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Position Paper

The 1st i-EUS consensus on the management of pancreatic fluid collections – Part 2

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ABSTRACT

Pancreatic fluid collections (PFCs), including pancreatic pseudocysts (PPs) and walled-off pancreatic necrosis (WON), are common complications of pancreatitis and pancreatic surgery. Historically, the treatment of these conditions has relied on surgical and radiological approaches. The treatment of patients with PFCs has already focused toward an endoscopy-based approach, and with the development of dedicated lumen-apposing metal stents (LAMS), it has almost totally shifted towards interventional Endoscopic Ultrasound (EUS)-guided procedures. However, there is still limited consensus on several aspects of PFCs treatment within the multidisciplinary management. The interventional endoscopy and ultrasound (i-EUS) group is an Italian network of clinicians and scientists with special interest in biliopancreatic interventional endoscopy, especially interventional EUS. This manuscript focuses on the second part of the results of a consensus conference organized by i-EUS, with the aim of providing evidence-based guidance on several intra- and post-procedural aspects of PFCs drainage, such as clinical management and follow-up.

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1. Background

The incidence of pancreatic disorders, including acute and chronic pancreatitis, and their sequelae is increasing [1,2]. Complications of acute pancreatitis (AP) are a major cause of bad outcomes and increased costs [3]. The most common local complications of pancreatitis are pancreatic fluid collections (PFCs), defined as either acute peripancreatic fluid collection (APFC), pancreatic pseudocysts (PPs), acute necrotic collection (ANC) or walled-off pancreatic necrosis (WON) [4]. The treatment of these conditions has been based on surgical and radiological procedures for a long time; however, in the past two decades, owing to the advent of interventional Endoscopic Ultrasound (EUS)-guided procedures, endoscopy has become the cornerstone for the initial treatment of PFCs [5,6]. This rapid paradigm change corresponds to the need for clear evidence regarding the indication of such procedures, the standardization of techniques, and the use of devices that are rapidly evolving [7-9].

Enforcement of novel approaches in daily practice must be verified and standardized. The interventional Endoscopy and Ultrasound (i-EUS) group was created in 2017 as a community of advanced Italian biliopancreatic endoscopists to promote data sharing, continuous updating and support education initiatives in order to optimize procedural outcomes and review execution methods, technical and clinical success, and long-term follow-up. Finally, to overcome the lack of guidelines on these topics, i-EUS has grown into a multidisciplinary stakeholder to organize consensus conferences regarding indications, techniques, clinical management, and follow-up of patients based on the available scientific evidence. The overall objective of this consensus guideline is to provide evidence-based recommendations for endoscopic treatment of PFCs. The second part hereby presented, gathers the statements on intra- and post-procedural aspects of PFCs drainage, such as clinical management and follow-up.

2. Methods

2.1. Organization

Four working groups (WGs) were created, each composed by 4 experts on managing PFCs and a WG leader. The WGs met online and prepared a list of questions and statements based on systematic reviews and related evidence tables regarding four main aspects (Supplementary Material 1). The third and fourth groups analyzed intra- and post-procedural aspects about clinical management and early follow-up of patients undergoing endoscopic drainage of PFCs (such as specific medication during or after the procedure, type and timing of refeeding). The consequent questions and statements were uploaded to a specific app (i-EUS) to be read by all experts involved and were eventually presented in a plenary session in a face-to-face meeting. All statements with less than 80% agreement were discussed again for possible amendments and excluded if the agreement level was not reached. Excluded questions and statements (one) are provided in Supplementary Material 2. The questions and statements that reached agreement were then checked and elaborated by the four WGs leaders. An updated literature review was conducted in January 2024; however, its content was only employed in the comments and voted statements. The target users of this document were clinicians involved in the care of patients with PFCs.

2.2. Grading of evidence

Based on the best available evidence, the four WGs provided the following for each clinical question, based on the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence levels and recommendation strengths (Supplementary Table 1) [10,11].

