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NARRATIVE REVIEW

Infected pancreatic necrosis—Current trends in management

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Abstract

Acute necrotizing pancreatitis is a common gastrointestinal disease requiring hospitalization and multiple interventions resulting in higher morbidity and mortality. Development of infection in such necrotic tissue is one of the sentinel events in natural history of necrotizing pancreatitis. Infected necrosis develops in around 1/3rd of patients with necrotizing pancreatitis resulting in higher mortality. So, timely diagnosis of infected necrosis using clinical, laboratory and radiological parameters is of utmost importance. Though initial conservative management with antibiotics and organ support system is effective in some patients, a majority of patients still requires drainage of the collection by various modalities. Mode of drainage of infected pancreatic necrosis depends on various factors such as the clinical status of the patient, location and characteristics of collection and availability of the expertise and includes endoscopic, percutaneous and minimally invasive or open surgical approaches. Endoscopic drainage has proved to be a game changer in the management of infected pancreatic necrosis in the last decade with rapid evolution in procedure techniques, development of novel metal stent and dedicated necrosectomy devices for better clinical outcome. Despite widespread adoption of endoscopic transluminal drainage of pancreatic necrosis with excellent clinical outcomes, peripheral collections are still not amenable for endoscopic drainage and in such scenario, the role of percutaneous catheter drainage or minimally invasive surgical necrosectomy cannot be understated. In a nutshell, the management of patients with infected pancreatic necrosis involves a multi-disciplinary team including a gastroenterologist, an intensivist, an interventional radiologist and a surgeon for optimum clinical outcomes.

Keywords Acute pancreatitis · Bleeding · Endoscopic ultrasound · LAMS · Mortality

Introduction

Acute pancreatitis is one of the most common gastrointestinal emergencies requiring admission globally. The incidence of acute pancreatitis has increased with 33.74 cases per person-years [1]. It is a dynamic disease with a fluctuating degree of systemic inflammation, which may lead to development of different local and systemic complications and therefore a varying clinical course [2]. Local complications are associated with significant morbidity in patients with acute pancreatitis. According to the revised Atlanta classification, local complications have been divided into acute peripancreatic fluid collection, pseudocyst, acute necrotic collection (ANC) and walled-off necrosis (WON) based on whether the patient has underlying acute interstitial pancreatitis or necrotizing pancreatitis and presence of surrounding fibrous wall or not [3]. Management of local complications has undergone a paradigm change in the last decade from open necrosectomy to minimally invasive therapies [4]. Infection develops in around one-third of patients with necrotizing pancreatitis with mortality reaching up to 30%. Infectious complications in acute pancreatitis and specifically infected pancreatic necrosis (IPN) usually peak during the second or third week of illness [5]. Various mechanisms have been postulated in the development of infection in the sterile necrosis. Increased intestinal permeability along with reduced motility causing bacterial overgrowth and bacterial translocation, early bacteremia, bowel ischemia and use of parenteral nutrition have been postulated as pathogenetic factors for infection

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in the initial sterile pancreatic necrosis [5–7]. It has been shown that IPN is related to a worse outcome compared to patients with severe acute pancreatitis without IPN [8].

Diagnostic criteria for IPN

Though various studies have explored the role of clinical, imaging and laboratory markers to diagnose or predict the development of IPN, there are no reliable clinical or laboratory parameters for the same with high accuracy. In a prospective multicentric study by Rau et al., procalcitonin was better than C-reactive protein (CRP) in predicting infected pancreatic necrosis and/or development of multi-organ dysfunction. A procalcitonin value of ≥ 3.5 ng/mL on two consecutive days had a sensitivity and specificity of 93% and 88% for predicting IPN [9]. In a recent systemic review, a procalcitonin value of > 0.5 ng/mL had a sensitivity and specificity of 80% and 91% for predicting IPN [10]. Apart from the static value of procalcitonin, Adachi et al. also showed that in patients with infected necrosis, the value of procalcitonin increases dynamically over time compared to patients with sterile necrosis [11]. Recently, Siriwardena et al. conduced a prospective study to explore the role of procalcitonin-based algorithm to guide antibiotic therapy in patients with acute pancreatitis. Decision to start or stop antibiotic was based on a procalcitonin value of 1.0 ng/mL. In the procalcitonin-based group, usages of antibiotics could be reduced without increasing risk of disease-related major adverse events or mortality [12]. Serum IL-6, phospholipase A2 and other serum markers are also under evaluation for assessing their role in predicting IPN [13]. The presence of gas bubbles in pancreatic or peripancreatic collection on contrast-enhanced CT scan is a useful sign to detect or predict IPN [14]. However, gas configuration is present in only 25% to 56% of patients with IPN [14–16]. Moreover, spontaneous fistulization in the gastrointestinal tract and prior intervention in any form can also lead to gas configuration within the collection. Image-guided ultrasonography (USG)/computed tomographic (CT) fine needle aspiration (FNA) followed by gram stain and culture is also very useful in the diagnosis of IPN. The timing of FNA during the disease process is also very important, as it is difficult to predict as to when the infection will develop in pancreatic necrosis. Nevertheless, studies have shown very high false-negative rates of 20% to 50% [17, 18]. Due to high false-negative rates, usefulness of negative FNA in clinically deteriorating patient remains questionable. Thus, the clinical use of FNA in all patients with suspected infection remains limited. Recently, positron emission tomography (PET)/CT with 18F-FDG-labeled autologous leukocytes have also been explored for the diagnosis of IPN with promising results; however, larger multi-centric studies are required to validate the results before its clinical use [19]. Finally, diffuse-weighted magnetic resonance imaging may have an added value in detecting infected pancreatic fluid collections, but results confirming its use in the diagnosis of IPN should still be demonstrated [20]. Despite these various laboratory and imaging markers, a majority of patients are diagnosed as having suspected IPN based on clinical and biochemical criteria. Persistence of organ failure or persistence of two inflammatory markers (temperature > 38.5 °C, elevated C-reactive protein or leukocytes) during three consecutive days after continuation of conservative management is usually considered a clinically suspected IPN. However, these clinical criteria are useful only after the second week from the onset of acute pancreatitis, as during the initial two weeks these signs may be secondary to disease process rather than secondary infection [15, 16].

