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Acute Pancreatitis: An Update of Evidence-Based Management and Recent Trends in Treatment Strategies

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ABSTRACT

Acute pancreatitis is a common gastrointestinal disease leading to hospitalisation. Recent advancements in its management have primarily focussed on the development of early phase medical interventions targeting inflammatory pathways, optimisation of supportive treatment (including fluid resuscitation, pain management and nutritional management), appropriate use of antibiotics, implementation of minimally invasive interventions for infected necrosis, and the necessity of follow-up for long-term complications. These advancements have significantly improved personalised management and overall outcomes of acute pancreatitis. Despite these efforts, early-phase medical interventions to mitigate disease progression are still lacking and acute pancreatitis remains a heterogeneous disease. Future research and clinical trials are imperative to further optimise current strategies and develop new therapeutic approaches. This review presents an evidence-based approach to the management of acute pancreatitis, highlighting recent developments.

1 | Introduction

Acute pancreatitis is a common gastrointestinal disease worldwide, often requiring hospital admission [1]. Over the past decades, the global incidence has increased with an average annual rise of 3% [2]. Common risk factors such as alcohol use, obesity, advancing age, and gallstone disease contribute to this increasing incidence. Acute pancreatitis can be categorised into mild, moderately severe, and severe diseases, as detailed in Table 1, with clinical manifestations ranging from self-limiting to life-threatening. On imaging, acute pancreatitis can be classified as acute interstitial pancreatitis or necrotising pancreatitis, each with distinct morphological features and treatment strategies [3, 4]. While abdominal ultrasound at admission is essential to identify gallstones or sludge, early computed tomography (CT) should only be performed in cases of diagnostic uncertainty. A CT can be considered if there is no clinical improvement after 3–5 days. About 20%–30% of patients develop a moderately severe to severe pancreatitis with considerable morbidity, and mortality up to 30% in cases of infected pancreatic necrosis. Early prediction of disease severity is desired to identify individuals who may require more intensive management for counselling and for stratification in clinical studies. However, current predictive tools, such as individual biomarkers (e.g., C-reactive protein) and

TABLE 1 | Overview of disease classification and local complications according to the revised Atlanta classification.

Disease severity	
Mild	No organ failure and local or systemic complications
Moderately severe	Transient organ failure (< 24 h), or, local or systemic complications
Severe	Persistent organ failure (> 48 h), and, local or systemic complications
Acute interstitial pancreatitis	
Acute peripancreatic fluid collection	Interstitial oedematous pancreatitis with a homogeneous non-encapsulated peri-pancreatic fluid collection in the first 4 weeks
Pseudocyst	Interstitial oedematous pancreatitis with an encapsulated acute fluid collection persisting beyond 4 weeks
Acute necrotising pancreatitis	
Acute necrotising pancreatitis	Diffuse or focal areas of nonviable (peri-)pancreatic tissue in the first 4 weeks
Walled off necrosis	Encapsulated heterogenous non-liquefied collection of (peri-)pancreatic necrosis with a well-defined wall (usually > 4 weeks after onset)

scoring systems (e.g., systemic inflammatory response syndrome (SIRS), Glasgow-Imrie criteria) do not accurately correspond with observed disease severity [5].

Substantial advancements in evidence-based management have been achieved over the last decade that have improved the prognosis of patients with acute pancreatitis; further changes are expected soon [6]. This review summarises the latest evidence-based management strategies for acute pancreatitis and future directions.

2 | Treatment of Acute Pancreatitis

The following chapters will cover the key aspects of management of acute pancreatitis, including early phase medical interventions, fluid resuscitation, nutrition, pain management, antibiotic therapy, invasive pancreatic interventions and (follow-up of) long-term sequelae. The core recommendations are summarised graphically in Figure 1 and a flow-chart for clinical decision-making that integrates these aspects is presented in Figure 2.

