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REVIEW

Controversies in the management of acute pancreatitis: An update

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Abstract

This review summarized the current controversies in the management of acute pancreatitis (AP). The controversies in management range from issues involving fluid resuscitation, nutrition, the role of antibiotics and antifungals, which analgesic to use, role of anticoagulation and intervention for complications in AP. The interventions vary from percutaneous drainage, endoscopy or surgery. Active research and emerging data are helping to formulate better guidelines. The available evidence favors crystalloids, although the choice and type of fluid resuscitation is an area of dynamic research. The nutrition aspect does not have controversy as of now as early enteral feeding is preferred most often than not. The empirical use of antibiotics and antifungals are gray zones, and more data is needed for conclusive guidelines. The choice of analgesic is being studied, and the recommendations are still evolving. The position of using anticoagulation is still awaiting consensus. The role of intervention is well established, although the modality is constantly changing and favoring endoscopy or percutaneous drainage rather than surgery. It is evident that more multicenter randomized controlled trials are required for establishing the standard of care in these crucial management issues of AP to improve the morbidity and mortality worldwide.

Key Words: Acute pancreatitis; Fluid resuscitation; Antibiotics; Analgesia; Anti coagulation; Intervention

Core Tip: The controversies in the management of acute pancreatitis are an area of dynamic research, and emerging data is assisting in guideline formulation. The current evidence favors crystalloids, although the choice and type of fluid resuscitation is an evolving research area. The empirical use of antibiotics and antifungals are gray zones and lack guidelines. The choice of analgesic lacks definite recommendations. The role of anticoagulation lacks agreement. The role of intervention is well established and favors endoscopy or percutaneous drainage rather than surgery. It is obvious that more evidence is essential for effective guidelines in these critical management issues of acute pancreatitis.

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process involving the pancreas, frequently affecting the peripancreatic tissue and less commonly the remote organ systems. It represents a spectrum of diseases ranging from a mild, self-limited course needing only brief hospitalization to moderate disease with increased morbidity and a rapidly progressive, severe illness culminating into multiorgan dysfunction, as categorized by the revised Atlanta Classification[1].

In 2019, the countries with the greatest number of incident cases of AP were India followed by China and the United States. The global estimate of AP incidence in 2019 was 33.7/per 100000 population and is rising in the Western world. The global burden of disease estimation is 1.4 deaths per 100000[2]. Therefore the disease burden is significant and requires more data and research in optimizing therapy. Although the revised Atlanta Classification has standardized the disease severity classification, there are a few controversies in the management of AP that are still evolving and are areas of active research.

In this review, we summarized the current controversies in the management of AP. The controversies are in the following areas: (1) Fluid resuscitation; (2) Nutrition; (3) Antibiotics and antifungals; (4) Analgesics; (5) Role of anticoagulation; (6) Endoscopic retrograde cholangiopancreatography (ERCP); and (7) Drainage in local complications. Certain issues like intra-abdominal hypertension (IAH) and persistent ascites also confound the management. Therefore, despite active research in many of these areas, the consensus is lacking. The data are still emerging, and guidelines are evolving.

FLUID MANAGEMENT IN AP

The pathophysiology of AP can broadly be classified into an early phase of systemic inflammatory response syndrome (SIRS), lasting 1-2 wk followed by a late phase characterized by disease sequelae and infection. There is a paucity of pharmacological options in the initial acute inflammatory phase; hence, treatment by and large remains supportive. Fluid management in the initial acute inflammatory phase becomes particularly important.

Which fluid? Crystalloids vs colloids

Our understanding of this vital management aspect is based on our understanding of altered pancreatic microcirculation in animal models. Studies have focused on using crystalloids as well as colloids to offset circulatory alterations. However, none of these studies conclusively established the superiority of one over the other[3,4].

Colloids (albumin, dextran, hexastarch) in animal studies have been shown to have better optimization of hemodynamic response. They have a larger molecular size and are better retained in the intravascular compartment. Their osmotic effect draws the fluid from the interstitium into the vascular compartment, thus maintaining better circulatory flow. These benefits, however, come at the cost of anaphylactic reactions, intravascular volume overload and renal impairment. Hypertonic saline, in particular, has shown promising results in animal models especially in modulating cytokine expression [5,6]. The use of balanced solutions like Ringer's lactate (RL) has demonstrated an inflammasome-mediated anti-inflammatory effect by acting on G-protein-coupled receptor 81, which is a cell surface lactate receptor[7]. The use of colloids in human studies include a combination of dextran with albumin in varying concentrations. A study using albumin after dilution with dextran has demonstrated reduced mortality (7.7%) and reduced progression of pancreatic necrosis (15.0%)[8]. The use of hydroxyethyl starch has not shown any benefit in reducing the risk of organ failure (OF) or mortality in AP[9]. Trials combining the colloids and crystalloids in different concentrations have also shown promising results

Table 1 Randomized controlled trials comparing resuscitation with Ringer's lactate *vs* normal saline in the initial acute phase of acute pancreatitis

Ref.	RL	NS	SIRS			CRP		
Wu *et al*[15], 2011	19	21	RL	84% at 24 h	P = 0.035	RL	Mean CRP 51 mg/L	P = 0.018
			NS	0% reduction at 24 h		NS	Mean CRP 104 mg/L	
de Madaria *et al*[13], 2018	19	21	RL	Median no of SIRS criteria at 48 h: 01 (0-1)	P = 0.060	RL	Mean CRP at 48 h: 28 mg/L	P = 0.037
			NS	Median no of SIRS criteria at 48 h: 01 (1-2)		NS	Mean CRP at 48 h: 166 mg/L	
Choosakul *et al*[14], 2018	23	24	RL	Reduction in SIRS at 48 h: 26.1%	P = 0.02	No difference in CRP		
			NS	Reduction in SIRS at 48 h: 26.1% 4.2%				
Karki *et al*[16], 2022	26	25	RL	SIRS at 24 h: 15.4%	P = 0.025	Median CRP at 72 h: 14.2 mg/L		P < 0.001
			NS	SIRS at 24 h: 44.0%		Median CRP at 72 h: 22.2 mg/L		

CRP: C-reactive protein; NS: Normal saline; RL: Ringer's lactate; SIRS: Systemic inflammatory response syndrome.

[10]. The American Gastroenterology Association recommends crystalloids as the initial fluid of choice for resuscitation in the acute inflammatory phase of AP, while it does not recommend the use of colloids like hydroxyl ethyl starch[11].

Which is better as the initial fluid of choice? RL vs normal saline

Traditionally, normal saline (NS) is the crystalloid of choice for critical illnesses like trauma or sepsis. Studies, however, have highlighted the adverse effects of NS therapy notably acute kidney injury (AKI) and non-anion gap acidosis. The landmark SMART trial provided valuable insight supporting the role of balanced crystalloids, *i.e.* RL and Plasma-Lyte A over NS alone in critically ill patients. Out of a total of 15802 adults admitted to intensive care units (ICUs), those receiving balanced crystalloids (n = 7942) had a lower incidence of major adverse kidney events (14.3%) *vs* 15.4% in patients receiving NS (n = 1211). Other notable benefits were reduced requirement of renal replacement therapy (2.5% *vs* 2.9%), persistent renal dysfunction (6.4% *vs* 6.6%), and 30 d in-hospital mortality (10.3% *vs* 11.1%) in the RL group compared to the NS group, respectively[12].

