Digestive Endoscopy 2023; **35**: 700–710 doi: 10.1111/den.14598

Review

Time to think prime times for treatment of necrotizing pancreatitis: Pendulum conundrum

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Pancreatic fluid collections (PFCs) typically develop as local complications of acute pancreatitis and complicate the clinical course of patients with acute pancreatitis and potentially fatal clinical outcomes. Interventions are required in cases of symptomatic walled-off necrosis (WON) (matured PFCs with necrosis) and pancreatic pseudocysts (matured PFCs without necrosis). In the management of necrotizing pancreatitis and WON, endoscopic ultrasound-guided transluminal drainage combined with on-demand endoscopic necrosectomy (i.e. the step-up approach) is increasingly used as a less invasive treatment modality compared with a surgical or percutaneous approach. Through the substantial research efforts and development of specific devices and stents (e.g. lumen-apposing metal stents), endoscopic techniques of PFC management have been standardized to some extent. However, there has been no consensus about timing of carrying out each treatment step; for instance, it is uncertain when direct endoscopic necrosectomy should be initiated and finished and when a plastic or metal stent should be removed following clinical treatment success. Despite emerging evidence for the effectiveness of noninterventional supportive treatment (e.g. antibiotics, nutritional support, irrigation of the cavity), there has been only limited data on the timing of starting and stopping the treatment. Large studies are required to optimize the timing of those treatment options and improve clinical outcomes of patients with PFCs. In this review, we summarize the current available evidence on the indications and timing of interventional and supportive treatment modalities for this patient population and discussed clinical unmet needs that should be addressed in future research.

Key words: acute necrotizing pancreatitis, drainage, endoscopic ultrasound, necrosectomy, pancreatic fluid collection

INTRODUCTION

ACUTE PANCREATITIS (AP) is one of the most common gastrointestinal (GI) diseases,[1] and approximately 20% of patients develop necrotizing pancreatitis, which is often complicated by pancreatic fluid collections (PFCs). According to the revised Atlanta classification,[2] PFCs are categorized into acute peripancreatic fluid collection, acute necrotic collection, pancreatic pseudocyst, and walled-off necrosis (WON) depending on the time after

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Received 10 February 2023; accepted 16 May 2023.

disease onset and the presence of necrosis. Because the presence of (peri)pancreatic necrotic tissue predisposes patients to the risk of developing infection and resultant mortality, surgical debridement of the necrotic tissue was historically carried out even in the early phase of AP in the 18th and 19th centuries.[3] In those days, the recovery from necrotizing pancreatitis was rare by nonsurgical management, but the mortality associated with surgery reached as high as 50%.[4] Since then, a technological paradigm shift has taken place from surgical interventions to the less invasive step-up approach. The step-up approach consists of initial endoscopic ultrasound (EUS)-guided or percutaneous drainage of PFCs followed by on-demand direct endoscopic necrosectomy (DEN) or video-assisted retroperitoneal debridement. Recent advent of lumen-apposing metal stents (LAMS) has supported this technological advance by facilitating endoscope insertion and removal of fragmented necrotic components by DEN.

However, there remains a controversy over the timing of intervention: that is, should we wait as long as possible or intervene proactively? In clinical practice, encapsulation of new-onset PFCs is observed around 4 weeks of AP onset, and a fraction of PFCs subside spontaneously. Therefore, it has been considered whether interventions should be postponed at least 4 weeks. The debate has resurged since the mortality rate decreased because of recent improvements of both invasive and noninvasive management of necrotizing pancreatitis. In addition, timing of the step-up procedures has been discussed without consensus.[5–7] Now that the procedural techniques for treatment of PFCs have matured,[8] we may consider nontechnical aspects (e.g. nutritional support, medications) involved in management of necrotizing pancreatitis[9] because those undergoing interventions for PFCs are in poor condition. Management of AP and PFCs has moved like a pendulum between early and delayed interventions or between nonsurgical and surgical interventions. On aggregate, it is now time to optimize the timing of starting and stopping various interventions and supportive treatment options.

In this review, we discuss the issues on timing of invasive and noninvasive treatment options in patients with necrotizing pancreatitis to summarize current evidence and propose future research. This review was conducted within the WON anD pERipancreatic FlUid coLlection (WONDERFUL) consortium, which consisted of expert endoscopists, gastroenterologists, interventional radiologists, and epidemiologists at high-volume centers in Japan.