2.1 | Early Phase Medical Interventions

Currently, no drugs or measures are available to intervene in the natural history of acute pancreatitis by modulating the initial inflammatory cascade. Early management is based on a combination of monitoring, supportive care, pain medication and management of complications in a multidisciplinary fashion. Various pharmacological targets have been explored, such as blocking the initial hyperinflammatory cascade, enhancing immune function, promoting gut barrier integrity, modifying the gut microbiome and targeting pathogenic bacteria [7]. Probiotics result in higher mortality rates in predicted severe pancreatitis and should be omitted from treatment [8]. Prophylactic antibiotics reduce overall infections but do not prevent pancreatic infection, pneumonia, urinary tract infection, complications, interventions, or mortality [9]. Besides being ineffective, the risk and global burden of antimicrobial resistance should also preclude the use of this therapy. Alternatively, selective decontamination of the digestive tract can be considered in critically ill patients in settings with a low prevalence of antibiotic resistance [10]. Finally, preliminary evidence shows that omega-3 fatty acids, short chain fatty acids (butyrate) and infliximab modulate the inflammatory response in acute pancreatitis, but their clinical benefits need to be demonstrated through the ongoing randomised trials [11–13]. Other targets may demonstrate their efficacy in future clinical trials. A medical intervention that successfully alters the course of potentially severe acute pancreatitis would significantly change the management and outcomes of acute pancreatitis.

2.2 | Fluid Resuscitation

The acute phase of acute pancreatitis is characterised by local hyperinflammation and vascular endothelial damage. In cases of moderately severe to severe pancreatitis, excessive systemic inflammation and vascular permeability lead to fluid accumulation in the third space, reduced organ perfusion and consequently pancreatic microcirculation [14, 15]. Early fluid resuscitation is a simple yet crucial supportive therapy to maintain adequate organ and pancreatic perfusion, and thereby reduce the risk of organ failure and shock. Retrospective studies have demonstrated improved clinical outcomes of early fluid resuscitation [16, 17], but its benefits seem to extend to late admissions (> 24 h) as well [18].

The relationship between the infusion rate of fluids and development of complications has long been under debate, especially concerning the infusion rate that maximises benefits before causing iatrogenic fluid overload. Guidelines previously advocated aggressive early hydration based on moderate-quality evidence [19, 20]. Recently, the WATERFALL trial provided high-quality evidence by randomising 249 patients to aggressive (3 mL/kg/h infusion following a bolus of 20 mL/kg) or moderate (1.5 mL/kg/h infusion following a bolus of 10 mL/kg in case of hypovolaemia) fluid resuscitation. The trial demonstrated no significant benefits of aggressive resuscitation compared with moderate resuscitation in terms of severity (22.1% vs. 17.3%

