Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines

Authors

Marianna Arvanitakis[1], Jean-Marc Dumonceau[2], Jörg Albert[3], Abdenor Badaoui[4], Maria Antonietta Bali[1], Marc Barthet[5], Marc Besselink[6], Jacques Deviere[1], Alexandre Oliveira Ferreira[7], Tibor Gyökeres[8], Istvan Hritz[9], Tomas Hucl[10], Marianna Milashka[11], Ioannis S. Papanikolaou[12], Jan-Werner Poley[13], Stefan Seewald[14], Geoffroy Vanbiervliet[15], Krijn van Lienden[16], Hjalmar van Santvoort[17], Rogier Voermans[18], Myriam Delhaye[1], Jeanin van Hooft[18]

Institutions

1 Department of Gastroenterology, Hepatology and Digestive Oncology, Erasme University Hospital Université Libre de Bruxelles, Brussels, Belgium
2 Gedyt Endoscopy Center, Buenos Aires, Argentina
3 Robert-Bosch-Krankenhaus, Abteilung für Gastroenterologie, Hepatologie und Endokrinologie, Stuttgart, Germany
4 Department of Gastroenterology and Hepatology, Université catholique de Louvain, CHU UCL Namur, Yvoir, Belgium
5 Service d'Hépato-gastroentérologie, Hôpital Nord, Marseille, France
6 Department of Surgery, Amsterdam Gastroenterology and Metabolism, Academic Medical Center Amsterdam, Amsterdam, The Netherlands
7 Gastroenterology Unit, Department of Surgery, Hospital Beatriz Ângelo, Loures, Portugal
8 Dept. of Gastroenterology, Medical Centre Hungarian Defense Forces, Budapest, Hungary
9 Semmelweis University, 1st Department of Surgery, Endoscopy Unit, Budapest, Hungary
10 Department of Gastroenterology and Hepatology, Institute of Clinical and Experimental Medicine, Prague, Czech Republic
11 Service de Gastroentérologie et Hépatologie, Hôpital Desgenettes, Lyon, France
12 Hepatogastroenterology Unit, Second Department of Internal Medicine, Propaedeutic, Research Institute and Diabetes Center, Medical School, National and Kapodistrian University, Attikon University General Hospital, Athens, Greece
13 Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
14 Gastroenterologie, Klinik Hirslanden, Zurich, Switzerland
15 Centre Hospitalier Universitaire de Nice, Pole D.A.R.E, Endoscopie Digestive, Nice, France
16 Department of Radiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
17 Department of Surgery, St. Antonius Hospital Nieuwegein, The Netherlands and Department of Surgical Oncology, University Medical Center Utrecht Cancer Center, The Netherlands
18 Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Corresponding author
Marianna Arvanitakis, MD PhD, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme University Hospital, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium
Marianna.Arvanitaki@erasme.ulb.ac.be

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MAIN RECOMMENDATION

1 ESGE suggests using contrast-enhanced computed tomography (CT) as the first-line imaging modality on admission when indicated and up to the 4th week from onset in the absence of contraindications. Magnetic resonance imaging (MRI) may be used instead of CT in patients with contraindications to contrast-enhanced CT, and after the 4th week from onset when invasive intervention is considered because the contents (liquid vs. solid) of pancreatic collections are better characterized by MRI and evaluation of pancreatic duct integrity is possible.
Weak recommendation, low quality evidence.

2 ESGE recommends against routine percutaneous fine needle aspiration (FNA) of (peri)pancreatic collections.
Strong recommendation, moderate quality evidence.
FNA should be performed only if there is suspicion of infection and clinical/imaging signs are unclear.
Weak recommendation, low quality evidence.

3 ESGE recommends initial goal-directed intravenous fluid therapy with Ringer's lactate (e. g. 5 – 10 mL/kg/h) at onset. Fluid requirements should be patient-tailored and reassessed at frequent intervals.
Strong recommendation, moderate quality evidence.

4 ESGE recommends against antibiotic or probiotic prophylaxis of infectious complications in acute necrotizing pancreatitis.
Strong recommendation, high quality evidence.

5 ESGE recommends invasive intervention for patients with acute necrotizing pancreatitis and clinically suspected or proven infected necrosis.
Strong recommendation, low quality evidence.
ESGE suggests that the first intervention for infected necrosis should be delayed for 4 weeks if tolerated by the patient.
Weak recommendation, low quality evidence.

6 ESGE recommends performing endoscopic or percutaneous drainage of (suspected) infected walled-off necrosis as the first interventional method, taking into account the location of the walled-off necrosis and local expertise.
Strong recommendation, moderate quality evidence.

7 ESGE suggests that, in the absence of improvement following endoscopic transmural drainage of walled-off necrosis, endoscopic necrosectomy or minimally invasive surgery (if percutaneous drainage has already been performed) is to be preferred over open surgery as the next therapeutic step, taking into account the location of the walled-off necrosis and local expertise.
Weak recommendation, low quality evidence.

8 ESGE recommends long-term indwelling of transluminal plastic stents in patients with disconnected pancreatic duct syndrome.
Strong recommendation, low quality evidence.
Lumen-apposing metal stents should be retrieved within 4 weeks to avoid stent-related adverse effects.
Strong recommendation, low quality evidence.

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE) on the management of acute necrotizing pancreatitis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

Introduction

Acute pancreatitis is the most common gastrointestinal disease requiring acute hospital admission [1]. In most cases (80 %), the outcome is rapidly favorable [2]. However, acute necrotizing pancreatitis (ANP) may develop in up to 20 % of cases and is associated with significant rates of early organ failure (38 %), need for intervention (38 %), and death (15 %) [3]. Among interventions, necrosectomy through the endoscopic route is increasingly performed.

This evidence-based guideline was commissioned by the European Society of Gastrointestinal Endoscopy (ESGE). It aims to address all major issues concerning the global management of ANP, the roles of radiology, endoscopy, and surgery in step-up strategies, and the technical modalities of endoscopic necrosectomy.

Methods

The ESGE commissioned this guideline and appointed a guideline leader (M.A.) who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating team (M.A., M.D.) and then approved by the other members. The coordinating team formed task force subgroups, each with their own leader, and divided the key topics among the subgroups. Topics included: diagnosis and initial management, indications and timing for intervention, treatment modalities (radiological, endoscopic, and surgical, as well as combined), complications, and outcome. The guideline development process included meetings and online discussions that took place from October 2015 to October 2016.

A literature search of PubMed/MEDLINE, the Cochrane Library, and Embase was performed by the authors for papers published on this topic up to December 2016. The search focused on fully published randomized controlled trials (RCTs) and meta-analyses. Retrospective analyses and case series were also included if they addressed topics not covered in the prospective studies. For important outcomes, articles were individually assessed by means of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) sys-

ABBREVIATIONS

ANP	acute necrotizing pancreatitis
APA	American Pancreatic Association
AUC	area under the curve
BISAP	bedside index of severity in acute pancreatitis
BUN	blood urea nitrogen
CE-CT	contrast-enhanced computed tomography scan
CI	confidence interval
CRP	C-reactive protein
CTSI	CT severity index
DBC	determinant-based classification
DEN	direct transluminal endoscopic necrosectomy
DPDS	disconnected pancreatic duct syndrome
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
EUS	endoscopic ultrasound
EXPN	extrapancreatic (peripancreatic) necrosis
FC-SEMS	fully covered self-expandable metal stent
FNA	fine needle aspiration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IAP	International Association of Pancreatology
ICU	intensive care unit
IPN	infected pancreatic and/or peripancreatic necrosis
LAMS	lumen-apposing metal stent
MPD	main pancreatic duct
MRCP	magnetic resonance cholangio-pancreatography
MRI	magnetic resonance imaging
MTGT	multiple transluminal gateway technique
OR	odds ratio
PCD	percutaneous catheter drainage
PFC	pancreatic fluid collection
RAC	revised Atlanta classification
RCT	randomized controlled trial
SIRS	systemic inflammatory response syndrome
VARD	video-assisted retroperitoneal debridement
WON	walled-off necrosis

tem for grading evidence levels and recommendation strengths [4].

Each subgroup developed draft proposals that were discussed electronically and then during a meeting held in May 2016 (Brussels, Belgium). After agreement on a final version following a meeting in October 2016 (Vienna, Austria), the manuscript was reviewed by two experts selected by the ESGE Governing Board and then sent to all ESGE-affiliated societies and individual members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised manuscript.

This Guideline will be considered for review in 2021 or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

1 Diagnosis

1.1 Classification systems for acute pancreatitis severity: revised Atlanta classification and determinant-based classification

RECOMMENDATION

ESGE suggests using the 3-tiered revised Atlanta classification rather than the 4-tiered determinant-based classification.

Weak recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests considering, besides the level of severity, the presence or absence of infected necrosis, as well as multiple vs. single persistent organ failure as further predictors of outcome.

Weak recommendation, low quality evidence.

Four levels of severity are distinguished in the determinant-based classification (DBC): (i) mild (absence of both [peri]pancreatic necrosis and organ failure), (ii) moderate (presence of sterile [peri]pancreatic necrosis and/or transient organ failure), (iii) severe (presence of either infected [peri]pancreatic necrosis or persistent organ failure), and (iv) critical (presence of infected [peri]pancreatic necrosis and persistent organ failure) [5]. On the other hand, the revised Atlanta classification (RAC) defines three degrees of severity: (i) mild (absence of organ failure and absence of local or systemic complications), (ii) moderate (presence of transient organ failure and/or local or systemic complications), and (iii) severe (presence of persistent organ failure, single or multiple) [6].