DRAINAGE AND NECROSECTOMY

ENDOSCOPIC ULTRASOUND-GUIDED TRANSLUMINAL approach currently serves as the cornerstone of treating symptomatic PFCs. With accumulated data and the increasing popularity of LAMS, the treatment sequence has almost been established: that is, EUS-guided drainage via LAMS, on-demand necrosectomy, and LAMS removal (with or without replacement with plastic stents).[10] However, there have been considerable variations in the timing of each treatment step among endoscopists (Fig. 1).

The timing of intervening symptomatic PFCs has been discussed since necrotizing pancreatitis was managed mainly by surgical interventions. Endoscopic or percutaneous drainage of symptomatic PFCs has been recommended 3–4 weeks after AP onset when well-defined walls of PFCs are formed.[10] However, as discussed later, intra-abdominal infection can occur earlier[11] and necessitate PFC drainage in cases with conservatively uncontrollable infection. The traditional threshold of 4 weeks has been defined in the Atlanta classification,[2] but some PFCs are considered as either partially or completely encapsulated on contrast-enhanced computed tomography (CT) even within 4 weeks.[12]

Although delayed interventions can avoid unnecessary drainage in approximately 60% of necrotizing pancreatitis,[13] early interventions may be necessary in cases with deteriorated infections even within 2–4 weeks of AP onset. A retrospective study of early percutaneous drainage suggested less need for necrosectomy and reduced in-hospital mortality,[14] but a recent randomized controlled trial (RCT)[15] comparing immediate and delayed drainage for infected necrosis failed to demonstrate the superiority of immediate drainage in terms of safety. Early endoscopic interventions[12,16–19] have been investigated (Table 1), but no studies have proved the superiority of early interventions over delayed interventions. Three meta-analyses[20–22] suggested routine early interventions do not necessarily lead to better outcomes and are not recommended in managing necrotizing pancreatitis. One of the reasons for delayed interventions is encapsulation of PFCs after 4 weeks. However, encapsulation can occur within 4 weeks in some cases and interventions might be safely performed.[23] Although early drainage is ineffective in PFCs without infection, clinical signs and symptoms of infected PFCs are similar to the ongoing AP without infection. To determine the indications for early drainage, biomarkers and imaging such as procalcitonin and encapsulation should be investigated in addition to EUS-guided fine needle aspiration (EUS-FNA) for bacterial culture. Because our meta-analysis[20] suggested the use of LAMS was not associated with clinical success or adverse events in early drainage, either LAMS or plastic stents can be selected in cases with partial or full encapsulation. However, in PFCs with

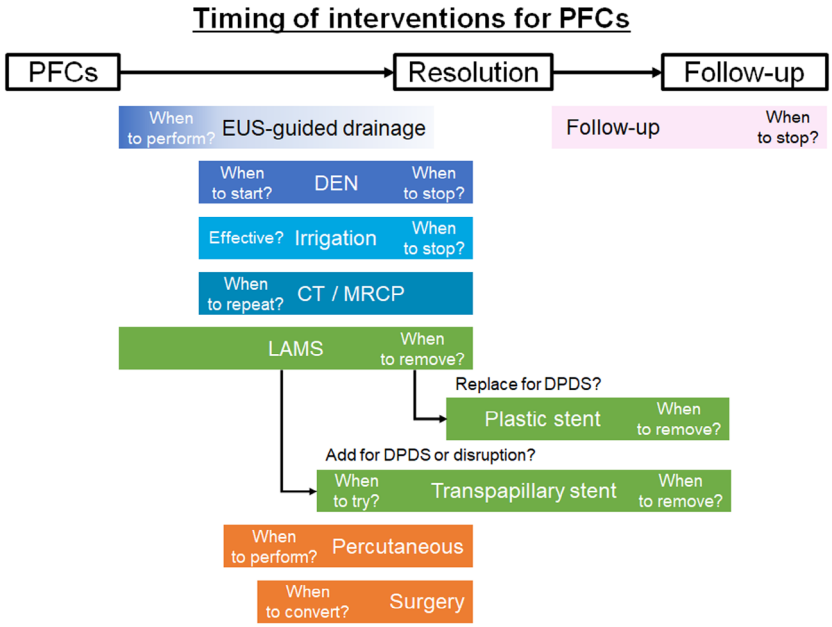

Figure 1 Timing of sequential interventional modalities for patients with pancreatic fluid collections (PFC). CT, computed tomography; DEN, direct endoscopic necrosectomy; DPDS, disconnected pancreatic duct syndrome; EUS, endoscopic ultrasonography; LAMS, lumen-apposing metal stent; MRCP, magnetic retrograde cholangiopancreatography.