Microbiological profile and antibiotic use

In patients with IPN, up to 32% of patients have extra-pancreatic infections especially during two weeks of disease [21]. The most common extra-pancreatic infections are respiratory infection, bacteremia or urinary infection [21]. Among patients with IPN, gram-negative bacilli including *E. coli*, *Klebsiella* species, *Pseudomonas* or *Proteus* species are the most common pathogens identified, followed by gram-positive cocci including *Staph aureus*, *Streptococcus* or *Enterococcus* spp. [22, 23]. Recently, studies have shown that the incidence of multi-drug resistance organisms can be as high as 38% to 57% and it is a risk factor for increased morbidity and mortality [24, 25]. So, careful use of antibiotics and antibiotic stewardship is essential for better outcomes [26, 27]. Risk of fungal infection is also increased in patients with IPN. Studies have shown incidence between 5% and 68.5% with the most common organism being *C. albicans* [28, 29]. However, a majority of studies are retrospective in nature and the clinical impact of fungal infection on overall disease morbidity and mortality has still not been explored prospectively yet. Regarding antibiotic selection, drugs with good penetration in pancreatic tissue or necrosum such as broad-spectrum penicillin (piperacillin-tazobactam), third-generation cephalosporins, carbapenems, cefepime or fluoroquinolones with anaerobic coverage such as metronidazole should be preferred in case of suspected or confirmed IPN depending on growth and local sensitivity pattern [30–32]. Though it is recommended to start antibiotics in patients with suspected IPN, prophylactic antibiotics have not been shown to prevent the occurrence of extra-pancreatic or pancreatic infection and therefore are not recommended [33, 34].

Interventional management

The management of IPN has undergone a paradigm shift over the last decade with wider adoption of different types of minimally invasive techniques such as endoscopic, radiological or surgical approach [33, 34]. The endoscopic approach includes endoscopic ultrasound (EUS)–guided transmural drainage (ETD) with plastic or metallic stents through single or multiple access ("single or multiple transluminal gateway drainage") with or without direct endoscopic necrosectomy (DEN). The radiological approach consists of inserting percutaneous catheter drainage (PCD) through retroperitoneal or transperitoneal route. Combined endoscopic and radiological approaches or "dual-modality drainage" (DMD) are also sometimes needed in patients with large or complex necrotic collections. Lastly, minimally invasive surgery using the video-assisted retroperitoneal debridement technique (VARD) or percutaneous sinus tract endoscopy and necrosectomy (PEN) can also be used if a previous PCD access is performed [35].

Timing of intervention in infected pancreatic necrosis

Timing of interventions in necrotizing pancreatitis has always been a matter of debate. An initial prospective randomized trial by Mier et al. showed that patients undergoing early surgical necrosectomy (within 48 to 72 hours of onset) had higher mortality (58% vs. 27%) compared to late necrosectomy (after 12 days of onset) [36]. Subsequently, a retrospective study by Besselink et al. showed that patients in whom interventions were done after 30 days had lower mortality compared to patients in whom interventions were done between one and 14 and 15 and 29 days (8% vs. 75% vs. 45%; $p < 0.001$) [18]. Delaying interventions or surgery in patients with acute pancreatitis gives time for collections to mature and organize by forming a surrounding inflammatory wall, which also helps in differentiating necrotic tissue from viable tissue [18]. A series including 639 patients with necrotizing pancreatitis and sequential abdominal CTs demonstrated clinically relevant walled-off necrosis (largely or fully encapsulated necrotic collections) was seen in 43% of patients within the first three weeks [14]. Recently, Boxhoorn et al. published a multi-center randomized controlled trial comparing immediate and postponed interventions in patients with suspected or confirmed IPN [15]. In the immediate group, patients underwent interventions within 24 hours following randomization, while in the postponed group, interventions were postponed until formation of an encapsulating wall and intervention was performed, if deemed necessary, at that point. Primary end point (comprehensive complication index) and mortality both were equal in both groups despite a higher number of interventions performed in the immediate group. Additionally, in the postponed group, 40% of patients improved with conservative management alone without requirement of any intervention. The authors concluded that immediate drainage is not superior to postponed drainage in regard to overall complications and mortality. Therefore, guidelines currently recommend delaying the interventions, if feasible, until at least four weeks after the onset of the disease [33, 34].

However, despite optimal supportive conservative therapy, more than half the patients still require interventions due to either persistence or worsening of systemic inflammatory response syndrome (SIRS) or organ failure. Trikudanathan et al., in a retrospective comparative study, described outcomes of early (< 4 weeks) vs. standard (> 4 weeks) endoscopic step-up approach in patients with necrotizing pancreatitis [37]. From 193 patients, 76 patients underwent an early step-up approach and 117 patients underwent a standard step-up approach. A majority of patients in the early group underwent interventions due to infected collection (91% vs. 39%; $p = 0.045$). Patients undergoing early interventions had a higher need for surgical intervention (7% vs. 1%; $p = 0.03$), adjuvant percutaneous intervention (42% vs. 21%; $p = 0.002$) and higher mortality (13% vs. 4%; $p = 0.02$) compared to patients undergoing interventions in the standard group. However, the observed mortality appears to be disease process-related rather than procedure-related [37]. Subsequently, in a recent meta-analysis involving six studies, early endoscopic interventions had similar technical and clinical success rates without increase in procedure-related adverse events as compared to interventions late in course of acute pancreatitis, suggesting that early endoscopic drainage could be performed if warranted [38]. Rana et al. compared endoscopic vs. percutaneous interventions in the early phase of acute pancreatitis. Patients undergoing percutaneous interventions had increased requirement of surgical necrosectomy (30% vs. 4%; $p = 0.01$), prolonged hospitalization and a higher rate of external pancreatic fistula (22% vs. nil; $p = 0.02$) [39]. The necrotic collections in the early course of disease are diffused, less organized and encapsulated, with more solid content and lacking a complete surrounding inflammatory wall [14]. Thus, interventions in the early course of illness should be done on an individual basis after careful review of indications. However, if required, central collections should ideally be intervened with endoscopic approach as compared to percutaneous approach in the presence of adequate expertise [40].