Researchers have strived hard to critically analyze the effects of RL *vs* NS in patients with AP. de Madaria *et al*[13] showed favorable anti-inflammatory effects of using RL *vs* NS in AP. Choosakul *et al* [14] showed a beneficial effect of using RL in reducing SIRS in the first 24 h of pancreatic injury as compared to those receiving NS. This beneficial effect, however, was not reciprocated at 48 h with no effect on disease-related mortality. This is in contrast to an earlier randomized controlled trial (RCT) by Wu *et al*[15] who demonstrated a statistically significant reduction in SIRS after 24 h of pancreatic injury in patients receiving RL *vs* those receiving NS. Karki *et al*[16] in their recent paper provided evidence of reduced systemic inflammation at 72 h in patients who received initial resuscitation with RL *vs* those who received NS (Table 1).

Four recent meta-analyses including the above-mentioned RCTs have drawn conflicting conclusions varying from reduced severity of AP, laparoscopic cholecystectomy and risk of ICU admission to no statistically significant benefit of resuscitating with RL compared to NS (Table 2)[17-20].

Which strategy of fluid resuscitation? Aggressive vs restricted fluid resuscitation

Recent human studies in AP have focused on two distinct aspects of fluid management, namely the aggressiveness of fluid therapy and the optimal fluid required for resuscitation.

Early aggressive resuscitation proposes to transfuse one-third of the body's 72-h fluid requirement within the first 24 h of presentation. This hypothesis was subsequently challenged by other investigators. Garg *et al*[21] aptly described that this clinical dilemma may require the services of an 'alchemist.' This clinical aspect thus required critical review. RCTs comparing aggressive *vs* restricted fluid resuscitation in the inflammatory phase of AP have been summarized in Table 3[22-26].

Recent systemic reviews and meta-analyses that included both RCTs and cohort studies on the use of aggressive *vs* restricted intravenous fluid resuscitation in the early acute phase (within the first 24 h from presentation) have weighed in favor of restrictive intravenous transfusion. This has shown that restricted intravenous fluid administration decreases the risk of AKI, pulmonary edema and the need for mechanical ventilation[27].

The recent 'waterfall trial' has provided valuable evidence supporting 'moderate resuscitation, *i.e.* up to 1.5 mL/kg/h and bolus of 10 mL/kg only in the presence of hypovolemia[28].

Table 2 Recent meta-analyses comparing resuscitation with Ringer's lactate *vs* normal saline in patients with acute pancreatitis

Ref.	Inclusion	Conclusion
Zhou *et al*[17], 2021	4 RCT, 7964 abstracts, 57 full-text documents	Patients resuscitated with RL were less likely to develop moderately severe/severe AP (OR: 0.49; 95%CI: 0.25-0.97), had reduced requirement of ICU admission (OR: 0.33; 95%CI: 0.13-0.81) and had reduced local complications (OR: 0.42; 95%CI: 0.20-0.88)
Aziz *et al*[18], 2021	4 RCT, 2 cohort studies	Patients resuscitated with RL had a lower rate of ICU admission (RR: 0.43; 95%CI: 0.22-0.84), a lower length of hospital stay (MD: 0.77 d; 95%CI: 1.44-0.09 d) and no difference in overall mortality and SIRS at 24 h
Vedantam *et al* [19], 2022	6 studies	Patients resuscitated with RL had a decreased need for ICU admission and no statistical difference in the risk of developing SIRS at 24 h (pooled OR: 0.59; 95%CI: 0.22-1.62, P = 0.31)
Chen *et al*[20], 2022	4 RCT	Patients resuscitated with RL had a reduced incidence of ICU admission (RR: 0.39; 95%CI: 0.18-0.85; P = 0.02), no significant reduction in SIRS at 24 h, 48 h and 72 h and no reduction in risk of mortality, severe disease or local complications

AP: Acute pancreatitis; CI: Confidence interval; ICU: Intensive care unit; MD: Mean difference; OR: Odds ratio; RCT: Randomized controlled trial; RL: Ringer's lactate; RR: Relative risk; SIRS: Systemic inflammatory response syndrome.

Table 3 Randomized controlled trials comparing aggressive *vs* restricted fluid resuscitation in the inflammatory phase of acute pancreatitis

Ref.	No. of patients	Disease severity	Aggressive resuscitation	Non-aggressive resuscitation
Mao *et al*[22], 2009	Aggressive: 36	SAP	Mortality: 94.4%	Mortality: 10.0%
	Non-aggressive: 40		Mechanical ventilation: 30.6%	Mechanical ventilation: 65.0%
Mao *et al*[23], 2010	Aggressive: 56	SAP	Mortality: 33.9%	Mortality: 15.3%
	Non-aggressive: 59		Sepsis: 78.6%	Sepsis: 57.6%
Wu *et al*[15], 2011	Aggressive: 19		Reduction in SIRS: 58%	Reduction in SIRS: 42%
	Non-aggressive: 21			
Buxbaum *et al*[24], 2017	Aggressive: 27	Mild AP	Clinical improvement: 70%	Clinical improvement: 42%
	Non-aggressive: 33		SIRS: 7.4%	SIRS: 21.1%
Cuellar-Monterrubeo *et al* [25], 2020	Aggressive: 43 Non-aggressive: 45	Mild, moderately severe and severe AP	SIRS at day 7: 13.3%	SIRS at day 7: 13.9%
Li *et al*[26], 2020	Total number (n = 912)	Hemoconcentration hematocrit > 44% *vs* < 44%	In hematocrit > 44%: increased NPPV	In hematocrit < 44%: reduced risk of NPPV

AP: Acute pancreatitis; NPPV: Non-invasive positive pressure ventilation; SAP: Severe acute pancreatitis; SIRS: Systemic inflammatory response syndrome.

To conclude, there is considerable heterogeneity in the study designs amongst various studies, the rate and type of fluids studied, study population and outcome measures. There is a paucity of evidence to recommend aggressive *vs* restrictive intravenous fluid administration. Most guidelines recommend RL as the initial fluid of choice intending to maintain urine output > 0.5 mL/kg[28,29]. The need of the hour is to incorporate non-invasive methods to assess the patient's hydration status before commencing intravenous fluid administration and dynamic hemodynamic monitoring and to determine a patient-centric treatment strategy.

NUTRITIONAL ASPECTS IN THE MANAGEMENT OF AP

There has been a paradigm shift in the management of AP from surgical management to conservative support. While judicious fluid therapy is imperative in the initial inflammatory phase, the concept of

Table 4 Meta-analysis on early enteral nutrition *vs* delayed enteral nutrition/total parenteral nutrition in acute pancreatitis