minimal encapsulation, the influx of gastric contents through LAMS can cause peritonitis, and the use of nasocystic drainage alone or in combination with plastic stents, should be considered. Future research should focus on the timing of interventions, in relation to encapsulation of PFCs. Furthermore, it is still unclear whether we should intervene in asymptomatic WON. In two retrospective studies,[24,25] 26% of the initially asymptomatic WON developed symptoms after 2–3 months. Infection and abdominal pain were major reasons for intervention in those cases but GI obstruction or perforation into GI lumens were also reported. Although proactive interventions in asymptomatic WON can be safely performed compared with those with infected and deteriorated WON, drainage of sterile WON could lead to bacterial contamination.[26] Thus, we should clarify the indications of interventions in asymptomatic or sterile WON, as well as the timing of interventions if indicated.

The timing of DEN is also under debate.[27] One retrospective study[28] showed immediate DEN at the time of LAMS placement was associated with resolution (odds ratio [OR] 2.3; 95% confidence interval [CI] 1.06–4.73) with fewer DEN sessions. On the contrary, in the other retrospective study,[29] immediate DEN was associated with longer hospital stay (7.5 vs. 3.0 days) and more DEN sessions (2.5 vs. 1.5). To clarify the appropriate timing of DEN, researchers launched RCTs to evaluate feasibility and efficacy of immediate DEN compared with the step-up approach for WON (NCT05043415, NCT05252897, NCT05451901). Recent studies examined prognostic factors for requirement of DEN as endoscopic step-up treatment as well. In an analysis of 136 PFCs undergoing EUS-guided LAMS placement, PFC size of ≥10 cm (OR 8.91; 95% CI 3.36–23.61), paracolic extension (OR 4.04; 95% CI 1.60–10.23), and ≥30% solid necrosis (OR 4.24; 95% CI 1.48–12.16) were independent predictors of requirement of the step-up therapy.[30] Another study[31] revealed air bubbles within necrotic tissues termed a "sponge sign" was associated with need for DEN. A further investigation is required to elucidate the appropriate timing of selecting the nonendoscopic step-up approach (percutaneous or surgical drainage) rather than the step-up DEN.

GOAL OF ENDOSCOPIC AND OTHER INTERVENTIONS

DESPITE SEVERAL STUDIES investigating the timing of interventions, no study has examined the timing of stopping DEN or the goal of DEN. In clinical practice, resolution of PFCs is defined based on improvements in symptoms, inflammatory markers (e.g. white blood cell

Table 1 Clinical outcomes in early (<4 weeks) and delayed (>4 weeks) endoscopic interventions

Author, year	No. of cases	ANC or WON, %	LAMS, %	Technical success, %	Clinical success, %	Adverse events, %	Mortality, %	Hospital stay, median (range), days	Recurrence, %
Chantarojanasiri, 2018[16]	35	80	54	100/100	NA	12/22	8/4	27.5 (5–58)/31 (15–271)	NA
Oblizajek, 2020[12]	38	100	21	100/100	89/89	21/32	0/5	26 (6–44)/6 (0–40)	NA
Khan, 2021[17]	188	43	100	100/97	88/88	31/31	19/5	NA	8/14
Rana, 2021[18]	170	100	14	100/100	94/100	21/1	6/0	NA	NA
Jagielski, 2022[19]	71	100	100	NA	92/96	28/24	4/4	NA	12/13

Numbers are shown in % or median (range).
ANC, acute necrotic collection; LAMS, lumen-apposing metal stent; NA, not available; WON, walled-off necrosis.

