with HTGP should fast for 48 hours because this reduces serum TG levels rapidly in most patients. A retrospective study of patients with severe HTG showed that intravenous insulin plus fasting for 24 hours reduced TG concentrations by 87 %, whereas insulin alone reduced levels by 40 % [389]. During fasting, chylomicrons rich in TG are metabolized rapidly after entering the blood circulation. Intravenous low-calorie infusion will also reduce the output of very low-density lipoprotein (VLDL) from the liver, further reducing serum TG levels. Thereafter, a low-fat oral diet or enteral tube-based nutrition should be initiated depending on the severity of AP. If parenteral nutrition is required, short-term withdrawal of the lipid fraction in the PN mixture is associated with a significant reduction of plasma triglyceride concentration [390]. The acceptable serum triglyceride concentration for those receiving PN is < 400 mg/dL [391]. In patients with TG $\geqq$ 400 mg/dL, intravenous fat emulsion should be discontinued [392].

Q 67 What level of TGs should be maintained after discharge to prevent relapse of hypertriglyceridemic associated AP?

Recommendation: The levels of serum TG should be maintained below 500 mg/dL after discharge to prevent relapse of HTGP. (Conditional recommendation; low-quality evidence).

Remarks: Serum TG should be kept consistently below 500 mg/dL to reduce the risk of recurrence of HTGP. A cohort study including 41,210 patients with severe HTG found that patients whose TG remained $\geq$500 mg/dL had a higher risk of pancreatitis episodes compared to those with TG levels <500 mg/dL [393]. A recent study of 3091 individuals with severe HTG found that 171 (6 %) developed AP, and TG levels of >500 mg/dL were independently associated with recurrent pancreatitis [394]. In a prospective cohort study of 317 HTGP patients, the 12-month and 18-month

cumulative recurrence rates were 8 % and 22 %, respectively [395].

Fenofibrate is the most commonly used medication to lower triglyceride levels, although no published clinical trial has shown its efficacy in preventing the recurrence of AP. In patients with familial hypertriglyceridemia and very high levels of triglycerides, newer therapies with an antisense oligonucleotide targeting messenger RNA for apolipoprotein C-III (APOC3), such as volanesorsen and olezarsen have been shown to reduce the recurrence of pancreatitis [396,397].

Prevention of post ERCP-pancreatitis

Q 68 **What is the recommendation for peri-procedure intravenous fluids to prevent post- ERCP-pancreatitis (PEP)?**

Recommendation: Moderate intravenous fluids with Lactated Ringer's solution should be given to patients undergoing ERCP during the periprocedural period in addition to rectal NSAIDs to prevent PEP. (Strong recommendation; moderate quality evidence).

Remarks: Periprocedural intravenous fluid hydration may help prevent PEP or help decrease its severity [87,398]. The ideal amount of LR that should be administered is unknown, but many centers administer at least 1L of fluid during an ERCP. Two retrospective studies found that peri-procedural administration of intravenous fluids was a protective factor against the development of moderate to severe PEP and was associated with a reduction in hospital stay [399,400]. Recent RCTs [401,402] and meta-analyses [403,404] have confirmed this benefit. Another RCT showed that the combination of LR and rectal indomethacin reduced the risk of PEP and hospital readmission rates compared to placebo and normal saline [405]. Most recently, a secondary analysis of a multicenter study on preventing PEP showed that periprocedural fluid use was associated with a significantly decreased risk of PEP and reduced hospital stay [406]. A recent multicenter study, the 'FLUYT' trial, showed no benefit of aggressive fluid administration over standard fluids when given in addition to rectal NSAIDs in decreasing the incidence of PEP [407].

Q 69 **What are the indications for rectal NSAIDs to prevent post-ERCP pancreatitis?**

Recommendation: Prophylactic rectal indomethacin or diclofenac is recommended for patients undergoing ERCP who are at high risk of post-ERCP pancreatitis. (Strong recommendation; high quality evidence).

Prophylactic rectal indomethacin or diclofenac is recommended for average-risk patients undergoing ERCP. (Strong recommendation; moderate quality evidence).

Remarks: Multiple RCTs and meta-analyses have confirmed the benefit of rectal NSAIDs (diclofenac or indomethacin) for preventing PEP in high-risk patients [408—410]. Host factors for high-risk include young age, a history of PEP, or suspected sphincter of Oddi dysfunction. A high-risk procedure includes difficult cannulation, repeated pancreatic duct cannulation, pancreatic duct injection, and pre-cut or needle knife sphincterotomy. The data in average-risk populations is also convincing, with multiple studies showing a decrease in PEP with rectal indomethacin [411—413]. It should preferably be given within 30 min before the procedure [411]. The mechanism of action of rectal NSAIDs is not well understood but may be related to the inhibition of Phospholipase A2 by NSAIDs.

Q 70 **What are the indications for Pancreatic Duct stent placement to prevent PEP?**

Recommendation: A prophylactic pancreatic duct stent should be placed in patients with inadvertent multiple pancreatic duct cannulation or injection of contrast into the pancreatic duct during ERCP. (Conditional recommendation; moderate quality evidence).

Remarks: The purpose of pancreatic duct placement is to reduce the pressure within the pancreatic duct and facilitate ductal drainage [414]. Prophylactic PD stent placement has been shown to significantly reduce the risk of PEP in RCTs and meta-analyses [413]. The common indications for prophylactic pancreatic stenting include pancreatic duct opacification or repeated pancreatic duct cannulation in patients with difficult bile duct access. Routine pancreatic duct stenting may be indicated in high-risk cases, e.g., suspected sphincter of Oddi dysfunction, but the benefit must be weighed against the potential for harm. A failed attempt at PD stent placement can increase the risk of PEP, an attempt to place a stent can cause injury to the pancreatic duct that may lead to stenosis or even disruption, and prolonged stenting can lead to chronic injury to the duct and pancreas [415,416]. A recent RCT showed prophylactic PD stent placement without rectal NSAID significantly reduced the incidence of PEP in unselected patients with inadvertent PD cannulation [417]. A 5-Fr diameter, 3—5 cm long stent, preferably a single pigtail without internal flanges, is recommended. The stent should be removed if it has not migrated out spontaneously within 2—3 weeks of ERCP.