Unlike the RAC, the DBC requires data on [peri]pancreatic necrosis status, sterile or infected, and is therefore less applicable during the early phase (1st week), being more suitable for post-hoc category allocation [7]. Both the RAC and the DBC were found to be similar in terms of predicting important clinical outcomes in acute pancreatitis (mortality, need for intensive care unit [ICU] management, need for intervention, and duration of hospital stay) [8 – 11]. The addition of a critical category in the DBC identifies patients with the most severe disease [7 – 13]. However, the proportion of patients included in this critical category was low (0.6 % – 12 %); therefore, the clinical significance of this group is probably limited.

In most studies, patients with infected pancreatic and/or peripancreatic necrosis (IPN) seemed to have poorer outcomes, independently of whether they were initially classified as moderate or severe [14 – 16]. Both classifications failed to account for the impact of persistent multiple-organ failure vs. persistent single-organ failure on mortality (56.3 % vs. 7.4 %; $P = 0.001$) [10] (**Table e1,** available online in Supplementary material).

1.2 Definition of local complications of acute pancreatitis

The local complications of acute pancreatitis are best defined in the RAC [6] and include acute (peri)pancreatic fluid collections (PFCs; within the first 4 weeks, with no well-defined wall, usually resolving spontaneously); acute necrotic collections (within the first 4 weeks, containing variable amounts of fluid and necrotic tissue, arising from ANP); pancreatic pseudocysts (≥ 4 weeks after onset of interstitial acute pancreatitis, fluid collection in the [peri]pancreatic tissues, surrounded by a well-defined wall, containing no solid material); and walled-off necrosis (WON; after ≥ 4 weeks, encapsulated collection containing partially liquefied [peri]pancreatic necrotic tissue). Other local complications include abdominal compartment syndrome, gastric outlet dysfunction, biliary obstruction, splenic and portal vein thrombosis, colonic necrosis, major bleeding, ascites, and pleural effusions [1, 17].

1.3 Definition of necrosis, extrapancreatic necrosis, and infected necrosis

In ANP, necrosis may involve the pancreatic parenchyma alone (< 5 % of cases), the pancreatic parenchyma and peripancreatic tissues (75 % – 80 % of cases), or peripancreatic tissues alone (approximately 20 % of cases) [18].

Pancreatic necrosis is the presence of non-viable pancreatic parenchyma. It is commonly assessed as a focal or diffuse area with no enhancement on contrast-enhanced computed tomography scanning (CE-CT) [6, 19]. By magnetic resonance imaging (MRI), pancreatic necrosis appears as well-marginated areas of lower signal intensity compared with the signal intensity of the normal pancreas and spleen in non-enhanced MRI and in the arterial, early venous, and late venous phases of enhancement after intravenous gadolinium injection [20].

Extrapancreatic (peripancreatic) necrosis (EXPN) is defined as the presence of heterogeneous, peripancreatic, ill-defined areas, commonly located in the retroperitoneum and lesser sac, while the pancreas enhances normally on CE-CT [21].

In a prospective study (639 patients), compared with patients with pancreatic necrosis, patients with EXPN alone had lower risks of organ failure (adjusted odds ratio [OR] 0.53), multiple-organ failure (adjusted OR 0.48), IPN (adjusted OR 0.30), need for intervention (adjusted OR 0.25), and mortality (adjusted OR 0.59). However, in the case of IPN, morbidity and mortality rates were similar among patients with EXPN and those with parenchymal pancreatic necrosis (with or without EXPN) [22].

IPN can be suspected based on clinical evidence of sepsis (e. g. fever > 38 °C, features of persistent systemic inflammatory response syndrome (SIRS), and deterioration or no improvement in clinical condition) or the presence of extraluminal gas in the pancreatic and/or peripancreatic tissues on CT [23]. IPN is diagnosed when sampling of (peri)pancreatic tissue by percutaneous, endoscopic, or surgical drainage is positive for bacteria and/or fungi on Gram stain or culture.

1.4 Scores and/or markers for the prediction of severe acute pancreatitis on admission and at 48 hours

RECOMMENDATION

ESGE suggests using the Bedside Index of Severity in Acute Pancreatitis (BISAP) score within the first 24 hours of presentation as an early predictor of severity and mortality in acute pancreatitis.
Weak recommendation, moderate quality evidence.

RECOMMENDATION

ESGE suggests using a blood urea nitrogen (BUN) level ≥ 23 mg/dL (8.2 mmol/L) as a predictor of persistent organ failure after 48 hours of admission.
Weak recommendation, moderate quality evidence.

Persistent organ failure is a good surrogate marker of severity in acute pancreatitis [6]. The overall accuracy of 11 scores/markers in predicting persistent organ failure has been evaluated in two prospective cohorts (n = 256 and n = 397) [24]. Overall, accuracy in predicting persistent organ failure was modest (area under the curve [AUC] 0.57 – 0.74 at admission and 0.57 – 0.79 at 48 hours).

Individual laboratory values showed accuracy similar to that of more complex scoring systems: for example, the AUC for BUN ≥ 23 mg/dL was 0.73 at admission and 0.76 at 48 hours [24]. In a post-hoc retrospective analysis of three prospectively enrolled cohorts of 1612 patients with acute pancreatitis, a hematocrit ≥ 44 % on admission and a rise in BUN at 24 hours showed the highest accuracy (0.67 and 0.71, respectively) for predicting persistent organ failure [25].

In two studies, a retrospective analysis of a prospective database including 759 patients with acute pancreatitis [26] and a prospective cohort study including 252 patients [27], persistent SIRS at 48 hours was significantly associated with higher mortality. Contrary to these results, a recent systematic review examining the performance of 11 predictors of persistent organ failure within the first 48 hours from admission suggested that SIRS did not perform well [28].

Four further studies have identified a BISAP score ≥ 2 within the first 24 hours of admission to be an accurate predictor of severe acute pancreatitis with an AUC ≥ 0.80 for prediction of severe acute pancreatitis and an AUC ≥ 0.82 for prediction of mortality [29 – 32] (**Table e2**, available online in Supplementary materials).

1.5 Indications, timing, and modalities of imaging in predicted severe acute pancreatitis

RECOMMENDATION
ESGE suggests performing cross-sectional imaging on admission where there is diagnostic uncertainty; within the first week from onset (after 72 hours from onset of symptoms) where there is failure to respond to conservative treatment; from the 2nd to the 4th week, to evaluate the evolution of complications; and, after the 4th week, to plan further management and to monitor the treatment response.
Weak recommendation, very low quality evidence.

RECOMMENDATION
ESGE suggests using contrast-enhanced CT as the first-line imaging modality on admission when indicated and up to the 4th week from onset in the absence of contraindications. MRI may be used instead in patients with contraindications to contrast-enhanced CT, and after the 4th week from onset when invasive intervention is considered because the contents (liquid vs. solid) of pancreatic collections are better characterized by MRI and evaluation of pancreatic duct integrity is possible.
Weak recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends use of the CT severity index as the preferred imaging severity score.
Strong recommendation, moderate quality evidence.

At admission, imaging with CE-CT is indicated where there is uncertainty about the diagnosis of acute pancreatitis [33–35]. Furthermore, abdominal ultrasound plays a role in determination of the etiology of acute pancreatitis (biliary vs. other origin), and should be performed on admission.

Within the first week from onset/hospital admission, patients with predicted severe acute pancreatitis who fail to improve clinically despite conservative treatment should have imaging in order to stage the extent of pancreatic necrosis (both parenchymal and extrapancreatic) and to identify early complications [34, 36]. CE-CT best detects parenchymal pancreatic necrosis 72 hours after symptom onset; before that time, it may underestimate or miss the presence of necrosis [35]. CE-CT is the first-line imaging modality used to assess the morphological features of ANP [19, 35, 37] because it is widely available with a short scan duration, a robust reproducibility (high interobserver and intraobserver agreement), and a high accuracy for predicting severe acute pancreatitis and clinical outcome [31, 37–39]. For example, the AUC of the CT severity index (CTSI) using a cutoff of 3 for predicting persistent organ failure is 0.84 [31], and 0.85 with a CTSI cutoff of 4 [38].

Non-enhanced MRI is similar to CE-CT for the early assessment of acute pancreatitis severity [20, 39–41]. MRI (without gadolinium) can be recommended when the injection of iodinated contrast medium is contraindicated (i. e. impaired renal function or allergy to iodinated contrast) or when radiation exposure is contraindicated (i. e. pregnant women). Contrast-enhanced ultrasound could also be used, potentially at the bedside, as it presents similar accuracy to CE-CT for the detection of severe acute pancreatitis [42–44]. However, its applicability may be more limited (e. g. obesity, meteorism).

From the 2nd to the 4th week after onset/hospital admission, imaging aims to detect local complications (e. g. vascular complications, main pancreatic duct [MPD] disruption), evaluate the evolution of (peri)pancreatic local complications (acute necrotic collection), or assess patients in whom a severe complication such as bleeding, bowel ischemia, or perforation is suspected [34]. MPD disruption is best diagnosed by secretin-enhanced magnetic resonance cholangiopancreatography (MRCP) [45].