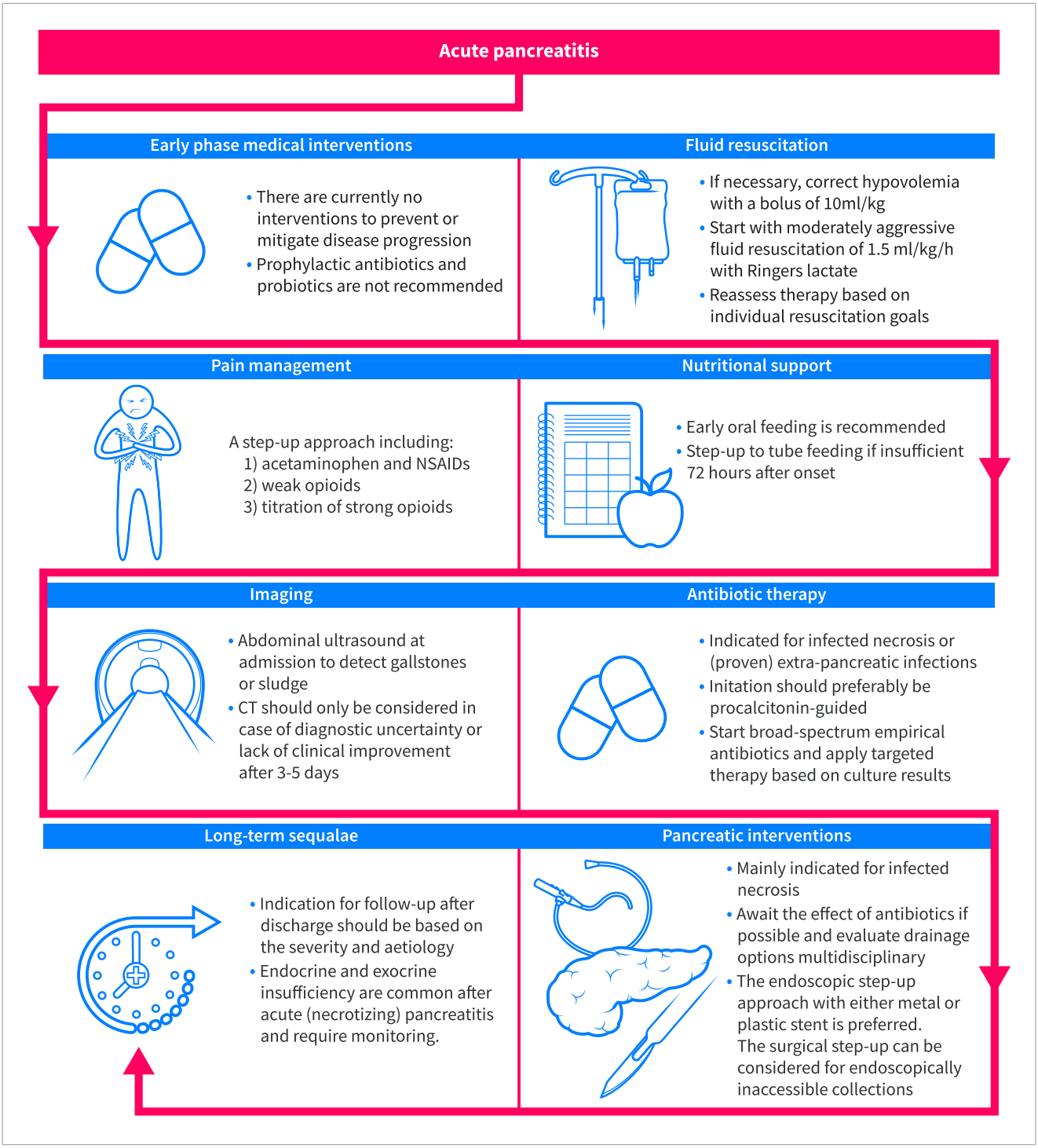

FIGURE 1 | Core recommendations for the management of acute pancreatitis. CT, computed tomography; NSAIDs, nonsteroidal anti-inflammatory drugs.

moderate to severe disease, respectively), but aggressive resuscitation was associated with increased fluid overload (20.5% vs. 6.3%). Recent meta-analyses confirmed that aggressive resuscitation is associated with significantly higher rates of organ failure, pulmonary and renal complications [21, 22]. Therefore, moderate fluid resuscitation with an individualised goal-directed approach is now the standard care. Clinicians should initiate an infusion of 1.5 mL/kg/h following a bolus of 10 mL/kg in case of hypovolaemia and reassess frequently, at least every 6 h in the first 24 h. A severe course has been associated with higher fluid needs and a higher risk of adverse outcomes, warranting closer monitoring of fluid responsiveness [15]. The strategy should be tailored to individual risk profiles (e.g., age, comorbidities) and individual resuscitation goals using a combination of clinical signs, physical examination, vital signs (e.g., heart rate < 120), urine output (e.g., > 0.5 mL/kg/h),