Q 71 **What are the indications for combined rectal indomethacin and pancreatic duct stent placement to prevent PEP?**

Recommendation: A prophylactic pancreatic duct stent should be considered in addition to rectal NSAID in high-risk patients for PEP prophylaxis.

(Conditional recommendation; moderate quality evidence).

Remarks: A post hoc analysis of an earlier RCT showed no difference in PEP rates between patients with rectal indomethacin alone or rectal indomethacin with additional PD stenting [418]. However, in a recent randomized trial of 1950 high-risk patients undergoing ERCP, PEP occurred in 145 (14·9 %) of 975 patients in the indomethacin alone group and 110 (11·3 %) of 975 patients in the indomethacin plus stent group (risk difference 3·6 %; 95 % CI 0·6-6·6; $p = 0·18$ for non-inferiority). The authors concluded that in high-risk patients, a strategy of indomethacin alone was not as effective as indomethacin plus prophylactic PD stenting [419]. If rectal NSAID has been given as prophylaxis and there is inadvertent multiple PD cannulation or contrast injection, prophylactic PD stenting should be considered.

Traumatic pancreatitis

Q 72 **What is the optimal imaging approach to diagnose traumatic pancreatitis? Is MRCP required to diagnose pancreatic ductal disruption?**

Good Practice Statement: A contrast-enhanced CT (CECT) is recommended for stable patients with suspected pancreatic trauma. MRI/MRCP should be reserved for situations when there is a persistent clinical suspicion of pancreatic ductal injury and equivocal findings on a CT scan.

Remarks: Pancreatic injury may occur in 2—6 % of patients with abdominal trauma [420]. The mainstay of diagnosis of pancreatic injury is abdominal imaging. Associated solid organs, hollow viscus, and vascular injuries may lead to hemodynamic instability. The hemodynamic stability of the trauma patient determines the optimal imaging protocol to diagnose pancreatic injuries. Focused Assessment with Sonography for Trauma (FAST) is a standard

investigation in trauma patients. Hemodynamically unstable patients with a positive FAST should undergo urgent surgery. Stable patients should undergo a CECT, which also rules out other abdominal injuries. Pancreatic injury is graded from grade 1 to grade 5 (Suppl. Table 16). The reported sensitivity of CECT in detecting pancreatic injuries ranges from 43 to 95 % due to variations in 'injury to CT' time and type of CT scanner [421,422]. An initial normal CT scan does not exclude pancreatic injury, and a repeat CT should be done after 24–48 hours if symptoms persist and the suspicion of pancreatic injury is high, especially if the initial scan was obtained within 12 hours of injury [423–425]. In a multicenter study involving 20 centers, the sensitivity of CT for pancreatic injury varied between 47 % and 60 % (depending on the type of scanner used), with a sensitivity of 52 %–54 % and specificity of 90 %–95 % to detect integrity of the main pancreatic duct (MPD) [426]. Recent techniques of CECT with multiplanar reconstruction (MPR) and minimum intensity projections (MinIPs) have higher diagnostic accuracy in detecting pancreatic ductal injury with a sensitivity and specificity of >90 % [425,427].

MRI with MRCP is also very useful to evaluate the extent of pancreatic injury. A recent single-center study found that the sensitivity, specificity, and diagnostic accuracy of CECT and MRCP were comparable in detecting pancreatic duct injury [427]. MRCP should be performed when CT findings regarding the pancreatic ductal integrity (PDI) are equivocal [428]. MRCP might be more useful in identifying the duct in the pediatric population, but it has no definite advantage over CT in determining PDI [429].

Q 73 When is ERCP indicated in patients with pancreatic trauma?

Recommendation: ERCP is not recommended for diagnostic purposes in patients with AP due to trauma. ERCP should be reserved only for therapeutic purposes to place a stent in the MPD, if indicated.

(Conditional recommendation; low-quality evidence).

Remarks: ERCP has been previously used to diagnose pancreatic ductal injury as it defines the location and extent of the injury and provides a route for therapy [430–434]. However, ERCP is an invasive procedure and is associated with complications. MDCT and MRCP have replaced ERCP as the diagnostic modality for assessing PDI [428]. The accuracy of MRCP for pancreatic ductal injury is comparable to ERCP [428,435]. ERCP should be performed with a therapeutic intent only [436–438] (Refer to question 75).

Q 74 How should pancreatic trauma be treated?

Recommendation: A hemodynamically unstable patient with pancreatic trauma should be treated with an exploratory laparotomy with a "damage control" approach. Grade 1 and 2 pancreatic injuries should be managed conservatively. For hemodynamically stable patients, early surgical resection is advised for grade 3 injuries. (Conditional recommendation; low-quality evidence).