1. Recommendation: the GRADE strength of recommendation (1 strong, 2 weak) and the quality of evidence (A high, B moderate, C low, D very low), together with the rate of agreement (Supplementary Table 2) [10,11].
   In the absence of studies specifically addressing a particular question, this had to be stated, and the recommendation was based on related studies or expert opinions.
2. Comments: These remarks could discuss any relevant aspect regarding the recommendation, such as important exceptions/contraindications, availability, lack of evidence, risks, and costs. In addition, given the time between the consensus conference and the publication of the document, any important additional evidence that could not be considered at the time of document preparation is presented and discussed in the comments. Additional details of the methodology are provided in Supplementary Material 1.

3. Results

The topics examined in the second part were presented consecutively, incorporating 15 questions and 18 related statements (Table 1). The GRADE strength of recommendation and quality of evidence are accordingly provided for each of them, together with the rate of agreement. For each recommendation, comments from the reviewers and attendees at the meeting are summarized.

2.1. Chapter 1

Question 1.1. *Should antibiotics always be administered when treating patients with DEN for WON?*

Statement 1.1. *I-EUS group suggests that prophylactic antibiotics should be administered during DEN for WON.*

Quality of evidence: very low; recommendation: weak; Agreement 91%

Comment

Infected necrosis can occur in up to 70% of patients with necrotizing pancreatitis, leading to a 1.5-fold increase in mortality [12-14]. In 2013, the American Pancreatic Association (APA) and International Association of Pancreatology (IAP) jointly produced evidence-based guidelines for the treatment of AP, stating that the prevention of infectious complications does not require intravenous antibiotic prophylaxis [14]. Overall, despite the high mortality due to infectious complications, the impact of prophylactic antibiotics on mortality in patients with severe pancreatitis has not been well established, even in RCTs and subsequent meta-analysis [15] (Supplementary Table 3). In 2022 a randomized, non-inferiority, placebo-controlled, and double-blinded clinical trial [16] investigated the role of antibiotic prophylaxis in endoscopic transmural drainage in 62 patients with symptomatic non-infected PFCs, concluding that the effective endoscopic drainage of sterile post-inflammatory PFCs requires no preventive or prophylactic use of antibiotics and, in the case of contaminated collections, the success of treatment depends on infection control driven by endoscopic drainage. However, as the WON content is often infected, in the absence of more definitive data, antibiotic prophylaxis at the time of DEN seems prudent.

Question 1.2. *Is it recommended to obtain a microbiological culture of pancreatic necrosis during DEN?*

Statement 1.2. *I-EUS group suggests obtaining a microbiological culture of pancreatic necrosis in presence of clinical signs of infection.*

Table 1
Agreement to the proposed statements (second part).

