81883_Auto_Edited.docx

WORD COUNT 6693
TIME SUBMITTED 06-FEB-2023 02:54PM
PAPER ID 96301448

Name of Journal: *World Journal of Clinical Cases*
Manuscript NO: 81883
Manuscript Type: REVIEW

Controversies in the management of acute pancreatitis

Manish Manrai, Saurabh Dawra, Anupam K Singh, Daya Krishna Jha, Rakesh Kochhar

Abstract

The review is an effort to summarize 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 (PCD), endoscopy or surgery. Active research and emerging data is helping in formulation of better guidelines. The available evidence favors crystalloids although the choice and type of fluid resuscitation is an area of dynamic research. The nutrition aspect is sans controversy as of now as early enteral feeding is preferred most often than not. The empirical use of antibiotics and antifungals are grey zones and more data is awaited for conclusive guidelines. The choice of analgesic is also 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 PCD rather than surgery. It is evident that more multi center 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.

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 disease ranging from 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 (RAC)(1).

In 2019, the countries with the greatest number of incident cases of AP were India followed by China and USA. The global estimate of AP incidence in 2019 was 33.7/per 100,000 population and is rising in the western world. The global burden of disease estimation is 1.4 deaths per 100,000(2). Therefore the disease burden is significant and requires more data and research in optimizing therapy. Although the RAC has standardized the disease severity classification, there are a few controversies in the management of AP which are still evolving and are areas of active research.

In this review, we endeavor to summarize the current controversies in the management of AP. The controversies are as follows: Fluid resuscitation –Which fluid? a balanced solution like Ringer's lactate (RL) or Normal saline (NS)?; How to give – Aggressive vs. slow, Nutrition – Timing and mode may create debate; Role of antibiotics and antifungals – when to give? ; Analgesics – What to give? How to monitor? , Role of anticoagulation – To give or not; ERCP in AP – Timing and indications and finally drainage in local complications of AP – How early? Which modality- endoscopic intervention or surgery?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 and even now the data is emerging and guidelines are evolving.

FLUID MANAGEMENT IN ACUTE PANCREATITIS

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 sequel 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, hence, 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, hence 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(GPR81) which is a cell surface lactate receptor(7). The use of colloids in human studies has used 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 %) (8). The use of hydroxyethyl starch has not shown any benefit in reducing the risk of organ failure(OF) or mortality in AP(9).Since the jury is still not out, trials combining the colloids and crystalloids in different concentrations have also shown promising results(10). The American Gastroenterology Association(AGA) 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).

Ringer's Lactate vs. Normal Saline as the initial fluid of choice: Which is better?

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., Ringer's Lactated solution (RL) and Plasma- Lyte A over NS alone in critically ill patients. Out of a total of 15, 802 adults admitted to intensive care units (ICU), 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%), and persistent renal dysfunction (6.4% vs. 6.6%) besides 30 days in hospital mortality(10.3% vs. 11.1%)) in the RL group as compared to 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, have shown favorable anti-inflammatory effects of using RL vs. NS in AP(13). Choosakul *et al* have shown a beneficial effect of using RL in reducing systemicinflammatory response syndrome (SIRS) inthe first 24 h of pancreatic injury as compared to those receiving NS. This beneficial effect, however, was not reciprocated at 48 hrs with no effect on disease-related mortality(14). This is in contrast to an earlier RCT by Wu *et al* who have demonstrated a statistically significant reduction in SIRS after 24 h of pancreatic injury in patients receiving RL vs. those receiving NS(15) (Table 1).

Four recent meta-analysis including the above-mentioned RCTs has drawn conflicting conclusions varying from reduced severity of AP, LC, 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 was proposed to transfuse one-third of the body's 72-hour fluid requirement within the first 24 h of presentation. This hypothesis originally proposed by Gardner *et al*. was subsequently challenged by other investigators. This clinical aspect thus required critical review. Randomized controlled trials (RCTs) comparing aggressive vs. restricted fluid resuscitation in the inflammatory phase of AP have been summarized in table 3.

Recent systemic review and meta-analysis which 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 acute kidney injury(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/hr and bolus of 10 mL/Kg only in the presence of hypovolemia (28).

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 besides dynamic hemodynamic monitoring and which should guide a patient-centric treatment strategy.