Remarks: The management of pancreatic trauma depends on the overall status of the patients, the timing of presentation, the grade of pancreatic injury, and associated injury to abdominal viscera and vessels. Hemodynamically unstable patients require immediate exploratory laparotomy. The pancreatic duct status is critical to plan management and predict the outcome [439]. Grade 1 and 2 injuries should be managed conservatively. The Eastern Association for the Surgery of Trauma (EAST) analyzed 14 articles involving 299 patients and found that for low-grade pancreatic injuries detected on exploratory laparotomy, patients undergoing resection had a higher incidence of intra-abdominal abscess formation than those managed only with drains [440]. For grade 3 injury, distal pancreatectomy (DP) is recommended as the treatment of choice [436]. A review of 314 patients from 19 studies showed that the mortality (27.2 % vs. 8.6 %, $p = 0.005$) and fistula formation rate (88.0 % vs. 17.7 %, $p < 0.0001$) were significantly greater in patients who underwent no resection procedure than in those who underwent resection [440]. If grade 3 injury is diagnosed late and the patient has no other indication for laparotomy, patients can be managed with non-operative management (NOM). In a systematic review of 365 pediatric pancreatic trauma patients with high-grade pancreatic injury, 167 patients underwent NOM initially with a success rate of 89 % [441].

For grade 4 and 5 injuries, scant literature is available. Distal pancreatic (body and tail) resection is not preferred for Grade 4 injuries because the remaining pancreatic stump (head region) would be small, with a high risk of postoperative endocrine and exocrine insufficiency. Thus, various approaches have been advocated, including non-operative management, drainage alone, pancreatico-gastrostomy, pancreatico-duodenectomy, and mid-segment pancreatectomy [420]. For grade 5 injuries (massive disruption of the pancreatic head), external drainage may be a safe option when the pancreatoduodenal complex is not devitalized with an intact ampulla of Vater, but a devitalized pancreatic head, combined pancreatoduodenal injury and destructive ampullary injury may require pancreatoduodenectomy [442–444].

Timing of surgical intervention: The complications and length of hospital stay are higher in patients whose diagnosis or management is delayed by more than 24 hours [445,446]. Thus, surgical intervention, if required, should be performed as soon as the diagnosis is made. There is no consensus regarding the ideal cut-off time, after which a non-operative approach should be considered in a high-grade pancreatic injury.

Q 75 What is the role of endoscopic therapy in pancreatic trauma?

Recommendation: ERCP with pancreatic stenting is recommended in stable patients with symptomatic main pancreatic duct disruption following trauma who do not have an indication for surgical treatment. Endoscopic transmural internal drainage is recommended for patients with symptomatic pseudocyst or walled-off necrosis after recovery from the initial injury.

(Conditional recommendation; low-quality evidence).

Remarks: Stable patients who are managed with non-operative treatment or have presented late with MPD injury and ductal leak may be managed with ERCP and pancreatic duct stenting in cases of partial MPD injury. A transpapillary 5 Fr stent should be placed to bridge the site of ductal injury. If it is not possible to bridge the site of injury, the stent should be left as far as possible to help drain the distal pancreas. During follow-up, the site of injury heals and may lead to a ductal stricture, which, if symptomatic, should be managed accordingly.

After the patients with pancreatic trauma recover from the initial illness, they might develop a pseudocyst or walled-off necrosis. Endoscopic transmural internal drainage is recommended for such patients, similar to patients with AP due to any other etiology.

Acute pancreatitis and pregnancy

Q 76 What is the impact of AP during pregnancy on fetal outcomes?

Good Practice Statement: Acute pancreatitis during pregnancy

results in higher rates of preterm delivery and perinatal mortality, including intra-uterine death. Fetal loss rates are higher in patients with severe pancreatitis as compared to those with mild pancreatitis.

Remarks: AP is rare during pregnancy, with an incidence of 1 in 10,000 pregnancies [447]. The most common etiology is gallstones [447—454]. There are 8 retrospective studies concerning maternal and fetal outcomes in patients with AP during pregnancy. The incidence of preterm delivery varied from 12.1 to 30.1 % and fetal loss from 0 to 33 % [447—454]. All maternal and fetal deaths occurred among patients with severe AP(454). Those with pancreatitis during the first trimester had more frequent adverse fetal outcomes.

In a retrospective analysis of hospital discharge records from the NIS database from 2009 to 2019, there were 40,887,659 eligible pregnancies beyond 20 weeks of gestation from 2009 to 2019, including 5439 pregnancies with AP and 40,882,220 pregnancies without AP. This study found an increased risk for women with AP for maternal mortality but no reported maternal deaths from 2012 to 2019. Preterm labor was present in 17.9 % of AP cases, compared to 5.8 % in the no AP group.

Q 77 What is the optimal imaging approach to identify AP in pregnancy?

Recommendation: Transabdominal USG is recommended as the initial imaging modality of choice to confirm the diagnosis of AP during pregnancy. MRI may be considered for patients with indeterminate sonographic findings. (Strong recommendation; low-quality evidence).

Remarks: Transabdominal USG should be used for suspected AP in pregnancy due to no risk of radiation and a high sensitivity for diagnosing gallstones. MRI is considered safe in all trimesters of pregnancy when performed without gadolinium contrast and may be considered when there are inconclusive findings on ultrasound [455—457]. A study comparing the diagnostic performance of CT and MRI in 94 pregnant patients with non-traumatic abdominal pain showed no difference between these two modalities [458]. The fetal risk from radiation is most significant between 2 and 20 weeks when the dose exceeds 0.05—0.15 Gy [459]. The radiation dose associated with an abdominal CT scan is 0.01 Gy (10 mSv). Iodinated contrast media should be avoided whenever feasible due to the risk of fetal hypothyroidism [456,458—461].

Q 78 Is there a difference in managing AP during pregnancy?

Good Practice Statement: Generally, pregnant patients with AP should be managed similarly to non-pregnant patients.

Remarks: The management of AP in pregnant patients should be similar to that in non-pregnant patients. Pregnant patients with AP should be managed in consultation with an obstetrician. Any medication that may have maternal or fetal adverse effects should be avoided. For stable patients with pseudocyst or walled-off necrosis, there is no specific guidance in the literature on the timing of intervention during pregnancy, but they should be managed as per clinical indication and local expertise.