counts), and imaging studies. The timing of stopping DEN should be determined considering multiple factors such as endoscopic findings of the intracystic wall, the feasibility of approaching residual necrotic tissue at peripheral regions of WON, and the risk of recurrence predicted based on cross-sectional imaging studies. There has also been controversy over the timing of follow-up images (i.e. CT and magnetic resonance imaging with cholangiopancreatography [MRCP]) after initial EUS-guided drainage of PFCs (Table 2).[8,32–38] CT is primarily used as follow-up imaging, but its timing varies significantly from 72 h to 8 weeks. The follow-up images are performed for two purposes: confirmation of PFC response/resolution and evaluation of disconnected pancreatic duct syndrome (DPDS). Although the initial response is evaluated on CT in the early phase (i.e. a few days after drainage to determine the necessity of additional interventions), resolution of PFCs may need weeks. As discussed later, DPDS is increasingly reported as a risk factor for recurrence, and MRCP or endoscopic retrograde cholangiopancreatography (ERCP), rather than CT, is preferred for evaluating DPDS. The precise evaluation of pancreatic duct is difficult in the presence of PFCs; MRCP is often performed at the time of resolution of PFCs and stent removal. Thus, the modality and the timing of imaging studies should be further integrated into the algorithm of endoscopic management of PFCs. The timing of stent removal after treatment success should also be discussed. It may be reasonable to remove plastic or metal stent(s) after PFC resolution. In cases with LAMS placement, one study suggested prolonged duration (>4 weeks) of LAMS placement might increase the risk of stent-related bleeding or buried stents.[39] In a prospective trial[40] evaluating LAMS removal after 4 weeks for pseudocyst and 6 weeks for WON, no delayed bleeding was observed; however, bleeding after LAMS placement does not necessarily occur as an early adverse event. In the accompanying literature review of 1378 cases,[40] bleeding was seen in 52 cases (3.8%), and most bleeding occurred within 4 weeks; 46% and 75% within 1 week and 4 weeks, respectively. In a recent large cohort study focusing on LAMS removal,[41] immediate (<24 h) and delayed (>24 h) bleeding rates were 1.1% and 1.9%, respectively. Buried stent by tissue overgrowth was the most frequent delayed adverse event (4.7%), followed by bleeding, but the timing of stent removal was not associated with buried stent or bleeding. Because endoscopic interventions such as necrosectomy may take >4 weeks after initial drainage, it is still unclear whether we should routinely remove LAMS at 4–6 weeks or consider LAMS removal after PFC resolution.

Accumulating evidence suggests that DPDS is associated with PFC recurrence. In a meta-analysis,[42] DPDS was present in 40% to 69%, and patients with DPDS were more likely to develop PFC recurrence after resolution of PFC, compared with patients without DPDS (OR 6.72; 95% CI 2.72–16.6). In addition, several studies suggest long-term placement of plastic stents may mitigate the risk of recurrence in patients with DPDS.[43–45] However, a recent RCT failed to demonstrate the efficacy of transmural plastic stents on prevention of recurrence in patients with DPDS.[38] On the other hand, there is a risk of intestinal perforation in long-term plastic stent placement.[46] Therefore, more evidence should be accumulated to standardize the treatment protocol (i.e. timing of stent removal or ERCP with pancreatic stent placement) in cases with DPDS.

In addition to timing of initiating DEN after EUS-guided drainage, appropriate timing to start and stop other interventional and noninterventional modalities should be examined (Fig. 2). Studies have suggested the effectiveness of irrigation combined with EUS-guided drainage. Irrigation may facilitate the washout of infectious components within the cavity and accelerate PFC resolution. However, the study results have been inconsistent in terms of its effectiveness,[36,47–52] and bacteremia may be provoked via the advertently increased intracystic pressure. Therefore, the starting time of irrigation should be determined with caution. Finally, the timing and necessity of ERCP have

Table 2 Timing of follow-up imaging studies after the initial endoscopic ultrasound-guided drainage of pancreatic fluid collections in major studies

Author, year	Diagnostic modality	Timing of imaging
Siddiqui, 2017[32]	Contrast-enhanced CT	4–8 weeks after stent placement
Mallick, 2018[33]	US or CT	Repeated at 2–4 weeks
Bang, 2019[34]	CT and ERCP	6 weeks postintervention; ERCP to assess for pancreatic duct integrity
Abu Dayyeh, 2021[35]	CT or MRI	Initially at 7 days, and 14 days after drainage and after each intervention
Maharshi, 2021[36]	US	3 weeks after drainage
Siddiqui, 2021[37]	Contrast-enhanced CT or US	4–8 weeks after stent placement
Chavan, 2022[38]	MRI with MRCP	4 weeks before removal of stents
Bang, 2022[8]	CT	72 h postintervention as initial evaluation

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; US, ultrasonography.