Step-up approach

In the landmark PANTER trial by the Dutch Pancreatitis Study Group, patients were randomized to open necrosectomy or a step-up approach to treatment [41]. The step-up approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. Patients having undergone the step-up approach had reduced risk of major complications such as new-onset organ failure (12% vs. 42%; $p=0.001$), incisional hernia (7% vs. 24%; $p=0.03$), endocrine (16% vs. 38%; $p=0.02$) or exocrine pancreatic insufficiency (7% vs. 33%; $p=0.002$) compared to patients who underwent open necrosectomy [41]. Subsequently, Bakker et al. also showed that patients undergoing transgastric necrosectomy had reduced incidence of composite of major complications (20% vs. 80%; $p=0.03$), new-onset organ failure (0% vs. 50%; $p=0.03$), development of pancreatic fistula (10% vs. 70%; $p=0.02$) and exocrine pancreatic insufficiency (50% vs. 0%; $p=0.04$) compared to patients undergoing surgical necrosectomy [42]. In a randomized study by Bang et al., endoscopic transluminal approach had lower incidence of composite of major complications (40.6% vs. 11.8%; $p=0.007$), new-onset SIRS (56.3% vs. 5.6%; $p=0.02$) and pancreatic fistula formation (28% vs. 0%; $p=0.001$) compared to the surgical step-up approach [43]. Similarly, a Dutch randomized controlled trial also comparing radiological/minimally invasive surgical step-up approach to endoscopic step-up approach confirmed similar outcomes, but a reduced rate of pancreatic fistulas and shorter length of hospital stay in the endoscopy step-up approach [16]. Currently, endoscopic or minimally invasive procedure and step-up approach are being recommended by all guidelines for the management of pancreatic collections depending on available expertise. Open surgical approaches are being reserved in case of failure of minimally invasive therapy and complications such as perforations or intestinal ischemia and in patients with abdominal compartment syndrome [33, 34].

Endoscopic step-up approach

Endoscopic transluminal drainage of pancreatic collections

Endoscopic ultrasound (EUS)-guided drainage has become the first line of therapy for the management of pancreatic necrotic collections. In a randomized trial by Varadarajulu et al., EUS-guided drainage was shown to have a higher technical success compared to a conventional endoscopic drainage group (100% vs. 33%; $p<0.001$) due to the ability of EUS-guided drainage to drain even non-bulging collection; additionally, it is supposed that rates of bleeding can also be reduced by avoiding vessels under Doppler guidance [44]. Endoscopic step-up approach includes initial transluminal drainage using plastic stents (double-pigtail stents) or metal stents followed by endoscopic necrosectomy, if required. Initially, Lee et al. compared biliary fully covered self-expandable metal stents (FCSEMS) and multiple plastic stents in patients with pseudocyst or walled-off necrosis (WON). Median procedure time was significantly shorter with the use of FCSEMS compared to plastic stent (15.0 minutes vs. 29.5 minutes; $p<0.01$), but overall similar technical and clinical success rates were observed [45]. Lumen-apposing metal stents (LAMS) present a dumbbell shape with bilateral flanges which allows close apposition of two structures, as well as including electrocautery in the deployment device, therefore facilitating stent insertion compared to FCSEMS and offering a larger diameter for drainage compared to plastic stents [46]. In a study by Bang et al., 60 patients with WON were randomized into two groups: LAMS or multiple plastic stent group. Both groups had similar clinical success; however, the LAMS group had higher stent-related adverse event rates in patients with indwelling LAMS for more than three weeks (32.3% vs. 6.9%; $p=0.01$). With modification of the protocol and timely removal of LAMS after collapse of the necrotic cavity, rates of stent-related adverse events (especially bleeding) could be reduced. The clinical success was equivalent across both groups with reduced procedure duration in the LAMS group (15 minutes vs. 40 minutes; $p<0.001$) [47]. Recently, Karstensen et al. compared LAMS vs. multiple plastic stents in patients with large (> 15 cm) WONs. Technical and clinical success rates, number of necrosectomies required (3.2 vs. 2.2; $p=0.42$) and overall adverse event rates (5% vs. 18.2%; $p=0.35$) were comparable between both groups [48]. However, multicentric trials comparing metal and plastic stents in drainage of WON are still pending. Moreover, due to ease of administration with the advent of cautery-enhanced LAMS, the learning curve with LAMS could be reduced, another issue which could yet be explored in subsequent studies. Nevertheless, it should be underlined that low number of procedures and hospital volume are related to a higher occurrence of adverse events related to LAMS use [49]. Recently, wider diameter LAMS (20 mm) are also available which provide 78% greater cross-sectional area compared to 15-mm LAMS [46]. In a comparative study by Parsa et al., 20-mm LAMS provides similar clinical efficacy with fewer requirement of necrosectomies (1.3 vs. 2.1; $p<0.001$) compared to 15-mm LAMS without increasing risk of overall or stent-related adverse events [50]. Another novel type of metal stent designed for collection drainage is a bi-flanged metal stent (BFMS). Siddiqui et al. did a multicentric retrospective study comparing BFMS ($n=205$) with LAMS ($n=182$) in drainage of WONs. Both groups had similar technical and clinical success rates. Patients with BFMS had higher frequency of stent occlusion (10.2% vs. 5.9%; $p=0.04$), but surprisingly lower requirement of procedures (2 vs. 3; $p<0.001$) compared to LAMS [51]. After the placement of BFMS or LAMS in patients with WON with significant solid debris, stent occlusion by debris remains a major challenge which can lead to the development of fever. Recently, Vanek et al. published a multi-centric randomized trial exploring the role of co-axial plastic stent insertion within the LAMS in patients with WON. It was shown that the use of a co-axial plastic stent can reduce the incidence of stent occlusion (14.7% vs. 36.3%; $p = 0.042$) and overall global adverse events (20.7% vs. 51.5%; $p = 0.008$) [52]. However, subsequently meta-analysis of eight studies ($n = 460$) did not show reduced incidence of stent occlusion or need for re-intervention in patients with use of a co-axial plastic stent (Fig. 1) [53].