NUTRITIONAL ASPECTS IN THE MANAGEMENT OF ACUTE PANCREATITIS

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 "nutritional support'' to prevent malnutrition is widely gaining acceptance. Inflammatory cytokines, higher ''Resting

Energy Expenditure"(REE), protein catabolism, ongoing pain, poor oral intake, complications like gastric outlet obstruction(GOO) and ileus in combination with micronutrient deficiency have all been postulated as contributing factors which 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 meta-analysis and systemic reviews(35-38).

Table 4 highlights the meta-analysis demonstrating the benefits of early EN in acute pancreatitis. The newer concept of ''Immediate EN" (immediately on admission vs. early EN has been shown to decrease the length of hospital stay and intolerance of feeding but no statistically significant decrease in the rate of progression to severe pancreatitis or incidence of complications(39).

Modality of enteral nutrition: Nasogastric vs. Nasojejunal feed

Oral nutritional support is the preferred mode of feeding in mild AP (37). The traditional approach of nasojejunal (NJ) feed 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 besides increasing the risk of developing aspiration pneumonia. However, there

is growing evidence that establishes the safety, feasibility, and tolerability of NG feed in AP (Table 5). Whether NG feed affects disease mortality or morbidity is debatable

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

ANTIBIOTICS IN ACUTE PANCREATITIS

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).

Pancreatic vs. Extra-pancreatic infections

Infections can be of pancreatic (infected pancreatic necrosis, infected pseudocyst, and infected walled-off necrosis) or extrapancreatic origin (pneumonia, bacteremia, urinary tract infection, or indwelling catheters). Etiologically, infections may be of bacterial origin, fungal origin or both may co-exist. Bacterial infections can complicate 30-50% of 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. 10-40 % of patients with infected necrosis mayharbor polymicrobial infection with gram-negative anaerobes being the most common(44).

The use of antibiotics for extra-pancreatic infections is less contested. Extra-pancreatic infection can complicate almost 1/3rd of patients. Respiratory infections are the commonest; however, their impact on mortality is less clear.(45-46).

Use of antibiotics and organ failure in AP

Patients with severe or moderately SAP who manage to tide over the initial onslaught of the inflammatory response maylater develop an infection. This timing is variable and unpredictable; however, the incidence peaks during 2ndto 4th week 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 drain samples. Cross-sectional imaging may demonstrate the presence of air in the collection. However, none of them provides absolute certainty. Recently there has been great emphasis on procalcitonin in guiding antibiotic treatment due to ease of applicability. Procalcitonin levels directly co-relate with levels of microbial toxins and indirectly to cytokine-mediated host inflammatory response. However, cut-off values indicating infection are not standardized(48). Recently procalcitonin-directed de-escalation of antibiotics has shown efficacy in the management of infections in the setting of AP. However, further RCTs may be required before definite conclusions can be drawn(49).

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 days 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). Prophylactic antibiotics increase the risk of MDR organisms and pancreatic fungal infection.

When to use antifungals in AP?

In critically ill patients with pancreatic fungal infection (PFI) 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 PFI like

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 and we will be restricting our discussion to the management of inflammatory pain. Most but not all guidelines on AP remain non-committal on analgesic management due to the paucity of high-quality evidence(11),(46),(50),(58). Japanese Guidelines recommend pain associated with AP is severe and persistent, requiring sufficient pain control; however, remain non-committal comments on the choice of analgesics(51). WSES guidelines for the management of SAP provide no evidence or recommendation about any restriction in available pain medications except that 'Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in cases with acute kidney injury(AKI)(53). None of the above guidelines provide sufficient recommendations on the type, route, dose, frequency, and duration of analgesics in AP.

Non-steroidal anti-inflammatory drugs vs. Opioids: Which is preferred?

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 WHO 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 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 acute kidney injury (AKI) and peptic ulcer disease, which should be avoided 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 severe and SAP warrants further studies before any clear-cut recommendations can be made.

Patient controlled analgesia and Epidural analgesia: Newer modalities?