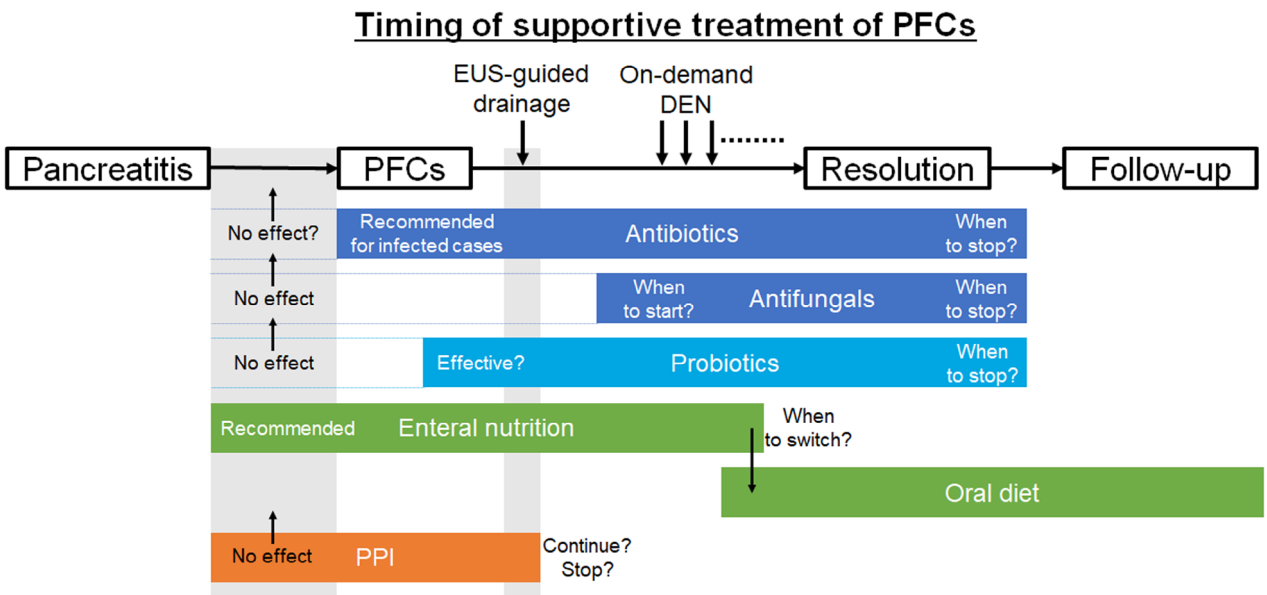

Figure 2 Timing of noninterventional treatment modalities for patients receiving endoscopic treatment for pancreatic fluid collections. DEN, direct endoscopic necrosectomy; EUS, endoscopic ultrasonography; PFC, pancreatic fluid collection; PPI, proton pump inhibitor.

been controversial. Transpapillary stent placement may enable the physiological outflow of pancreatic juice, prevent DPDS, and decrease PFC recurrence, but in turn harbors an inherent risk of provoking or deteriorating infection by bacterial contamination.[53] An RCT evaluating the role of prophylactic pancreatic stent in acute necrotizing pancreatitis was terminated early because of the high infection rate in the stent group (63.6% in intention-to-treat analysis).[54] Thus, future research should focus on the indication and timing of transpapillary pancreatic intervention in acute necrotizing pancreatitis.

Finally, it is also unclear how long we should follow patients after resolution of necrotizing pancreatitis. Follow-up data of two RCTs revealed that pancreatic function can be affected, especially in cases with surgical necrosectomy. The incidence of pancreatic endocrine insufficiency defined as the use of oral antidiabetic and/or insulin therapy was reportedly 36% to 56%, and pancreatic exocrine replacement treatment was required in 16% to 42% after treatment of necrotizing pancreatitis.[55,56] Given the improved short-term outcomes, further research is warranted to optimize the strategies of acute-phase treatment and posttreatment surveillance to ensure the long-term quality of life. Furthermore, AP is a risk factor for pancreatic cancer, which remains high as long as 10 years after AP.[57,58] Thus, it might be difficult to stop surveillance of pancreatic cancer

or pancreatic function deficiency at this moment, and we need to define high-risk patients who need long-term follow-up.