Direct endoscopic necrosectomy (DEN)

After initial successful transluminal drainage, about half of the patients still require DEN for the removal of solid debris. Studies have shown that the presence of significant solid debris within the collection, especially more than 30% to 40%, increases need for endoscopic step-up approach in terms of DEN [54–57]. Chandrasekhara et al. did a retrospective study of 163 patients with pancreatic fluid collections undergoing drainage with lumen-apposing metal stent (LAMS). Predictors for the need of necrosectomy included size of collection > 10 cm, para-colic extension of collection and > 30% solid debris within the collection [56]. In a study by Seicean et al., the presence of more than 50% solid debris was predictive of need for multiple (more than two) necrosectomies [57]. Recently, Baroud et al. did a retrospective study and classified the pancreatic necrotic collection based on quadrant involved, necrotic content of the collection and the presence/absence of infection (quadrant, necrosis and infection [QNI] classification). They showed that patients with diffuse collections (extending in > 2 abdominal quadrants) and/or a higher percentage of solid debris (> 30%) were associated with a more complicated course requiring necrosectomies and prolonged length of stay [58]. A study by Tsujimae et al. also observed that fluid occupying > 2 regions, ≥ 35% remaining collection post initial drainage and a positive "sponge sign" on CT scan are predictive factors for need for necrosectomy [59]. In conclusion, size, site and the extent of collection and degree of solid debris are factors that determine the need for endoscopic step-up therapy and subsequent necrosectomies. Timing of endoscopic step-up approach after EUS-guided drainage has also been explored. A recent retrospective study by Pawa et al. showed that patients undergoing delayed DEN had a shorter index hospital stay and fewer necrosectomies than immediate necrosectomy [60]. However, another multi-centric retrospective study concluded that the mean number of DEN sessions for WON resolution was significantly lower in the immediate necrosectomy group compared to that of the delayed group (3.1 vs. 3.9, $p < 0.001$). Performing necrosectomy at the time of stent placement was an independent predictor for the resolution of WON with a lower number of necrosectomy sessions (odds ratio 2.3; $p = 0.004$) [61]. It is believed that performing early necrosectomy has an advantage of removal of solid debris and

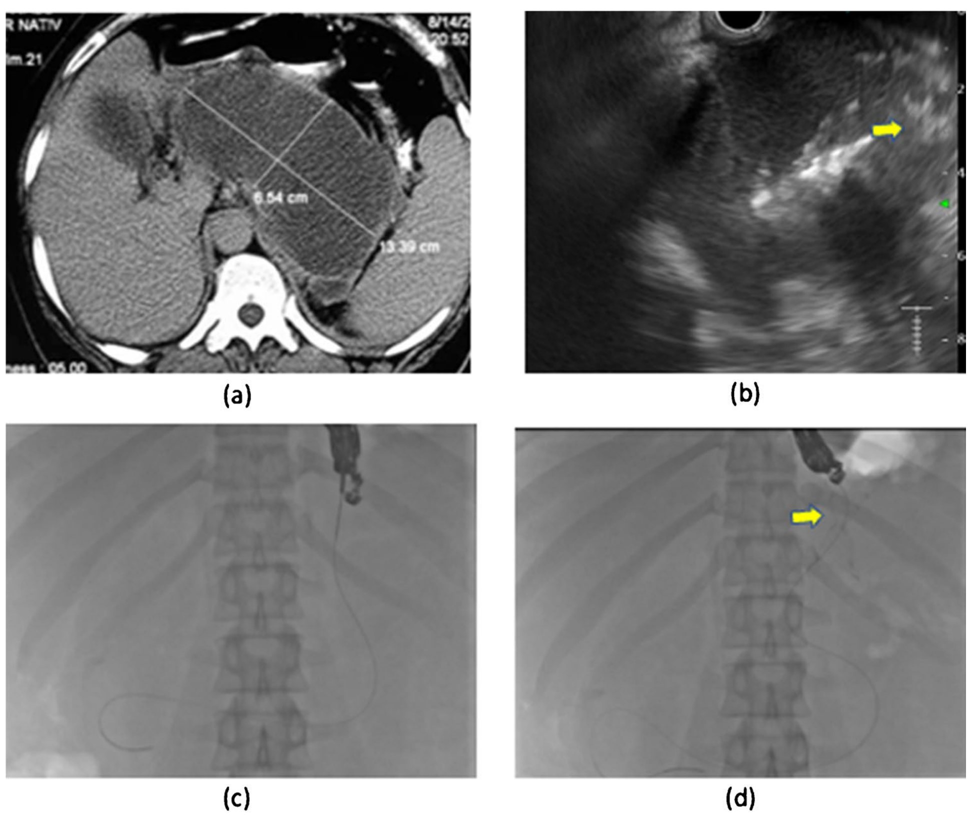

Fig. 1 **a** Axial scan of a patient of acute pancreatitis showing large 14 cm * 7 cm peripancreatic collection in lesser sac. The patient had presented with systemic inflammatory response syndrome (SIRS) not responding to trial of antibiotic drainage for 72 hours and planned for endoscopic ultrasound (EUS)-guided transluminal drainage. **b** EUS showing same collection with < 30% solid debris (yellow arrow). **c** The collection was punctured with a 19-G EUS needle followed by passage of a 0.025-inch guidewire. **d** After dilation of track with 6F cystotome, 16 mm * 30 mm Nagi stent (Taewoong Medical, Gyeonggi-do, South Korea) could be placed (arrow showing stent with waist in the middle of the stent)

therefore resulting in faster resolution of SIRS and organ failure [61]. Nevertheless, many patients with solid debris may not require necrosectomy due to the large caliber of the metal stent. Recently, a multi-centric randomized trial has been conducted by Bang et al. showing that upfront DEN is associated with lower requirement of re-intervention (1 vs. 2; $p = 0.0027$) and reduced hospital stay (16.2 ± 15.4 vs. 22.9 ± 16.9; $p = 0.048$) compared to "step-up" DEN with overall equivalent clinical success rates, procedure-related adverse events and mortality (Fig. 2) [62].

Adverse events related to endoscopic step-up approach

Overall, endoscopic transmural drainage of pancreatic collections is associated with > 95% technical and clinical success rates [63]. Adverse events (AE) varied between 0% and 12% across various studies among which bleeding (intra-procedural or delayed), stent mal-deployment or perforation are the most common peri-procedural complications. A majority of the complications are minor and can be tackled endoscopically; however, in the presence of significant bleeding due to erosion of surrounding vessel or free peritoneal perforation, a few patients might require additional radiological or surgical interventions [64].