Q 79 What is the optimal timing for cholecystectomy for gallstones in pregnant patients with acute biliary pancreatitis?

Recommendation: Early cholecystectomy is recommended for pregnant patients with mild acute biliary pancreatitis, preferably in the second and early third trimester. (Strong recommendation; moderate quality evidence).

Remarks: Acute biliary pancreatitis is more common among patients with advanced gestational age. The management of gallbladder stones should be similar to that in non-pregnant patients with pancreatitis [448,449,453,462]. The recurrence rate of acute biliary pancreatitis during pregnancy is as high as 70 % as compared to 20—30 % in the general population [463,464]. In a review of 113 patients from 12 studies, which compared conservative management versus cholecystectomy in pregnant patients with acute biliary pancreatitis, there was a higher fetal mortality seen in the conservative group (8.0 % vs 2.6 %, $p = 0.28$), [465]. Another retrospective series, which included 112 pregnant patients with acute biliary pancreatitis, showed that the number of emergency visits, hospitalizations, and recurrent biliary events were higher in the conservatively treated group as compared to those who underwent intervention (cholecystectomy and/or ERCP), [466]. Hence, early cholecystectomy is recommended for patients with mild acute biliary pancreatitis. Laparoscopic cholecystectomy is safe in all trimesters of pregnancy. However, it should be done preferably in the second or early third trimester as organogenesis is completed by that time, and the gravid uterus is not large [465,467—469]. The timing of cholecystectomy in patients with severe acute biliary pancreatitis remains unclear, similar to non-pregnant patients [470]. The decision of cholecystectomy should be taken based on the overall risk profile, trimester, and local complications. In patients suspected to have bile duct stones, an abdominal ultrasound should be done to assess choledocholithiasis before performing a therapeutic intervention such as ERCP. In doubtful cases, an MRI or EUS should be used to confirm the presence of choledocholithiasis before ERCP. If ERCP is indicated in the second and third trimester of pregnancy, the patient should be placed in the left pelvic tilt and left lateral position to avoid aortic or vena cava compression during the procedure. Fetal monitoring should be considered. Radiation exposure should be minimized by limiting exposure, using a lead cover over the abdomen to protect the fetus, and avoiding hard-copy X-ray films [471—473].

Patients' viewpoints and suggestions: Patients include trauma as a common etiology in children. Patients think that in children the same tests as in adults could be used to assess severity, including SIRS, CRP and IL-6. Patients recommend that treatment for children with specific differences from treatment for adults be identified, e.g., analgesia, and fluid requirements.

XIV. Targeted therapy for acute pancreatitis

Q 80 Is any targeted therapy indicated for patients with AP?

Good Practice Statement: At present, no effective targeted therapy is available, and thus, no targeted therapy is recommended for patients with AP.

Remarks: The treatment for AP during the first week is limited to general supportive measures. The need for a development pipeline testing specific therapeutic agents targeting local and systemic inflammation to reduce the morbidity and mortality of AP is compelling. New agents should be evaluated in well-designed randomized clinical trials [474,475]. The setup of a master protocol allowing for a trial platform that includes adaptive designs, as in cancer precision medicine, could speed up development and be desirable [476—478].

Q 81 Are there some promising therapeutic options to target inflammation in AP?

Good Practice Statement: A few therapeutic agents to mitigate inflammation are currently undergoing trials, which could effectively reduce the severity of AP.

Remarks: Many previous attempts to reduce morbidity and mortality have been unsuccessful. These include PAF antagonist lexipafant [479], pentoxifylline [480], protease inhibitors (ulinastatin and mesilates of gabexate, camostat and nafomastat), somatostatin receptor ligands (somatostatin, octreotide), and continuous regional artery infusion (CRAI of protease inhibitors ± antibiotics) [481]. Low molecular weight heparin and Cox-2 inhibitors have shown promise in reducing the severity of AP and need further confirmation [128,482,483]. Some other therapeutic agents undergoing randomized trials include ORAI1 channel inhibitor, omega-3 fatty acids, anti-IL-6 receptor antibody tocilizumab, steroids, and anti-TNF-α infliximab [484].

Patients' viewpoints and suggestions: Patients attest that they are extremely keen and supportive for effective, targeted drugs to be developed and authorized for worldwide use in AP, to reduce the huge burdens of AP, currently without any internationally agreed disease modifying therapy.

XV. Discharge criteria for patients with acute pancreatitis

Q 82 What clinical features and laboratory markers indicate that it is safe to discharge a patient with AP?

Recommendation: Stable patients who tolerate an oral diet, demonstrate improvement of inflammatory markers (C-reactive protein) and/or total leukocyte count, absence of persistent fever, and require no or minimal non-opioid analgesia are suitable candidates for discharge following AP.

(Conditional recommendation; low quality evidence).

Remarks: Large population studies suggest that readmission for pancreatitis occurs in more than 20 % of patients following an initial episode [485]. This is similar to other high-burden conditions, such as congestive heart failure [486]. Readmission following AP correlates with increased mortality [487]. The median cost of an AP readmission may exceed the cost of the index hospitalization [485]. Therefore, it is vital to identify predictors for readmission and standards for discharge after AP.

Risk factors for readmission include the presence of GI symptoms (nausea, vomiting, diarrhea) at the time of discharge, tolerating less than a solid diet at discharge, moderate to heavy alcohol use, and pancreatic necrosis [488]. Tolerance of oral intake, good pain control with first-step analgesia according to the WHO (World Health Organization) scale, C-reactive protein <150 mg/dL, and blood urea nitrogen increasing no more than 5 mg/dL in two consecutive samples separated by an interval of 24 hours, were associated with safe early discharge (first 24–48 hours) of patients with mild AP [489]. Another multicenter study from the Hungarian study group showed that a protocol based on tolerance to oral diet and decrease in CRP levels resulted in the shortest length of hospital stay of 6 (5-9) days and low rate of readmittance (5 %) [490].