ANTIBIOTICS FOR INFECTION DURING THE CLINICAL COURSE OF ACUTE PANCREATITIS AND PFCS

INFECTION IS A prognostic factor in acute necrotizing pancreatitis because it deteriorates the patient's condition with a potential risk of sepsis. The mortality rate was as high as 20% to 30% in cases with infected pancreatic necrosis.[59] The timing of infection was investigated in a cohort of 731 cases with AP.[60] Overall, intra- and extra-pancreatic infectious complications were observed in 23.7%; infected pancreatic necrosis in 13.4%, bacteremia in 14.6%, and pneumonia in 11.5%. The median time to the diagnosis of infection was 26 days in infected necrosis, 10 days in bacteremia, and 9 days in pneumonia. In 114 surgical cases with necrotizing pancreatitis,[11] surgically obtained necrotic material was contaminated with bacteria in 23.8% in the first week, 71.4% in the third week, and 32.5% after the fourth week. In another study of 205 cases with necrotizing pancreatitis,[61] the mean time to infection was 13.9 days in pancreatic infection and 9.1 days in extrapancreatic infection. Furthermore, fungal infection occurred significantly later, with a median time to the event of 31.6 days.

Because pancreatic infection occurs in the early phase of AP, the role of prophylactic antibiotics has long been investigated. In a meta-analysis of seven RCTs,[62] prophylactic antibiotics did not significantly reduce mortality (risk ratio [RR] 0.60; 95% CI 0.34–1.05) or infected pancreatic necrosis (RR 0.85; 95% CI 0.57–1.26). Meanwhile, another meta-analysis,[63] which included only RCTs investigating antibiotics administration within 48–72 h, showed reduced mortality with antibiotics (OR 0.48; 95% CI 0.25–0.94) as well as reduced infected pancreatic necrosis (OR 0.55; 95% CI 0.33–0.92). Prophylactic antibiotics may increase the risk of infection with multidrug-resistant bacteria, although there have been no data suggesting an increase in nonpancreatic infection or fungal infection. Although early administration of prophylactic antibiotics might decrease mortality, there is no strong evidence to support the routine use of prophylactic antibiotics in acute necrotizing pancreatitis. European Society of Gastrointestinal Endoscopy (ESGE) guidelines[64] recommend antibiotics use only in patients with suspected or proven infected necrosis. A recent RCT suggested the use of procalcitonin to stop or continue antibiotics could reduce antibiotic use without increase in infection.[65] In cases with proven infection, the type of antibiotics can be customized based on the profile of cultured bacteria. Future research is warranted to elucidate empiric antibiotics for patients with pending culture results or suspected pancreatic necrosis.

It is also controversial whether we should routinely puncture PFCs to prove infection before drainage. ESGE guidelines[64] argue against routine percutaneous or EUS-FNA of PFCs because its false-negative rate was reportedly 12% to 25%.[66–68] The false negatives can be more problematic if prophylactic antibiotics were administered since the onset of AP. In clinical practice, a decision for PFC drainage is made based on clinical symptoms, regardless of a definite proof of infection. In an expert survey,[69] EUS-FNA is not routinely performed at any centers but is performed on a case-by-case basis in 85%; in case of clinical signs of infected necrosis without gas on CT in 18%, clinical signs of infected necrosis regardless of CT findings in 22%, and rarely in 45%. Because PFC drainage is often performed even in sterile cases, it should be further explored if antibiotics guided by proactive FNA can lead to better outcomes compared with empiric or no antibiotics in necrotizing pancreatitis.[70] To overcome low sensitivity of culture tests, emerging evidence points to the potential of the metagenomic approach based on next-generation sequencing technologies in identifying microbial pathogens in blood samples.[71] Because this new assay has other strengths, including shorter turnaround time and the potential of identifying a large number of pathogens, a cost-effective analysis is warranted. We should also investigate the usefulness and appropriate interval of follow-up culture tests in patients undergoing drainage of infectious PFCs.

The appropriate timing of antibiotics discontinuation should be clarified in patients receiving endoscopic treatment of PFCs. In clinical practice, antibiotics are stopped 48 h after stent or catheter removal according to the ESGE guidelines.[64] However, this practice results in prolonged antibiotics administration (>1–2 months in case of PFC drainage and subsequent necrosectomy), which may increase the risk of infection with multidrug-resistant bacteria or fungi. In addition, prolonged antibiotics use may cause *Clostridium difficile*-related colitis. Thus, we need to explore whether we can stop antibiotics once clinical signs of infection are controlled by adequate drainage/necrosectomy or should continue antibiotics until PFC resolution.