Impact of disconnected pancreatic duct syndrome (DPDS)

In a multi-centric study including 361 patients with pancreatic fluid collections (149 [41%] WONs), DPDS was observed in 68.3% of patients with WON. Patients with DPDS had more requirement of hybrid treatment (31.1% vs. 4.8%; $p < 0.001$), re-intervention (30% vs. 18.5%; $p = 0.03$) and rescue surgery (13.2% vs. 4.8%; $p = 0.02$). Moreover, collection recurrence was higher in patients without permanent transmural stents (17.4% vs. 1.7%; $p < 0.001$) [65]. On the other hand, a randomized trial by Chavan et al. on evaluating the role of maintaining a transmural plastic stent to prevent collection concludes that both groups had similar recurrence rates at three (5.8% vs. 5.8%; $p > 0.05$) and 12 months (13.5% vs. 25%; $p > 0.05$). However, trial limitations included a short follow-up, a lower technical success rate in placing plastic stent after the removal of metal stents and higher migration of plastic stents during follow-up [66]. Moreover, keeping transmural plastic stent in situ has shown excellent long-term (> 3 years) safety and efficacy [67, 68]. Therefore, it is still suggested to attempt replacing the metal stent with plastic stent after resolution of the cavity or to keep the initial plastic stent in situ indefinitely [34].

Combined techniques in endoscopic step-up approach

Presence of diffuse collection with para-colic gutter extension may require dual-modality drainage combining both endoscopic and percutaneous approach. Dual-modality drainage may reduce duration of indwelling percutaneous catheter time, length of stay and need for endoscopic retrograde pancreatography for preventing external pancreatic fistula [69]. Similarly, in the presence of diffuse pancreatic collection with extension in both the head and body, multiple transluminal gateway technique can also be applied resulting in multiples EUS-guided orifices between the collection and the digestive tract. This technique has shown to improve clinical success (91.7% vs. 52.1%) with decrease in requirement of endoscopic necrosectomy or surgery compared to standard drainage technique [70]. Despite availability of wider diameter of metal stents and increased expertise of DEN, such modified methods can be of help in the management of complex and large pancreatic necrotic collections (Figs. 3 and 4; Table 1).

Adjuvant therapies along with EUS-guided drainage of pancreatic necrosis

Naso-cystic irrigation Placement of a naso-cystic catheter alongside a previously placed plastic stent or through metal stents can be used for irrigation of the necrotic cavity. In a study by Siddiqui et al., irrigation using a naso-cystic tube reduced the risk of stent blockage (33% vs. 13%; $p = 0.03$)

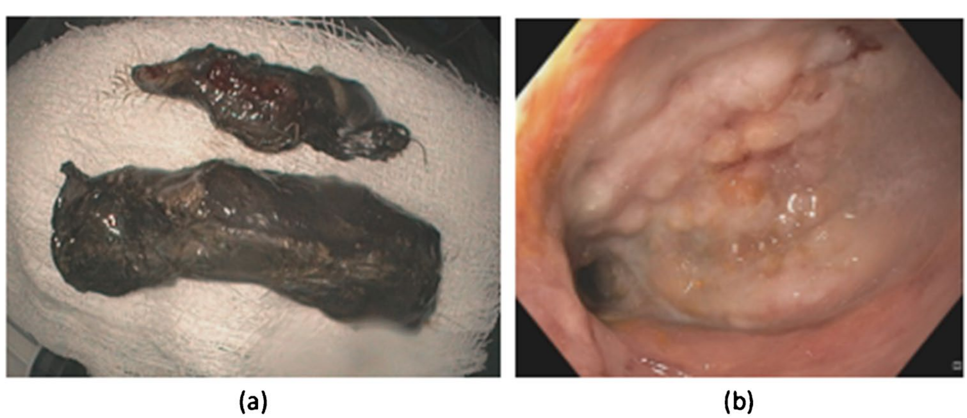

Fig. 2 With conventional accessories such as snare and foreign body forceps, adequate necrosectomy could be achieved with retrieval of large chucks of necrosum (**a**) along with visualization of healthy granulation tissue in the cavity at the end of the procedure (**b**)

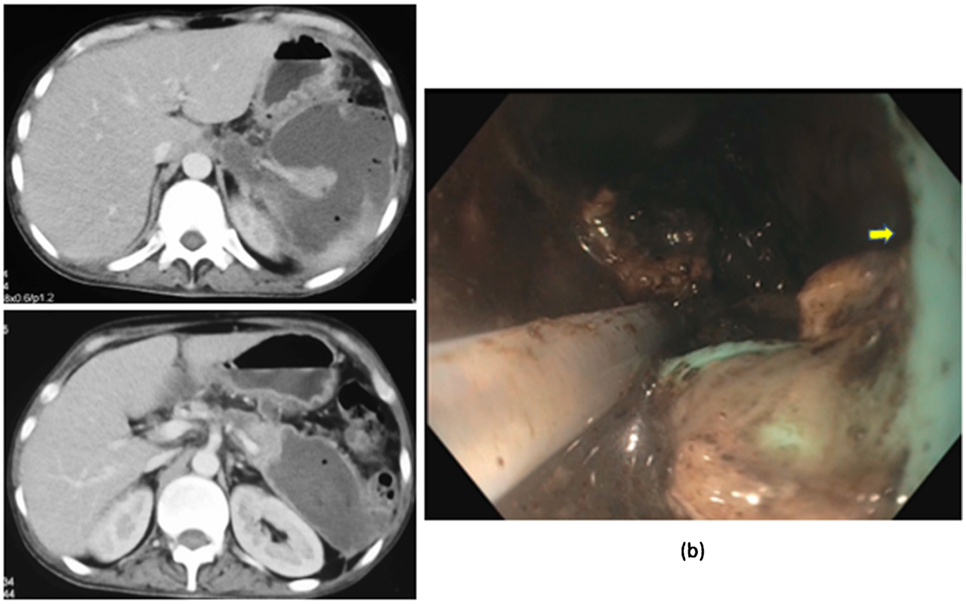

Fig. 3 Dual-modality drainage in the presence of diffuse collection extending from lesser sac to the left para-renal area. The patient had gallstone induced acute pancreatitis with clinically suspected infected pancreatic necrosis (IPN) and persistent organ failure. Axial computed tomography (CT) scan showing large collection in the lesser sac extending until the right para-renal and para-colic gutter (**a**). The central collection was drained using endoscopic ultrasound (EUS)-guided endoscopic approach and peripheral collection was drained using percutaneous approach. After initial stabilization of the patient, complete endoscopic necrosectomy could be performed. Image **b** shows visualization of percutaneous catheter (yellow arrow) during endoscopic necrosectomy. Percutaneous catheter could be removed after 10 days along with clinical improvement of the patient