Ref.	Inclusion	Conclusion
Li *et al*[35], 2013	6 studies	Early EN *vs* delayed EN: reduced incidence of all infections (OR: 0.38; 95%CI: 0.21–0.68, P < 0.05); reduced incidence of catheter-related sepsis (OR: 0.26; 95%CI: 0.11–0.58, P < 0.05); reduced pancreatic infection (OR: 0.49; 95%CI: 0.31–0.78, P < 0.05); reduced risk of hyperglycemia (OR: 0.24; 95%CI: 0.11–0.52, P < 0.05); reduced length of hospitalization (mean difference: -2.18; 95%CI: -3.48-(-0.87); P < 0.05); reduced mortality (OR: 0.31; 95%CI: 0.14–0.71, P < 0.05); and no difference in pulmonary complications (P > 0.05)
Feng *et al*[36], 2017	4 RCTs, 2 retrospective studies	Early EN (within 48 h) *vs* delayed EN (after 48 h): reduced risk of multiple organ failure (RR: 0.67; 95%CI: 0.46-0.99; *P* = 0.04); decreased systemic inflammatory response syndrome but not significant (RR: 0.85; 95%CI: 0.71-1.02; *P* = 0.09); and no significant difference in mortality (RR: 0.78; 95%CI: 0.27-2.24; *P* = 0.64)
Qi *et al*[37], 2018	8 studies (727 patients)	Early EN *vs* late EN and TPN: risk of mortality (OR: 0.56; 95%CI: 0.23-1.34); multiple OF (OR: 0.40; 95%CI: 0.20-0.79); infectious complications: (OR: 0.57; 95%CI: 0.23-1.42); adverse events (OR: 0.45; 95%CI: 0.17-1.21); and pancreatitis-related infections (OR: 0.83; 95%CI: 0.59-1.18)
Zeng *et al*[38], 2019	17 RCTs	Early EN *vs* delayed EN: lower mortality (9.21% *vs* 11.22%) but no statistical significance between the two groups (RR: 0.86; 95%CI: 0.60-1.23; *P* = 0.42); reduced risk of complications (RR: 0.81; 95%CI: 0.70-0.93; *P* = 0.002); reduced incidence of infections (RR: 0.68; 95%CI: 0.51-0.91, *P* = 0.009); and no difference in risk of multi OF (RR: 0.82; 95%CI: 0.59-1.14; *P* = 0.23)

CI: Confidence interval; EN: Enteral nutrition; OF: Organ failure; OR: Odds ratio; RCT: Randomized controlled trial; RR: Relative risk; TPN: Total parenteral nutrition.

Table 5 Summary of the meta-analysis highlighting the feasibility of nasogastric feeding in acute pancreatitis

Ref.	Inclusion	Conclusion
Zhu *et al*[40], 2016	4 RCTs	NG *vs* NJ feed: mortality (RR: 0.71; 95%CI: 0.38-1.32; *z* = 1.09; *P* = 0.28); infectious complications (RR: 0.77; 95%CI: 0.45-1.30; *z* = 0.99; *P* = 0.32); digestive complications (RR: 1.02; 95%CI: 0.57-1.83; *z* = 0.08; *P* = 0.93); achievement of energy balance (RR: 1.00; 95%CI: 0.97-1.03; *z* = 0.00; *P* = 1.00)
Dutta *et al*[41], 2020	5 RCTs	NG *vs* NJ feed: mortality (RR: 0.65; 95%CI: 0.36-1.17; no difference in the rate of OF, procedure-related complications, the requirement of surgical intervention and the requirement of PN

CI: Confidence interval; NG: Nasogastric; NJ: Nasojejunal; OF: Organ failure; PN: Parenteral nutrition; RCT: Randomized controlled trial; RR: Relative risk.

“nutritional support’’ to prevent malnutrition is widely gaining acceptance. Inflammatory cytokines, higher ‘’resting energy expenditure,” protein catabolism, ongoing pain, poor oral intake and complications like gastric outlet obstruction and ileus in combination with micronutrient deficiency have all been postulated as contributing factors that precipitate a state of malnutrition in AP[30].

When to initiate enteral nutrition? Early enteral nutrition vs delayed enteral nutrition

The earlier concept of “pancreatic rest” (*i.e.* initiation of enteral feeding on the complete resolution of pain abdomen) has given way to the concept of “early enteral nutrition (EN)”. This concept is based on experimental evidence demonstrating that pancreatic enzyme secretion reduces with increased severity of AP. Thus, injured acinar cells may not respond to an increased physiological stimulus[31].

Early EN has shown a reduced incidence of bacterial translocation thus reducing systemic inflammation and maintaining gut integrity and gut microbiota composition[32-34]. The benefits of early EN have been confirmed in a meta-analysis and systemic reviews[35-38].

Table 4 highlights the meta-analysis demonstrating the benefits of early EN in AP. The newer concept of “immediate EN” *vs* early EN has been shown to decrease the length of hospital stay and intolerance of feeding but with no statistically significant decrease in the rate of progression to severe pancreatitis or incidence of complications[39].

Which modality of EN? Nasogastric vs nasojejunal feed

Oral nutritional support is the preferred mode of feeding in mild AP[37]. The traditional approach of nasojejunal feeding is based on the premise that it bypasses the inflamed pancreas. On the other hand, it was believed that nasogastric (NG) nutrition stimulates pancreatic secretion, thereby causing an exacerbation of the inflammatory process and increasing the risk of developing aspiration pneumonia. However, there is growing evidence that establishes the safety, feasibility and tolerability of NG feeding in AP (Table 5)[40,41]. Whether NG feeding affects disease mortality or morbidity is debatable.

The ESPEN guidelines recommend early initiation of oral feeding in predicted mild AP and EN in preference to parenteral nutrition in those who are unable to take an oral feed with an initial energy requirement of 15-20 kcal/kg/d and protein requirement of 1.2-1.5 g/kg/d.

Table 6 Guidelines on the use of antibiotics in acute pancreatitis

Societies	Prophylactic antibiotics	Indications of therapeutic antibiotics	Probiotics
ACG, 2013[50]	Not recommended	Extrapancreatic infections. Cholangitis, catheter-acquired infections, bacteremia, urinary tract infection, pneumonia. Infected pancreatic necrosis	Not recommended
IAP/APA, 2013[46]	Not recommended	Infected pancreatic necrosis	No recommend-ations
Japanese guidelines, 2021 [51]	Not recommended	Not addressed	No recommend-ations
AGA, 2018[11]	Not recommended	Not addressed	No recommend-ations
ESGE, 2018[52]	Not recommended	Infected pancreatic necrosis	Not recommended
World Society of Emergency Surgery, 2019[53]	Not recommended	Infected pancreatic necrosis	No recommend-ations

ACG: American College of Gastroenterology; AGA: Androgenetic Alopecia; APA: American Pancreatic Association; ESGE: European Society of Gastrointestinal Endoscopy; IAP: International Association of Pancreatology.

ANTIBIOTICS IN AP

Diagnosis of infection in AP and judicious use of antimicrobials is a challenge faced by clinicians with very limited tools available for decision-making. Infections and OFs are critical determinants of outcome in cases of AP[42].

What is the origin of the infection? Pancreatic vs extrapancreatic

Infections can be of pancreatic [infected pancreatic necrosis, infected pseudocyst and infected walled-off necrosis (WON)] or extrapancreatic origin (pneumonia, bacteremia, urinary tract infection or indwelling catheters). Etiologically, infections may be of bacterial origin, fungal origin or both may coexist. Bacterial infections can complicate 30%-50% of severe AP (SAP), and the presence of infected necrosis increases the risk of mortality by 50% *vs* those with sterile necrosis[43]. Bacterial infections are monomicrobial in 60%-87% of patients. Infected necrosis may harbor polymicrobial infection in 10%-40% of patients, with Gram-negative anaerobes being the most common[44].

The use of antibiotics for extrapancreatic infections is less contested. Extrapancreatic infection can complicate almost one-third of patients. Respiratory infections are the commonest; however, their impact on mortality is less clear[45,46].

When to use antibiotics for patients with OF in AP?

Patients with SAP or moderate SAP who manage to tide over the initial onslaught of the inflammatory response may later develop an infection. This timing is variable and unpredictable; however, the incidence peaks during weeks 2 to 4 of illness, presumably secondary to increased gut translocation of bacteria and reduced immunity[47]. Tools that are readily available for diagnosis of infection are based on cultures, pancreatic necrotic aspirate or drainage samples. Cross-sectional imaging may demonstrate the presence of air in the collection. However, none provides absolute certainty. Recently there has been great emphasis on procalcitonin in guiding antibiotic treatment due to ease of applicability. Procalcitonin levels directly correlate with levels of microbial toxins and indirectly to cytokine-mediated host inflammatory response. However, cutoff values indicating infection are not standardized[48]. Recently procalcitonin-directed deescalation of antibiotics has shown efficacy in the management of infections in the setting of AP. Although, further RCTs may be required before definite conclusions can be drawn [49].