Statement	*Agreement (%)*
Statement # 1.1 **I-EUS group suggests that prophylactic antibiotics should be administered during DEN for WON.** *Quality of evidence: very low; recommendation*	91
Statement # 1.2 **I-EUS group suggests obtaining a microbiological culture of pancreatic necrosis in presence of clinical signs of infection.** *Quality of evidence: very low; recommendation: weak*	85
Statement # 1.3 **I-EUS group suggests evaluation by an infectious disease specialist for patients with infected WON.** *Low quality evidence; Recommendation weak*	72
Statement # 1.4 **In patients with WON, I-EUS suggests the insertion of a naso-cystic tube for additional irrigation, or between DEN sessions.** *Quality of evidence: very low; recommendation: weak*	81
Statement # 1.5 **I-EUS group suggests that the use of H2O2 during DEN could improve clinical outcomes without increasing the risk of adverse events.** *Quality of evidence: low; recommendation: weak*	89
Statement #1.6 **I-EUS group suggests against routine use of PPI in patients with acute pancreatitis and/or peripancreatic collections unless indicated for other clinical reasons** *Quality of evidence: very low; recommendation: weak*	82
Statement #2.1 **I-EUS recommends offering oral feeding on a hunger basis, if clinically tolerated, in patients with pancreatic fluid collection.** *Quality of evidence: moderate; recommendation: strong*	95
Statement #2.2a **I-EUS suggests enteral nutrition in patients with pancreatic collections and inability to be fed orally.** *Quality of evidence: moderate; recommendation: weak*	98
Statement #2.2b **I-EUS suggests PN feeding only in cases of intolerance or contraindications to EN in patients with pancreatic fluid collection.** *Quality of evidence: very low; recommendation: weak*	97
Statement #2.3 **I-EUS suggests starting enteral nutrition within 24–48 h in patients with pancreatic fluid collections and inability to be fed orally.** Quality of evidence: moderate; recommendation: weak	80
Statement #2.4 **I-EUS suggests a nasojejunal route for enteral nutrition in patients with pancreatic fluid collection.** Quality of evidence: very low; recommendation: weak	89
Statement #2.5 **I-EUS suggests that either a semi-elemental or polymeric formula might be employed for Enteral Nutrition In patients with pancreatic fluid collections.** Quality of evidence: very low; recommendation: weak	93
Statement #2.6 **I-EUS suggests against the routine use of probiotics in patients with acute pancreatitis and pancreatic fluid collection.** *Quality of evidence: low; recommendation: weak*	93
Statement #2.7 **I-EUS suggests against the routine use of pancreatic enzyme replacement therapy in patients with pancreatic fluid collection unless otherwise indicated.** *Quality of evidence: low; recommendation: weak*	93
Statement #2.8a **I-EUS suggests oral food intake after endoscopic drainage. Oral feeding may be initiated within the first few days of the procedure.** *Quality of evidence: moderate; recommendation: weak*	97
Statement #2.8b **I-EUS suggests that in patients undergoing endoscopic necrosectomy who are unable to be fed orally (hemodynamic instability, septic parameters, gastric emptying), enteral nutrition is indicated via the nasojejunal route as the preferred route.** *Quality of evidence: moderate; recommendation: weak*	100
Statement #2.8c **I-EUS recommends parenteral nutrition in patients undergoing necrosectomy who do not tolerate Enteral Nutrition, are unable to tolerate targeted nutritional requirements, or have contraindications for Enteral Nutrition.** *Quality of evidence: moderate; recommendation: weak*	92
Statement #2.9 **I-EUS suggests that patients with a complicated peri-pancreatic collection should be managed with multidisciplinary discussion in a center with availability of expertise in pancreatic surgery, pancreatobiliary endoscopy including therapeutic ERCP-EUS, interventional radiology, intensive care, infectious disease, and nutrition, or otherwise transferred to a center with these characteristics.** *Level of evidence: low; strength of recommendation: weak*	91

Quality of evidence: very low; recommendation: weak; Agreement 85%

Comment

Data on the microbial spectrum of infected pancreatic necrosis are limited. Only a few studies have addressed this issue in a large, consecutive group of patients treated by a standardized algorithm [17-20] (Supplementary Table 4). The differentiation between sterile and infected PFCs in pancreatitis according to clinical appearance and laboratory parameters remains difficult because both may present with fever, leukocytosis, and severe abdominal pain. In the presence of worsening clinical conditions, cultures of the pancreatic fluid can be performed by targeted antibiotic

therapy. In a multicenter study, colonization of PFCs was found in 59% of PFC cultures, whereas all but two (13%) concomitant blood cultures showed no microbial growth. In addition, in 23 (72%) patients with fluid colonization despite empiric antibiotic therapy, the treatment required adjustment in 18 patients (78%) according to the antibiotic susceptibility profile [17]. Another study of AP patients showed that nearly 50% of the involved patients acquired extremely drug-resistant bacterial infection and emerged as a key reason for prolonged hospital and intensive care unit (ICU) stay [19]. In a retrospective study evaluating 56 consecutive ICU patients admitted with infected necrosis, infection was confirmed in 48 patients (86%) through the identification of bacteria in pancreatic samples [18]. Despite the lack of evidence and considering the frailty of these patients, I-EUS suggests obtaining a microbiological culture when PFC drainage is achieved.

Question 1.4. *Is naso-cystic tube (NCT) placement indicated in patients treated with DEN for WON?*

Statement 1.4. *In patients with WON, I-EUS suggests the insertion of a naso-cystic tube for additional irrigation, or between DEN sessions.*

Quality of evidence: very low; recommendation: weak; Agreement 81%

Comment

Management of peripancreatic collections has gradually introduced the use of naso-cystic tubes (NCT). The justification is based on the dual goals of aspirating the collection contents and injecting liquids, H2O2, or antibiotics into the collection to clean it [21,22]. Through the suction function, it is also possible to obtain fluid that can be analyzed by carrying out biochemical dosages and microbiological examinations to define the possible infecting pathogen with the relative antibiogram. According to some authors, the removal of this material would reduce the possibility of superinfection of the collection and would allow for faster dimensional reduction [23] (Supplementary Table 5).