Finally, no study has investigated the indication of antifungal agents in case of PFC drainage. In a pooled analysis,[72] fungal infection was noted in 572 (26.6%) of 2151 patients with necrotizing pancreatitis and was associated with worse outcomes including higher in-hospital mortality. In a culture-based analysis of 123 patients receiving EUS-guided drainage and necrosectomy for WON,[73] local fungal contamination was observed in 46%, and the most common fungi were *Candida* species. Therefore, management of fungal infections, which are often

underestimated, would likely have a substantial impact on clinical outcomes of this population. Additionally, the optimal timing of testing beta-D-glucan needs to be elucidated, too.

NUTRITION AND PROBIOTICS

IN MANAGING AP, the importance of enteral nutrition has been emphasized because it can prevent bacterial overgrowth in the GI tract, maintain gut mucosal integrity, and reduce the risk of infectious complications from bacterial translocation. In a meta-analysis,[74] enteral nutrition significantly reduced mortality, multiple organ failure (MOF), infections, and need for interventions compared with total parenteral nutrition. Of note, the timing of initiation of enteral nutrition might influence clinical outcomes in comparison with parenteral nutrition.[75] When started within 48 h of admission, enteral nutrition was associated with significant reductions in mortality (RR 0.46; 95% CI 0.20–0.99), MOF (RR 0.44; 95% CI 0.23–0.84), and pancreatic infection (RR 0.46; 95% CI 0.27–0.77), but such clinical benefits were not evident in cases receiving enteral nutrition after 48 h: RR of 0.67 (95% CI 0.22–2.10) in mortality, 0.73 (95% CI 0.33–1.63) in MOF, and 0.31 (95% CI 0.07–1.34) in pancreatic infection. These data were in line with abovementioned studies implicating the occurrence of local infection at the early stage of AP.[11,60,61] Meanwhile, an RCT failed to demonstrate the superiority of early enteral feeding over oral diet at 72 h in terms of infection and mortality.[76] In this study, oral diet was well tolerated in 69% of the patients at 72 h. Thus, it is still controversial whether we should start enteral nutrition immediately in cases with severe AP.[77]

Additional effects of prophylactic probiotics on prevention of bacterial translocation via early enteral nutrition have also been investigated. Although an RCT of 45 cases with AP[78] suggested that probiotics might decrease infectious complications (4.5% with probiotics and 30.4% without probiotics), a subsequent RCT, the PROPATRIA trial, including 298 cases[79] did not demonstrate any differences in infectious complications (30% with probiotics and 28% without probiotics). Unexpectedly, the mortality rate was higher in the probiotics group than in the placebo group (16% and 6%). In a subanalysis of PROPATRIA trial,[80] urinal excretion of nitric oxide (NOx) was evaluated as a marker for bacterial translocation. Although probiotics significantly decreased NOx in the total cohort, NOx increased in patients with organ failure, suggesting probiotics might provoke enterocyte damage and bacterial translocation in cases with organ failure. Meanwhile, the study suggested that intestinal barrier dysfunction may occur at the early phase of AP and be related to infectious complications, organ failure, and mortality. The causes of unexpectedly high mortality have been speculated and discussed,[81] but the process how probiotics works needs further investigation to clarify the role of probiotics in AP. Because there are various strains of probiotics and other microbial modulation strategies (e.g. prebiotics, symbiotics, bacterial cocktails, fecal microbiota transplantation),[82] there are several unanswered questions to be addressed before clinical use of those treatments.

Nutritional support may also be beneficial for patients receiving interventions for PFCs, in that it might facilitate patients' recovery from infection. In the setting of endoscopic transmural treatment of PFCs using large-bore metal stents including LAMS, technical issues should be considered. Transmural stents might clog with food debris or allow the food influx into PFCs. These adverse events might cause recurrent inflammation in PFCs and hinder DEN procedures. Although its incidence is unknown, it should be investigated whether to prescribe a low-residue diet for patients with LAMS. A newly developed LAMS with an S-shaped antireflux valve[83] potentially prevents food influx while maintaining the outflow of fluid and debris from the PFC cavity. Feasibility of this antireflux LAMS was reported in 10 patients, and data are desired to demonstrate the superiority over commercially available LAMS.