Q 83 Should any specific scoring system or algorithm be used to determine whether a patient with AP is eligible for discharge?

Recommendation: No validated specific scoring system is recommended to determine safe discharge, although PASS and SNAPP scores may be used as guidance. (Conditional recommendation; low-quality evidence).

Remarks: According to an international survey, 87.5 % (49/56) of the centers had no discharge protocol [490]. Approximately half of readmissions are early (≤30 days) and half late (>30 days) after discharge [491]. The former likely reflects smoldering pancreatitis, while the latter signifies complications or new discrete attacks. Several models to predict early readmission have been proposed. In a study, 21 % of patients had early readmission, which correlated with ongoing symptoms of nausea, vomiting, and intolerance of solid diet [486]. The authors designated these factors along with three other predictors, such as the SNAPP (Symptoms, nutrition on less than solid diet, antibiotic use, pancreatic necrosis, pain at discharge) model, to predict readmission [486,488].

Readmission occurred in 68 % of those with high SNAPP scores and 4 % with a low score in a testing cohort. This score has been validated [491]. The Pancreatitis Activity Scoring System (PASS) was developed to quantitatively gauge disease activity during the clinical course [492]. A validation study demonstrated that a PASS score correlated with 30-day readmission; a score of >60 had a modest sensitivity of 68 % and specificity of 71 % for readmission [493]. The Hungarian study group's score may also be useful but needs to be externally validated. [490]. These scoring symptoms aim to identify patients whose discharge should be delayed or who may benefit from additional outpatient support such as home nursing care. Implementation studies to gauge the impact of SNAPP, PASS, and other scoring systems on early readmission rates and other outcomes, including cost and mortality, are needed.

Scoring systems to predict late readmission are lacking. It is known that late readmission is strongly correlated with alcohol use, which is a potential target for intervention [485]. Same admission cholecystectomy and induction of aggressive lipid control may prevent readmission in those with biliary and hypertriglyceridemia-associated pancreatitis [494,495].

Patients' viewpoints and suggestions: Patients value clear descriptions of when they can be discharged and what criteria will be used to determine this, including those listed. Patients are concerned about the development of complications and if there are recommended time slots for follow-up. Patients highlight the importance of support for both mental health and physical health whilst still in hospital and after discharge. They describe how acute pancreatitis brings with it life changes that have significant impacts on mental health, including being in hospital, unable to undertake normal activities, coping with recovery, and a continuing risk of recurrent attacks. They also state this is compounded by the impact of a prolonged hospital stay with e.g. muscle wastage. They recommend that support for both mental and physical health should be addressed both before and after a patient is discharged.

XVI. Prevention of recurrent acute pancreatitis

Q 84 What is the optimal timing of cholecystectomy after mild acute biliary pancreatitis?

Recommendation: Early cholecystectomy during index admission for mild biliary pancreatitis is safe and is recommended to prevent recurrence of AP. (Strong recommendation; moderate quality evidence).

Remarks: The timing of cholecystectomy after an attack of mild acute biliary pancreatitis is critical to minimize the risk of recurrence of AP and biliary complications. In a multicenter RCT evaluating the timing of cholecystectomy at the time of index episode of AP versus interval cholecystectomy, 9 % of those in the interval group developed recurrent pancreatitis as opposed to 2 % in the same admission group [495]. Significant improvements in patient-reported outcomes, cost savings, and a reduced incidence of post-pancreatitis diabetes mellitus have also been reported [496–498]. Systematic reviews and meta-analyses have also shown that early cholecystectomy reduces biliary complications and recurrent pancreatitis [499,500].

Endoscopic sphincterotomy (ES) might prevent recurrent pancreatitis in patients with severe biliary pancreatitis who cannot undergo early cholecystectomy, but it needs further confirmatory

studies [501]. ES alone may be a reasonable option in patients with high surgical risk, especially elderly patients with co-morbidities who are at high risk for cholecystectomy, although a subset of such patients might develop recurrent biliary colic [502].

Q 85 **What is the optimal timing of cholecystectomy after severe acute biliary pancreatitis?**

Recommendation: Cholecystectomy should be delayed in patients with moderate and severe AP, in particular, those with necrotizing pancreatitis and peripancreatic fluid collections, until the collections nearly resolve. (Conditional recommendation; low-quality evidence).

Remarks: In patients with severe acute biliary pancreatitis with necrosis and fluid collections, surgery should be delayed till the PFCs have resolved or drained. If the PFCs persist beyond 6 weeks, the timing of cholecystectomy should depend on the resolution of pancreatic inflammation and may be combined with other surgical drainage procedures as appropriate. Even with current advances in endoscopic drainage of collections, it is recommended that cholecystectomy be delayed till the complications resolve, though robust data are lacking [469]. In a retrospective study of 108 patients with moderately severe and severe ABP, early cholecystectomy was associated with an increased risk of mortality, morbidity, and infections compared with delayed cholecystectomy [503].

Another study with post-hoc analysis of acute necrotizing pancreatitis suggested that the mean time to cholecystectomy should be within 8 weeks after discharge to reduce recurrent pancreatitis and biliary complications [504]. Adequately powered randomized trials are required to define the optimal timing of cholecystectomy in patients with moderate-severe ABP.

Q 86 **What is the role of cholecystectomy in patients with acute biliary pancreatitis who have undergone ERCP and endoscopic sphincterotomy?**

Recommendation: Cholecystectomy is recommended in patients with acute biliary pancreatitis who have undergone ERCP and endoscopic sphincterotomy and are fit for surgery. (Conditional recommendation; moderate quality evidence).