The use of antibiotics may be considered empirically in a subset of patients with pancreatic or extrapancreatic necrosis specifically in those patients who fail to improve or develop new onset OF after 7-10 d of initial hospitalization[50]. Empirical antibiotics should cover Gram-negative, Gram-positive and anaerobic microorganisms effectively, giving adequate cognizance to nosocomial infections and local antibiotics policy. The role of prophylactic antibiotics is contested routinely in clinical practice, with most of the guidelines and evidence recommending against its usage except for Japanese guidelines, which recommend prophylactic antibiotics in SAP and necrotizing pancreatitis within 72 h (Table 6)[11,46,50-53]. Prophylactic antibiotics increase the risk of multidrug resistant organisms and pancreatic fungal infection.

When to use antifungals in AP?

In critically ill patients with pancreatic fungal infection, echinocandins and liposomal amphotericin are the first-line drugs. However, differentiating invasive fungal infection from colonization can be perplexing[54]. Modalities available for diagnosing fungal infection are histological (aspirate samples or perioperative samples), cultures (drain catheters or blood cultures) and biomarkers[55]. Clinical judgment should be exercised when starting antifungals based on the likely diagnosis of invasive fungal infection, whereas it should be started in all cases with a definitive diagnosis[55]. Antifungals may be added considering clinical profile and risk factors for pancreatic fungal infection, such as prolonged intensive care, antibiotic administration, total parenteral nutrition and indwelling catheters[55].

In conclusion, antibiotics in AP should be initiated whenever a definite indication exists along with source control. However, there is no role for prophylactic antibiotics. Prophylactic antifungals especially with new-onset OF requires further evaluation.

ANALGESICS IN AP

Pain is a cardinal symptom and one of the diagnostic criteria for AP[1]. It not only contributes significantly to patient distress but also prognosticates the course of disease[56,57]. Alleviation of pain is an essential component in the management of the early phase of AP. We will be restricting our discussion to the management of inflammatory pain. Most, but not all, guidelines on AP remain noncommittal on analgesic management due to the paucity of high-quality evidence[11,46,50,58]. Japanese guidelines recommend that if pain associated with AP is severe and persistent, then it requires sufficient pain control; however, they remain noncommittal on the choice of analgesic[51]. The World Society of Emergency Surgery guidelines for the management of SAP provide no evidence or recommendation about any restriction in available pain medications except that nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in cases with AKI[53]. None of the above guidelines provide sufficient recommendations on the type, route, dose, frequency and duration of analgesics in AP.

Which is preferred? NSAIDs vs opioids

NSAIDs and opioids are the most frequently prescribed analgesic for pain in AP. Thirteen RCTs and multiple meta-analyses have failed to provide any conclusive data on the analgesic management of AP, which hinges on the World Health Organization analgesic ladder (Figure 1, Table 7)[59-61]. Opioids have been the most studied analgesic for AP in RCTs, establishing good efficacy, and are the agent of choice for rescue analgesia in all of the trials. NSAIDs have been reported to be beneficial in mitigating the inflammatory cascade thus improving outcomes. However, their analgesic potency as compared to opioids remains controversial[62]. NSAIDs have been studied in only a few RCTs where it was found to be better than placebo but similar efficacy to weak opioids[63-65].

NSAIDs and opioids have different safety profiles. Opioids are known to cause bowel dysfunction and ileus, which may induce or exacerbate ileus in AP[66]. There is some evidence that opioid use is associated with sphincter of Oddi dysfunction as well as the risk of overuse and addiction[67]. The problem with NSAIDs is a risk of AKI and peptic ulcer disease, which should be avoided in AP with AKI[53]. Based on the better safety profile and comparable efficacy, NSAIDs may be preferred as first-line analgesia in patients with mild AP, keeping opioids as a reserve in refractory pain[62]. Monitoring of response using a visual analog scale and the need for rescue analgesia should be monitored regularly before consideration for escalation of therapy[21,68]. Lack of relevant and high-quality data on analgesics in cases of moderately SAP and SAP warrants further studies before any clear-cut recommendations can be made.

Newer modalities? Patient-controlled analgesia and epidural analgesia

Patient-controlled analgesia (PCA) and epidural analgesia are emerging therapies in AP. PCA allows adequate pain control allowing patients to control their medication doses. Intravenous protease inhibitor nafamostat mesilate is one of the newer agents that has been used in an open label RCT. The analgesic effect was analyzed based on 24 h cumulative dose of fentanyl required and any administration of intravenous PCA. Results showed encouraging analgesic effect. An ongoing clinical trial is studying the use of PCA in AP[69,70]. Epidural analgesia has been used infrequently in patients with SAP and has shown a beneficial effect on mortality and pancreatic arterial perfusion[71,72]. However, it bears the risk of catheter-related hypotension and epidural abscess and is presently not recommended for mild to moderate AP. Further studies assessing the efficacy and safety of epidural analgesia in SAP are needed to make a definite conclusion.

In conclusion, we would suggest using the World Health Organization analgesic ladder for the management of pain in AP keeping in mind the safety profile of drugs[59-61,73]. It begins with low-potency NSAIDs (*e.g.*, paracetamol, indomethacin and diclofenac), which is usually sufficient in mild to moderate AP. If NSAIDs are not sufficient for pain relief, then upgrading to weak opioids (*e.g.*, tramadol and codeine) or strong opioids (*e.g.*, pentazocine, fentanyl and buprenorphine) appears logical. PCA and

Table 7 Important randomized controlled trials on analgesics in acute pancreatitis