Patient-controlled analgesia (PCA) and epidural analgesia (EA) are emerging therapies in AP. PCA allows adequate pain control allowing patients to control their medication doses. Two RCTs have studied the role of PCA in establishing efficacy for pain management but cost, availability, and similar efficacy to other parenteral therapy limits generalization (69-70). Epidural analgesia has been used infrequently in patients with severe AP 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 severe AP are needed to make a definite conclusion.

In conclusion, we would suggest using WHO 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 acute pancreatitis. If NSAIDs are not

sufficient for pain relief upgrading to weak opioids (e.g. Tramadol, codeine) or strong opioids (e.g. pentazocine, fentanyl, buprenorphine) appears logical. (Figure 1) PCA and EA are promising therapies but need validation in larger cohorts and may be suited best as individualized therapy due to cost and limited availability.

ANTICOAGULATION IN ACUTE PANCREATITIS

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 a 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 (SV) 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 per se. 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 which have just been unmasked because of pancreatitis. Understanding this rare disease 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 non-cirrhotic patients 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 PV in 39 % of those who were initiated on anticoagulation in the acute phase of PV

thrombosis. Gastrointestinal (GI) 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 complication i.e. pseudoaneurysm bleeding from large vessels and retroperitoneal bleeding. Moreover, many of these patients with SAP end up undergoing 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. Also noteworthy is the fact that SV 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 on this aspect have been attempted to address this pertinent management dilemma. Hajibandeh *et al* in their systemic review of 05 observational studies and 252 patients demonstrated no significant difference in the rate of resolution of thrombus or formation of varices/collaterals. The study however had a major drawback of low study heterogeneity between anticoagulation and no anticoagulation group(90). Another systemic review by Norton *et al* included 16 studies (09 case reports, 02 case series, and 05 single-center studies). 46.5% of a total of 198 affected patients received anticoagulation. 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(91).

The most recent meta-analysis has included 07 retrospective cohort studies (233 patients of AP suffered from splanchnic venous thrombosis). SVT thrombosis was seen in 33-82 %, PV thrombosis in 4-32%, and SMV thrombosis in 5-9% of all patients with

splanchnic thrombosis. A combination of SVT, PVT, and or SMV thrombosis has also been reported in variable combinations. Moderate to SAP was resent in 89 % of patients who had some evidence of splanchnic vein thrombosis. A common drawback of these systemic reviews and meta-analysis is 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 (PE), extrahepatic portal vein obstruction (EHPVO), and deep vein thrombosis (DVT). Low molecular weight heparin (LMWH) followed by Vit. K antagonist, Fondaparinaux, and Apixaban have been used in different studies. 47 % of affected patients who received therapeutic anticoagulation showed no statistically significant rates of recanalization (92-95).

INTERVENTIONS IN ACUTE PANCREATITIS

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

Endoscopic Retrograde Cholangiopancreatography (ERCP)

Endoscopic retrograde cholangiopancreatography (ERCP) is an invasive intervention with a complication rate of 5 % to 15 % (90). The current use of ERCP in AP is limited to relieve of biliary obstruction. In AP patients 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 ERC in these patients with ABP without cholangitis. Neoptolemos *et al* showed that patients with predicted severe AP had fewer complications with an early ERCP (within 72 h of admission) (24% vs. 61%, *P* <0.05)(96). On the other hand, Folsch *et al* reported that early ERCP was not beneficial in patients with ABP without obstructive jaundice(97). 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). Schepers *et al* also compared the urgent ERCP with a conservative approach in patients with predicted severe ABP(98). The study showed that urgent ERCP with sphincterotomy did not reduce the major complication or mortality (38% vs. 44%, risk ratio 0·87, 95% 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.

Interventions for drainage: What are the options?

The management of the pancreatic and peri-pancreatic collections has evolved over the last 2 decades. The indications to drain (peri-) pancreatic collections in AP are infection and symptomatic sterile necrosis **(Table 8)**. The choice of interventions includes percutaneous, endoscopic, minimally invasive surgery, or a combined approach, and 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 acute pancreatitis. The approach involves initial conservative management and then either percutaneous drainage or endoscopic transluminal drainage can be selected.

Timing of drainage: Is there an ideal time?