Remarks: Biliary complications, including biliary colic, cholecystitis, and recurrent pancreatitis, are seen in up to 10 % of those patients awaiting interval cholecystectomy post-endoscopic sphincterotomy (ES) [499]. Data on the role of ES in severe acute biliary pancreatitis are lacking. There is limited data regarding the role of ES in reducing the recurrence of acute biliary pancreatitis in patients in whom cholecystectomy cannot be performed. In a study, subgroup analysis showed that ERCP with ES before cholecystectomy decreased the rate of recurrent pancreatitis but not of biliary events [505].

Patients' viewpoints and suggestions: Patients state lifestyle management, including abstinence from alcohol and cessation of smoking, should be included in prevention. Patients identify dietary recommendations as particularly important for those who have had triglyceride-associated acute pancreatitis. Patients question a lack of consideration of underlying chronic pancreatitis and think follow-up for patients identified to have chronic pancreatitis would be different. Patients note a few differences in discharge strategies between individual countries, e.g., earlier or later, with differing medications, whilst recognizing that these guidelines address the major and important areas of common ground.

XVII. Long-term complications and long-term care after AP

Q 87 **Is there a need for periodic follow-up of patients with AP after discharge to assess short- and long-term complications?**

Recommendation: Patients who recover from an attack of AP should be followed up periodically after discharge to assess short- and long-term complications. (Strong recommendation; moderate quality evidence).

Remarks: Patients recovering from AP might develop short- and long-term complications. These complications include recurrent acute and chronic pancreatitis (CP), recurrence of PFCs, pancreatico-cutaneous fistula, and biliary and gastric outlet obstructions and functional consequences [4]. Up to one-third of patients might develop recurrent acute pancreatitis, and 10 % of patients develop CP. The risk of progression to CP is four times greater in men, in those with alcohol etiology and in those with recurrent AP. Other important risk factors for progression include smoking [506], genetic mutations [507–509], and hypertriglyceridemia [494,510].

AP can be an initial manifestation of pancreatic cancer in a small subset of patients. A recent large cohort study noted that pancreatic cancer might be a late complication in patients with AP [511]. In 41,669 patients with first-time AP, the authors noted that the long-term (>5 years) risk of pancreatic cancer was more than 2-fold greater (HR 2.02, 95 % CI 1.57–2.61). However, the association of AP with an increased long-term risk of pancreatic cancer is debatable [512].

Recent studies have shown that there is a risk of premature mortality after discharge. One study from the Dutch group showed that 26 % of patients died during long-term follow-up of 13 years [513]. Another population-based cohort study from Hungary showed a threefold higher mortality among 2613 patients with AP than in the general population up to 8 years after hospital discharge [514]. Older age, comorbid conditions, frailty due to the adverse effects of the index AP, and pancreatic cancer are the likely causes of mortality. These observations suggest a need for regular follow-up of patients with AP after discharge.

Q 88 **Should patients with AP be screened for diabetes mellitus (DM) during follow-up?**

Recommendation: Screening for pre-diabetes and DM after AP is recommended in all patients. Blood glucose and hemoglobin A1c levels should be tested every 12 months, starting 3–6 months after recovery from AP. (Strong recommendation; moderate quality evidence).

Remarks: Many studies have shown that AP, irrespective of severity, increases the risk of DM [515,516]. A systematic review of 24 prospective clinical studies consisting of 1102 patients estimated the pooled prevalence of newly diagnosed DM after the first episode of AP to be 23 % (95 % CI 16–31 %) and the need for insulin to be 15 % (9–21 %), [517]. An updated systematic review of 31 studies found similar estimates for DM [518] but noted the risk of DM to be significantly greater in patients with severe AP vs. mild AP (39 % vs. 14 %), necrotizing pancreatitis vs. non-necrotizing AP (37 % vs. 11 %) and in those with alcohol vs. biliary etiology (28 % vs. 12 %). The mechanisms leading to post-pancreatitis DM include loss of islets due to necrotizing AP, inflammation, insulin resistance, the unmasking of autoimmunity, and genetic predisposition [519]. These data support routine screening for DM after AP with yearly testing of blood sugar and hemoglobin A1c levels starting 3–6 months after an episode of AP [520].

Q 89 How should pancreatic exocrine insufficiency (PEI) be evaluated and managed following recovery from AP?

Recommendation: PEI may occur due to extensive pancreatic necrosis in patients with acute pancreatitis. Patients with clinical symptoms of steatorrhea or severe undernutrition with low fecal elastase (<100 μg/g) may be treated with Pancreatic Enzyme Replacement Therapy (PERT). (Conditional recommendation; moderate quality evidence).

Remarks: Patients with necrotizing AP are at an increased risk of PEI. PEI may develop in the setting of AP as the result of parenchymal necrosis as well as secondary phenomena such as impaired regulation of enzyme secretion [521]. Two systematic reviews and meta-analyses have evaluated the prevalence of PEI among patients with AP [522,523]. In the first analysis of 32 studies of 1495 patients, the pooled prevalence of PEI at 36 months post-discharge from index episodes of AP was 27.1 % (95 % CI 20.3—35.1 %). PEI prevalence in a more recent meta-analysis of 39 studies and 1795 patients was 35 % (95 % CL 27—43 %). In this meta-analysis, the pooled prevalence of PEI during hospitalization was also determined in 10 studies and was much greater at 62 % (95 % CI 39—82 %). In both meta-analyses, the risk of PEI increased with disease severity, necrosis, and alcohol etiology [7]. Two RCTs tested the role of pancreatic enzyme replacement therapy (PERT) during the convalescent phase of AP. The first enrolled a small number of subjects (n = 23) and failed to show any benefit [524], while the other was prematurely stopped due to insufficient recruitment [525]. Based on available evidence, patients with necrotizing AP may be considered for evaluation of PEI using an indirect test after the resolution of the disease. Patients with clinical symptoms of steatorrhea should be treated with PERT. Those with low fecal elastase (<100 mcg/gm of stool) may also be treated with PERT if they are undernourished.