Currently, no studies have determined the patient population that would benefit from its use. The use of NCT is left to the discretion of the endoscopist, and in the various published studies, it was adopted for several reasons, either in all patients, or in patients with collections containing a substantial amount of necrotic tissue, with fever or signs suggesting an infection of the peripancreatic collection, or, finally, in very large collections.

One RCT was conducted to compare naso-cystic irrigation with hydrogen peroxide (H2O2) versus a bi-flanged metal stent (BMS) in the management of WON [21]. Fifty patients were randomized 1:1, and no differences were observed in technical success, clinical success, requirement for additional procedures, or AEs. In addition, the time to clinical success and the procedure time were longer with the use of NCT [21]. This RCT was a single-center study, without an attempt to stratify confounding at randomization, with a small sample size, and designed on a different outcome measure rather than NCT vs. no-NCT.

Question 1.5. *Does hydrogen peroxide (H2O2) irrigation-assisted direct endoscopic necrosectomy (DEN) improve the clinical outcome of patients affected by WOPN?*

Statement 1.5. *I-EUS group suggests that the use of H2O2 during DEN could improve clinical outcomes without increasing the risk of adverse events.*

Quality of evidence: low; recommendation: weak; Agreement 89%

Comment

The rationale for using hydrogen peroxide (H2O2) is based on H2O2′s ability to decompose organic tissues, facilitating the removal of necrotic debris and irritation of the WON wall, which leads to the formation of granulation tissue and fibrosis, favoring cavity obliteration. However, there are issues with its use, most notably the possibility of air embolism and vessel erosion within collections. It is typical to use a 3% H2O2 solution that is further diluted with saline solution at a ratio ranging from 1:10 to 1:2. The endoscopist has complete discretion over the irrigation volume, which can range from 100 to 1000 cc per session. H2O2 irrigation-assisted DEN may reduce the time and number of DEN sessions required to achieve WON resolution and clinical success [24-26]. In this regard, the largest study to date available is a multicenter retrospective comparative study of 204 patients, of whom 122 were treated with H2O2-assisted DEN (Supplementary Table 6) [27]. In this study, H2O2 was an independent factor for higher clinical success rate (Odds Ratio=3.30; $p = 0.003$) and earlier resolution (Odds Ratio=2.27; $p < 0.001$). A meta-analysis including seven studies and 186 patients who underwent H2O2 assisted DEN reported pooled technical success, clinical success, and cumulative rates of overall adverse events of 95.8%, 91.6%, and 19.3%, respectively. The pooled bleeding rates were 7.9%, stent migration was 11.3%, 5.4%, 5.7%, and pulmonary adverse event 2.9%, respectively. However, no adverse events attributable to H2O2 were reported. The mean number of sessions ranged from two to five [28].

Question 1.6. *Does PPI discontinuation improve necrosis digestion and reduce the number of re-interventions in patients undergoing DEN for WON?*

Statement 1.6. *I-EUS group suggests against routine use of PPI in patients with acute pancreatitis and/or peripancreatic collections unless indicated for other clinical reasons.*

Quality of evidence: very low; recommendation: weak; Agreement 82%

Comment

Proton pump inhibitors (PPI) reduce the risk of bleeding and gastric ulceration. However, acid suppression might accelerate bacterial duodenal overgrowth and subsequent superinfections and might delay the time until solid necrosis dissolves, suggesting that PPI interruption is required to facilitate digestion of the remaining necrotic tissue [29]. A multicenter retrospective study investigated the effectiveness of PPI therapy in patients receiving DEN for WON [30] in 272 patients (136 on PPI and 136 off PPI during the interval of DEN). The PPI and non-PPI groups had similar clinical success rates (78.7% vs. 77.9%), and the PPI group required a median of 4.6 procedures, compared to 3.2 in the non-PPI group ($p < 0.01$). The PPI group had a 14.0% resolution after the initial LAMS placement without requiring subsequent procedures compared to 22.1% in the non-PPI group ($p = 0.14$). In contrast, stent occlusion occurred significantly more frequently in the non-PPI group (9.5% vs. 20.1%, respectively). $P = 0.012$) occurred more frequently in the non-PPI group [30]. This study has limitations, owing to its retrospective nature, heterogeneity in follow-up, and endoscopic technique. Additional studies did not confirm this finding [31] (Supplementary Table 7).