During the treatment course of AP and subsequent PFCs, antacid medications such as proton pump inhibitors (PPIs) are often used to suppress the activity of pancreatic acinar cells or prevent complications including peptic ulcer bleeding. However, prolonged PPI use may cause dysbiosis in the GI tract[84] and lead to infectious complications, as shown in its association with cholangitis.[85–88] In the early phase of severe AP, PPI-induced alterations in the low-pH environment were reported to result in duodenal dysbiosis, although infectious complications did not increase in patients receiving PPIs in an RCT.[89] Furthermore, the reduced secretion of gastric acid resulting from PPIs may impair gastric acid-based chemical debridement of necrotic tissue in WON drained by LAMS. In a retrospective study of LAMS for WON,[90] PPI use was associated with increases in stent occlusion (20.1% vs. 9.5%) and the mean number of DEN sessions (4.6 vs. 3.2 sessions).

CONCLUSIONS

IN THIS REVIEW, we summarized the current evidence on indications and timing of interventional and non-interventional treatment options for PFCs. Overall, there has been a paucity of high-quality data for clinical decision-

making of starting and stopping various treatment modalities for necrotizing pancreatitis; therefore, prospective studies are required for each topic. First, there is an urgent need for investigations of the timing of interventions for symptomatic PFCs (i.e. drainage, necrosectomy, stent removal). We then need to devote research resources to investigations of supportive treatment options (e.g. irrigation, antibiotics). Given the rarity of symptomatic PFCs and the heterogeneity in clinical practices between centers, a multicenter collaboration is required to provide robust evidence for treatment selections with reasonable generalizability. Through accumulation of these lines of evidence, we may further improve clinical outcomes of patients presenting with PFCs who are associated with substantial morbidities and mortality.

ACKNOWLEDGMENTS

THE AUTHORS WOULD like to thank the following members of the WONDERFUL study group for their valuable comments on the manuscript: Ryota Nakano, Shogo Ota, Division of Gastroenterology and Hepatobiliary and Pancreatic Diseases, Department of Internal Medicine, Hyogo Medical University, Hyogo, Japan; Kensaku Yoshida, Department of Gastroenterology, Gifu Prefectural General Medical Center, Gifu, Japan; Ryuichi Tezuka, Senju Akihiko, Shinya Uemura, First Department of Internal Medicine, Gifu University Hospital, Gifu, Japan; Mitsuru Okuno, Yuhei Iwasa, Department of Gastroenterology, Gifu Municipal Hospital, Gifu, Japan; Shunsuke Omoto, Department of Gastroenterology and Hepatology, Faculty of Medicine, Kindai University, Osaka, Japan; Masahiro Tsujimae, Arata Sakai, Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan; Keito Nakagawa, Department of Gastroenterology and Hepatology, Saitama Medical Center, Saitama Medical University, Saitama, Japan; Nobuhiko Hayashi, Third Department of Internal Medicine, University of Toyama, Toyama, Japan; and Toshio Fujisawa, Sho Takahashi, Department of Gastroenterology, Graduate School of Medicine, Juntendo University, Tokyo, Japan.

CONFLICT OF INTEREST

AUTHOR Y.N. RECEIVED research grants from Boston Scientific Japan, Fujifilm Corporation, and HOYA Corporation and honoraria from Boston Scientific Japan, Fujifilm Corporation, Olympus Corporation, and Gadelius Medical. H.I. received research grants from Boston Scientific Japan, Fujifilm Corporation, Fujifilm Healthcare Corporation, Gadelius Medical, Japan Lifeline Corporation, and Zeon Medical and honoraria from Boston Scientific Japan, Fujifilm Corporation, Olympus Corporation, Gadelius Medical, and Century Medical. Y.N., T.I., and M.T. are Associate Editors of *Digestive Endoscopy*. I.Y. is an Associate Editor of *DEN Open*. The other authors declare no conflict of interest for this article.

FUNDING INFORMATION

THIS WORK WAS supported in part by grants from the Japanese Foundation for Research and Promotion of Endoscopy (T.Saito and Y.N.). T.H. was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI grants (JP19K08362 and JP22H02841) and a grant from Takeda Science Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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