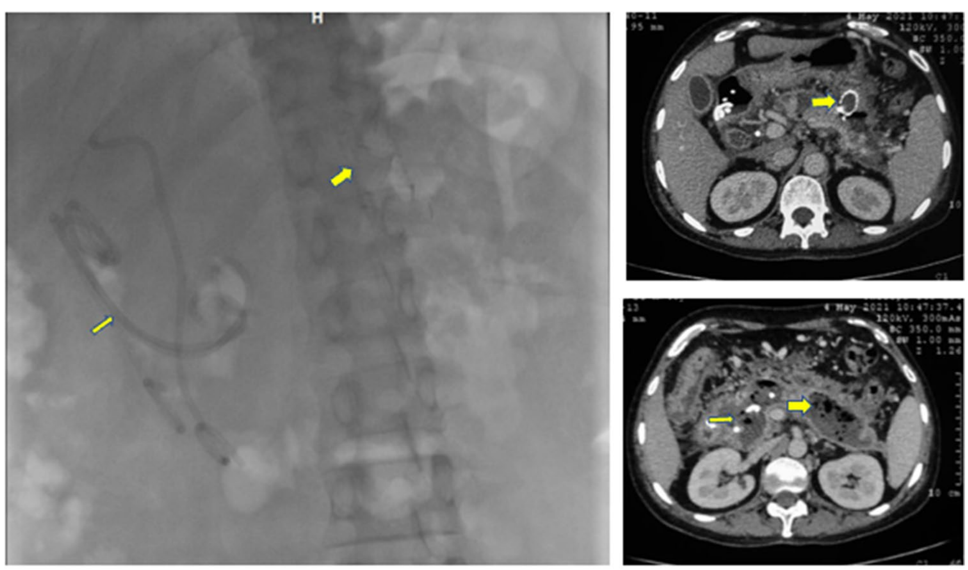

Fig. 4 **a**, **b** Multiple transluminal gateway technique in a patient of acute biliary pancreatitis with infected pancreatic necrosis (IPN) and walled-off necrosis (WON) extending in both head and body of the pancreas. The central collection was drained using Nagi stent (thick yellow arrow) (Taewoong Medical, Gyeonggi-do, South Korea) and collection near the head of the pancreas was drained using multiple plastic stents (thin yellow arrow). Endoscopic retrograde cholangiopancreatography (ERCP) was performed for concurrent cholechodolithalsis with placement of biliary stent. After four weeks of drainage and single session of endoscopic necrosectomy, the metal stent was removed and plastic stents were kept in situ

[71]. Reports on the local administration of antibiotics (imipenem) were done in small retrospective series, showing reduced need for necrosectomy and low mortality in cases of IPN; however, further studies are needed [72]. However, the routine use of a naso-cystic catheter or local installation of antibiotic is still to be explored in a prospective study.

Hydrogen peroxide irrigation Hydrogen peroxide (H_2O_2) rapidly dissociates into oxygen and water when in contact with organic tissues, producing soft foam that aids in debridement of necrotic tissue. Also, it may promote wound healing by stimulating granulation and fibrosis. In a retrospective comparative multi-centric study by

Table 1 Summary of landmark published studies in management of pancreatic necrosis/infected pancreatic necrosis

Study	Study design	Major findings
van Santvoort et al. [4]	Multi-centric RCT comparing minimally invasive step-up approach ($n=43$) vs open necrosectomy ($n=45$) in patients with necrotizing pancreatitis	Composites of major complications were less common in minimally invasive approach (69% vs. 40%; $p=0.006$) with less frequent new-onset organ failure (12% vs. 40%; $p=0.002$), new-onset diabetes (16% vs. 38%; $p=0.02$) and lower rate of incisional hernia (7% vs. 24%; $p=0.03$) in step-up approach. Mortality was equal in both arms (19% vs. 16%; $p=0.70$)
Bakker et al. [42]	Multi-centric RCT comparing endoscopic transgastric necrosectomy ($n=10$) vs. surgical necrosectomy ($n=12$) in patients with IPN	Endoscopic necrosectomy had reduced incidence of composite of major complications (20% vs. 80%; $p=0.03$), new-onset organ failure (0% vs. 50%; $p=0.03$), development of pancreatic fistula (10% vs. 70%; $p=0.02$) and exocrine pancreatic insufficiency (50% vs. 0%; $p=0.04$) compared to surgical necrosectomy
Bang et al. [43]	Single center RCT comparing minimally invasive surgery ($n=32$) vs. an endoscopic step-up approach ($n=34$) in patients with necrotizing pancreatitis	Endoscopic step-up approach had lower incidence of composite of major complications (40.6% vs. 11.8%; $p=0.007$), new-onset SIRS (56.3% vs. 5.6%; $p=0.02$) and pancreatic fistula formation (28% vs. 0%; $p=0.001$) compared to surgical step-up approach
van Brunschot et al. [16]	Multi-center RCT comparing surgical ($n=47$) vs. an endoscopic ($n=51$) step-up approach in patients with IPN	Composites of major complications (47% vs. 45%; $p=0.88$) and mortality (18% vs. 13%; $p=0.50$) were equal among both groups
Boxhoorn et al. [15]	Multi-center RCT comparing immediate drainage ($n=55$) vs. post-poned drainage ($n=49$) in patients with IPN	Comprehensive complication index was equal among both groups (57 vs. 58; $p=0.90$). Both groups had equal mortality (13% vs. 10%). The post-poned group had lower mean interventions (4.4 vs. 2.2) and 39% of patients in the post-poned group could be treated conservatively without need for intervention
Bang et al. [47]	Single center RCT comparing LAMS ($n=31$) vs plastic stent ($n=29$) for EUS-guided transluminal drainage in patients with WON	Both groups had similar number of procedure requirement, treatment success, clinical adverse events, and overall treatment costs. Stent-related adverse events were higher with the LAMS group especially if stent was kept in situ for more than three weeks
Karstensen et al. [48]	Single center RCT comparing LAMS ($n=20$) vs. plastic stent ($n=22$) during EUS-guided transluminal drainage in patients with large WON (> 15 cm)	Both groups had similar number of total number of procedures performed (2.2 vs. 3.2; $p=0.42$), clinical success (95.5% and 94.7%; $p=1.0$), adverse events
Bang et al. [62]	Multi-center RCT comparing upfront endoscopic necrosectomy ($n=37$) vs. step-up endoscopic approach ($n=33$) in patients with IPN	The median number of re-interventions was significantly lower for upfront necrosectomy (1 vs. 2; $p=0.0027$). Both groups had equal adverse events and mortality
Chavan et al. [66]	Single center trial comparing impact of transmural plastic stent on recurrence of pancreatic fluid collection in patients with disconnected pancreatic duct	Recurrence of PFC was equal with and without transmural stent in situ at three, six and 12 months. Moreover, both groups had equal requirement of re-intervention during follow-up period