2.2. Chapter 2

Question 2.1. *Which feeding route should be preferred for patients with pancreatic fluid collection?*

Statement 2.1. *I-EUS recommends offering oral feeding on a hunger basis, if clinically tolerated, in patients with pancreatic fluid collection.*

Quality of evidence: moderate; recommendation: strong; Agreement 95%

Comment

Patients with severe AP should be considered at nutritional risk because of the catabolic nature of the underlying disease, the risk

of metabolic sequelae, and the risk of gastric outlet obstruction due to pancreatic collections [32]. As no studies have specifically addressed the topic of nutrition in patients with pancreatic collections, the whole body of evidence has been extrapolated from studies regarding "nutrition in patients with moderate and severe AP" with high levels of evidence, mostly randomized controlled trials (RCTs) with a low to moderate risk of bias (Supplementary Table 8). Hunger-based refeeding is preferred to conventional refeeding (mostly based on clinical and biochemical remission) because it significantly reduces the length of hospitalization, health costs, and fasting duration [33-35]. Moreover, even in patients with predicted severe AP, among those at high risk of complications, oral diet has been compared to nil-per-mouth or nasoenteric tube feeding, showing no differences in the appearance of necrosis, infections, systemic inflammatory response syndrome (SIRS), or death [36,37].

Question 2.2. *Which feeding route should be used when oral feeding is not feasible?*

Statement 2.2a. *I-EUS suggests enteral nutrition in patients with pancreatic collections and inability to be fed orally.*

Quality of evidence: moderate; recommendation: weak; Agreement 98%

Statement 2.2b. *I-EUS suggests PN feeding only in cases of intolerance or contraindications to EN in patients with pancreatic fluid collection.*

Quality of evidence: very low; recommendation: weak; Agreement 97%

Comment

Several studies have highlighted the benefits of enteral nutrition (EN) versus parenteral nutrition (PN) in patients with predicted severe acute pancreatitis (SAP) who cannot be fed orally [36,38-42].

EN appears to be preferable because it maintains the integrity of the gut mucosa, stimulates bowel motility, prevents bacterial overgrowth, and increases splanchnic blood flow [43]. Several RCTs, systematic reviews, and meta-analyses have clearly demonstrated that EN is safe and well-tolerated in patients with SAP, with significant improvements in several clinical outcome measures such as infectious and digestive complications, tracheal aspiration, exacerbation of pain, achievement of energy balance, need for surgery, length of hospital stay, multi-organ failure, and mortality. A recent meta-analysis of 11 RCTs published by Wu et al. [44] with 562 patients with SAP focused on efficacy comparisons of EN and PN, showing that EN significantly decreased the relative risk (RR) of death (RR=0.43; $P = 0.006$), infections, and complications (RR=0.53; $P = 0.000$), with a lower rate of surgical intervention and shorter mean hospitalization time compared with patients who received PN. There was no significant difference in multiple organ failure (MOF) rates between the EN and PN groups (RR=0.63; $p = 0.059$). EN has also been shown to be crucial in preventing infection of the pancreatic necrotic collection in patients with SAP [45-48]. A recent RCT that enrolled 107 patients with SAP (randomly assigned 53 EN vs. 54 PN) [48] reported a significantly higher rate of organ failure in the PN group than in the EN group (80% vs. 21%). The risk of infection in the pancreatic collection (72% vs. 23%) and the risk of mortality (43% vs. 11%) were also higher in the PN group than in the EN group. Only one outdated RCT [49], based on a relatively low number of patients (24 EN vs. 26 PN), went in the opposite direction, showing that in predicted SAP the overall early complication rate was higher in the EN group, with no differences in gastrointestinal symptoms or abdominal pain.

Approximately 20% of patients with SAP have complications that can represent absolute or relative contraindications to EN, such as bowel obstruction, prolonged paralytic ileus, and mesenteric ischemia [50]. Abdominal compartment syndrome, one of the main contraindications for EN, can occur in 45% of patients with SAP [51]. In critically ill patients, those at high nutritional risk, or severely malnourished, exclusive PN should be initiated as soon as possible when EN is not feasible [50].

Question 2.3P. *What is the optimal timing to start enteral nutrition in patients with pancreatic fluid collection and inability to be fed orally?*

Statement 2.3. *I-EUS suggests starting enteral nutrition within 24–48 h in patients with pancreatic fluid collections and inability to be fed orally.*

Quality of evidence: moderate; recommendation: weak; Agreement 80%

Comment

Many studies have been published regarding the appropriate timing for starting EN, examining the clinical consequences, and tolerance of early EN in patients with AP (Supplementary Table 9); however, the definition of the time interval as "early" is not always univocal, as it is sometimes defined as within 24 h [52-54] or 48 h [55-57] or 72 h [58]. Meta-analyses clearly show that early EN, compared with delayed EN, leads to considerable benefits in terms of clinical outcomes, such as rate of mortality, organ failure or pancreatic related infections, so it should be considered feasible, safe and well-tolerated. Nevertheless, a potential confounding factor could be that in several studies included in meta-analyses, control groups were characterized by patients receiving PN [52-56]. In a recent meta-analysis of ten randomized controlled trials [55] containing 1051 patients with SAP comparing early EN to late EN or total PN, the pooled risk ratios were 0.53 (p=.003) for mortality, 0.58 (p=.0002) for MOF, 0.50 ($p = 0.0008$) for operative intervention, 0.75 ($p = 0.009$) for systemic infection, 0.42 ($p = 0.0005$) for local septic complications, 0.84 ($p = 0.01$) for gastrointestinal symptoms. 0.87 ($p = 0.08$) for SIRS, and 1.24 ($p = 0.50$) for other local complications. No direct prospective comparison can be found in the literature between 24 and 48 h, which could represent a significant item in clinical practice. A Multicenter Retrospective Study published in 2021 [59] divided patients with SAP into 3 groups depending on the starts of enteral nutrition: within 24 h, between 24 and 48 h, and >48 h. Regarding the primary outcome, in-hospital mortality was better with EN within 48 h vs. >48 h (adjusted OR=0.49; $p < 0.001$); EN initiation between 24 and 48 h was significantly associated with a reduced rate of surgical intervention but did not reduce mortality or fewer pancreatic infections than the group with EN initiation within 24 h. Two recent meta-analyses [60,61] have confirmed that immediate EN is associated with a shorter length of hospital stay, relief of feeding intolerance, and lower costs.

Question 2.4. *Which route should be preferred for enteral nutrition in patients with pancreatic collections?*

Statement 2.4. *I-EUS suggests a nasojejunal route for enteral nutrition in patients with pancreatic fluid collection.*

Quality of evidence: very low; recommendation: weak; Agreement 89%

Comment

In the literature, there are RCT and meta-analyses comparing the nasojejunal versus nasogastric route for EN in patients with SAP, suggesting no significant difference in outcomes [62-68], but no data are available for patients with pancreatic collections. Nevertheless, almost 15% of patients with SAP complain of digestive discomfort, mainly characterized by delayed gastric emptying and gastric outlet syndrome (GOO) [66], because pancreatic inflam-

mation itself predisposes to gastric stasis and because PFCs may cause or worsen gastric compression. A recent retrospective study of 60 patients with PFCs [69] showed that 55% (33/60) developed GOO in the first 4 weeks and 45% (27/60) developed GOO 4 weeks after onset. Pancreatic necrosis compression and gastric outlet gastrointestinal edema were the main causes of early onset GOO, whereas WON was the leading cause in the late phase. Therefore, even if there is no clear evidence on the preferred route of EN in this group of patients, we may speculate that in the case of PFCs, which may enhance the risk of GOO, an increase in abdominal distension due to gastric feeding may limit tolerance. Postpyloric delivery of nutrition through the nasojejunal tube is, therefore, suggested (Supplementary Table 10).