Ref.	Country	Comparison drugs	Study design	Patients, *n*	Rescue agent	Primary outcome	Results	Conclusion
Blamey *et al*[74], 1984	United Kingdom	IM buprenorphine *vs* IM pethidine	RCT, blinding not mentioned	32	Pethidine	Pain relief at 24 h	No significant difference in pain relief at 24 h and no significant difference in pain-free period	No superiority established
Ebbehøj *et al*[75], 1985	Denmark	Indomethacin suppository *vs* placebo	Placebo-controlled, double-blind RCT	30	Opiate not specified	Pain relief using VAS; Pain-free days	Indomethacin provided better pain control, a lesser number of painful days and lesser need for rescue analgesia	Indomethacin suppository favored over placebo
Jakobs *et al* [76], 2000	Germany	IV buprenorphine *vs* IV procaine	Open-label RCT	39	Procaine group–pethidine; buprenorphine group–pethidine	Pain relief: VAS ever 8 hr for 3 d; rescue demand	Buprenorphine provided better pain relief on days 1 and 2 with lesser need for rescue analgesia; comparable side effects, complications, mortality	Buprenorphine favored
Stevens *et al*[77], 2002	United States	Transdermal fentanyl IM pethidine *vs* placebo and IM pethidine	Double-blind placebo-controlled RCT	32	IM pethidine	Pain relief: Self-reported 0-5 scale; self-reported satisfaction 1-5 at discharge	Fentanyl provided no significant difference in pain relief at 24 h but better pain relief at 36 h and a shortened hospital stay	Fentanyl favored
Kahl *et al* [78], 2004	Germany	Infusion procaine *vs* IV pentazocine	Open RCT	101	IM pethidine	Pain relief based on VAS and rescue analgesia	Pentazocine provided better pain relief until day 3 and required fewer rescue doses	Pentazocine favored
Peiró *et al* [79], 2008	Spain	IV metamizole *vs* SC morphine	Open RCT	16	Pethidine	Pain relief based on VAS and time to pain relief	Metamizole showed better pain relief at 24 h and faster pain relief, which was nonsignificant	A favorable trend towards metamizole but a small sample size
Wilms *et al* [80], 2009	Germany	IV procaine *vs* IV placebo	Double-blind placebo-controlled RCT	42	Buprenorphine	Pain relief and need for rescue analgesia over 3 d	Failed to show better pain relief as compared to placebo, and the need for rescue analgesia was similar in both groups	Procaine is not superior to placebo
Layer *et al* [81], 2011	Germany	IV procaine *vs* IV placebo	Double-blind placebo-controlled RCT	44	Metamizole or buprenorphine	Pain relief at 3 d; rescue analgesia; proportion achieving > 67% drop in VAS	Procaine showed higher analgesic superiority with greater pain relief at 72 h, lesser need for rescue analgesia and more patients achieving VAS drop > 67%	Procaine favored over placebo
Sadowski *et al*[82], 2015	Switzerland	Epidural analgesia *vs* PCA	Open RCT	35	Not applicable	Safety and efficacy of EA; pancreatic perfusion on CT; pain relief VAS	EA was safe, provided faster pain relief and increased pancreatic perfusion	EA favored over PCA
Gülen *et al* [83], 2016	Turkey	Tramadol *vs* paracetamol + dexketoprofen	Single-blind RCT	90	Morphine	Pain relief at 30 min	No significant drop in VAS at 30 min for both agents and a similar need for rescue analgesia for both groups	No superior analgesia
Mahapatra *et al*[84], 2019	India	IV pentazocine *vs* IV diclofenac	Double blind RCT	50	Fentanyl PCA	Pain relief; pain-free period; rescue analgesia	Higher rescue analgesia needed with diclofenac; longer pain-free period and lower need for PCA with	Pentazocine favored

							pentazocine	
Kumar *et al*[85], 2019	India	IV diclofenac *vs* IV tramadol	Double-blind RCT	41	IV morphine	Pain relief VAS over 7 d; painful days; rescue demand; time for significant VAS drop	No significant difference among both groups except time to a significant drop in VAS was quicker with diclofenac	No superior agent
Chen *et al* [86], 2022	China	Hydromorphone PCA *vs* IM pethidine	Open-label RCT	77	IM dezocine	Change in VAS score over 72 h; rescue analgesia; organ failures; local complic-ations; ICU admission LOH; mortality	No significant difference in VAS score deduction was noted with PCA as compared to pethidine, but a higher dose of hydromorphone needed for similar pain relief; need for rescue analgesia similar	No superior agent

CT: Computed tomography; EA: Epidural analgesia; ICU: Intensive care unit; IM: Intramuscular; IV: Intraveneous; LOH: Loss of heterozygosity; PCA: Patient-controlled analgesia; RCT: Randomized controlled trial; SC: Synovial chondromatosis; VAS: Visual analog scale.

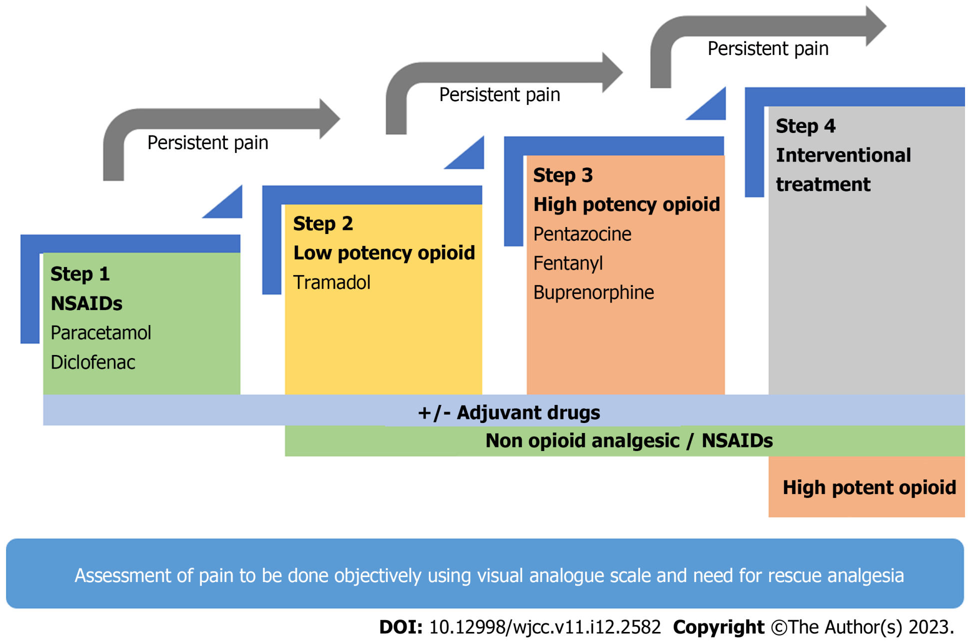

Figure 1 Pain management in acute pancreatitis. NSAIDs: Nonsteroidal anti-inflammatory drugs.

epidural analgesia are promising therapies but need validation in larger cohorts and may be suited best as individualized therapy due to cost and limited availability (Figure 1). Table 7 summarizes the RCTs evaluating the role of different analgesics in management of pain in AP[74-86].

ANTICOAGULATION IN AP

The use of anticoagulation in AP is perhaps the least studied in the literature. This is because the disease can give rise to two different complications: Splanchnic thrombosis and retroperitoneal bleeding. Management of these two opposing complications poses a unique challenge for a clinician. Pancreatitis is an acute inflammatory condition coupled with systemic response to inflammation, fluid shifts and subsequent hypovolemia. These pathophysiological mechanisms in unison precipitate a prothrombotic milieu. Thrombosis involving the splanchnic vasculature may involve the portal vein (PV), superior mesenteric vein (SMV) and splenic vein either separately or in combination.

Splanchnic vein thrombosis in AP, with a reported incidence of 1%-2%, has been poorly studied in clinical trials[87] partly because thrombosis in splanchnic vasculature is often incidentally detected on imaging. Clinical presentation of splanchnic vein thrombosis may overlap with that of AP. Our understanding of the natural history of splanchnic vein thrombosis in AP is still evolving. Some of these patients may have underlying prothrombotic risk factors that have just been unmasked because of pancreatitis. Understanding this rare complication is important because of prominent life-threatening manifestations, namely bowel gangrene, chronic portal hypertension and hepatic failure.

Thus, should we use anticoagulation in patients presenting with splanchnic vein thrombosis? Experience gained from the use of anticoagulation in patients without cirrhosis who present with acute PV thrombosis has been summarized in the European network of vascular diseases of the liver study. This study has shown the recanalization of the PV in 39% of those who were initiated on anticoagulation in the acute phase of PV thrombosis. Gastrointestinal bleeding and intestinal infarction occurred in 9.4% and 2.1% of anticoagulated patients, respectively[88]. This has led to some researchers advocating the use of anticoagulation in those with documented thrombosis of splanchnic vasculature in AP.