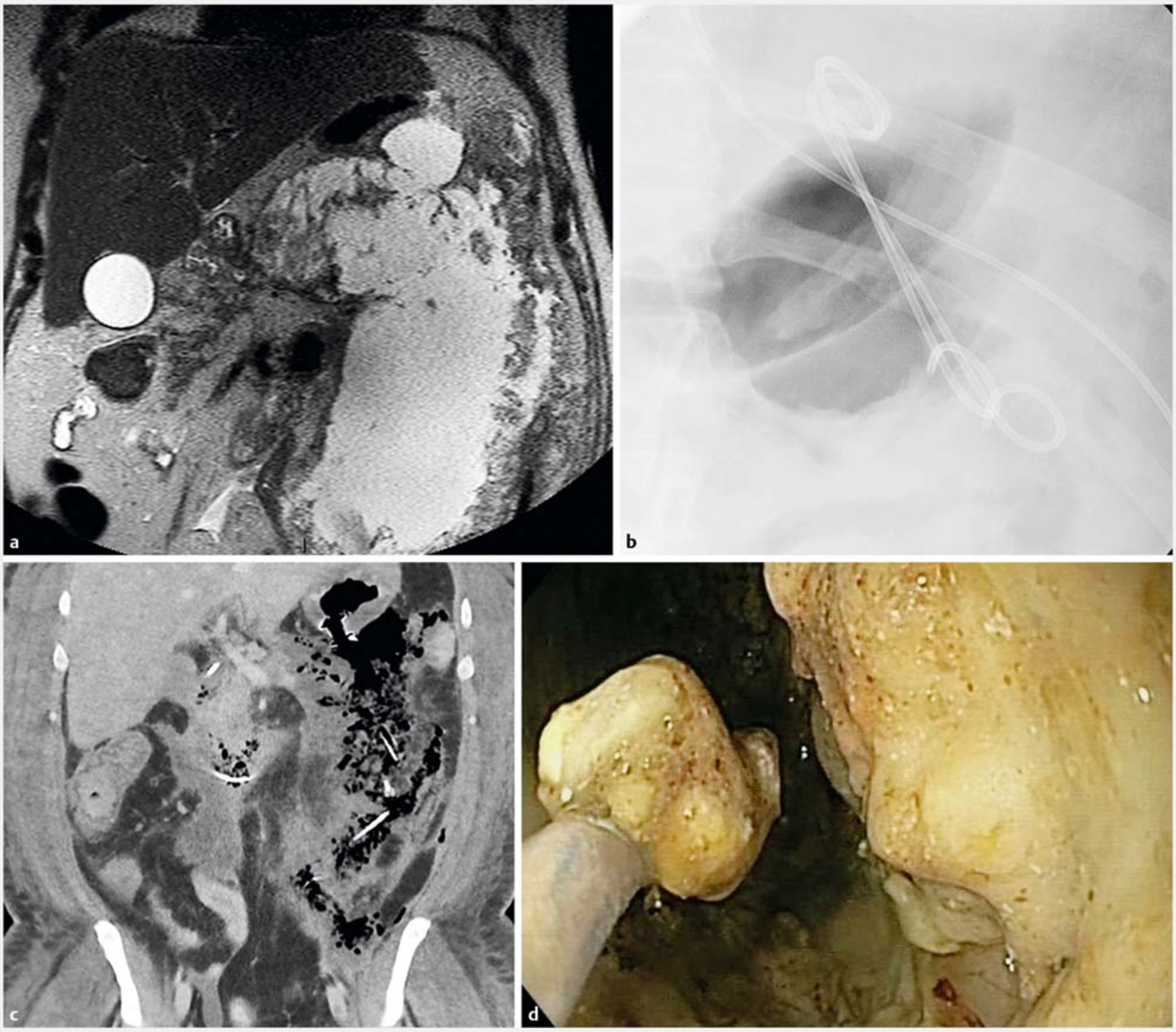
After the 4th week, imaging is used in patients with no clinical improvement, if invasive intervention is considered, and to monitor treatment response. MRI is preferred to assess whether WON can be drained because it is better at detecting non-liquefied material than CT, with a better interobserver agreement [46, 47] (▶ **Fig. 1a**). Albeit more invasive, endoscopic ultrasound (EUS) is also accurate in assessing the content of WON [48, 49].

1.6 Differentiating between sterile and infected necrosis (including clinical, biological, and imaging modalities)

RECOMMENDATION
ESGE recommends against routine percutaneous fine needle aspiration (FNA) of (peri)pancreatic collections.
Strong recommendation, moderate quality evidence.
FNA should be performed only if there is suspicion of infection and clinical/imaging signs are unclear.
Weak recommendation, low quality evidence.

A Dutch post-hoc retrospective analysis of a prospective multicenter database (208 patients) found that clinical deterioration (persisting sepsis, new/prolonged organ failure, increased need for cardiovascular and/or respiratory and/or renal support, leukocytosis, elevated or increasing C-reactive protein [CRP], and fever) despite adequate support, in the absence of an alternative source of infection, was caused by IPN in 74 of 92 patients (80.4 %; false-positive rate 19.6 %) [50].

A systematic review suggested that the best biological predictor of IPN is procalcitonin. With a cutoff value of 3.5 ng/mL, procalcitonin had a sensitivity and specificity of 0.90 and 0.89, respectively [28]. However, procalcitonin is a non-specific marker of infective complications in critically ill patients and



► **Fig. 1** Management of a 35-year-old man with severe acute alcoholic pancreatitis and walled-off necrosis who was referred for management 30 days after his symptoms had begun. **a** Coronal magnetic resonance imaging T2 sequence showed a large, mostly fluid-filled walled-off necrosis, extending into the left iliac fossa. **b** Initial endoscopic ultrasound-guided drainage was performed with insertion of two double-pigtail stents and a nasocystic catheter for lavage. **c** Subsequently, after dilation of the orifice, a lumen-apposing metal stent was inserted and necrosectomy was performed. A coronal computed tomography image illustrates the stent with the nasocystic catheter passing through it. **d** Endoscopic image of the cavity, as seen during the necrosectomy sessions. A snare is used to retrieve the necrotic debris.

therefore other coexisting sources of infection need to be excluded [51].

The presence of gas in parenchymal or extrapancreatic necrosis on CT showed poor performance for assessing IPN in the abovementioned study (sensitivity 45.9 %; specificity 81.5 %; accuracy 50.5 %) [50]. Diffusion-weighted MRI can be used to detect IPN, but large studies are still lacking [52, 53].

The added value of fine needle aspiration (FNA) for diagnosing IPN is limited if clinical and/or imaging signs are taken into consideration [50]. Furthermore, there are a considerable number of false-negative (20 % – 29 %) and false-positive results (4 % – 10 %) [50, 54].

2 Conservative management of acute necrotizing pancreatitis

2.1 Fluid resuscitation

RECOMMENDATION

ESGE recommends initial goal-directed intravenous fluid therapy with Ringer’s lactate (e. g. 5 – 10 mL/kg/h) at onset of the pancreatitis. Fluid requirements should be patient-tailored and reassessed at frequent intervals.
Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE suggests that fluid resuscitation assessment should be based on one or more of the following: (i) clinical targets (heart rate < 120 beats/min, mean arterial pressure of 65 – 85 mmHg, urinary output > 0.5 – 1 mL/kg/h), (ii) laboratory targets (hematocrit < 44 %, declining BUN levels, maintainence of normal serum creatinine levels during the first day of hospitalization) and, (iii) in the intensive care setting, invasive targets (central venous pressure of 8 – 12 mmHg, stroke volume variation, and intrathoracic blood volume determination).

Weak recommendation, moderate quality evidence.

2.1.1 Type of fluid for initial resuscitation

In a multicenter RCT (40 patients with severe acute pancreatitis), resuscitation with Ringer's lactate decreased the incidence of SIRS when compared to resuscitation with normal saline [55]. Intravenous hydration with Ringer's solution was found to be equivalent to nasojejunal hydration in a recent RCT (49 patients with severe acute pancreatitis) [56] (**Table e3**, available online in Supplementary materials).

2.1.2 What is the optimal fluid infusion rate?

Retrospective studies have demonstrated that aggressive early hydration in patients with severe acute pancreatitis is associated with decreased morbidity and mortality [57 – 60]. Three RCTs in endoscopic retrograde cholangiopancreatography (ERCP) patients showed that aggressive fluid administration reduced post-ERCP acute pancreatitis [61 – 63].

In contrast, three studies (2 RCTs) in patients with severe acute pancreatitis by Mao et al. supported that rapid hemodilution increased morbidity and mortality, although criticisms regarding design, randomization, and power were raised [64 – 66]. Recently, Weitz et al. reported higher disease severity and more complications with aggressive hydration in patients with severe acute pancreatitis [67]. Patients with diminished cardiac reserve should be administered fluids cautiously, given their risk of pulmonary edema [68]. A study in 9489 patients with acute pancreatitis concluded that high volume fluids in the initial 48 hours were associated with increased mortality [69]. A prospective study demonstrated that administration of > 4.1 L of fluids during the initial 24 hours was linked to increased morbidity, while < 3.1 L had no unfavorable consequences [70]. Obviously, selection biases (i. e. severe cases have worse outcomes despite vigorous management) should be considered when evaluating the results of non-randomized studies.

2.1.3 What are the best non-invasive and invasive measures to assess appropriate fluid resuscitation in patients with acute pancreatitis?