There are multiple dilemmas while contemplating the drainage of necrotic collection. Should 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 till 4 wk after the disease onset to allow liquefaction and encapsulation of the collection(46),(100). The cut-off 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 to 75 days, between the onset of the disease and the first drainage procedure **(Table 9)**. The older studies suggested that delaying percutaneous drainage till encapsulation may improve the outcome (101- 105). Other recent studies have suggested the usefulness of early drainage in improving outcomes (106). However, a recent multicentre randomized study (POINTER trail), which compared early *vs* delayed drainage in AP,did not show the superiority of early drainage (107-108). 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%, RR: 0.94, 95%CI 0.77 to 1.14) in early and delayed drainage. Studies have shown that early drainage required a higher number of re-interventions compared to delayed strategy. Trikudanathan *et al* have demonstrated that early endoscopic drainage (< 4 wk) required higher percutaneous drainage compared with patients with walled-off collections(108).

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 organ failure may require early drainage.

Modality of drainage

Percutaneous catheter drainage (PCD)

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 (CT) guidance. Percutaneous catheter drainage is important in patients where early drainage is required and necrotic collection is not well encapsulated. Freeney *et al* for the first time demonstrated the safety and efficacy of PCD in AP in 1998 with a successful outcome in 47% of patients with PCD only(111). Subsequently, Baril *et al*. and Mortele *et al* also confirmed the success of PCD in AP (112-113).

In 2010 Van Santvoort *et al* (PANTER trial)did a randomized controlled trial of the step-up approach and primary surgery and found a significant success rate of PCD(99). The first step in "the step-up approach" became the PCD and remain 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** summaries 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 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 done using conventional endoscopic drainage or under endoscopic ultrasound (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).

Percutaneous or endoscopic drainage or combined approach: Which modality to choose?

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 AGA guidelines also suggest that an endoscopic approach may be preferred. However, the choice of drainage method should be individualized and guided by multiple factors: 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.

Choice of stent: Plastic or metal stents?

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 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 pseudo aneurysm formation(122). **Table 10** summaries the studies for the outcome of endoscopic drainage with plastic and metal stents

The retrospective studies compared to metal and plastic stents showed that BFMS performed better than multiple plastic stents for draining walled-off collection(126)(128). On the other hand, 2 RCTs showed similar clinical efficacy with metal and multiple plastic stents for WON (122-123). Furthermore, a meta-analysis concluded no difference in clinical success and adverse events between LAMS and

multiple PS for symptomatic WON(129). 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 vs. 10 d) (127).

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 stent 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),(130). Studies have shown variable results with the use of different agents. Agents used for irrigation include normal saline, antibiotics, hydrogen peroxide, and streptokinase. Werge *et al* showed that local instillation of antibiotics in infected pancreatic necrosis improves the eradication of infection(43). Similarly, Larino-Noia showed that the addition of local infusion of antibiotics avoids the need for necrosectomy in half of the patients with infected pancreatic necrosis not responding to drainage and systemic antibiotics(130). 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* suggested that these agents such agents can be used in the management of necrotic pancreatitis if there is no clinical and imaging improvement after drainage alone (131).

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 naso-cystic tube and irrigation (chemical necrolysis), and direct endoscopic necrosectomy (DEN). Lakhtakia *et al* showed that after initial drainage with a biflanged metal stent, 74.6 % of patients had clinical success. Re-intervention with a step-up approach improved the overall clinical success to 96.5% with DEN required only in 9.2 % of the patients (132)

Several studies have confirmed the safety and efficacy of DEN in patients with infected pancreatic collections (133-134).PENGUIN trial compared the DEN and surgical necrosectomy (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 (135). 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 video-assisted retroperitoneal debridement (VARD) (136). The major complications and mortality rates with 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 the DEN after initial drainage. Earlier thought was to perform the DEN after 3-7 days to allow maturation of the cystogastrostomy/cystoenterostomy tract. However, with the advent of LAMS, DEN can be performed immediately after the placement of the stent. Yan *et al* in a muti-centric study compared the immediate and delayed DEN for WON. The study showed no difference in clinical success and adverse events (137). 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.

Minimally invasive approach and Surgery: When to consider?