RCT randomized control trial, *IPN* infected pancreatic necrosis, *LAMS* lumen-apposing metal stent, *WON* walled-off necrosis, *EUS* endoscopic ultrasound

Messallam et al., H_2O_2-assisted necrosectomy provided earlier resolution of the collection with higher clinical success rates [73]. Moreover, a recent meta-analysis involving seven studies also concluded that H_2O_2-assisted necrosectomy is associated with high technical success rates and without increase in incidence of overall adverse events [74]. However, there is a heterogeneity in the concentration (range 0.1% to 3%) and amount of H_2O_2 utilized (20 mL to 1 L) which needs to be standardized before its routine clinical use [74].

OTSG Xcavator Recently, a dedicated device for necrosectomy (OTSG Xcavator, OVESCO Endoscopy AG, Tuebingen, Germany) has been introduced. It has a conical transparent cap with two atraumatic scoups which are mounted on the standard gastroscope. An external control with a grasper allows gasping of tissue, allowing the scope channel to be used for other necrosectomy devices (snare, rat tooth forceps) and an effective irrigation and suction [75]. In a recent multi-centric retrospective study, it was shown that necrosectomy using this device has a technical success rate of around 97% [76]. However, a prospective comparative study with standard necrosectomy tools is still pending.

Powered endoscopic debridement (PED) The EndoRotor PED device (EndoRotor PED System; Interscope, Inc., Northbridge, MA, US) is a novel device for direct endoscopic necrosectomy which provided simultaneous cutting and suction using EndoRotor catheters [77]. In a recent multi-centric retrospective study by Stassen et al., out of 30 patients with WON with > 30% solid debris, 15 achieved completed necrosectomy in one session. Mean number of sessions was 1.5 using a 3.2-mm catheter [78]. Recently, a new 6.0-mm EndoRotor catheter is available which provides 4.4 times larger cutting window and 2.5 times larger inner lumen for faster suction. However, technical feasibility and safety and efficacy of the newer 6.0-mm catheter are still to be evaluated in prospective studies [79].

Role of discontinuing proton pump inhibitors It is hypothesized that gastric acid exposure can help in digestion of necrotic debris after endoscopic drainage for WON and therefore, interruption of proton pump inhibitors (PPI) may be beneficial. In a multicentric retrospective study by Powers et al., it has been shown that patients in the non-PPI group had a lower incidence of stent occlusion (9.5% vs. 20.1%; $p = 0.012$) and required a lower number of necrosectomies (4.6 vs. 3.2; $p < 0.01$) compared to patients in the PPI group, without increasing the rate of gastrointestinal bleeding [80]. Although the evidence is very limited, judicious use of PPI is recommended in patients with WON requiring endoscopic drainage and DEN.

Percutaneous step-up approach

Despite advancement in endoscopic techniques, PCD of pancreatic necrosis still plays an indispensable part in the management of patients with IPN. Percutaneous approach is of use when collection is not amenable for endoscopic drainage (para-colic gutter, para-renal, mesenteric or pelvic location) or when endoscopic expertise is not available [81, 82]. PCD can be performed under ultrasound or CT guidance depending on the location and complexity of the procedure. Route of the drain placement usually depends on the location of the collection. However, a retroperitoneal approach via the left or right posterolateral site is preferred, as it allows the upgrade of the drainage catheter and future necrosectomy without the risk of peritoneal contamination [83]. Transperitoneal or transluminal approach can also be used when retroperitoneal route is not accessible. PCD is placed using the Seldinger technique where the collection is initially punctured with an 18-G needle followed by insertion of a 0.035-inch hydrophilic guidewire. The track is dilated serially followed by insertion of the pigtail catheter [82]. After initial successful drainage, the catheter is intermittently flushed with saline to maintain patency of the catheter [83]. Apart from saline irrigation, studies have also explored the role of irrigating the cavity with antibiotics for better local availability or with hydrogen peroxide or streptokinase for the faster resolution of necrosum [83–85]. However, in the absence of robust data, their routine clinical use is still limited.

Regarding selection of initial catheter size, a retrospective study has shown that initial large bore catheter (> 12 F) is associated with reduction in hospitalization duration, intensive care unit (ICU) stay and need for readmission [86]. Ke et al. performed a systemic review, including 15 studies and 577 patients, on success rates and the complications of PCD in IPN. The overall clinical success rate for PCD was 56.2%; 38.5% of patients required additional surgical intervention, of which surgical necrosectomy was the most common. Overall adverse event rate was 25.1%, of which external pancreatic fistula was the most common [87]. The presence of organized collection (> 50% solid debris), failure to reduce in size of collection, absence of improvement in organ failure a week after drainage and multiple necrotic collections have been identified as predictors for failure in different studies [88, 89]. After initial drainage, PCD can be upgraded gradually for providing wider diameter for drainage in case of clinical nonresponse. One retrospective study has shown more aggressive upgradation at every four to six days until 28 Fr and complete resolution of the cavity results in reduced overall hospital and ICU stay, albeit with higher number of required percutaneous catheters and interventions [90].

Apart from upsizing the percutaneous catheter, the percutaneous track can also be used for performing PEN using a snare, a basket, forceps or nets. Recent meta-analysis involving six studies and 282 patients has shown that success rate of PEN is 82% with long-term morbidity of 23% and overall mortality of 16% [81]. However, prospective studies evaluating the risk of complications and pancreatic fistula after PEN are still lacking.