Q 90 Is the quality of life worse in patients with AP after discharge?

Good Practice Statement: Patients who recover from an attack of AP may have a poor quality of life, especially in those with acute necrotizing pancreatitis.

Remarks: A systematic review of 16 studies showed that the general health and vitality domains were significantly worse in patients with AP [526]. One study noted considerable improvement at the follow-up time point [527]. Factors associated with impaired QOL included the presence of abdominal pain, analgesic use, current smoking, and disability [528]. Patients require continued care and psychological support during follow-up.

Q 91 How to prevent complications of AP after discharge?

Good Practice Statement: Elimination of treatable causes of AP, including behavioral therapy for de-addiction, is recommended for preventing recurrent AP and progression to CP.

Remarks: The risk of progression to CP increases with alcohol, smoking [506], genetic factors [507—509], and hypertriglyceridemia [494,510]. The primary strategies to prevent recurrence and disease progression are behavior modification [529] and addressing treatable causes [494,495]. Alcohol and tobacco cessation are important therapeutic goals.

Patients' viewpoints and suggestions: Patients are concerned about abdominal pain that may relapse and that the causes of continuing problems are identified and addressed. While some patients may recover their quality of life readily, others report their quality of life to have been markedly, or even profoundly, reduced by having had acute pancreatitis. They emphasize the need for effective communication, nutrition, physical and mental therapies, and follow-up alongside the recommendations of these guidelines to reduce the impacts of this disease. If the etiology is identified to be hereditary pancreatitis, patients recommend that cancer screening should be advised according to internationally agreed guidelines.

XVIII. Disconnected pancreatic duct syndrome

Q. 92 What are the clinical presentations of the disconnected pancreatic duct?

Good Practice Statement: Patients with acute necrotizing pancreatitis may develop disconnected pancreatic duct syndrome (DPDS). Most patients with DPDS remain asymptomatic. DPDS may present with persistent external pancreatic fistula (EPF), recurrent pseudocyst, and/or recurrent acute or chronic pancreatitis involving the upstream pancreatic parenchyma.

Remarks: Disconnected pancreatic duct syndrome (DPDS) is characterized by complete disruption of the main pancreatic duct by central pancreatic necrosis, leading to discontinuity between viable secreting pancreatic tissue upstream and the gastrointestinal tract [141]. DPDS is seen in 10—75 % of necrotizing pancreatitis, and these patients may need therapeutic interventions, reintervention, rescue surgery, and/or longer hospital stays [530]. The diagnosis of DPDS is usually made months to years after resolution of acute necrotic fluid collections [531].

EPF is defined as persistent exocrine output [increased fluid amylase concentration (≥3 times the serum value)] and could be low output (<200 ml/day) or high output (>200 ml/day). EPF may develop in patients who have undergone external drainage and may cause substantial morbidity [532,533]. Residual or recurrent PFC is a more common clinical presentation. Recurrent acute or chronic pancreatitis may be a consequence of DPDS(141,531), but pancreatitis confined to the upstream pancreatic gland is uncommon and difficult to diagnose. Recurrence of pancreatitis is more likely to be due to the same etiology as the index episode of AP. However, most patients with a disconnected duct are asymptomatic [534].

Q 93 How is disconnected pancreatic duct/syndrome diagnosed?

Good Practice Statement: A contrast-enhanced CT scan showing central pancreatic necrosis during the acute phase of AP may suggest the development of DPDS. Later in the disease course, MRCP should be used to diagnose DPDS**.**

Remarks: It is important that DPDS be considered in a patient with necrotizing pancreatitis [530,535]. Central necrosis of the pancreas, persistent fluid collections, fistula formation, and/or recurrent bouts of pancreatitis in the residual upstream gland are suggestive features of DPDS. A contrast-enhanced CT scan is important to diagnose central pancreatic necrosis and can suggest disconnected pancreatic duct [536]. A significant amount of upstream pancreatic tissue (i.e., the tail) is often present in patients with central pancreatic necrosis and DPDS. A MRCP should be performed to diagnose DPDS during the later course of illness [537,538]. Secretin can also be used as an adjunctive measure to highlight the pancreatic duct [538]. ERCP can be used for the diagnosis but fails to show the upstream pancreatic duct and cannot differentiate between a high-grade stenosis and a disconnected pancreatic duct. EUS may also be a valuable tool for evaluating the presence of disconnected viable pancreatic tissue [539].

Q 94 **What is the natural history of disconnected pancreatic duct syndrome?**

Good Practice Statement: There is limited data on the natural history of disconnected pancreatic duct syndrome, but it remains asymptomatic in most patients.

Remarks: The natural history of DPDS is poorly understood [540]. The incidence of DPD has been reported in 10 %—75 % [540]. The recurrence of PFC was reported in 13 %—50 % of patients with DPDS [534]. In a study of 256 patients with walled-off necrosis, 189 (73.8 %) developed DPDS, but only 13 % of patients had recurrent events, either AP or fluid collections requiring intervention. Most patients with DPD are, therefore, asymptomatic and do not require reintervention. In the long-term follow-up, the tail of the pancreas may undergo changes suggestive of "chronic pancreatitis" with dilatation of the upstream pancreatic duct and loss of pancreatic parenchyma.