Apart from vital signs, serial measurements of hematocrit, BUN, and serum creatinine can serve as surrogate markers of hydration status and their use has been widely recommended [24, 31, 71, 72]. Sole central venous pressure measurement is rather unreliable [63, 73] and inferior to assessment by technologically advanced intravascular monitoring systems, such as the continuous cardiac output monitoring system (PiCCO), in optimizing fluid management in acute pancreatitis [74, 75].

2.2 Antibiotics

RECOMMENDATION

ESGE recommends against antibiotic or probiotic prophylaxis of infectious complications in acute necrotizing pancreatitis.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends, in patients with suspected or proven infected necrosis, the use of antibiotics targeting gut-derived bacteria and adapted to culture and antibiogram results if available.

Strong recommendation, low quality evidence.

2.2.1 Antibiotic prophylaxis in acute necrotizing pancreatitis

Meta-analyses published since 2008 [76 – 83] have shown no benefit from the routine use of prophylactic antibiotics in patients with severe acute pancreatitis. Furthermore, prophylactic antibiotic use might increase the risk of intra-abdominal fungal infection [84, 85].

A meta-analysis (4 RCTs, 428 patients) showed no reduction in the risk of IPN or associated mortality with vs. without probiotic prophylaxis [86].

2.2.2 Selection of antibiotics in patients with suspected infected pancreatic necrosis

Intravenous antibiotics should be administered and further intervention considered once IPN is suspected. Antibiotics are useful in IPN to delay or even avoid intervention in mild cases [3, 33]. Translocation of bacteria from the small bowel is thought to be the major source for infection of necrosis [87]. Empirically, antibiotics effective on gut-derived bacteria and known to penetrate into the pancreas (carbapenems, quinolone, metronidazole, and high dose cephalosporins) seem the most appropriate [77, 88, 89]. Once blood/FNA culture results have been obtained, antibiotic therapy should be adjusted accordingly.

2.2.3 Duration of antibiotic therapy for infected pancreatic necrosis

There are no data on the adequate duration of antibiotic therapy in patients with IPN (e. g. stopping rules for antibiotic administration) [77]. Antibiotics are commonly stopped 48 hours after the removal of the last drainage catheter, if all cultures remain negative. Improvement of clinical, biochemical, and imaging features may help guide the decision to stop antibiotic therapy [90–92].

2.3 Nutrition

RECOMMENDATION

ESGE recommends enteral tube feeding with polymeric enteral nutrition in all patients with predicted severe acute pancreatitis who cannot tolerate oral feeding after 72 hours.
Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE suggests initiating enteral nutrition via a nasogastric tube, except in patients with hemodynamic instability, and to switch to the nasojejunal route in patients with digestive intolerance.
Weak recommendation, moderate quality evidence.
Parenteral nutrition should be commenced if there is persistent digestive intolerance or if the caloric goal is not met.
Weak recommendation, low quality evidence.

2.3.1 Effects of enteral tube feeding in severe acute pancreatitis

Gut-barrier dysfunction may occur in a significant percentage of patients with severe acute pancreatitis; it is thought to lead to bacterial translocation and infection of necrosis [93]. Enteral feeding is supposed to preserve the integrity of the gut mucosa, stimulate intestinal motility, prevent bacterial overgrowth, and increase the splanchnic blood flow [94].

Twelve RCTs and eight meta-analyses have been performed regarding enteral and parenteral nutrition in acute pancreatitis [95]. The three most recent meta-analyses showed that, in patients with predicted severe acute pancreatitis, enteral nutrition as compared to parenteral nutrition decreases systemic infections, multiple-organ failure, need for surgical intervention, and mortality [96–98]. However, the RCTs have several limitations such as heterogeneity in the severity of acute pancreatitis and in the delay before nutritional intervention; other limitations include small sample sizes, poor glycemic control in the parenteral groups in the older studies, and suboptimal calorie goal attainment [95].

2.3.2 Timing of enteral tube feeding in severe acute pancreatitis

Previously, non-randomized studies involving patients with predicted severe acute pancreatitis, including two systematic reviews (775 and 451 patients) [99, 100], have shown that nasoenteric tube feeding started within 48 hours after admission, as compared with after 48 hours, significantly reduces the rate of major infection and in some studies even reduces mortality [101, 102]. Nevertheless, a multicenter RCT (208 patients with predicted severe acute pancreatitis) found no difference in the rate of major infection or death between early nasoenteric tube feeding, started within 24 hours after admission, and an oral diet initiated 72 hours after admission [103].

The abovementioned trial challenges the gut mucosa-preserving effect of early enteral nutrition during acute pancreatitis and is in line with the "permissive underfeeding" concept [104]. A second RCT (214 patients with acute pancreatitis) confirmed these results, showing no significant reduction in persistent organ failure and mortality in patients receiving early enteral nutrition compared with patients receiving no nutritional support [105].

2.3.3 Type of enteral nutrition

Two meta-analyses, involving previous RCTs comparing enteral to parenteral nutrition, focused on the effect of different formulations by means of secondary analysis [106, 107]. Both reviews found no differences between polymeric vs. (semi)elemental nutrition, in terms of feeding intolerance, infectious complications, or death.

2.3.4 Should enteral nutrition be administered via the nasojejunal or nasogastric route?

Four studies (3 RCTs) compared nasojejunal with nasogastric feeding in patients with severe acute pancreatitis [108–111] (**Table e4**, available online in Supplementary material), and an RCT compared nasogastric tube feeding vs. parenteral nutrition [112]. Based on these trials, four meta-analyses found no differences between nasogastric and nasojejunal enteral feeding regarding tolerance and mortality [113–116]. One study reported a higher pulmonary complication rate in patients receiving nasogastric enteral feeding [111]. Limitations of the abovementioned RCTs include heterogeneity with regard to timing and severity of acute pancreatitis, exclusion of patients with hemodynamic instability and likely very severe disease, and absence of routine confirmation of the nutrition tube position [95].

2.4 Specific treatment of biliary acute pancreatitis

RECOMMENDATION

ESGE recommends urgent (≤ 24 hours) ERCP and biliary drainage in patients with acute biliary pancreatitis combined with cholangitis.
Strong recommendation, high quality of evidence.
ERCP should be performed within 72 hours in patients with ongoing biliary obstruction.
Weak recommendation, moderate quality evidence.
It should not be performed in patients with acute biliary pancreatitis and neither cholangitis or ongoing bile duct obstruction.
Weak recommendation, moderate quality evidence.

2.4.1 What are the indications for early ERCP and sphincterotomy in the setting of biliary acute pancreatitis?

Based on the initial RCTs, ERCP was shown to be effective in decreasing the incidence of complications in biliary acute pancreatitis [117, 118]. These trials included patients with cholangitis, who may benefit more than those without cholangitis. For this reason, a multicenter RCT excluding patients with cholangitis was performed; it failed to show a benefit of early ERCP in the community hospital setting [119]. Three other RCTs also failed to show a benefit from ERCP in this group of patients [120 – 122] (**Table e5**, available online in Supplementary materials).

The Cochrane meta-analysis of these trials showed no difference in outcomes with vs. without ERCP, independently of acute pancreatitis severity and ERCP timing, except for patients with cholangitis [123]. A trend toward a decreased complication rate was observed for patients without cholangitis but with ongoing biliary obstruction (common bile duct stone and/or abnormal bilirubin and/or common bile duct dilatation). However, significant group heterogeneity, the lack of systematic sphincterotomy in the absence of common bile duct stones, and a type II statistical error could be potential biases.

2.4.2 Optimal timing for ERCP in the setting of biliary acute pancreatitis with and without cholangitis

No study has been specifically designed to assess the timing of ERCP in biliary acute pancreatitis. The available RCTs that have evaluated ERCP in acute pancreatitis have used variable time frames, from < 24 hours [118] to 72 hours after the beginning of the symptoms [119], or after admission [117, 120, 121] (**Table e5**, available online in Supplementary materials).

In the 2012 Cochrane systematic review, there were no significant differences in mortality between the early ERCP strategy and the early conservative management strategy regardless of time to ERCP (within 24 hours vs. within 72 hours of admission) [123]. The International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guideline states that urgent ERCP (< 24 hours) should be performed in patients with biliary pancreatitis and cholangitis [1].

3 Invasive (radiological, endoscopic, or surgical) interventions

RECOMMENDATION

ESGE recommends invasive intervention for patients with acute necrotizing pancreatitis and clinically suspected or proven infected necrosis.
Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests considering an invasive intervention in patients with acute necrotizing pancreatitis and persistent organ failure or “failure to thrive” for several weeks.
Weak recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests considering an invasive intervention after failure of conservative treatment in patients with sterile necrosis and adjacent organ compression or persistent pain late in the course of the disease.
Weak recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests that the management plan should be individualized, considering all of the available data (clinical, radiological, and laboratory) and taking into account the available expertise.
Weak recommendation, moderate quality evidence.

Indications for intervention (radiological, endoscopic, or surgical) in ANP are [1]:

- Proven IPN.
- Clinically suspected IPN: in the absence of documented IPN, ongoing organ failure or persisting unwellness (“failure to thrive”) for several weeks after the onset of acute pancreatitis, despite optimal medical therapy, preferably when the necrosis has become walled off, as a retrospective study (164 patients) found that 42 % of these patients had IPN [54].
- Organ compression, in the absence of IPN, including gastric outlet syndrome, intestinal, or biliary obstruction, and pain due to mass effect from large WON (intervention should preferably be performed > 4 – 8 weeks after the onset of acute pancreatitis) [124, 125]. Secondary infection is a major concern regarding these indications.
- Abdominal compartment syndrome: this situation is less common but it may require radiological or surgical decompression early in the course of acute pancreatitis. Nevertheless, it is advised to refrain from exploring the lesser sac or performing a necrosectomy at the same time, because there is a risk of bleeding and of introducing infection into sterile necrosis [126, 127].

Data from small cohort studies as well as a recent meta-analysis, including studies with significant heterogeneity, suggest that a proportion of patients with IPN (6/42; 14 %) [128] can be treated with antibiotics alone [23, 128 – 131] (**Table e6**, available online in Supplementary materials). However, the exact subgroup of these clinically stable patients has not been clearly defined. Furthermore, conservative treatment included percutaneous catheter drainage (PCD) in some studies, making it difficult to identify a group receiving only antibiotics [23, 131].

4 Technical modalities of invasive interventions

4.1 Radiology

4.1.1 Technique of percutaneous catheter drainage

In a systematic review including 10 retrospective series and one RCT with a total of 384 patients undergoing PCD, the procedures were performed under CT (8 studies) or ultrasound guidance (2 studies), where this was reported [132]. Ultrasound guidance in combination with fluoroscopy is often preferred during the initial PCD procedure. Real-time imaging during puncture can prevent puncture of interpositioned bowel loops. After initial puncture, guidewires can be steered under fluoroscopic guidance. If the necrotic collections cannot be visualized with ultrasound because of limited liquid content, a CT-guided drainage can be performed. If possible, a retroperitoneal access route should be chosen, between the spleen, descending colon, and left renal upper pole for left-sided drainage, or between the ascending colon and upper pole of the right kidney for right-sided drainage.

No comparative data have been published regarding the use of sedation, local, or general anesthesia. PCD is usually performed with local infiltration of lidocaine combined with moderate/conscious sedation with midazolam and fentanyl, while deep propofol sedation is given if multiple large-bore catheters are to be placed.

In the aforementioned systematic review, drain diameter varied from 8 to 28 Fr [132]. There is no comparative trial regarding catheter diameter, but large-bore catheters (> 14 Fr) seem to obstruct less frequently [132]. Drains may need upgrading to a larger diameter or replacement in about half of the patients [133]. Regular silicone pigtail drains are used, placed according to the Seldinger or the tandem trocar technique [132].

4.1.2 Use of percutaneous catheter drainage (drainage and flushing)

Flushing of the catheters with saline can be performed to improve drainage efficacy and avoid catheter obstruction. In the aforementioned systematic review, drains were flushed with saline every 8 hours [132]. Where there is inadequate drainage of necrotic material, additional flushing catheters may be placed to create a continuous flushing/drainage system.

4.2 Endoscopy

Various endoscopic techniques are used to treat WON; all of these include transmural access to the cavity, using either an echoendoscope (EUS-guided drainage) or, for bulging collections, a standard endoscope (conventional transmural drainage); the former approach has nowadays largely replaced conventional transmural drainage ("blind" access) [134].

The available endoscopic approaches include: (i) endoscopic drainage (placement of a transmural drain such as double-pigtail or metal stents into the cavity, performed through a single or several access sites, the latter technique being termed the multiple transluminal gateway technique [MTGT]) [135]; (ii) transluminal endoscopic necrosectomy (removal of necrotic debris using devices such as a stone-retrieval basket introduced from the digestive lumen into the cavity), and (iii) direct transluminal endoscopic necrosectomy (DEN; insertion of the endoscope into the cavity to remove necrotic debris) [136, 137]. Endoscopic drainage has been combined with PCD in the "dual-modality drainage technique" [138].

Furthermore, an intervention is said to be primary if it is the first intervention performed to access WON and secondary if it is preceded by another intervention (e. g. endoscopic necrosectomy following PCD).

4.2.1 What is the preferred modality for establishing transmural access (EUS-guided vs. non-EUS)?

RECOMMENDATION

ESGE recommends that EUS-guided access should be preferred over conventional transmural drainage for initial endoscopic transmural drainage.
Strong recommendation, moderate quality evidence.

The main advantage of EUS-guided puncture is to allow treatment of PFCs that do not bulge into the gastrointestinal lumen [139]. A prospective comparative study showed no differences between conventional (n = 53) and EUS-guided (n = 46) drainage for patients with pseudocysts regarding success rates in both the short (94 % vs. 93 %) and long term (91 % vs. 84 %), nor in complications rates (18 % vs. 19 %) [140]. Nevertheless, only patients with bulging PFCs and without obvious portal hypertension were drained by the conventional method [140].

Later on, two RCTs confirmed the superiority of EUS-guided access regarding technical success (100 % vs. 33 % and 94 % vs. 72 %) [141, 142]. In patients where conventional drainage failed because of non-bulging PFCs, EUS-guided access succeeded. Both trials included pancreatic pseudocysts only, but results can be generalized to patients with WONs (**Table e7**, available online in Supplementary materials).

4.2.2 Is there a benefit of using a forward-viewing vs. a standard EUS scope in some settings?

The feasibility of endoscopic drainage of PFCs using forward-viewing EUS has been described in a few small retrospective case series [143, 144]. Only one RCT including PFCs requiring transgastric drainage is available. This study did not show a difference in technical success or ease of the procedure when using the forward-viewing EUS scope compared with the standard oblique-viewing EUS scope [145].

4.2.3 What are the optimal access dilation modalities?

RECOMMENDATION

ESGE suggests performing progressive balloon dilation of the cystoenterostomy fistula starting at 6 – 8 mm, potentially increasing during the days following endoscopic transmural drainage, with stent placement, if direct endoscopic necrosectomy is required.
Weak recommendation, low quality evidence.

After endoscopic puncture of WON, balloon dilation (6 – 8 mm) of the access site is performed over a 0.035-inch guidewire to create a fistula between the digestive lumen and WON in order to facilitate stent insertion [146]. Puncture with an electrocautery needle followed by dilation of the cystogastrostomy or cystoduodenostomy with a cautery-tip catheter can also be performed over the guidewire, before further balloon dilation and stent insertion [147].

Where DEN is undertaken, a progressive dilation with a controlled radial expansion balloon of the WON entry is performed, usually after removing the double-pigtail stent(s), a few days after the initial endoscopic drainage [148, 149]. DEN performed during the initial WON endoscopic access in a single-step procedure has also been described [150 – 152].

4.2.4 Types of stent for maintaining transmural access

RECOMMENDATION

ESGE suggests either plastic stents or lumen-apposing metal stents for initial endoscopic transmural drainage; however, long-term data on lumen-apposing metal stents are still sparse.
Weak recommendation, moderate quality evidence.

After transmural access of WON has been established, maintainence of a large open access is required to allow the evacuation of debris, pus, and necrotic tissue, and eventually to allow repeated DEN when needed [153]. Two options are available: multiple plastic double-pigtail stents or self-expandable metal stents (SEMSs). Plastic stents are usually double-pigtail stents in order to avoid migration, with various diameters (7 Fr – 10 Fr). SEMSs are either fully covered biliary metal stents (FC-SEMSs), lumen-apposing metal stents (LAMSs; Axios stent, Boston Scientific, Natick, Massachusetts, USA; Nagi stent or Spaxus stent, Taewoong, Seoul, South Korea), or esophageal SEMSs (► **Fig. 1 b,c**).

A systematic review (17 studies, 881 patients, 183 with WON) showed no differences regarding treatment success for drainage by plastic stents or metal stents in PFCs, including pancreatic pseudocysts and WONs [154]. In addition, in a retrospective comparative study including 70 patients with WON, there was no difference between plastic stents (n = 27 patients) and SEMSs (mix of LAMS and FC-SEMS; n = 43), except for a shorter procedure time for SEMSs (28.8 vs. 42.6 minutes; *P* < 0.001) [155]. On the other hand, another recent retrospective comparative study, including 133 patients with WON treated with multiple plastic stents (n = 61) or LAMSs (n = 72), showed a superior clinical success rate for LAMSs (94 % vs. 74 %; *P* < 0.05) [156] (**Table e8**, available online in Supplementary materials).

A US single-center RCT comparing LAMSs vs. multiple plastic stents for patients with WON is ongoing but interim analysis has revealed an important rate of delayed stent-related adverse effects in the LAMS group (6/12; 50 %), consisting of bleeding and embedded LAMSs [157]. The authors have since changed the study protocol and underline the need for CT imaging to exclude vascular complications, such as pseudoaneurysms, and retrieval of the LAMS within 4 weeks.

4.2.5 What type of scope is preferred for use during subsequent necrosectomy sessions?

RECOMMENDATION

ESGE suggests performing subsequent necrosectomy with a therapeutic gastroscope.
Weak recommendation, low quality evidence.

There are no data comparing types of scopes used for subsequent necrosectomy. Most often the use of a gastroscope is stated in the literature for this procedure, without however differentiating between double-channel, pediatric, standard, or therapeutic gastroscopes. From a technical perspective, a scope with a larger working channel that facilitates evacuation of fluids and entry of equipment to be used for necrosectomy is preferred [149, 152, 158 – 164] (**Table e9**, available online in Supplementary materials).