However, the benefits of giving anticoagulation have to be weighed in light of another potentially life-threatening complications (*i.e.* pseudoaneurysm-related bleeding from large vessels and retroperitoneal bleeding). Moreover, many of these patients with SAP undergo interventions (percutaneous/endoscopic drainage of collections or surgical interventions). Thus, from a clinician's point of view, using therapeutic anticoagulation in patients with AP may be a risky proposition. The lack of RCTs on the efficacy of anticoagulation in AP needs special attention. Then splenic vein lies in close anatomical proximity to the inflamed pancreas. Researchers have shown a direct correlation between the degree of peripancreatic inflammation, direct venous compression by collections and the incidence of splanchnic vein thrombosis. Thus, drainage of collections has been postulated to be the most ideal way of treating and preventing splanchnic vein thrombosis in AP[89].

Systematic reviews have been attempted to address this pertinent management dilemma. Hajibandeh *et al*[90] in their systemic review of 5 observational studies and 252 patients demonstrated no significant difference in the rate of resolution of thrombus or formation of varices/collaterals. The study had a major drawback of low study heterogeneity between the anticoagulation and no anticoagulation groups. Another systemic review by Norton *et al*[91] included 16 studies (9 case reports, 2 case series and 5 single-center studies); among the total of 198 affected patients, 46.5% received anticoagulation therapy. The rate of venous recanalization was 14% in the anticoagulated group *vs* 11% in the untreated group, while 16% and 5% of patients had bleeding manifestations, respectively.

The most recent meta-analysis included 7 retrospective cohort studies (233 AP patients suffered from splanchnic venous thrombosis). Splanchnic vein thrombosis was seen in 33%-82%, PV thrombosis in 4%-32% and SMV thrombosis in 5%-9% of all patients with splanchnic vein thrombosis. A combination of splanchnic vein thrombosis, PV thrombosis and/or SMV thrombosis has also been reported in variable combinations. Moderate AP to SAP was resent in 89% of patients who had some evidence of splanchnic vein thrombosis. Several drawbacks of these systemic reviews and meta-analysis include the absence of RCTs and the serious risk of bias, imprecision and indirectness[92].

There are no guidelines on the management of splanchnic vein thrombosis in AP. Management issues have been extrapolated from existing guidelines on pulmonary embolism, extrahepatic PV obstruction and deep vein thrombosis. Low molecular weight heparin followed by vitamin K antagonist, fondaparinaux and apixaban have been used in different studies. Approximately 47% of affected patients who received therapeutic anticoagulation showed no statistically significant rate of recanalization[92-95].

INTERVENTIONS IN AP

Interventions in AP could be an emergency or may be delayed. The emergency interventions in AP include ERCP to relieve the biliary obstruction. Non-emergency or delayed interventions include percutaneous catheter drainage or endoscopic drainage of necrotic or walled-off collections.

When to consider ERCP?

ERCP is an invasive intervention with a complication rate of 5% to 15%[90]. The current use of ERCP in AP is limited to relief of biliary obstruction. In patients with AP who present with acute cholangitis, emergency ERCP (within 24 h) is the recommended first-line treatment[46,50]. However, the role and timing of ERCP in biliary obstruction without cholangitis in AP is not clear[46].

Multiple studies have looked at the role and timing of ERCP in these patients of acute biliary pancreatitis (ABP) without cholangitis[96]. Neoptolemos *et al*[97] showed that patients with predicted SAP had fewer complications with an early ERCP (within 72 h of admission) (24% *vs* 61%, $P < 0.05$). On the other hand, Fölsch *et al*[98] reported that early ERCP was not beneficial in patients with ABP without obstructive jaundice. Furthermore, a meta-analysis showed no significant difference in mortality rate according to the timing of ERCP (< 24 h *vs* < 72 h) in patients with persistent biliary obstruction without cholangitis[6]. Fölsch *et al*[98] also compared urgent ERCP with a conservative approach in patients with predicted severe ABP. This study showed that urgent ERCP with sphincterotomy did not reduce the major complication or mortality [38% *vs* 44%, risk ratio: 0.87; 95% confidence interval (CI): 0.64–1.18].

The available studies suggest that emergency ERCP (within 24 h) is indicated in patients with ABP with cholangitis or persistent cholestasis. For the rest of the patients with ABP, the role of urgent ERCP is controversial, and a conservative approach should be considered.

What are the options for interventions for drainage?

The management of the pancreatic and peripancreatic collections has evolved over the last two decades. The indications to drain (peri-) pancreatic collections in AP are the presence of infection and symptomatic sterile necrosis (Table 8). The choice of interventions includes percutaneous, endoscopic, minimally invasive surgery or a combined approach. The approach depends on multiple factors including the time elapsed since the onset of the disease, condition of the patient, anatomy of the collection and expertise available. An open surgical approach is no longer the preferred strategy due to the higher risk of mortality and major complications[99].

Across the world, the step-up approach remains the standard of care for the management of collections in AP. The approach involves initial conservative management, and then either percutaneous drainage or endoscopic transluminal drainage can be selected.

Is there an ideal time for drainage?

There are multiple dilemmas while contemplating the drainage of necrotic collection. Should the drainage be performed early (*i.e.* before encapsulation of the collection) or should it be delayed? Most guidelines suggest delaying drainage as much as possible and preferably until 4 wk after the disease onset to allow liquefaction and encapsulation of the collection[46,100]. The cutoff of 4 wk is arbitrary, and studies have shown variable results for early and delayed drainage.

Various studies have reported a widespread time window, varying from a median of 9 d to 75 d, between the onset of the disease and the first drainage procedure. The older studies suggested that delaying percutaneous drainage until encapsulation may improve the outcome[101-106]. Other recent studies have suggested the usefulness of early drainage in improving outcomes[107]. However, a recent multicenter randomized study (POINTER trail), which compared early *vs* delayed drainage in AP, did not show the superiority of early drainage[108]. The study showed similar rates of mortality (13% *vs* 10%, relative risk: 1.25; 95%CI: 0.42-3.68) and adverse events (76% *vs* 82%, relative risk: 0.94; 95%CI: 0.77-1.14) in early and delayed drainage. Studies have shown that early drainage required a higher number of reinterventions compared to a delayed strategy[108]. Trikudanathan *et al*[109] demonstrated that early endoscopic drainage (< 4 wk) required higher percutaneous drainage compared with patients with walled-off collections. Navalho *et al*[110] demonstrated the benefits of early drainage of infected pancreatic collections in patients in ICU settings[110,111]. Table 9 summarizes the studies highlighting timing of first catheter drainage and outcome in various studies of AP[99,101,103-104,110,112-122].

The available literature suggests that the correct timing of intervention in AP requires careful clinical judgment. A subset of patients with infected collections, sepsis and persistence or new onset OF may require early drainage.

Which modality of drainage? Percutaneous drainage vs endoscopic drainage

Percutaneous drainage: Percutaneous catheter drainage is an important treatment modality for acute necrotizing pancreatitis. The percutaneous procedure could be done safely under ultrasound (US) or computed tomography guidance. Percutaneous catheter drainage is important in patients where early drainage is required and the necrotic collection is not well encapsulated. Freeny *et al*[112] for the first time demonstrated the safety and efficacy of percutaneous drainage in AP in 1998 with a successful outcome in 47% of patients with percutaneous drainage only. Subsequently, Mortelé *et al*[113] and Baril *et al*[114] also confirmed the success of percutaneous drainage in AP.

In 2010 van Santvoort *et al*[99] (PANTER trial) performed an RCT of the step-up approach and primary surgery and found a significant success rate of percutaneous drainage. The first step in the step-up approach is percutaneous drainage, and it remains the standard of care for early drainage. Several studies have also confirmed the safety of early percutaneous catheter drainage in sick patients[109,110]. Table 10 summarizes the important studies and outcomes after percutaneous catheter drainage in AP.