The indications of surgery are limited in the setting of acute pancreatitis. 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* (PANTER trial) compared the 'step-up' approach with primary open surgical necrosectomy surgery(99). The study concluded that a minimally invasive step-up approach reduces 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 (MIRP) and video-assisted retroperitoneal debridement (VARD) (138-139). Both MIRP and VARD retroperitoneal techniques are modifications of the open lateral approach initially described in the 1980s by Fagniez *et al*(140). 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 intra-abdominal hypertension (IAH) and persistent ascites may require a multipronged approach predominantly revolving around timely drainage

Management of intra-abdominal hypertension (IAH): What to do?

In AP, high intra-abdominal pressures 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 intra-abdominal hypertension (IAH) or abdominal compartment syndrome (ACS). IAH is defined as sustained intra-abdominal pressure (IAP) above 12 mmHg and occurs frequently in AP (51). Several studies have observed poor outcomes in patients with IAH(141-142).

The management of increased abdominal pressure should follow the standard algorithm proposed by the various societies irrespective of the etiology (143-144). The management includes the frequent monitoring of IAP, evacuation of intraluminal contents using nasogastric 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* in a retrospective study showed that the presence of intra-abdominal hypertension increases the risk of development of multiple organ failure and was associated with higher mortality(142). At 48 h post-PCD, the mean reduction in intra-abdominal pressure was significantly higher (6.87 mmHg vs. 3.21 mmHg, p-value <0.001) in patients with baseline IAH than in patients without IAH. The study also identified that post-PCD, a pressure reduction of >40% was associated with better survival.

Persistent Ascites: How to manage?

Ascites are commonly described in patients with AP but its association and effect on outcome are poorly understood. Samanta *et al* identified that the presence of ascites

was associated with higher rates of OF and increased mortality in AP(145). Mortality rates were 4 times higher in the presence of ascites compared to non-ascites patients (34.1% vs. 8.4%, p-value 0.001). The study showed that the presence of moderate to gross ascites was associated with intra-abdominal hypertension and higher rates of OF. Though the presence of ascites increases intra-abdominal pressure, 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 greater than 1 may indicate underlying portal hypertension while pancreatic ascites (SAAG less than 1) may require drainage and/ or endoscopic placement of trans papillary 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 as even though there are several guidelines the jury is still out and 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 intriguing the investigators to date. The intervention is tending towards endoscopy or PCD rather than surgery; with the progressive development of technology and expertise, more data is likely to emerge which may help in the formulation of more conclusive indications and guidelines.

81883_Auto_Edited.docx

ORIGINALITY REPORT

5%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	141 words — 2%
2	Guru Trikudanathan, Udayakumar Navaneethan, Santhi Swaroop Vege. "Current Controversies in Fluid Resuscitation in Acute Pancreatitis", Pancreas, 2012 Crossref	55 words — 1%
3	Gaurav Muktesh, Jayanta Samanta, Jahnvi Dhar, Roshan Agarwala et al. "Endoscopic Ultrasound–guided Drainage of Patients With Infected Walled-off Necrosis", Surgical Laparoscopy, Endoscopy & Percutaneous Techniques, 2022 Crossref	31 words — < 1%
4	Ichiro Yasuda, Kosuke Takahashi. "Endoscopic management of walled‐off pancreatic necrosis", Digestive Endoscopy, 2020 Crossref	20 words — < 1%
5	Jose Lariño-Noia, Daniel de la Iglesia-García, Jaime González-Lopez, Javier Díaz-Lopez et al. "Endoscopic drainage with local infusion of antibiotics to avoid necrosectomy of infected walled-off necrosis", Surgical Endoscopy, 2020 Crossref	20 words — < 1%

6	Sergio Pinto, Saverio Bellizzi, Roberta Badas, Maria Laura Canfora et al. "Direct Endoscopic Necrosectomy: Timing and Technique", Medicina, 2021 Crossref	18 words — < 1%
7	journals.lww.com Internet	16 words — < 1%
8	Prediction and Management of Severe Acute Pancreatitis, 2015. Crossref	13 words — < 1%
9	docksci.com Internet	13 words — < 1%
10	www.wjgnet.com Internet	13 words — < 1%
11	Pramod K. Garg, Soumya Jagannath Mahapatra. "Optimum Fluid Therapy in Acute Pancreatitis Needs an Alchemist", Gastroenterology, 2020 Crossref	12 words — < 1%
12	fg.bmj.com Internet	12 words — < 1%
13	pure.uva.nl Internet	12 words — < 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS