Endoscopic Management of Acute Necrotizing Pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Evidence-based Multidisciplinary Guidelines

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).

(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
(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.
**Abbreviation list**

AP: Acute pancreatitis

ANP: Acute necrotizing pancreatitis

AUC: Area under the curve

BUN: Blood urea nitrogen

CE-CT: contrast enhanced-CT scan

CTSI: CT severity index

DBC: Determinant-Based Classification

DEN: Direct transluminal endoscopic necrosectomy

DPDS: Disconnected pancreatic duct syndrome

ESGE: Endoscopic Society of Gastrointestinal Endoscopy

EXPN: Extra-pancreatic (peri-pancreatic) necrosis

FC-SEMS: fully covered self-expandable metal stent

FNA: Fine needle aspiration

GRADE: Grades of Recommendation Assessment, Development, and Evaluation

ICU: Intensive Care Unit

IN: Infected necrosis (pancreatic and/or peri-pancreatic)

LAMS: Lumen apposing metal stent

MPD: Main pancreatic Duct

MRCP: Magnetic resonance cholangiopancreatography

MRI: Magnetic Resonance Imaging

MTGT: Multiple transluminal gateway technique

NPV: Negative predictive value

OF: Organ failure

OR: Odds ratio
PCD: Percutaneous catheter drainage
PFC: Pancreatic Fluid collection
PN: Pancreatic necrosis
PPV: positive predictive value
RAC: Revised Atlanta Classification
RCT: Randomized controlled trial
sens: sensitivity
spec: specificity
SIRS: Systemic inflammatory response syndrome
VARD: Video-assisted retroperitoneal debridement
WON: Walled-off necrosis
Main recommendations

- 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 absence of contra-indication. Magnetic resonance imaging may be used instead of CT in case of contraindications to contrast-enhanced CT and after the 4th week from onset when invasive intervention is considered, because contents (liquid vs solid) of pancreatic collections are better characterized and evaluation of pancreatic duct integrity is possible (weak recommendation, very low quality evidence).

- ESGE recommends against routine percutaneous fine needle aspiration of (peri)pancreatic collections (strong recommendation, moderate quality evidence) and suggests to use it only if there is suspicion of infection and clinical/imaging signs are unclear (weak recommendation, low quality evidence).

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

- ESGE does not recommend systemic antibiotic or probiotic prophylaxis in preventing infectious complications in acute necrotizing pancreatitis (strong recommendation, high quality evidence).

- ESGE recommends invasive intervention for patients with acute necrotising pancreatitis in case of clinical suspicion or proven infected necrosis (strong recommendation, low quality evidence). The 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).
• ESGE recommends performing endoscopic drainage or percutaneous drainage of (suspected) infected walled-off necrosis as the first interventional method taking into account walled-off necrosis location and local expertise (strong recommendation, moderate quality evidence).

• 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) to be preferred over open surgery as the next therapeutic step, taking into account walled-off necrosis location and local expertise (weak recommendation, low quality evidence).

• ESGE recommends long term indwelling of transluminal plastic stents in case of a disconnected pancreatic duct syndrome but retrieval of lumen-apposing metal stents within 4 weeks to avoid stent related adverse effects (strong recommendation, low quality evidence).
Introduction

Acute pancreatitis (AP) is the most common gastrointestinal disease requiring acute hospital admission. In most cases (80%), the outcome is rapidly favorable. However, acute necrotizing pancreatitis (ANP) may develop in up to 20% of cases, and is associated with significant rates of early organ failure (OF) (38%), need for intervention (38%) and death (15%). 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 global management of ANP, the roles of radiology, endoscopy and surgery in step-up strategies and the technical modalities of endoscopic necrosectomy.

Methods

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 guidelines development process included meetings and online discussions taking place from October 2015 to October 2016.

A literature search of PubMed/MEDLINE, Cochrane Library, and Embase, was performed by the authors for papers published up to December 2016 on this topic. 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 Grades of Recommendation Assessment, Development, and Evaluation (GRADE) system for grading evidence levels and recommendation strengths (Appendix 1)\(^4\). 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

A. Classifications systems for acute pancreatitis severity: Revised Atlanta Classification (RAC) and Determinant-Based Classification (DBC)

- ESGE suggests using the 3-tiered Revised Atlanta Classification rather than the 4-tiered Determinant-Based Classification (weak recommendation, low quality evidence).