Endoscopic drainage: Endoscopic drainage involves the internal drainage of collection by creating a temporary fistula and placing a stent between the collection and the gastrointestinal lumen. Internal drainage carries the advantage of a lower risk of infection of collections and eliminates the risk of pancreatic-cutaneous fistula. However, these benefits come with a risk of anesthesia-related complications. Internal drainage could be completed using conventional endoscopic drainage or under endoscopic US (EUS) guidance. Though the studies have established the efficacy and safety of the conventional technique, its use is limited by a visible bulge in only 40%-50% of patients, and most endoscopists prefer EUS-guided drainage.

As with percutaneous drainage, the appropriate timing of drainage for endoscopic drainage is a matter of research. Though few studies have suggested the safety and efficacy of early endoscopic drainage for necrotic collections, most of the guidelines and reviews suggest the endoscopic drainage of collections with a well-defined wall[46,100].

Table 8 Indications of drainage of collection in acute pancreatitis

Clinical suspicion or documented infected pancreatic collection
Presence of gas in the fluid collection on imaging
Systemic signs of infections
Increasing leucocytes and worsening clinical condition
Persistent or new onset organ failure
Pressure symptoms
Gastric outlet obstruction
Intestinal obstruction
Biliary obstruction
Persistent symptoms (*e.g.*, pain, persistent unwellness)
Disconnected pancreatic duct (*i.e.* full transection of the pancreatic duct) with ongoing symptoms

Which modality to choose? Percutaneous drainage vs endoscopic drainage vs combined approach

The percutaneous method is a time-tested method of drainage of infected pancreatic collections. Endoscopic drainage is an alternative approach to draining such collections in AP. Compared to percutaneous drainage it carries less risk of secondary infection and pancreatic-cutaneous fistula. Recent American Gastroenterology Association guidelines also suggest that an endoscopic approach may be preferred. However, the choice of drainage method should be individualized and guided by multiple factors including the time elapsed since the onset of disease, encapsulation of the collection, location of the collection, solid contents of the collection, hemodynamic condition of the patient and available expertise. In early pancreatic collection with an ill-defined wall, sicker patients and peripherally located collections or when expertise is not available, percutaneous drainage should be considered. Endoscopic drainage is preferable for centrally located pancreatic collections in patients with a well-defined wall. A combined approach can be used for larger central collections extending into the periphery or when a single modality fails.

Which stent should be used? Plastic stent vs metal stent

Endoscopic drainage of a collection could be performed with multiple plastic stents or metal stents. Historically, plastic stents were the mainstay of endoscopic drainage. However, their placement is time-consuming and challenging when multiple stents are required. On the other hand, the insertion of transmural metal stents ensures a short procedure time and wider transmural fistula and provides a more efficient way of drainage compared to plastic stents**.** Though the larger diameter of metal stents allows rapid drainage and facilitates endoscopic necrosectomy through the stent, the metal flanges may increase the risk of pseudoaneurysm formation[123]. Table 10 summarizes the studies for the outcome of endoscopic drainage with plastic and metal stents[123-128].

The retrospective studies comparing metal and plastic stents showed that the biflanged metal stent performed better than multiple plastic stents for draining WON[127,129]. On the other hand, two RCTs showed similar clinical efficacy with metal and multiple plastic stents for WON[123,124]. Furthermore, a meta-analysis concluded no differences in clinical success and adverse events between lumen- apposing metal stents and multiple plastic stents for symptomatic WON[130]. A recent study of EUS-guided drainage of infected WON identified that the use of metal stents was associated with higher clinical success (96.2% *vs* 81.8%, $P = 0.04$) and shorter hospital stays (6 d *vs* 10 d)[128].

The current evidence suggests that the choice of a stent for draining the collection is a matter of ongoing research and depends on multiple factors including the hemodynamic condition of the patients, size of the collection, solid contents of the collection and cost associated with metal stents. In patients with pseudocysts and limited solid contents, multiple plastic stents can be considered. While in patients with large collections, significant solid contents and peripherally extending collections metal stents should be preferred.

What is the role of irrigation?

The concept of irrigating the collection to remove the solid necrotic debris is a less popular and debatable approach. It is based on the principle of chemical debridement using necrolytic agents to accelerate the drainage of pancreatic necrosis. The irrigation technique has been used for either percutaneous or endoscopic transmural drainage[43,131]. Studies have shown variable results with the use of different agents. Agents used for irrigation include NS, antibiotics, hydrogen peroxide and streptokinase. Werge *et al*[43] showed that local instillation of antibiotics in infected pancreatic necrosis improves the eradication of infection. Similarly, LarinoNoia *et al*[131] showed that the addition of local

Table 9 Timing of first catheter drainage and outcome in various studies of acute pancreatitis

Ref.	Number of days after the onset of the disease when PCD was performed, mean (range)	Patients, *n*	IPN, %	Mortality, %
Infected necrotic collection				
Freeny *et al*[112], 1998	9 (1-48)	34	100	12
Navalho *et al*[110], 2006	18	30	100	17
Mortelé *et al*[113], 2009	12 (2-33)	13	100	17
Baril *et al*[114], 2000	24 (18-30)[a]	7	100	0
Bala *et al*[115], 2009	26 (18-88)	8	100	13
Baudin *et al*[116], 2012	19.8 ± 15.7	48	100	29
Tong *et al*[101], 2012	PCD only = 30.74 ± 5.67; PCD + surgery = 27.80 ± 6.00	34	100	0 and 7
Pascual *et al*[117], 2013	28 ± 17	13	100	23
Wroński *et al*[102], 2013	PCD only = 33 (27-46); surgery = 35 (8-116)	18	100	0 and 17
Wang *et al*[118], 2016	11.7 ± 8.1	59	100	18.6
Infected or sterile necrotic collection				
Lee *et al*[103], 2007	10 (1-58)[a]	23	12	4
Bruennler *et al*[119], 2008	3.5 (median 7)	80	65	23
van Santvoort *et al*[99], 2010	30 (11-71)[a]	43	91	19
Kumar *et al*[104], 2014	36.4 ± 7	12	67	8
Bellam *et al*[120], 2019	Median: 20 d	51	33.3	29.4
Gupta *et al*[121], 2020	Median: 22 d (range: 3–267 d)	146	47.9	20.5
Lu *et al*[105], 2020	15.26 ± 7.08	43	86	13.9
	50.86 ± 19.58	55	56.3	10.9
Sterile necrotic collection				
Walser *et al*[122], 2006	NR	22	0	9.1

[a]Some patients underwent endoscopic transluminal drainage.
IPN: Infectious pancreatic necrosis; NR: Not reported; PCD: Percutaneous catheter drainage.

Table 10 Outcome on endoscopic drainage of a pancreatic collection with various types of stents

Ref.	Collection	*n*	Success
Lee *et al*[124], 2014	WON and pseudocyst	PS = 25; FCMS = 25	PS: 90%; FCMS: 87%
Mukai *et al*[125], 2015	WON	PS = 27; BFMS = 43	PS: 90.6%; FCMS: 97.7%
Siddiqui *et al*[126], 2017	WON	PS = 106 FCMS = 121; LAMS = 86	PS: 81%; FCMS: 95%; LAMS: 90%
Bapaye *et al*[127], 2016	WON	PS = 61; BFMS = 72	PS: 73.7%; BFMS: 94.0%
Bang *et al*[123], 2019	WON	PS = 29; LAMS = 31	PS: 96.6%; LAMS: 93.5%
Muktesh *et al*[128], 2022	WON 108	PS = 45; BFMS = 53	PS: 81.8%; BFMS: 96.2%

BFMS: Biflanged metal stent; FCMS: Fully covered self-expandable metal stent; LAMS: Lumen-apposing metal stent; PS: Plastic stent; WON: Walled-off necrosis.

infusion of antibiotics avoids the need for necrosectomy in half of the patients with infected pancreatic necrosis not responding to drainage and systemic antibiotics. Hydrogen peroxide and streptokinase are other adjunctives for the management of necrotic collections.