Q 95 **What are the indications for intervention in a Disconnected Pancreatic Duct Syndrome?**

Recommendation: Indications for interventions for DPDS include persistent high-output external pancreatic fistula and symptomatic recurrent fluid collections and/or recurrent acute pancreatitis confined to the upstream pancreas. (Conditional recommendation; low-quality evidence).

Remarks: Spontaneous closure of low-output EPF in the setting of DPDS is known to occur in most patients because of cessation of pancreatic juice secretion due to glandular atrophy of the upstream pancreas [541,542]. Conservative management with naso-jejunal feeding, high-dose pancreatic enzymes, downsizing the percutaneous catheter, and converting the gravity-assisted drainage to a colostomy bag should be pursued for 2—3 months. Interventions are indicated if the EPF continues with a poor quality of life. Indications for intervention in recurrent PFCs are the same as in necrotizing pancreatitis and include pain, infection, gastric outlet obstruction, and persistent unwellness due to the PFCs.

Q 96 **What are the treatment options for the management of Disconnected Pancreatic Duct Syndrome?**

Recommendation: Endoscopic management is the preferred option for symptomatic DPDS in the post-acute setting if conservative treatment is unsuccessful. (Conditional recommendation; low-quality evidence).

Remarks: Endoscopic transluminal interventions for necrotizing pancreatitis result in significantly fewer external or internal pancreatic fistulae due to DPDS than percutaneous step-up or surgical approaches [141,250,251]. Following endoscopic internal drainage of WON using plastic stents, a small RCT showed higher recurrence after removal of the plastic stent [543]. If a LAMS has been placed for internal drainage of WON, it may be replaced by a plastic stent to prevent the recurrence of PFC if there is a presence of DPD at the time of removal of LAMS. However, an RCT showed no difference in the recurrence of fluid collections between replacing LAMS with a plastic stent versus no plastic stent after removing LAMS [544]. In patients with recurrence of symptomatic fluid collections after removal of the plastic stents placed at the index intervention, if the imaging is suggestive of DPD, repeat internal drainage is recommended with double pigtail plastic stents, which can be left in place for long [545,546]. In patients with symptomatic DPDS, pancreaticogastrostomy with placement of an indwelling plastic stent between the stomach and the dilated pancreatic duct in the distal pancreas may be tried to maintain a duct-enteric fistula [547]. Similarly, in patients with persistent external fistula due to DPD, either a rendezvous technique or EUS-guided placement of a double pigtail plastic stent between the stomach and the fistulous tract has been shown to be successful in a case series [548]. Transpapillary pancreatic stenting to bridge pancreatic strictures is generally not possible [549]. Surgical treatment may be done in symptomatic patients with recurrent fluid collections and/or recurrent pancreatitis in the upstream pancreatic gland. Surgical approaches include either resection of the left (upstream) pancreas or, if the upstream duct is of adequate size (typically >5 mm), Roux-en-Y pancreatojejunostomy, and have been shown to provide a durable response in 90 % of patients [550].

Patients' viewpoints and suggestions: Patients recognize and trust the specialist's expertise and recommendations for the management of this complex complication.

Future directions

Good Practice Statement: A group of clinical and basic science pancreatitis experts provide their insights into the state of the field and suggestions for future research into how to design best clinical research guided by mechanistic and therapeutic basic science research.

Remarks: We recognize the challenges in performing pancreatitis-related therapeutic trials, including patient availability, assessment of severity, measurable end-points, and costs. The understanding we gain from filling the current gaps in knowledge must be applied to future clinical trial designs. Such knowledge must be periodically and critically summarized, and disseminated to pancreatologists [551]. Concerning endpoints for clinical trials of new treatment agents, patient-reported outcomes are increasingly recognized as essential for FDA approval. Clinical research should focus on identifying accurate biomarkers/systems and using them to select patients predicted to derive maximum benefit from a particular treatment. Appropriate and achievable primary and secondary outcomes must be assessed, including those that extend beyond six months, and better dynamic disease monitoring systems like PASS score should be used [551]. In this context, methods for identifying biochemical and immune biomarkers for selecting patients and monitoring therapy should be developed with the hope that trials will consider concepts of precision medicine. Similarly, quality indicators should be developed and utilized to measure quality for the management of AP with the aim of improving patient outcomes [552].

Some mechanisms are particularly important for future drug development, including disordered calcium signaling, impaired autophagy, endoplasmic reticulum stress, mitochondrial dysfunction, cell death, and pathways of inflammatory and immune mechanisms emanating from the injured pancreas. The efficacy of many potential agents has been tested in preclinical models. Targeted therapies are required for controlling systemic inflammation and mitigating organ dysfunction to improve clinical outcomes. Control of pain is an important endpoint, especially since some pain pathways link to inflammation. Some potential therapies are in early-stage clinical trials, and in preliminary studies, some have shown considerable promise [553]. Basic and clinical researchers should work side by side to develop better management and interventions to improve outcomes in patients with AP.

Patients' viewpoints and suggestions: Patients consider these guidelines to be most welcome, with what they consider some great statements and recommendations, appreciating the huge amount of work it has taken to pull them together. The patients hope that their contributions add to the value and impact on the guidelines, to improving patient outcomes from acute pancreatitis, and that they will have further opportunity to contribute to the future directions of these guidelines.

Footnote

One expert (JN) did not agree with (a) the specific rate of fluid infusion (Q11) and suggested instead that general guidelines for fluids should be followed as in any general ITU and (b) suggested that surgical decompression should not be performed in patients with ACS and worsening organ dysfunctions if non-operative modalities have failed (Q48).

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- Aliye Uc declares funding from NIH and as a consultant for the Cystic Fibrosis Foundation
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- Vijay Singh declares that they are the inventor of RABI-767; an investor in Arrivo Biopharma; and has received funding from Arrivo Biopharma.
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Appendix A. Supplementary data

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