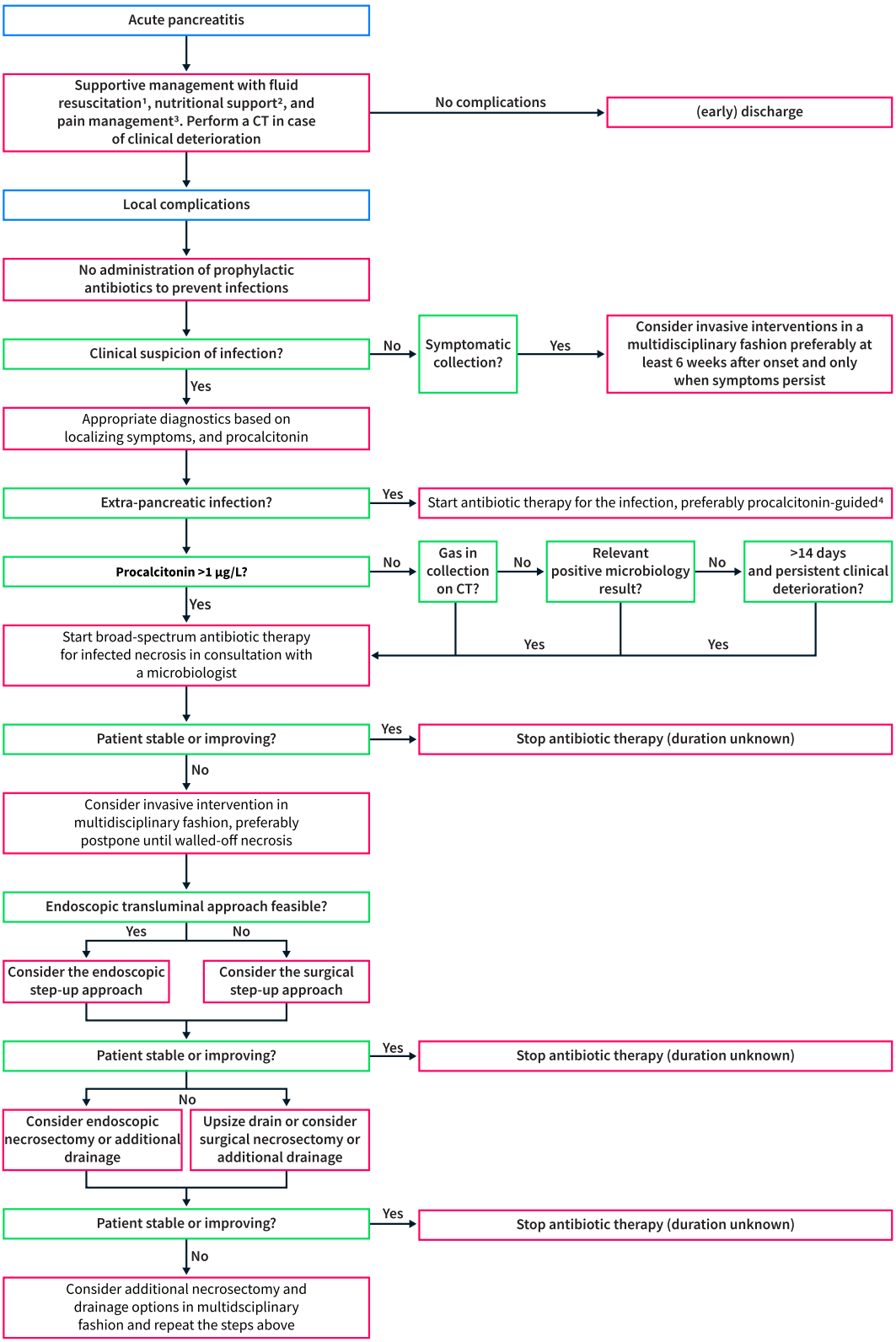

FIGURE 2 | Evidence-based management of acute pancreatitis flow diagram. [1] 1.5 mL/kg/h with Ringer's lactate, [2] early oral feeding and step-up to tube feeding if insufficient after 72 h, [3] according to World Health Organisation (WHO) ladder, [4] start antibiotics if procalcitonin > 1 µg/L and stop if < 1 µg/L.

biochemical markers (e.g., haematocrit < 44%), imaging results and advanced (non-)invasive targets in case of intensive care unit (ICU) admission.

Limited and heterogenous evidence is available concerning the type of fluids that should be used. The use of balanced crystalloids, such as Ringer's lactate, in acute pancreatitis is

described to be superior to normal saline due to a reduced risk of disease severity, ICU admission and hospital stay [23]. Both fluids have similar tonicity, but Ringer's lactate contains an electrolyte composition more similar to plasma. In theory, colloid fluids could effectively expand the intravascular compartment by oncotic pressure and restore albumin levels affected by hyperinflammation and nutritional status. However, no benefits of colloids could be demonstrated in acute pancreatitis and sepsis patients in ICU settings [24, 25]. Therefore, moderate fluid resuscitation with balanced crystalloids (Ringer's lactate) remains the standard approach. In 2026, the WATERLAND trial is expected to provide final evidence on which type of fluid should be ideally used [26].

2.3 | Nutritional Support

Historically, patients were advised a period of fasting to allow the pancreas to rest and inflammation to subside. However, basic research has shown that adenosine triphosphate (ATP) is crucial for restoring mitochondrial damage and cell function in the early phase of acute pancreatitis [27]. Additionally, clinical trials have demonstrated that early oral feeding supports recovery and leads to shorter hospital stays in patients with predicted mild and moderate pancreatitis [28, 29]. Very early (< 24 h) was not superior to early (> 72 h) on demand enteral feeding in severe pancreatitis. Furthermore, tube feeding was not required in 69% of the on demand group [30]. Therefore, tube feeding can be commenced after 72 h if on demand feeding is insufficient. Based on limited evidence, nasogastric feeding is non-inferior to nasojejunal feeding unless gastric outlet obstruction or severe vomiting is present [31]. When both oral and enteral tube feeding is not feasible, parenteral nutrition should be considered [32], but this is rarely necessary.