Although not developed in the currently available literature, the position of the initial puncture is also important when DEN is foreseen. Access that is too proximal (i. e. fundus or cardia) or too distal (i. e. from the antrum) may compromise the direct introduction of a gastroscope into the cavity and render its manipulation more difficult.

4.2.6 What are the modalities of use of nasocystic catheters (duration, type, frequency of flushing, and removal)?

It is necessary to distinguish between insertion of a nasocystic catheter with irrigation during the access phase of the WON, between each necrosectomy session, and finally during a session of necrosectomy to facilitate debridement.

During the access phase, the nasocystic catheter can be placed in parallel to the plastic stents [147, 149, 151, 160 – 163, 165, 166] or through the deployed metal stent [159, 164]. The most frequently described protocol involves the constant instillation of normal saline solution via a 5- to 7-Fr catheter at a daily volume of 500 – 1000 mL [160, 161, 165]. Only two studies have reported their experience of sequential irrigation with a flushing volume ranging from 50 to 500 mL three to six times per day during the access phase and between each necrosectomy session [160, 162]. This protocol was associated with a clinical success of 89 % after a median of four endoscopic procedures in a retrospective analysis of 81 patients [160].

Some authors suggest antibiotic irrigation according to the microbiological findings is an alternative to the use of normal saline [150, 158, 160]. Endoscopic lavage through the working channel of the endoscope is also proposed during the necrosectomy session, occasionally with a large volume of warmed antibiotic (1 – 2 L of bacitracin – saline, 25 000 Units/L) or with 100 – 300 mL of 0.1 % – 0.3 % hydrogen peroxide directly sprayed over the necrotic material [150, 152, 161].

No prospective randomized trials exist that have assessed the duration, type, and volume of irrigation. Furthermore, no significant difference in terms of clinical success was found with or without nasocystic tube placement in a large multicenter study (90.9 % vs. 95.6 %; $P = 0.59$) [167]. High clinical resolution (86 % – 94 %) was also reported by authors without any instillation protocol or when only performed during the debridement phase [150, 164] (**Table e9**, available online in Supplementary materials).

Finally, nasocystic irrigation seems to be safe. With the exception of a peritoneal perforation during a forced irrigation with 1000 mL saline that led to subsequent organ failure and death, no severe adverse events have been reported [160].

4.2.7 What different necrosectomy devices are available and how do they compare?

Endoscopic necrosectomy is performed by a combination of sucking debris through the working channel, removing necrotic material with a removal device, and applying irrigation. No endoscopic accessory is specifically dedicated to the removal of pancreatic necrosis and/or infected debris. A variety of auxiliary instruments have been used for endoscopic necrosectomy, including polypectomy snares, Dormia and other stone-removal baskets, balloons, nets, tripod retrieval forceps, or grasping/rat-tooth/pelican forceps [91, 136, 151, 168 – 171].

Any device needs to balance the efficacy of removing debris with safety (i. e. the avoidance of injury to vital tissues and retroperitoneal vessels). Comparative trials of endoscopic necrosectomy devices do not exist. Snares and baskets might be preferred for the primary attempt to remove pancreatic necrosis as they are safe and quite effective (▶ **Fig. 1d**).

4.2.8 What other auxiliary methods are available?

RECOMMENDATION

ESGE suggests restraint regarding the use of high-flow water-jet systems, hydrogen peroxide, or vacuum-assisted closure systems to facilitate debridement of necrosis in walled-off necrosis because of insufficient evidence.
Weak recommendation, low quality evidence.

Unconventional methods, such as using a high-flow water-jet system [159, 172 – 175], hydrogen peroxide (0.1 % – 3 %) application [161, 176, 177], and a vacuum-assisted closure system [178 – 180], to facilitate debridement of necrosis in WON have been described. However, none of these case series included the minimal required number of patients to qualify for inclusion in the current Guideline.

4.2.9 Use of CO_2 vs. air for insufflation

RECOMMENDATION

ESGE recommends exclusive use of CO_2 instead of air for insufflation during necrosectomy to reduce the risk of gas embolism.
Strong recommendation, low quality evidence.

CO_2 is a gas that is rapidly absorbed and highly soluble in water and/or blood. For endoscopic interventions, CO_2 might reduce the risk of air embolism, which is a rare but well-known severe event that occurs when air enters the systemic venous circulation. The risk of gas embolism can be significantly reduced by insufflating CO_2 instead of air, because of the higher capacity of blood to absorb CO_2 compared with air or other gases. When air insufflation was used during endoscopic necrosectomy, suspected or likely air embolism occurred in 0.9 % – 2 % of procedures according to published series [149, 151, 163, 168]. Air embolism has not been documented in later reports after the introduction of CO_2 insufflation. Nevertheless, gas insufflation should be minimized during necrosectomy to maintain minimal gas pressure within the retroperitoneum.

4.2.10 Association of transpapillary pancreatic drainage with transmural drainage of WON

RECOMMENDATION

ESGE suggests that, in the case of endoscopic transmural drainage of walled-off necrosis, transpapillary drainage of the main pancreatic duct should not be routinely attempted.
Weak recommendation, low quality evidence.

One retrospective study suggested a better outcome for combined transpapillary and transmural PFC drainage where there was partial MPD disruption [181]; another showed no difference [182]. Both studies included only a few patients with WON. A third study reported a negative association between an attempt at transpapillary drainage being made and long-term radiological resolution [183] (**Table e10**, available online in Supplementary materials).

4.2.11 Technique and indications for the multiple transluminal gateway technique

RECOMMENDATION

ESGE suggests drainage of walled-off necrosis using the single transluminal gateway technique; the multiple transluminal gateway technique should be considered in patients with either multiple or large (> 12 cm) walled-off necrosis, or in the case of suboptimal response to single transluminal gateway drainage.

Weak recommendation, low quality evidence.

Three retrospective case series compared MTGT (with up to three puncture sites) with single-access endoscopic drainage for WON [135, 165, 184]. In total, 41 of 211 patients (19 %) received MTGT and the two series that reported the results separately for each technique found that clinical success was seen more frequently after MTGT [135, 182]. The authors who described the MTGT initially used it when there was minimal drainage after initial puncture of WON [135]. They then used a step-up algorithm where MTGT was performed for WON > 12 cm in size and for unilocular WON ≤ 12 cm that had responded suboptimally to single transluminal drainage [134] (**Table e11**, available online in Supplementary materials). Furthermore, additional access is sometimes necessary when the first access is in such a position that it does not allow easy scope introduction into the cavity for DEN.

4.2.12 How many sessions are required and how long is the length of hospitalization?

For endoscopic drainage, a comparative series reported that 25 % and 50 % of patients treated according to the single and multiple transluminal gateway techniques, respectively, required endoscopic re-intervention (median 1.3 and 1.5 sessions, respectively) [135]. For endoscopic necrosectomy, the mean number of sessions varied between 1 and 15 (weighted mean 4) in a meta-analysis [185]. For dual-modality drainage, a mean of 1.9 endoscopic sessions, plus an unspecified number of EUS sessions and a mean of 6.2 PCD studies were performed [186].

In two RCTs, the median hospital stays after randomization to endoscopic necrosectomy were 45 days [91] and 39 days [187]. Following dual-modality drainage, a mean hospitalization of 24 days was reported [186].

4.3 Surgery

The surgical approach to infected necrotizing pancreatitis has evolved: the traditional procedure of choice, direct open necrosectomy, has been replaced by a step-up approach in which PCD of the retroperitoneum is first performed, preferably via the left flank. Where insufficient clinical improvement occurs despite adequate drainage of all (peri)pancreatic necrotic collections (45 % – 65 % of patients), minimally invasive surgical necrosectomy is performed [132, 133].

Two techniques are used: in sinus tract endoscopy, a flexible or rigid endoscope is introduced into the PCD tract following dilation and the solid debris is removed using grasping forceps [188]; in video-assisted retroperitoneal debridement (VARD), sinus tract endoscopy is combined with a 5-cm lumbotomy that makes the procedure easier to conduct and allows for the removal of larger pieces of necrotic material [189]. Following sinus tract endoscopy or VARD, a continuous lavage system is maintained until the lavage fluid becomes clear or until the next procedure. The drains stay in place for several weeks until the drainage product becomes clear and there is no evidence of a pancreaticocutaneous fistula.

5 Outcome of invasive interventions

5.1 Drainage interventions

5.1.1 How do percutaneous and combined percutaneous and endoscopic drainage compare in terms of success, duration of hospitalization, number of interventions, and number of diagnostic imaging studies?

RECOMMENDATION

ESGE suggests considering concurrent endoscopic transmural drainage and percutaneous drainage in patients with walled-off necrosis with extension to the pelvic paracolic gutters.

Weak recommendation, low quality evidence.

A systematic review focusing on PCD as a primary treatment for ANP, including 10 retrospective series and one RCT (total 384 patients), concluded that no additional surgical necrosectomy was required in 55.7 % of patients (214/384) [132]. Similarly, a systematic review evaluating conservative treatment (including antibiotics and PCD if required) reported a successful outcome in 64 % of patients; a separate analysis including four studies that reported outcomes of non-consecutive patients with IPN following PCD reported similar results (50 % had a successful outcome, mortality was 18 %, and 38 % required surgery) [190].

Three recent retrospective studies from a single center reported on the use of dual-modality drainage to treat WON [138, 186, 191]. A potential advantage of dual-modality drainage is the absence of a pancreaticocutaneous fistula (0 of 103 patients in the most recent study) [191]. One of these studies (94 patients) was comparative [186]; it showed that, compared with PCD alone, dual-modality drainage was associated with fewer drain studies (6.2 vs. 13.0), endoscopic procedures (1.9 vs. 2.6), and CT scans (7.8 vs. 14.0), shorter hospitalization (24 vs. 54 days), and fewer pseudoaneurysm bleeds (0 % vs. 11 %). Overall mortality and the requirement for surgery were similar in both groups. Of note, patients in the dual-modality group presented less frequently with paracolic gutter extension of the WON (39 % vs. 60 %) and had a longer delay between acute pancreatitis and drainage (53 vs. 34 days), suggesting selection bias.

In the published series on dual-modality drainage the procedures were performed on the same day [191].

5.1.2 Factors predictive of the need for necrosectomy

A retrospective analysis (53 patients) reported that larger size of WON (median diameter 18 cm [12 – 21 cm] vs. 14 cm [3 – 46 cm]; $P = 0.01$), extension of WON to the paracolic gutters, and preexisting diabetes were associated with the need for surgical interventions after initial endoscopic treatment [192]. In a post-hoc analysis of a prospective multicenter database (639 patients with ANP), the need for intervention was lower in patients with only EXPN than in patients with parenchymal necrosis with or without EXPN (18 % vs. 57 %; $P < 0.001$) [22]. In a retrospective study (43 patients with WON), the extent of the necrosis ($r = 0.703$; $P < 0.001$), increasing size of the WON ($r = 0.320$; $P = 0.047$), and the amount of solid debris ($r = 0.800$; $P < 0.001$) measured by EUS correlated with the need for more aggressive therapeutic methods [48].

In a prospective cohort of 109 patients with acute pancreatitis (including 80 with ANP and 39 with WON) who underwent CE-CT within the first 5 to 7 days of onset, an admission BUN of ≥ 20 mg/dL and a baseline necrotic collection > 6 cm were associated with the development of WON, with ORs of 10.96 (95 % confidence interval [CI] 2.57 – 46.73; $P = 0.001$) and 14.57 (CI 1.60 – 132.35; $P = 0.017$), respectively [193]. In a post-hoc analysis of 130 prospectively included patients who underwent catheter drainage (113 percutaneously, 17 endoscopically) for suspected IPN, the percentage of pancreatic necrosis (< 30 %, 30 % – 50 %, and > 50 %; OR 0.44; CI 0.23 – 0.83; $P = 0.01$), and heterogeneous collection (OR 0.19; CI 0.06 – 0.61; $P = 0.005$) were the two imaging factors shown to be associated with a lower rate of success (success being defined as survival without necrosectomy) [194] (**Table e12**, available online in Supplementary materials).

Two other studies identified the factors that predicted failure of catheter drainage and the need for subsequent surgery: persistent organ failure and multiple-organ failure, higher CRP levels, and extent of necrosis (> 50 % of the pancreas) [190, 195].

5.2 Various approaches to necrosectomy

5.2.1 How do the various surgical approaches (open surgery, laparoscopy, and minimally invasive surgery) compare in terms of success, morbidity/mortality, cost-effectiveness, hospital stay duration, and technical knowledge requirement?

RECOMMENDATION

ESGE suggests minimally invasive surgery should be preferred to open surgery.
Weak recommendation, moderate quality evidence.

A meta-analysis (4 studies including one RCT, 336 patients) found that minimally invasive surgery was better than open surgery in terms of multiple-organ failure, incisional hernias, enterocutaneous fistula or perforation of visceral organs, and pancreatic insufficiency, but the high heterogeneity of the data did not permit a definitive conclusion to be drawn [196].

5.2.2 How does endoscopic necrosectomy compare with other approaches in terms of success, morbidity, mortality, and cost-effectiveness?

RECOMMENDATION

ESGE suggests that, in the absence of improvement following endoscopic transmural drainage of walled-off necrosis, endoscopic necrosectomy or minimally invasive surgery (if percutaneous drainage has already been performed) is to be preferred over open surgery as the next therapeutic step, taking into account the location of the walled-off necrosis and local expertise.
Weak recommendation, low quality evidence.

Endoscopic necrosectomy was examined in three meta-analyses [153, 197, 198]; the largest one included 455 patients and found a success rate of 81 % with endoscopy alone and a complication rate of 36 % [153].

There are no comparative studies of early (during initial access) vs. delayed DEN. Possible clinical improvement with WON drainage alone (in a recent RCT, drainage was sufficient in 41 %) [187] supports delaying DEN for a few days after endoscopic drainage [91, 198].

Endoscopic necrosectomy has been compared with various interventions.

- Compared with VARD, endoscopic necrosectomy was associated with a better outcome in a small RCT including 22 patients with IPN, as assessed by a composite endpoint including major morbidity or mortality (80 % vs. 20 %) [91]. Moreover, endoscopic necrosectomy was associated with less major morbidity (new onset multiple-organ failure 0 % vs. 50 %; $P = 0.03$) and a nonsignificant difference in mortality (10 % vs. 40 %) in this trial [91]. Nevertheless, a second larger trial (98 patients) comparing endoscopic (drainage and necrosectomy if required) and surgical (PCD and VARD if required) step-up did not show superiority of endoscopic necrosectomy with regard to major complications and death, but there were fewer occurrences of fistulas and a shorter length of stay [187] (**Table e13**, available online in Supplementary materials).
- Compared with PCD (matched cohort study; n = 24), endoscopic necrosectomy was associated with more frequent clinical resolution (92 % vs. 25 %), shorter length of stay, and lower healthcare utilization [152].
- Compared with minimally invasive retroperitoneal necrosectomy (retrospective study; n = 32), endoscopic necrosectomy was associated with a similar success rate but fewer interventions and a shorter length of stay (21 vs. 63 days) [199] (**Table e14**, available online in Supplementary materials).
- Compared with open necrosectomy, endoscopic necrosectomy was associated with similar success rates but fewer

complications (27 % vs. 86 % and 44 % vs. 90 %) and shorter length of stay (32 vs. 74 days and 21 vs. 52 days) [199, 200]. In both studies, mortality was also lower with endoscopic necrosectomy (0 % vs. 14 % and 6 % vs. 63 %) [199, 200].

5.3 Step-up approaches

RECOMMENDATION

ESGE recommends performing endoscopic or percutaneous drainage of (suspected) infected walled-off necrosis as the first interventional method, taking into account the location of the walled-off necrosis and local expertise.
Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE suggests delaying the first intervention for 4 weeks if tolerated by the patient.
Weak recommendation, low quality evidence.

5.3.1 How do step-up and open necrosectomy compare in terms of death or major morbidity, new onset multiple-organ failure, and long-term morbidity?

A Cochrane meta-analysis (8 RCTs, 306 patients) found that: (i) compared with open necrosectomy, the minimally invasive step-up approach was better in terms of both overall and serious adverse events and mean costs; and (ii) compared with the video-assisted (VARD) minimally invasive step-up approach, the endoscopic-assisted (DEN) minimally invasive step-up approach was better in terms of adverse events, but required more procedures (median difference 2) [201]. It also concluded that the differences in short-term mortality were imprecise for all comparisons.

One of the RCTs included in the meta-analysis showed, in 88 patients, that the step-up strategy was superior to open necrosectomy in terms of new-onset multiple-organ failure (12 % vs. 40 %) and long-term morbidity (new-onset pancreatic insufficiency), but not in terms of mortality (19 % vs. 16 %) [133]. In this RCT, the step-up approach used PCD or endoscopic (2 patients only) drainage followed by VARD if necessary. A recent RCT revealed that a step-up approach using transmural endoscopic drainage followed by DEN if necessary was comparable to the PCD/VARD step-up approach with regard to major complications and death. However, the rate of pancreatic fistula formation (5 % vs. 32 %), length of stay, and costs were significantly reduced in the endoscopic group [187].

5.4 Complications

5.4.1 What are the adverse effects of endoscopic necrosectomy and how often do they occur?

Based on a systematic review including 13 retrospective cohort series (n = 455) and the aforementioned RCT (n = 98), the overall complication rate was 36 % [153]. Bleeding was the most common complication with an incidence of 18 %. Perforation (excluding gastric/duodenal perforation) occurred in 4 % of patients, and a pancreatic fistula developed in 5 %.

6 Late outcomes of invasive interventions

6.1 When and how should follow-up imaging be performed after invasive procedures for WON?

RECOMMENDATION

ESGE suggests deciding on follow-up imaging based on clinical findings or when invasive treatment is contemplated, in which case contrast-enhanced CT is the imaging method of choice.
Weak recommendation, low quality evidence.

Though evidence relating to the specific timing of follow-up imaging is lacking, it appears most feasible to conduct these follow-up studies based on relevant clinical findings or when invasive treatment is contemplated, instead of offering routine follow-up [1]. Relevant clinical findings include: sudden-onset or increase of abdominal pain, organ failure, signs of sepsis, and other signs of local complications (e. g. sudden drop of hemoglobin).

CE-CT is considered the imaging method of choice for the assessment of evolving local complications, guidance on when and how to employ invasive treatment, and monitoring response to treatment, as well as for successful placement of stents and drains.

6.2 When should percutaneous drains be removed?

RECOMMENDATION

ESGE suggests removing percutaneous drains when the effluent is clear and production is less than 50 mL per 24 hours, with no evidence of a pancreaticocutaneous fistula.
Weak recommendation, very low quality evidence.