- 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 DBC: (1) mild (absence of both [peri]pancreatic necrosis (PN) and organ failure (OF), (2) moderate (presence of sterile [peri]PN and/or transient OF), (3) severe (presence of either infected [peri] PN or persistent OF), and (4) critical (presence of infected [peri] PN and persistent OF). On the other hand, the RAC defines three degrees of severity: mild (absence of OF and absence of local or systemic complications), moderate (presence of transient OF and/or local or systemic complications) and severe (presence of persistent OF, single or multiple). Contrary to the RAC, the DBC requires data on [peri] PN status, sterile or infected, and it is therefore less applicable during the early phase (1st week) and is more suitable for post-hoc category allocation. Both the RAC and the DBC were found to be similar in predicting important clinical outcomes in AP (mortality, need for intensive care unit (ICU), need for intervention, and hospital stay duration). The addition of a critical category in the DBC identifies patients with the most severe disease. However the proportion of patients included in the critical category of severity was low (0.6-12%); therefore the clinical significance of this group is probably limited. In most studies, patients with infected necrosis (IN) seemed to have worse outcomes,
independently if they were initially classified as moderate or severe\textsuperscript{14,15,16}. Both classifications failed to account for the impact of persistent multiple OF vs persistent single OF on mortality (56.3\% vs 7.4\%, \(p=0.001\))\textsuperscript{10} (Table 1-on line).

B. Definition of local complications of AP

Local complications of AP are best defined in the RAC \textsuperscript{6} and include acute (peri)pancreatic fluid collections (PFC) (within the first 4 weeks, with no well-defined wall, usually resolve spontaneously), acute necrotic collections (within the first 4 weeks, containing variable amounts of fluid and necrotic tissue, arising from ANP), pancreatic pseudocysts (after \(\geq 4\) weeks after onset of interstitial AP, fluid collection in the [peri]pancreatic tissues, surrounded by a well-defined wall, containing no solid material), and walled-off necrosis (WON) (after \(\geq 4\) 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\textsuperscript{1,17}.

C. Definition of necrosis, extra-pancreatic necrosis and infected necrosis

In ANP, necrosis may involve the pancreatic parenchyma alone (PN), (<5\% of the cases), pancreatic parenchyma and peripancreatic tissues (PN + EXPN) (75-80\% of the cases) or peripancreatic tissues alone (EXPN) (approximately 20\% of the cases)\textsuperscript{18}.

PN is the presence of non-viable pancreatic parenchyma and it is commonly assessed as a focal or diffuse area with no enhancement at contrast enhanced-CT scan (CE-CT)\textsuperscript{6,19}. By magnetic resonance imaging (MRI), PN appears as well-marginated areas of lower signal intensity compared with the signal intensity of the normal pancreas and of the spleen in non-enhanced MRI and in the arterial, early venous, and late venous phases of enhancement after IV gadolinium injection\textsuperscript{20}. 
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 to patients with PN, patients with EXPN alone had a lower risk of OF (adjusted OR 0.53), multiple OF (adjusted OR 0.48), IN (adjusted OR 0.30), need for intervention (adjusted OR 0.25) and mortality (adjusted OR 0.59). However, in the case of IN, morbidity and mortality rates were similar among patients with EXPN and those with PN (with or without EXPN) \(^{22}\).

IN can be suspected based on clinical evidence of sepsis (e.g. fever > 38°C, features of persistent systemic inflammatory response syndrome (SIRS), deterioration or no improvement of clinical condition) or if extraluminal gas is evidenced in the pancreatic and/or peri-pancreatic tissues on CT \(^{23}\). IN is diagnosed when percutaneous / endoscopic / surgical drainage sampling procedure of (peri)pancreatic tissue is positive for bacteria and/or fungi on Gram stain or culture.

D. Scores and/or markers for the prediction of severe AP on admission and at 48h

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

- ESGE suggests using a blood urea nitrogen level ≥ 23 mg/dL (8.2mmol/L) for predicting persistent organ failure after 48 hours of admission (\textbf{weak recommendation, moderate quality evidence}).

Persistent OF is a good surrogate marker of severity in AP \(^{6}\). The overall accuracy of 11 scores/markers predicting persistent OF has been evaluated in two prospective cohorts (n=256 and n=397) \(^{24}\). Overall, accuracy in predicting persistent OF 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 blood urea nitrogen (BUN) ≥23 mg/dL was 0.73 and 0.76 at admission and at 48h, respectively 24. In a post-hoc retrospective analysis of three prospectively enrolled cohorts of 1612 patients with AP, a hematocrit ≥44% on admission and a rise in BUN at 24h showed the highest accuracy (0.67 and 0.71 respectively) for predicting persistent OF 25. In two studies, a retrospective analysis of a prospective database including 759 patients with AP 26 and a prospective cohort study including 252 patients27, persistent SIRS at 48h was significantly associated with higher mortality. Contrary to these results, a recent systematic review examining the performance of 11 predictors of persistent OF within the first 48h from admission suggested that SIRS did not perform well 28.