Though such agents have been used with modest success to improve the outcome of AP and collections, the optimal dose, volumes, concentration and timing for use of these agents are still not known. A recent review by Trikudanathan *et al*[132] suggested that these agents can be used in the management of necrotic pancreatitis if there is no clinical and imaging improvement after drainage alone.

When to contemplate and what role is played by direct endoscopic necrosectomy?

The term direct refers to the access of necrotic collection directly by endoscope through the gastric or duodenal wall. The direct endoscopic necrosectomy (DEN) forms the last step of the endoscopic step-up approach and involves direct access to the collection and debridement of the necrotic material. The step-up approach includes declogging of the blocked stent lumen, placement of a nasocystic tube and irrigation (chemical necrolysis) and DEN. Lakhtakia *et al*[133] showed that after initial drainage with a biflanged metal stent, 74.6% of patients had clinical success. Reintervention with a step-up approach improved the overall clinical success to 96.5% with DEN required in only 9.2% of the patients.

Several studies have confirmed the safety and efficacy of DEN in patients with infected pancreatic collections[134,135]. The PENGUIN trial compared DEN and surgical necrosectomy [video-assisted retroperitoneal debridement (VARD) or open] in patients with infected WON and showed significantly lower IL-6 levels and lower rates of complication (20% *vs* 80%) in the DEN group[136]. Subsequently, the TENSION trial compared the endoscopic step-up approach (EUS-guided stent placement followed by DEN) with the surgical step-up approach (percutaneous catheter drainage followed by VARD)[137]. The major complications and mortality rates were similar in both groups. However, the incidence of pancreatic fistula formation was higher with the percutaneous approach.

Though DEN has been shown to improve the outcome with a reduced need for surgical intervention. A relevant point of discussion is the timing of DEN after initial drainage. It was initially thought that performing DEN after 3-7 d would allow maturation of the cystogastrostomy/cystoenterostomy tract. However, with the advent of lumen-apposing metal stents, DEN can be performed immediately after the placement of the stent. Yan *et al*[138] in a multicentric study compared immediate and delayed DEN for WON. The study showed no difference in clinical success and adverse events. The study also showed the mean number of necrosectomy sessions for WON resolution was significantly lower in the immediate DEN group compared to the delayed DEN group (3.1 *vs* 3.9, $P < 0.001$).

The studies suggest that DEN remains the cornerstone of the endoscopic step-up approach with similar or lower complication rates than the percutaneous step-up approach. After initial endoscopic drainage, DEN can be performed immediately post-drainage, or delayed DEN can be considered depending on the clinical status of the patients. Post-endoscopic drainage of collection, a step-up approach of initial chemical necrolysis followed by DEN or upfront DEN can be considered depending on the available expertise, clinical status of the patient and residual collection.

When to consider a minimally invasive approach and surgery?

The indications of surgery are limited in the setting of AP. Surgery is usually required for necrosectomy and rarely for acute compartment syndrome. As a general rule of thumb, any surgical intervention should not be done before 4 wk of the onset of the disease to enable the walling-off of the collections.

The approach for surgical necrosectomy could be minimally invasive, laparoscopic or open. In 2010 van Santvoort *et al*[99] (PANTER trial) compared the step-up approach with primary open surgical necrosectomy surgery. The study concluded that a minimally invasive step-up approach reduced the rate of major complications and mortality in patients with infected pancreatic necrosis. In the step-up approach, initial drainage is followed by debridement and necrosectomy using minimally invasive surgical methods. Several minimally invasive approaches are described and popularly utilized including minimally invasive retroperitoneal percutaneous necrosectomy and VARD[139,140]. Both minimally invasive retroperitoneal percutaneous and VARD retroperitoneal techniques are modifications of the open lateral approach initially described in the 1980s by Fagniez *et al*[141]. The aim of these minimally invasive approaches is not complete necrosectomy but to remove loosely adherent pieces of necrosis, thus minimizing the risk of hemorrhage. Open surgical necrosectomy is only indicated when a minimally invasive approach fails or in the absence of expertise.

MISCELLANEOUS ISSUES

Certain issues like the management of IAH and persistent ascites may require a multipronged approach predominantly revolving around timely drainage.

How to manage IAH

In AP, high intra-abdominal pressures (IAPs) are a common finding and occur through multiple mechanisms (*i.e.* pancreatic and/or peri-pancreatic inflammation, third space fluid loss and retention in the abdominal cavity and ileus). The pressure can reach the extent to produce IAH or abdominal compartment syndrome. IAH is defined as sustained IAP above 12 mmHg and occurs frequently in AP

[51]. Several studies have observed poor outcomes in patients with IAH[142,143].

The management of increased abdominal pressure should follow the standard algorithm proposed by the various societies irrespective of the etiology[144,145]. The management includes the frequent monitoring of IAP, evacuation of intraluminal contents using NG or rectal tubes, improving abdominal wall compliance by use of adequate analgesia and sedation, goal-directed use of fluid and release of intra-abdominal fluid or collection using percutaneous drainage.

Singh *et al*[143] in a retrospective study showed that the presence of IAH increases the risk of development of multiple OF and was associated with higher mortality. At 48 h post-percutaneous drainage, the mean reduction in IAP was significantly higher (6.87 mmHg *vs* 3.21 mmHg, $P < 0.001$) in patients with baseline IAH than in patients without IAH. The study also identified that post-percutaneous drainage a pressure reduction of > 40% was associated with better survival.

How to manage persistent ascites?

Ascites are commonly described in patients with AP, but its association and effect on outcome are poorly understood. Samanta *et al*[146] identified that the presence of ascites was associated with higher rates of OF and increased mortality in AP. Mortality rates were four times higher in the presence of ascites compared to non-ascites patients (34.1% *vs* 8.4%, $P = 0.001$). The study showed that the presence of moderate to gross ascites was associated with IAH and higher rates of OF. Though the presence of ascites increases IAP, several unidentified mechanisms could contribute to the poor outcome in the presence of ascites in AP. Serum ascites albumin gradient (SAAG) can be used to differentiate the underlying pathophysiological process in addition to history and diligent physical examination. SAAG > 1 may indicate underlying portal hypertension, while pancreatic ascites (SAAG < 1) may require drainage and/or endoscopic placement of transpapillary pancreatic duct stent. Hence, the decision of drainage of persistent ascites should be considered before drainage of the collection.

CONCLUSION

The management of AP is still a work in progress. Even though there are several guidelines, there is a lack of consensus on certain issues. The choice and type of fluid resuscitation are still evolving. The nutrition aspect is settled with ample evidence for early enteral feeding. The judicious use of antibiotics is always debatable, and the ideal analgesic is unknown. The intervention is tending towards endoscopy or percutaneous drainage rather than surgery. With the progressive development of technology and expertise, more data is likely to emerge that may help in the formulation of more conclusive indications and guidelines.

FOOTNOTES

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