There are no studies available regarding this subject.

6.3 When should transluminal stents be removed?

RECOMMENDATION

ESGE recommends retrieval of lumen-apposing metal stents within 4 weeks to prevent stent-related adverse effects, and long-term indwelling of double-pigtail plastic stents in patients with disconnected pancreatic duct syndrome.
Strong recommendation, low quality evidence.

Regarding drainage of WON with plastic stents and long-term indwelling of stents in patients with disconnected pancreatic duct syndrome (DPDS), data from retrospective series have indicated a low rate of recurrence, as well as a low rate of spontaneous stent migration [202, 203]. Regarding complications, data were however not homogeneous. In one series, two serious adverse events occurred due to small-bowel obstruction as a consequence of spontaneous stent migration [203]. The available RCT included patients with mainly pseudocysts and with MPD rupture in half of the studied population. This study revealed a significant reduction in recurrence in those in whom the stent was left in situ (0 % vs. 38 % recurrence), with MPD rupture seeming to predispose to recurrent pseudocysts in patients having the stent removed [204]. Infectious complications due to permanent stent indwelling did not occur in any of the aforementioned series.

Regarding LAMSs, although a study reported that stents were removed after a median of 32 days (range 2 – 178), with no LAMS-related adverse effects [205], an interim analysis of an ongoing RCT revealed a worrisome rate of LAMS-related adverse effects (50 %; 6/12) in the group of patients who had undergone LAMS insertion [157]; this incited investigators to modify the protocol so that LAMSs were retrieved within 4 weeks. A consequence of this is that, in patients with suspected DPDS, LAMSs should be replaced by plastic stents at this time.

6.4 Is imaging of the pancreatic duct necessary before transluminal stents are retrieved?

RECOMMENDATION

ESGE suggests performing imaging (preferably secretin-enhanced magnetic resonance cholangiopancreatography) of the main pancreatic duct prior to stent removal after endoscopic drainage of walled-off necrosis.
Weak recommendation, very low quality evidence.

An MPD rupture could lead to a recurrent collection after removal of the transluminal stents [184, 204]. Some centers therefore perform imaging of the MPD by CE-CT, MRCP with secretin, and/or ERCP prior to drainage of and/or stent removal from WON. No studies have investigated if management based on standard imaging of the MPD prior to removal of transluminal stents decreases the number of recurrent PFCs [206].

CE-CT has been reported as adequately visualizing the MPD in 75 % – 100 % of patients, but probably this is an overestimation because of the low quality of the studies [207, 208]. Imaging with MRCP provides a non-invasive and precise evaluation of the pancreatic parenchyma and MPD morphology. Secretin injection increases the sensitivity of the assessment of MPD integrity from 47.1 % to 66.4 % [45, 209, 210].

6.5 What proportion of patients develop recurrence after treatment?

Recurrence in the form of a necrotic cavity or pseudocyst has been reported in approximately 10 % of patients after any type of endoscopic treatment; for WON, it was reported to be 9.4 % after endoscopic transmural drainage (single or multiple transluminal gateway technique) in 53 patients [184], 7.8 % after combined percutaneous and endoscopic drainage in 103 patients [191], and 10.9 % (7 % – 15 %) after endoscopic necrosectomy in a meta-analysis (8 studies, 233 patients) [197].

6.6 How should disconnected pancreatic duct syndrome be managed?

RECOMMENDATION

ESGE recommends long-term indwelling of transluminal plastic stents after transluminal drainage of walled-off necrosis in patients with proven disconnected pancreatic duct syndrome.
Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE suggests against combining transluminal drainage with routine stenting of the pancreatic duct in patients with disconnected pancreatic duct syndrome. Where partial main pancreatic duct disruption has occurred, bridging of the disruption with a stent can be considered.
Weak recommendation, low quality evidence.

If endoscopic drainage of WON has been performed in a patient with a disrupted MPD, long-term indwelling of transluminal plastic stents is indicated [184, 204]. One retrospective study that included only a small number of patients with WON suggested that combining transpapillary and transluminal drainage would improve outcome [181].

If drainage of WON has not yet been performed or is not indicated, there is no indication for transpapillary stenting. Where partial MPD disruption has occurred, transpapillary stenting can be considered, preferably with the stent bridging the MPD disruption [211, 212]. If transpapillary stenting of a partial disruption fails or where there is complete disruption, EUS-guided MPD drainage can be considered [213 – 215]. However, high quality data are scarce at the moment.

If endoscopy fails and a recurrent PFC occurs, surgery (distal pancreatectomy or Roux-en-Y drainage) can offer an alternative with success rates over 90 %, but diabetes ensues in the vast majority of patients [216 – 218] (**Table e15**, available online in Supplementary material).

A recent retrospective study showed that DPDS occurred more frequently in patients with WON compared with other PFCs (68.3 % vs. 31.7 %) and was associated with a greater need for hybrid treatment (31.1 % vs. 4.8 %; $P < 0.01$), re-interventions (30 % vs. 18.5 %; $P = 0.03$), and rescue surgery (13.2 % vs. 4.8 %; $P = 0.02$), and a longer length of stay [219].

6.7 How should external pancreatic fistulas be managed?

RECOMMENDATION
ESGE suggests that the initial management for external pancreatic fistulas should be conservative; intervention can be considered for patients who develop associated complications and in patients with persistent external pancreatic fistulas.
Weak recommendation, low quality evidence.

RECOMMENDATION
ESGE suggests considering endoscopic transluminal drainage (possibly in the setting of hybrid procedures) for an external pancreatic fistula associated with a partial or complete main pancreatic duct disruption and an adjacent pancreatic fluid collection.
Weak recommendation, low quality evidence.

An external pancreatic fistula is defined as the output of any measurable volume of fluid (via a percutaneous drain, a drainage canal after removal of a percutaneous drain, or from a surgical wound) with an increased fluid amylase concentration (≥ 3 times the serum value) [220 – 222]. Initial management of pancreatic fistulas can be conservative unless sepsis is present because most will close spontaneously after a median interval of 70 days [220, 221].

Where an external pancreatic fistula is associated with partial MPD disruption and no PFC larger than 5 cm exists, transpapillary stenting can be considered. However, bridging the site of leakage with a pancreatic stent is successful in only 27 % of patients (9 % – 69 %) [221 – 223]. In the only study comparing endoscopic transpapillary stenting and conservative management, the rate of external pancreatic fistula closure was not significantly different: 84 % after stenting vs. 75 % after conservative management ($P = 0.18$) [221]. The median times to closure were 71 days after stenting and 120 days with conservative management, which were not significantly different ($P = 0.13$) [221].

One of the aims of dual-modality (percutaneous and endoscopic) drainage is to achieve a lower incidence of external pancreatic fistulas than occurs after PCD or surgical necrosectomy (incidence approximately 30 %, ranging from 7 % to 79 %) [91, 187, 220 – 226]. In a retrospective review of 103 patients who completed dual-modality drainage, the rate of external pancreatic fistulas was 0 % [191].

Endoscopic transluminal drainage can also be considered in patients with an established external pancreatic fistula associated with a partial or complete MPD disruption, with or without a PFC. With this procedure, an external pancreatic fistula can be transformed into an internal fistula, with consequent closure of the cutaneous orifice [227]. If a PFC is present, it can be drained under EUS guidance and, if this is not possible, a transient collection can be created by injecting saline into the external fistula; the collection is then punctured, so internalizing the tract of the pancreatic juice [227].

In patients with a persistent or recurrent external pancreatic fistula or where there has been failure of conservative and less invasive treatment, surgery (e. g. tail resection or ultimately a pancreaticojejunostomy) is still indicated as a last-resort treatment [220 – 222] (**Table e16**, available online in Supplementary materials).

Disclaimer

ESGE guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply to all situations and should be interpreted in the setting of specific clinical situations and resource availability. They are intended to be an educational tool to provide information that may support endoscopists in providing care to patients. They are not rules and should not be utilized to establish a legal standard of care.

Competing interests

J. Albert has received speaker's honoraria from Fujifilm (2015 – 2016), Falk foundation, and Covidien/Medtronic (2015 – 2017), and both research and speaker's honoraria from Olympus Europe (2015 – 2017). A. Badaoui received a travel grant from Boston Scientific (2016). M. Barthet is a consultant for and receives research support from Boston Scientific (2016 to present). J. Devière has received research support from Cook Medical (until 2016) and from Boston Scientific (ongoing); his department is receiving research support from Olympus (ongoing). I. Hritz is a consultant (speaker/tutor) for Olympus Europe (ongoing). I. Papanikolaou is co-editor for social media with the *Endoscopy* journal. J.-W. Poley has received consultancy, travel, and speaker's fees from Cook Endoscopy and Boston Scientific (ongoing). S. Seewald has received consultancy fees from Boston Scientific (until 2016), and from Olympus and Cook Medical (ongoing). J. van Hooft received lecture fees from Medtronics (2014 – 2015) and a consultancy fee from Boston Scientific (2014 – 2016); her department received research grants from Cook Medical and Abbott (2014 – 2017). K. van Lienden is receiving consultancy and speaker's fees from Cook Medical (ongoing). M. Arvanitakis, M. A. Bali, M. Besselink, M. Delhaye, J.-M. Dumonceau, A. Ferreira, T. Gyökeres, T. Hucl, M. Milashka, H. van Santvoort, G. Vanbiervliet, and R. Voermans have no competing interests.

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