Surgical step-up approach

Surgical step-up approach involves minimally invasive therapy in the form of VARD or minimally invasive retroperitoneal pancreatic (MIRP) necrosectomy, laparoscopic cyst drainage to open necrosectomy [35]. In minimally invasive necrosectomy of either MIRP or VARD, around 5–7 cm incision is placed on the left loin at the midaxillary line near the percutaneous drain. Using a previously placed percutaneous drain as a guidance, the retroperitoneal space is entered with blunt dissection using either finger or non-compliant dilator balloon or trocar depending on the technique. The cavity is then irrigated using warm normal saline along with suction to remove all liquid components. Loose necrotic debris is grasped by long-grasping forceps or sponge-holding forceps. Visualization during necrosectomy is usually provided by a laparoscope or nephroscope. After successful debridement, a 24-F catheter is placed in situ for adequate drainage and irrigation of the necrotic cavity [35, 91]. Studies have shown that, compared to open necrosectomy, minimally invasive surgery has lower post-operative mortality and shorter hospital stay. However, due to the more invasive nature compared to DEN, the risk of new-onset organ failure, bleeding and external pancreatic fistula formation is still higher [91]. So, careful selection of patients, with peripheral and superficial necrotic collections not amenable for endoscopic necrosectomy, is of utmost importance. Studies have also compared laparoscopic vs. endoscopic drainage of pancreatic collection and showed that both approaches are equivalent in terms of technical and clinical success so choice of mode of drainage should be based on available expertise [92, 93]. Apart from minimally invasive surgical options, open necrosectomy is still required in the presence of failure of the abovementioned minimally invasive options. Moreover, open laparotomy might be required in the presence of complications of pancreatic necrosis or iatrogenic complications such as perforation, bleeding or stent mal-deployment in peritoneum [94]. Gastrointestinal fistulization of the necrosis is quite a common complication of pancreatic necrosis. Studies have shown its prevalence up to 7% to 8% with colonic fistulization being the most common site. Though upper gastrointestinal fistulization can be treated conservatively, colonic fistula usually requires surgical intervention in the form of ileostomy or colostomy [95]. Apart from treatment of complications, laparotomy can also provide good access to perform complete necrosectomy with packing of cavity or putting large bore catheters for irrigation of the cavity in case of failure of conservative therapy or in the presence of multiple organized collections non-amenable for endoscopic or percutaneous route [94].

Multi-disciplinary team management

Management of patients with IPN is quite a complex matter which requires inputs from all stakeholders, including medical gastroenterologist, surgical gastroenterologist and interventional radiologist. The input from an ICU physician, as well as an infectious disease specialist, is crucial. Careful evaluation of symptoms, indications of drainage, location and character of the collection, route of drainage and plan for step-up therapy in case of requirement should be discussed with a multi-disciplinary team for each patient for optimum clinical outcomes (Fig. 5).

Future direction

Management of local complications associated with AP has undergone a drastic change from early and open necrosectomy to delayed and minimally invasive/endoscopic interventions. Subsequently, morbidity and mortality associated with local complications have also been drastically reduced as shown in recent studies. With widespread adoption of EUS and cautery-enhanced stents, endoscopic approach is now the most commonly used modality whenever feasible for drainage of IPN. However, as with pancreatic surgeries, whether hospital volume in management of IPN does make a difference in overall outcome or not is still not clear. Moreover, with introduction of cautery-enhanced stents, learning curve for EUS-guided transluminal drainage has now become steep. Subsequently, performing optimal endoscopic necrosectomy becomes the “Achilles Heel” for clinical success. An automated device such as EndoRotor (Interscope Medical, Inc., Worcester, MA, United States) can be helpful in optimizing debridement and reducing number of the necrosectomy sessions required in near future. Despite the endoscopic revolution for centrally located collection, minimally invasive radiological/surgical procedures remain the cornerstone in the management of peripherally placed collections. However, multi-centric prospective studies are still required for procedure optimization and combination for better clinical outcome.

To conclude, the management of IPN requires multi-disciplinary team management involving an intensivist, gastroenterologist, surgeon and interventional radiologist. After careful expectant management, need for intervention should be decided with the involvement of all stakeholders, especially in patients who are in the early phase of acute pancreatitis. Moreover, route and mode of drainage should be decided based on its location and feasibility. In view of high technical and clinical success rates, centrally placed collections should be drained using endoscopic approach. Need and timing of step-up approach should be decided based on the complexity and nature of the collection and

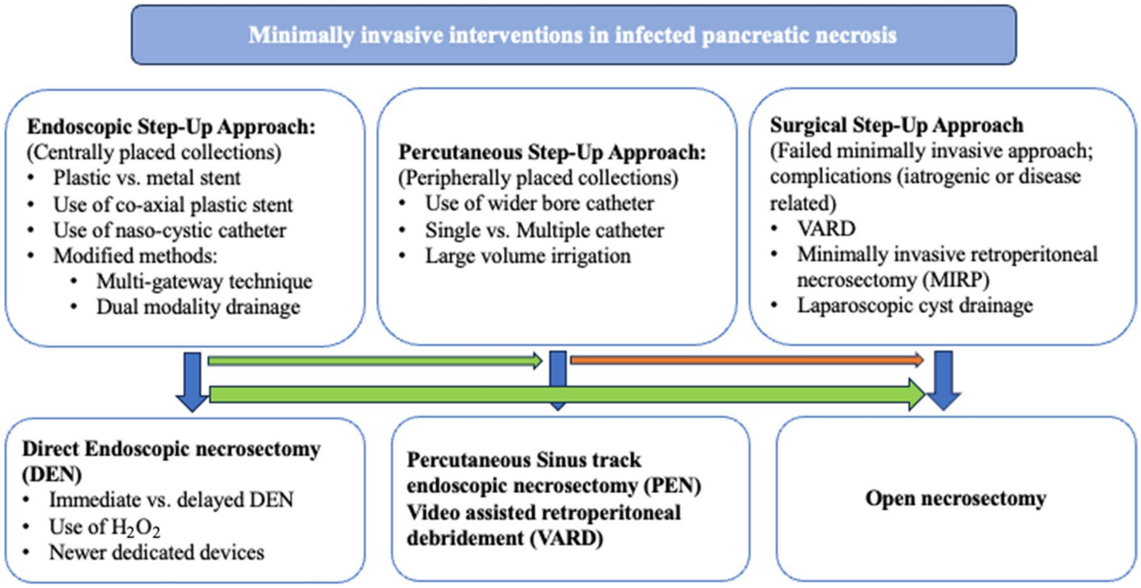

Fig. 5 Showing role of multi-modality management of infected pancreatic necrosis based on location and character of the collection. It should involve a multi-disciplinary team involving a medical gastroenterologist, surgical gastroenterologist and interventional radiologist for better clinical outcomes

clinical response after the initial intervention. Lastly, the role of surgical intervention cannot be underestimated, especially in the presence of disease/procedure-related complications or in the presence of failure of minimally invasive interventions.

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Declarations

Conflict of interest JS, MFYV, RJ and MA declare no competing interests.

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