2.4 | Pain Management

Abdominal pain is the most common and burdensome symptom of acute pancreatitis. Its intensity may be linked with disease severity [33]. Neither nonsteroidal anti-inflammatory drugs (NSAIDs) nor opioids have shown significant impact on preventing the progression of acute pancreatitis after onset in humans. In randomised trials, opioids had similar pain control, adverse events and clinical outcomes compared with other analgesics [34]. In a recent large international prospective observational cohort study, opioid treatment was associated with increased severity; however, no cause-effect relationships can be drawn from these data and a probable explanation is that severe pancreatitis patients require opioids more frequently [35]. Considering the risk of dependence, even with short-term use of opioids, pain management according to the step-up approach of the World Health Organisation (WHO) is recommended for acute pancreatitis [36]. This includes starting with non-opioid analgesics such as acetaminophen and NSAIDs, adding a weak opioid as second step, and if necessary, titration of strong opioids. For (predicted) severe acute pancreatitis, both a step-up and a step-down approach have been suggested. Arguments for the step-down approach include the increased pain intensity and higher risk of renal insufficiency, which contraindicate NSAIDs. Notably, in an open-label single-centre RCT with predicted severe pancreatitis, COX-2 inhibitors were useful in pain control and reduced local complications and severity [37], but double-blind multicentre confirmatory studies are needed. Smaller studies showed the safety and feasibility of epidural anaesthesia in severe pancreatitis and hypothesised the benefits of epidural analgesia on clinical outcomes by improving splanchnic perfusion. However, this could not be demonstrated in a multicentre randomised study of acute pancreatitis in the ICU [27, 28]. Currently, the step-up approach according to the above-mentioned WHO ladder remains the advised evidence-based pain management method.

2.5 | Antibiotic Therapy

Following the hyperinflammatory phase, an excessive anti-inflammatory response can cause relative immunosuppression, increasing the risk of (secondary) pancreatic and extrapancreatic infections [38]. Nevertheless, sterile SIRS is also common during the early phase of acute pancreatitis and can be misclassified as infection. In daily practice, antibiotics are initiated in 31%–82% of patients with acute pancreatitis, often early during admission (< 7 days) without a clear source of infection [39–41]. Appropriate diagnostics for (extra-) pancreatic infections should be performed based on localising symptoms prior to the initiation of antibiotics. Recently, a single-centre randomised trial found that the use of procalcitonin, a biomarker specific to infection rather than inflammation, to guide antibiotic decisions reduced antibiotic use compared to standard care (45% vs. 63%, respectively) without affecting clinical outcomes [42]. Infected necrosis mainly (> 80%) occurs after 14 days and can be identified by persistent clinical deterioration in the absence of other infections, gas configurations in the (peri-) pancreatic collections, and positive cultures from the pancreatic tissue [43]. For infected necrosis, antibiotics are the first step of treatment alongside supportive care. Generally, empirical broad-spectrum intravenous antibiotics that cover gram-negative and gram-positive microorganisms are recommended for a minimum of one to 2 weeks. However, evidence regarding the choice, timing and duration of antimicrobials is lacking. Blood cultures and cultures of the necrotic tissue during pancreatic interventions are essential to facilitate targeted antibiotic therapy in consultation with a microbiologist. Additionally, a fine-needle aspiration can be considered in case of diagnostic uncertainty or to apply targeted therapy [44]. An upcoming randomised trial of the Dutch Pancreatitis Study Group will investigate whether an optimised and standardised antimicrobial treatment based on antimicrobial stewardship principles can improve clinical outcomes. Finally, long-term broad-spectrum antibiotics increase the risk of fungal infections, but no randomised studies on antifungal prophylaxis in infected necrosis are available.

2.6 | Invasive Pancreatic Interventions

In acute biliary pancreatitis, endoscopic retrograde cholangiopancreatography (ERCP) is only indicated in cases of

cholangitis and can be considered in cases of biliary obstruction [45, 46].

Sterile (peri) pancreatic fluid collections are often self-limiting and rarely require invasive interventions. Only in case of persistent symptoms, preferably at least 6 weeks after onset, drainage can be considered keeping in mind the risk of secondary infection of necrosis and the associated need for additional necrosectomy procedures [47].

Drainage of infected pancreatic necrosis is indicated when antibiotic therapy fails to achieve source control. In the POINTER trial, 39% of patients with infected pancreatic necrosis did not require any intervention to achieve clinical success and postponed drainage (> 4 weeks) resulted in fewer interventions and similar clinical outcomes compared with early drainage [48]. Ideally, the intervention is delayed until the infected necrotic collection is more mature and demarcated or completely walled-off [49]. For critically ill patients with persistent organ failure, there is also no evidence to support early drainage. Their treatment should be personalised and managed by a multidisciplinary team at a specialised centre. Patients with parenchymal necrosis, as compared to extrapancreatic necrosis, are prone to complications that require interventions [50]. A disrupted or disconnected pancreatic duct (DPD) is a frequent complication of parenchymal, especially central gland, necrosis and is associated with worse clinical outcomes, higher rate of pancreatic interventions, complications and recurrence [51]. An evidence-based algorithm for diagnosis of, indication for and type of intervention for DPD is hampered by lack of data [51–53]. Prophylactic pancreatic duct stenting is not recommended to prevent DPD [54]. Given the invasive nature of other modalities a, preferably secretin enhanced, magnetic resonance cholangiopancreatography (MRCP) is recommended as the first diagnostic modality [52]. Indication for an intervention is based on symptoms related to the consequences of DPD. In case of a symptomatic pancreatic fluid collection, long-term internal drainage with double pigtail stents is preferred [55]. For other indications, such as pancreatic enterocutaneous fistula or pancreatic ascites/pleural fluid, an ERP can be considered with, if possible, a leak bridging stent. It needs to be underlined that all these patients should be discussed in a multidisciplinary team meeting to consider other options such as surgical drainage procedures or, in case of DPD located in the tail of the pancreas, a distal pancreatectomy [53].

Over time, drainage strategies have shifted significantly. First, a minimally invasive surgical step-up approach showed superiority over open necrosectomy in terms of major complications and mortality (40% vs. 69%) [56]. More recently, two step-up approaches were compared: the surgical approach, with percutaneous catheter drainage and surgical necrosectomy if needed, and the endoscopic approach, with transluminal drainage and endoscopic necrosectomy if needed. The endoscopic step-up approach demonstrated better short-term as well as long-term outcomes in major complications (RR 0.69, 95% CI 0.49–0.97), organ failure (RR 0.29, 95% CI 0.11–0.82), and especially pancreatic fistula development (RR 0.14, 95% CI 0.05–0.45) [57, 58]. The endoscopic step-up approach is now the first-choice strategy. Collections that are difficult to access from the upper gastrointestinal tract, such as collections deep in the pelvis or paracolic gutter, still need percutaneous drainage. Furthermore, multiple drainages may be necessary for extensive or multiple unconnected collections.

For endoscopic drainage, either a lumen-apposing metal stent (LAMS) or double-pigtail plastic stents are used. It was hypothesised that metal stents with larger diameters would enhance drainage and facilitate subsequent necrosectomy. However, no benefit of LAMS over plastic stents could be demonstrated [59–62]. It can be argued that plastic stents are cheaper and more patient-friendly (as no reintervention is necessary to remove/replace the stent) and provide the opportunity of long-term internal drainage for patients who develop DPD. In contrast, the placement of LAMS is easier and can be performed without fluoroscopy. When using LAMS, the addition of a plastic stent through the LAMS reduces the risk of adverse events and stent occlusion [63].

When insufficient clinical improvement is achieved after initial drainage, an endoscopic necrosectomy or video-assisted retroperitoneal debridement is indicated. Multiple endoscopic necrosectomy procedures are often required for clinical success [64]. Direct endoscopic necrosectomy during the initial procedure, rather than as a subsequent intervention following drainage, was recently investigated in a randomised trial in stabilised patients with walled-off collections treated with LAMS [65]. Direct necrosectomy reduced the number of interventions needed to achieve clinical success. However, 21% of patients achieved clinical success without necrosectomy in the step-up arm. Moreover, in other trials this number was 36%–63% [48, 59]. Subjecting a subset of patients to an unnecessary and time-consuming procedure remains questionable. Optimised patient selection might further improve the clinical utility of this approach. Furthermore, future clinical trials are needed to evaluate new technology and devices to perform endoscopic necrosectomy more efficiently, such as powered endoscopic debridement [66].