Question 2.5. *Which formula is indicated for enteral feeding in patients with pancreatic fluid collections*

Statement 2.5. *I-EUS suggests that either a semi-elemental or polymeric formula might be employed for Enteral Nutrition In patients with pancreatic fluid collections*

Quality of evidence: very low; recommendation: weak; Agreement 93%

Comment

Enteral nutrition formulations can be classified broadly as semi-elemental, comprising amino acids or oligopeptides, maltodextrins, and medium- and long-chain triglycerides, and polymeric, comprising non-hydrolyzed proteins, maltodextrins, oligofructosaccharides, and long-chain triglycerides. In AP, the use of semi-elemental polymeric formulations presents a number of theoretical advantages, as it is believed that semi-elemental formulations have superior absorption from the intestine, stimulate pancreatic secretions to a lesser degree, and are better tolerated [70]. However, the major disadvantage of semi-elemental formulations is their high cost. Petrov et al. conducted a systematic review and meta-analysis of ten RCTs comprising 428 patients, comparing semi-elemental and polymeric formulations indirectly using parenteral nutrition as a reference treatment [71]. In all patients with AP, the use of semi-elemental formulation did not result in a significant difference in the risk of infectious complications (RR=0.48; $p = 0.482$), death (RR=0·63; $p = 0.741$) and feeding intolerance (RR=0.62; $p = 0.611$).

A more recent meta-analysis that included 15 trials (1376 participants) showed no evidence to support a specific enteral formula [72].

Nevertheless, in a pilot randomized study conducted on 30 patients affected by SAP, semi-elemental nutrition was associated with decreased weight loss and a shorter length of hospital stay, suggesting a possible benefit of a semi-elemental diet in this subgroup of patients (Supplementary Table 11) [70].

Question 2.6. *Should probiotics be administered to patients with acute pancreatitis and pancreatic fluid collection?*

Statement 2.6. *I-EUS suggests against the routine use of probiotics in patients with acute pancreatitis and pancreatic fluid collection.*

Quality of evidence: low; recommendation: weak; Agreement 93%

Comment

Intestinal barrier dysfunction and subsequent bacterial translocation from the intestinal tract to the bloodstream and necrotic tissues play a critical role in infection of necrotic tissues [73]. In animal studies, probiotics stabilized the intestinal barrier and stimulated host cell production of antimicrobial peptides, thus minimizing bacterial translocation and preventing infection in AP [74]. A meta-analysis conducted by Gou et al. [75] of six RCTs including 536 patients showed that probiotics did not significantly affect the pancreatic infection rate (RR= 1.19; $p = 0.47$), total infections (RR=1.09; $p = 0.57$), operation rate (RR=1.42,; $p = 0.71$), length of hospital stay or mortality (RR=0.72; $p = 0.25$). Significant heterogeneity was observed in the type, dose, and treatment duration of probiotics used in these trials. Another relevant result comes from a randomized, double-blind, placebo-controlled trial [76] which showed that the probiotics group had a significant reduction in the length of hospital stay of patients with mild AP compared to the placebo group (5.36 vs 6.02; $p < 0.05$). Moreover, the probiotics group was associated with a shorter time to abdominal pain relief and time to successful oral feeding ($p < 0.01$).

A recent meta-analysis by Gao et al. (published in 2023, subsequent to the consensus) [77] confirmed that probiotics do not significantly affect mortality or the risk of organ failure in patients with SAP. Hence, there are insufficient data to support the routine use of probiotics in this context.

Question 2.7. *Is there any role of pancreatic enzyme replacement therapy in patients with pancreatic fluid collection?*

Statement 2.7. *I-EUS suggests against the routine use of pancreatic enzyme replacement therapy in patients with pancreatic fluid collection unless otherwise indicated.*

Quality of evidence: low; recommendation: weak; Agreement 93%

Comment

Pancreatic exocrine insufficiency (PEI) is a significant complication associated with pancreatitis. The severity of and recovery PEI appears to depend on the severity of AP, the extent of pancreatic parenchymal necrosis, and possibly on AP etiology, especially when comparing biliary and alcoholic AP [78]. A recent meta-analysis conducted by Huang et al. observed a prevalence of PEI during admission for AP of 65%, more commonly seen with SAP, which persisted during follow-up in 35% of the cases [79].

There were only two RCTs with a total of 78 patients randomized to either pancreatic enzyme supplementation or placebo. The study conducted by Kahl et al. included 56 patients with moderate and severe AP, 20 of whom had low fecal elastase levels [80]. There was no statistically significant difference in the recovery from PEI between the two treatment groups (pancreatic enzyme supplementation vs. placebo; $p = 0.641$). Although enzyme supplementation positively affected the course of the disease and the global health status (less weight loss, less flatulence, and improved quality of life), this did not reach statistical significance. In the second small study by Patankar et al., there was no significant difference in the laboratory or clinical outcomes [81].

There is insufficient evidence to support the generalized use of pancreatic enzyme replacement therapy in patients with AP; however, this should be considered in patients with proven or obvious PEI.

Question 2.8. *Which feeding route is preferred in patients with AP and PFC after endoscopic drainage?*

Statement 2.8a. *I-EUS suggests oral food intake after endoscopic drainage. Oral feeding may be initiated within the first few days of the procedure.*

Quality of evidence: moderate; recommendation: weak; Agreement 97%

Statement 2.8b. *I-EUS suggests that in patients undergoing endoscopic necrosectomy who are unable to be fed orally (hemodynamic instability, septic parameters, gastric emptying), enteral nutrition is indicated via the nasojejunal route as the preferred route.*

Quality of evidence: moderate; recommendation: weak; Agreement 100%

Statement 2.8c. *I-EUS recommends parenteral nutrition in patients undergoing necrosectomy who do not tolerate Enteral Nutrition, are unable to tolerate targeted nutritional requirements, or have contraindications for Enteral Nutrition.*

Quality of evidence: moderate; recommendation: weak; Agreement 92%

Comment

The "step-up" approach has proven benefits over the "open" approach for the management of pancreatic collections [82], and endoscopic techniques have been progressively adopted compared with surgical approaches [83]. Unfortunately, to date, there have been no published studies specifically addressing the topic of nutritional support in patients with pancreatic collections treated using minimally invasive approaches. In a large Dutch trial showing the benefits of the endoscopic approach over the surgical step-up approach [84], although no specific nutrition-related data were reported, all patients received oral nutrition, if tolerated. EN was administered through a nasojejunal feeding tube in cases of oral feeding intolerance, and if EN was contraindicated, the patient received PN.

Moreover, when extrapolating data from studies regarding nutrition in patients with moderate/severe AP who underwent interventional procedures due to PFCs (21), early (first 24 h) EN was not superior to late (>72 h) oral feeding (Supplementary Table 12). Finally, as previously discussed, PN remains indicated in patients with contraindications to EN, those who do not tolerate EN, or those who are unable to meet the targeted nutritional requirements with EN (Supplementary Table 13 and Supplementary Table 14). Definitive data were unavailable.

Question 2.9. Should patients with complicated peri–pancreatic collections be managed in centers with specific expertise?

Statement 2.9. *I-EUS suggests that patients with a complicated peri–pancreatic collection should be managed with multidisciplinary discussion in a center with availability of expertise in pancreatic surgery, pancreatobiliary endoscopy including therapeutic ERCP-EUS, interventional radiology, intensive care, infectious disease, and nutrition, or otherwise transferred to a center with these characteristics.*

Level of evidence: low; strength of recommendation: weak. Agreement: 91%

Comment

Patients with complicated PFCs that require invasive treatment are at high risk of death and should be referred to centers with high volumes of expertise, as better outcomes have been reported. The American Gastroenterology Guidelines (AGA) on the management of patients with pancreatic necrosis have already recommended such an approach in 2020 [85]. Since then, it has become clear that the mortality in AP is lower in hospitals with higher volumes of disease care [86] and that there is a specific hospital volume threshold for LAMS placement for the drainage of PFCs, which is associated with better outcomes, further supporting the need to centralize these patients in expert centers [87].

Conflict of Interest

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Supplementary materials

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