Splanchnic vein thrombosis is a frequent and early complication of acute necrotising pancreatitis [67]. While pancreatologists generally support the use of therapeutic anticoagulation such as low molecular weight heparin for 3–6 months, the clinical benefits relative to the risk of bleeding remain uncertain [68]. High-quality prospective trials are necessary to explore the impact of anticoagulants on clinical outcomes, as well as to determine the optimal timing and duration of therapy, if indicated. Other complications associated with necrotising pancreatitis, such as fistulisation and perforation, are beyond the scope of this review.

2.7 | Follow-Up and Long-Term Sequalae

To prevent recurrence and biliary complications after acute biliary pancreatitis, cholecystectomy is preferred during the same admission for mild cases and generally within 8 weeks for necrotising pancreatitis [69,70]. In a mild acute pancreatitis, discharge usually takes place within 1 week. However, multiple prospective studies indicate that early discharge within 24–48 h, with enhanced outpatient services or remote monitoring, may be feasible and safe in these patients [71]. Many patients prefer home care for recovery and this approach would significantly

TABLE 2 | Overview of follow-up recommendations for acute pancreatitis, dependent on aetiology and severity.

	Follow-up recommendations	Intervals
Based on severity		
Mild	• Examinations should be based on aetiology, symptoms related to endocrine or exocrine insufficiency, pain and intake, and risk profile (e.g., recurrent pancreatitis, comorbidity)	At least once after 3–6 months, then as needed For patients discharged very early (< 24–48 h), outpatient (telephone) monitoring within the first days can be considered
Moderate-severe	• Monitor recovery and complications • Screening for endocrine and exocrine insufficiency • Imaging in persistent symptomatic patients	Every 3–6 months for the first year, then annually for the first 5 years after the event
Based on aetiology		
Idiopathic	• Perform additional diagnostics (e.g., EUS, MRI) to identify other potential aetiologies • Inform on risk of recurrence	At least once after 3–6 months, then as needed
Alcoholic	• Recommend and evaluate abstinence from alcohol. Referral to addiction services as necessary • Monitor liver function and nutritional status as necessary	At least once after 3–6 months, then as needed
Biliary		
Mild	• Cholecystectomy should be performed during the same admission. If not feasible, at least within 14 days post-discharge	At least once after 3–6 months, then as needed
Moderate severe	• Cholecystectomy is recommended within 8 weeks post-discharge after necrotising biliary pancreatitis	Every 3–6 months for the first year, then annually for the first 5 years after the event

reduce the healthcare demand. Nevertheless, across all disease severities, long-term complications can develop within years post-admission. Endocrine and exocrine insufficiency represent the most frequent long-term sequalae of acute pancreatitis. New onset endocrine insufficiency develops in approximately 14% and 39% of patients following mild or severe acute pancreatitis, respectively, within 5 years [72]. Similarly, the development of exocrine insufficiency has been reported in 16% and 30% of patients following mild or severe pancreatitis, respectively [73]. This underlines the necessity of annually checking for exocrine and endocrine insufficiency in the years following acute, especially necrotising, pancreatitis. Early appropriate management can reduce their burden and improve the quality of life [74]. Additionally, the development of recurrent acute pancreatitis (25%) and chronic pancreatitis (6%) are common, especially for alcoholic aetiology [75]. Adjusting lifestyle could be one of the most effective interventions to improve long-term outcomes and clinicians should ensure patients recognise the potential benefits of preventive health measures. Table 2 summarises the follow-up considerations based on disease severity and aetiology of acute pancreatitis, though the provided intervals lack strong evidence-based support.

3 | Conclusion

We summarised the key components of evidence-based management of acute pancreatitis resulting from most recent studies. The choice of management and the intervention strategy will be influenced by global variations in resource availability, healthcare systems, local expertise, and preferences. Future trials are particularly needed to explore early phase medical interventions to prevent disease progression, optimised conservative treatment with antibiotics of infected necrosis and more efficient endoscopic necrosectomy devices.

Author Contributions

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Conflicts of Interest

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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