Four further studies have identified a Bedside Index of Severity for Severity in Acute Pancreatitis Score (BISAP) score ≥2 within the first 24h of admission as an accurate predictor of severe AP with an AUC ≥0.80 for prediction of severe AP and with an AUC ≥0.82 for prediction of mortality 29,30,31,32. (Table 2 on-line)

E. Indications, timing and modalities of imaging in predicted severe AP

- ESGE suggests performing cross-sectional imaging on admission in case of diagnostic uncertainty, within the first week from onset (after 72 hours from onset of symptoms) in case of 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 further plan management and to monitor the treatment response (weak recommendation, very low quality evidence).

- 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
contra-indication. Magnetic resonance imaging may be used instead in case of contraindication to CT and after the 4th week when invasive intervention is considered, because contents (liquid vs solid) of pancreatic collections are better characterized and evaluation of pancreatic duct integrity is possible (weak recommendation, low quality evidence).

- ESGE recommends the use of CT severity index as the preferred imaging severity score (strong recommendation, moderate quality evidence).

**At admission**, imaging with CECT is indicated in case of diagnostic uncertainty, relative to the diagnosis of AP. Furthermore, abdominal ultrasound (US) plays a role in the determination of AP etiology (biliary vs other origin), and should be performed on admission.

Patients with predicted severe AP who fail to improve clinically within the first week from onset/hospital admission despite conservative treatment should have imaging in order to stage the extent of PN/EXPN and to identify early complications. CECT best detects parenchymal PN 72 hours after symptom onset; before that time it may underestimate or miss the presence of necrosis. CECT is the first-line imaging modality used to assess the morphologic features of ANP because it is widely available with a short scan duration, a robust reproducibility (high inter and intraobserver agreement) and a high accuracy for predicting severe AP and clinical outcome. For example, the AUC of a CT severity index (CTSI) at the cut-off of 3 for predicting persistent OF is 0.84 and 0.85 with a CTSI cut-off of 4.

Non-enhanced MRI is similar to CECT for the early assessment of AP severity. MRI (without gadolinium) can be recommended when iodinated contrast medium injection is contraindicated (i.e. impaired renal function or allergy to iodinated contrast) or, when radiation exposure is contraindicated (i.e. pregnant women). Contrast-
enhanced US could also be used, potentially at bedside, as it presents similar accuracy compared to CECT for the detection of severe AP. 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), to evaluate the evolution of (peri)pancreatic local complications (acute necrotic collection) or in patients in whom a severe complication is suspected such as bleeding, bowel ischemia or perforation. MPD disruption is best diagnosed by secretin-enhanced magnetic resonance cholangiopancreatography (MRCP).

**After the 4th week**, imaging is used in patients with no clinical improvement, if invasive intervention is considered, and to monitor the treatment response. MRI is preferred to assess if WON can be drained because it better detects non-liquefied material than CT, with a better interobserver agreement (Figure 1A). Albeit more invasive, EUS is also accurate to assess the content of WON.

**F. Differentiating between sterile and infected necrosis (including clinical, biological and imaging modalities)**

- ESGE recommends against routine percutaneous fine needle aspiration of (peri)pancreatic collections (strong recommendation, moderate quality evidence) and suggests to use it 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 OF, increased need for cardiovascular and/or respiratory and/or renal support, leukocytosis, elevated or increasing CRP and fever) despite adequate support in the
absence of an alternative source of infection was caused by IN in 74 (80.4%) of 92 patients (false positive rate, 19.6%) \(^{50}\).

A systematic review suggested that the best biological predictor of IN is procalcitonin. With a cut-off 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 therefore, other co-existing sources of infection need to be excluded \(^{51}\).

The presence of gas in the PN/EXPN on CT had a low performance for assessing IN in the abovementioned study (sensitivity, 45.9%; specificity, 81.5%; accuracy 50.5%) \(^{50}\). Diffusion weighted-MRI can be used to detect IN, but large studies are still lacking \(^{52, 53}\). The added value of FNA for diagnosing IN 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 ANP

**Fluid resuscitation**

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

- ESGE suggests that fluid resuscitation assessment should be based on one or more of the following: 1) clinical targets (heart rate <120/min, mean arterial pressure of 65-85 mmHg, urinary output >0.5-1 mL/kg/h), 2) laboratory targets (Hct <44%, declining blood urea nitrogen levels, maintaining normal serum creatinine levels during the first day of hospitalization) and, in intensive care setting, 3) invasive targets (central venous pressure of 8-12 mmHg, stroke volume variation and intra-thoracic blood volume determination) (weak recommendation, moderate quality evidence).

**A. Fluid to use for initial resuscitation**

In a multicenter RCT (40 patients with severe AP), resuscitation with Ringer’s lactate decreased the incidence of SIRS when compared to resuscitation with normal saline. Intravenous hydration with Ringer's solution was found equivalent to naso-jejunal hydration in a recent RCT (49 patients with severe AP). Table 3-on line

**B. What is the optimal fluid infusion rate?**

Retrospective studies have demonstrated that aggressive early hydration in patients with severe AP is associated with decreased morbidity and mortality. Three RCTs in ERCP patients showed that aggressive fluid administration reduced post-ERCP AP. However, 3 studies (2 RCTs) in patients with severe AP by Mao et al supported that rapid hemodilution increased morbidity and mortality, although
criticisms regarding design, randomization and power were raised \(^{64, 65, 66}\). Recently, Weitz et al reported higher disease severity and more complications with aggressive hydration in patients with severe AP \(^{67}\). Patients with diminished cardiac reserve should be administered fluids cautiously, given their risk of pulmonary oedema \(^{68}\). A study in 9489 patients with AP concluded that high volume in the initial 48 hours was associated with increased mortality \(^{69}\). A prospective study demonstrated that administration of more than 4.1L of fluids during the initial 24 hours was linked to increased morbidity, while less than 3.1L had no unfavorable consequences \(^{70}\). Obviously, selection biases (i.e. severe cases have worse outcomes despite vigorous management) should be considered when evaluating results of non-randomized studies.

C. **What are the best non-invasive and invasive measures to assess appropriate fluid resuscitation in patients with AP?**

Apart from vital signs, serial measurements of hematocrit, BUN and serum creatinin 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 continuous cardiac output monitoring system (PiCCO) in optimizing fluid management in AP \(^{74, 75}\).

**Antibiotics**

- ESGE recommends against antibiotic or probiotic prophylaxis of infectious complications in acute necrotizing pancreatitis (**strong recommendation, high quality evidence**).

- ESGE recommends, in the case of 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).**

A. Antibiotic prophylaxis in ANP

Meta-analyses published since 2008 showed no benefit of the routine use of prophylactic antibiotics in patients with severe AP. Furthermore, prophylactic antibiotics use might increase the risk of intra-abdominal fungal infection.

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

B. Selection of antibiotics in the case of suspected IN

Intravenous antibiotics should be administered and further intervention considered once IN is suspected. Antibiotics are useful in IN to delay or even avoid intervention in mild cases. Translocation of bacteria from the small bowel is thought to be the major cause source for infection of necrosis. 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. Once blood/FNA culture results have been obtained, antibiotic therapy should be adjusted accordingly.

C. Antibiotic therapy duration for IN

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

- 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).*

- ESGE suggests initiating enteral nutrition via a nasogastric tube, except in cases with hemodynamic instability, and to switch to the naso-jejunal route in case of digestive intolerance *(weak recommendation, moderate quality evidence)* and then to parenteral nutrition in case of persistent digestive intolerance or if the caloric goal is not met *(weak recommendation, low quality evidence).*

**A. Effects of enteral tube feeding in severe AP**

Gut barrier dysfunction may occur to a significant percentage of patients with severe AP, and it is thought to lead to bacterial translocation and infection of necrosis. Enteral feeding is supposed to preserve the integrity of the gut mucosa, stimulate intestinal motility, prevent bacterial overgrowth and increase the splanchnic blood flow. Twelve RCT and 8 meta-analyses have been performed regarding enteral and parenteral nutrition in AP. The three most recent meta-analyses showed that in patients with predicted severe AP, enteral nutrition as compared to parenteral nutrition decreases systemic infections, multiple OF, need for surgical intervention and mortality. However, the RCTs have several limitations such as heterogeneity of severity grades of AP and of the delay before nutritional intervention; other limitations include small sample sizes, poor glycemic control in the parenteral groups in the older studies, and sub-optimal calorie goal attainment.

**B. Timing of enteral tube feeding in severe AP**

Previously, non-randomized studies involving patients with predicted severe AP, including two systematic reviews (775 and 451 patients) have shown that
nasoenteric tube feeding started within 48 hours after admission, as compared with after 48 hours, significantly reduced the rate of major infection and in some studies even reduced mortality\textsuperscript{101,102}. Nevertheless, a multicenter RCT (208 patients with predicted severe AP), 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\textsuperscript{103}. The abovementioned trial challenges the gut mucosa-preserving effect of early enteral nutrition during AP and goes in the line of the “permissive underfeeding” concept\textsuperscript{104}. A second RCT (214 patients with AP) confirmed these results, showing no significant reduction of persistent OF and mortality in patients receiving early enteral nutrition compared to patients receiving no nutritional support\textsuperscript{105}.

C. 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\textsuperscript{106,107}. Both reviews found no differences between polymeric vs (semi) elemental, in terms of feeding intolerance, infectious complications or death.

D. Should enteral nutrition be administered via a nasojejunal or nasogastric route?

Four studies (3 RCTs) compared nasojejunal with nasogastric feeding in patients with severe AP\textsuperscript{108,109,110,111} (Table 4 on-line), as well as a RCT comparing nasogastric tube feeding vs parenteral nutrition\textsuperscript{112}. Based on these trials, four meta-analyses found no differences between nasogastric and nasojejunal enteral feeding regarding tolerance and mortality\textsuperscript{113,114,115,116}. One study reported a higher pulmonary complication rate in patients receiving nasogastric enteral feeding\textsuperscript{111}. Limitations of the abovementioned RCTs include heterogeneity regarding timing and severity of AP, exclusion of patients
with hemodynamic instability and probably very severe disease, and absence of routine confirmation of the nutrition tube position.\textsuperscript{95}

**Specific treatment of biliary AP**

- ESGE recommends urgent (≤ 24 hours) ERCP and biliary drainage in patients with acute biliary pancreatitis combined with cholangitis (**strong recommendation, high quality of evidence**) while this should be performed within 72 hours in patients with ongoing biliary obstruction (**weak recommendation, moderate quality evidence**) and not in patients with acute biliary pancreatitis and neither cholangitis nor ongoing bile duct obstruction (**weak recommendation, moderate quality evidence**).

A. **What are the indications for early ERCP and sphincterotomy in the setting of biliary AP?**

Based on the initial RCTs, ERCP was shown to be effective in decreasing the incidence of complications in biliary AP.\textsuperscript{117,118} These trials included patients with cholangitis, who may benefit more than those without. For this reason a multicenter RCT excluding patients with cholangitis was performed; it failed to show a benefit of early ERCP in the setting of community hospitals.\textsuperscript{119} Three other RCTs also failed to show a benefit from ERCP in this group of patients.\textsuperscript{120,121,122} (Table 5 on-line)

The Cochrane meta-analysis of these trials showed no difference in outcomes with vs without ERCP, independently of AP severity and ERCP timing except for patients with cholangitis.\textsuperscript{123} A trend for 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 dilation). 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.
B. Optimal timing for ERCP in the setting of biliary AP with and without cholangitis

No study was specifically designed to assess the timing of ERCP in biliary AP. The available RCTs that evaluated ERCP in AP use variable time frames, from <24 hours \[118\] to 72 hours after the beginning of the symptoms \[119\] or after admission \[117, 120, 121\]. (Table 5 on line) 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 vs within 72 hours of admission) \[123\]. The IAP/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

- ESGE recommends invasive intervention for patients with acute necrotizing pancreatitis and clinically suspected or proven infected necrosis (strong recommendation, low quality evidence).
- 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).
- 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).
- ESGE suggests that the management plan should be individualized, considering all of the available data (clinical, radiologic, 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 IN
- Clinically suspected IN: in the absence of documented IN, ongoing OF or persisting unwellness ("failure to thrive") for several weeks after the onset of AP, despite optimal medical therapy, preferably when the necrosis has become walled-off, as a retrospective study (164 patients) has found that 42% of these patients had IN.

- Organ compression, in the absence of IN, 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 AP). Secondary infection is a major concern regarding these indications.

- Abdominal compartment syndrome: this situation is less common and may require radiological or surgical decompression early in the course of AP. 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 in sterile necrosis.

Data from small cohort studies as well as a recent meta-analysis, including studies of significant heterogeneity, suggest that a proportion of patients with IN (6/42, 14%) can be treated with antibiotics alone. 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.

4. Technical modalities of invasive interventions

Radiology

A. Technique of percutaneous catheter drainage (PCD)

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 US...
guidance (2 studies), when reported. US guidance in combination with fluoroscopy is often preferred during the initial PCD procedure. Real time imaging during puncture can prevent puncture of inter positioned bowel loops. After initial puncture, guide wires can be steered under fluoroscopic guidance. If the necrotic collections cannot be visualized with US 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 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 performed if multiple, large bore catheters are placed.

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

B. Use of PCD (drainage and flush)

Flushing 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. In the case of inadequate drainage of necrotic material, additional flushing catheters may be placed to create a continuous flushing/drainage system.

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). The available endoscopic approaches include: endoscopic drainage (placement of a transmural drain such as double pigtail or metal stents into the cavity, performed through a single access site or several ones, the latter technique being termed as the multiple transluminal gateway technique [MTGT]), transluminal endoscopic necrosectomy (removal of necrotic debris using devices such as a stone retrieval basket introduced from the digestive lumen into the cavity), and direct transluminal endoscopic necrosectomy or DEN (insertion of the endoscope into the cavity to remove necrotic debris). Endoscopic drainage has been combined with PCD in the dual-modality drainage technique. Furthermore, an intervention is said primary if it is the first intervention performed to access WON and secondary if it is preceded by another one (e.g., endoscopic necrosectomy following PCD).

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

- ESGE recommends preferring EUS-guided 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. A prospective comparative study showed no differences between conventional (n=53) and EUS-guided (n=46) drainage for patients with pseudocysts regarding short (94% vs 93%) and long-term (91% vs 84%) success.
rates, as well as complications rates (18% vs 19%)\textsuperscript{140}. Nevertheless, only patients with bulging PFCs and without obvious portal hypertension were drained by the conventional method\textsuperscript{140}. Later on, two RCTs confirmed the superiority of EUS-guided access regarding technical success (100% vs. 33% and 94% vs. 72%)\textsuperscript{141, 142}. In cases 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 2)

B. Is there a benefit of using a forward view EUS scope vs standard EUS in some settings?

Feasibility of endoscopic drainage of PFCs using forward viewing EUS has been described in a few small, retrospective, case series\textsuperscript{143, 144}. Only one RCT including PFCs requiring transgastric drainage is available. This study did not show a difference in technical success and ease of the procedure when using the forward-viewing EUS-scope over the standard oblique viewing EUS-scope\textsuperscript{145}.

C. What are the optimal access dilation modalities?

- 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 (\textit{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 guide-wire to create a fistula between the digestive lumen and WON and to facilitate stent insertion\textsuperscript{146}. Puncture with an electrocautery needle followed by dilation of cystogastrostomy or cysto-duodenostomy with a cautery tip catheter can also be performed over the guide-wire before further balloon dilation and stent insertion\textsuperscript{147}.
In the case of DEN, a progressive dilation with 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. DEN performed during the initial WON endoscopic access in a single step procedure has also been described.

D. Stents used for maintaining transmural access

- 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 establishing transmural access of WON, maintaining a large open access is required to allow the evacuation of debris, pus and necrotic tissue, and for allowing eventually repeated DEN when needed. Two options are available: multiple plastic double pigtail stents or self-expandable metal stents (SEMS). Plastic stents are usually double pigtail stent in order to avoid migration, with various diameters (7Fr-10Fr). SEMS are either fully covered biliary metal stents (FC-SEMS), lumen apposing metal stents (LAMS) (Axios stent, Boston Scientific, USA; Nagi stent or Spaxus stent, Taewong Seoul, Korea), or esophageal SEMS. A systematic review (17 studies, 881 patients, 183 with WON) showed no differences regarding treatment success for plastic stent or metal stent drainage in PFCs including pancreatic pseudocysts and WONs. Also in a retrospective comparative study including 70 patients with WON, there was no difference between plastic (n=27 patients) and SEMS (mix of LAMS and FC SEMS) (n=43), except for a shorter procedure time for SEMS (28.8 min vs 42.6 min, p<0.001). On the other hand, another recent retrospective comparative study including 133 patients with WON, treated with multiple plastic stents (n=61) or LAMS (n=72), showed
a superior clinical success rate for LAMS (94% vs 74%, p<0.05) \(^{156}\) (Table 3). A US single center RCT comparing LAMS vs multiple plastic stents for patients with WON is ongoing but interim analysis revealed an important rate of delayed stent-related adverse effects in the LAMS group (6/12, 50%) consisting of bleeding and embedded LAMS \(^{157}\). The authors 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 (Figure 1B, Figure 1C).

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

- ESGE suggests performing subsequent necrosectomy with a therapeutic gastroscope (**weak recommendation, low quality evidence**).

There are no data comparing types of scopes to be used for subsequent necrosectomy. Most often the use of a gastroscope is stated regarding this procedure in the literature however without differentiation between double channel, pediatric, standard or therapeutic gastroscope. From a technical perspective, a scope with a larger working channel facilitating evacuation of fluids and equipment to be used for necrosectomy is preferred \(^{149, 152, 158, 159, 160, 161, 162, 163, 164}\) (Table 4). Although not developed in the currently available literature, the position of the initial puncture is also important when DEN is foreseen. A too proximal (ie fundus or cardia) access as well as too distal (ie from the antrum) may compromise direct introduction of a gastroscope into the cavity and render its manipulation more difficult.

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

It is necessary to distinguish the insertion of the nasocystic catheter with irrigation during the access phase of the WON, between each necrosectomy session and finally during the session of necrosectomy to facilitate debridement. During the access phase,
the nasocystic catheter can be placed in parallel to the plastic stents or through the deployed metal stent. The most frequent protocol described involves the constant instillation of normal saline solution with a 5 to 7-Fr catheter at daily volume of 500-1000 mL. Only two studies report the experience of sequential irrigation with flushing volume ranged from 50 to 500 ml three to 6 times per day during the access phase and between each necrosectomy sessions. This protocol was associated with a clinical success of 89% after a median of 4 endoscopic procedures in a retrospective analysis of 81 patients. Some authors suggest the antibiotic irrigation according to microbiological findings in alternative to the normal saline. The endoscopic lavage through the working channel of the endoscope is also proposed during the necrosectomy session occasionally with large volume of warmed antibiotic (1 to 2L of Bacitracin-saline 25,000 Units/L) or with 100–300 cc of 0.1–0.3 % hydrogen peroxide directly sprayed over the necrotic material. There exists no prospective randomized trial assessing the duration, type and volume of the irrigation. Furthermore no significant difference in terms of clinical success with or without nasocystic tube placement was found in a large multicenter study (90.9% vs. 95.6% (p=0.59)). High clinical resolution (86 to 94%) was also reported by authors without any instillation protocol or only performed during the debridement phase (Table 4). Finally nasocystic irrigation seems to be safe. With the exception of a peritoneal perforation during a forced irrigation with 1000 ml saline with subsequent OF and death, no severe adverse event was reported.

G. What are the different necrosectomy devices available and how do they compare?

Endoscopic necrosectomy is performed combining sucking debris through the working channel, removing necrotic material by use of a removal device, and by applying irrigation. No endoscopic accessory is specifically dedicated to remove PN 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. Any device needs to balance efficacy of removing debris and safety, i.e. to avoid injury to vital tissue and retroperitoneal vessels. Comparative trials of endoscopic necrosectomy devices do not exist. Snares and baskets might be preferred for the primary attempt to remove PN, as they are safe and quite effective (Figure 1D).

H. What other auxiliary methods are available?

- ESGE suggests restraint regarding the use of high-flow water-jet system, hydrogen peroxide or a vacuum-assisted closure system to facilitate debridement of necrosis in walled-off necrosis due to insufficient evidence (weak recommendation, low quality evidence).

Unconventional methods have been described, such as using a high-flow water-jet system, application of hydrogen peroxide (0.1%-3%) and a vacuum-assisted closure system 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.

I. Use of CO2 vs air for insufflation

- ESGE recommends exclusive use of CO2 instead of air insufflation for necrosectomy to reduce the risk of gas embolism (strong recommendation, low quality evidence).

CO2 is a gas that is rapidly absorbed and highly soluble in water and/or blood. For endoscopic interventions, CO2 might reduce the risk of air embolism, which is a rare but well-known severe event, occurring when air enters the systemic venous circulation. The risk of gas embolism might significantly be reduced by insufflating CO2 instead of
air, because of the higher capacity of blood to absorb CO2 compared to air or other gases. Using air insufflation during endoscopic necrosectomy, suspected or likely air embolism occurred in 0.9%-2% according to published series 149, 151, 163, 168. Air embolism has not been reported after introducing CO2 insufflation in later reports. Nevertheless, gas insufflation should be minimized during necrosectomy to maintain minimal gas pressure within the retroperitoneum.

J. Association of transpapillary pancreatic drainage with transmural drainage of WON

- 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 of combined transpapillary and transmural PFC drainage in the case of partial MPD disruption 179 and another showed no difference 180. Both studies included only a few patients with WON. A third study reported a negative association between attempting transpapillary drainage and long-term radiological resolution 181 (Table 5).

K. Technique and indications of the multiple transluminal gateway technique (MTGT)

- 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 3 puncture sites) with single access endoscopic drainage for WON 135, 165, 182. In total, 41 (19%) of 211 patients received MTGT and the two series that reported the results separately for each
technique found that clinical success was more frequent with MTGT 135,182. The authors who described the MTGT initially used it when there was minimal drainage after initial puncture of WON 135, and then used a step-up algorithm where MTGT was performed for WON >12 cm in size and for unilocular WON ≤12 cm that responded suboptimally to single transluminal drainage 134 (Table 6). Furthermore, an additional access is sometimes necessary when the first is in such a position that it does not allow easy scope introduction into the cavity for DEN.

L. 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 transmural gateway technique, respectively, required endoscopic reintervention (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 183. 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 184. In two RCTs, median hospital stay after randomization to endoscopic necrosectomy was 45 91 and 39 days 185. Following dual-modality drainage, a mean hospitalization of 24 days was reported 184.

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. In the case of insufficient clinical improvement 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 are removed using grasping forceps \(^{186}\); 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 necrosis \(^{187}\). Following sinus tract endoscopy or VARD, a continuous lavage system is maintained until the lavage fluid becomes clear or until the next procedure. Drains stay in place for several weeks until drain production becomes clear and there is no evidence of a pancreaticocutaneous fistula.

5. Outcome of invasive interventions

*Drainage interventions*

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

- 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% (214/384) patients \(^{132}\). Similarly, a systematic review evaluating conservative treatment (including antibiotics and PCD if required), reported a successful outcome in 64%; a separate analysis including 4 studies that reported outcomes of non-consecutive patients with IN following PCD reported
similar results (50% had successful outcome, mortality was 18%, and 38% required surgery)\textsuperscript{188}.

Three recent retrospective studies from a single center reported on the use of dual-modality drainage to treat WON \textsuperscript{138, 184, 189}. A potential advantage of the dual-modality drainage is the absence of pancreaticocutaneous fistula (0 of 103 patients in the most recent study)\textsuperscript{189}. One of these studies (94 patients) was comparative\textsuperscript{184}; it showed that, compared with PCD alone, dual-modality drainage was associated with fewer drain studies (6.2 vs. 13.0) and endoscopic procedures (1.9 vs. 2.6), fewer CT-Scans (7.8 vs. 14.0), a shorter hospitalization (24 vs. 54 days), and fewer pseudoaneurysm bleedings (0 vs. 11%). Overall mortality and requirement for surgery were similar in both groups. Of note, patients in the dual-modality group presented less frequently a 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\textsuperscript{189}.

B. Predictive factors for the need of necrosectomy

A retrospective analysis (53 patients) reported that the larger size of WON (median diameter: 18(12-21) cm vs 14(3-46) cm; \(p=0.01\)), extension of WON to paracolic gutters and preexisting diabetes were associated with the need for surgical interventions after initial endoscopic treatment\textsuperscript{190}. 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 PN with or without EXPN (18% vs 57%, \(p<0.001\))\textsuperscript{22}. In a retrospective study (43 patients with WON), the extent of necrosis (\(r=0.703, p<0.001\)), an 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. In a prospective cohort of 109 patients with AP (including 80 with acute necrotizing pancreatitis and 39 with WON) who underwent CECT within the first 5 to 7 days of onset, an admission BUN of ≥ 20 mg/dL and a baseline necrotic collection larger than 6 cm were associated with the development of WON with an OR of 10.96 (CI: 2.57-46.73, p=0.001) and of 14.57 (CI: 1.60-132.35, p=0.017), respectively. In a post hoc analysis of 130 prospectively included patients who underwent catheter drainage (113 percutaneously, 17 endoscopically) for suspected IN, the percentage of PN (<30%/30%-50%/>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 2 imaging factors shown to be associated with less success (success being defined as survival without necrosectomy) (Table 7). Two other studies identified factors that predicted failure of catheter drainage and need for subsequent surgery: persistent OF and multiple OF, higher CRP levels, and extent of PN >50% of the pancreas.

**Various approaches of necrosectomy**

A. How do the various surgical approaches (open surgery, laparoscopy, and minimal invasive surgery [sinus tract endoscopy or video-assisted retroperitoneal debridement (VARD)]) compare in terms of success, morbi/mortality, cost-effectiveness, hospital stay duration, and technical knowledge requirement?

- ESGE suggests preferring minimally invasive surgery 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 OF, incisional
hernias, enterocutaneous fistula or perforation of visceral organs, and pancreatic insufficiency but the high heterogeneity of the data did not permit to draw a definitive conclusion 194.

B. How does endoscopic necrosectomy compare to other approaches in terms of success, morbidity, mortality and cost effectiveness?

- 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) to be preferred over open surgery as the next therapeutic step, taking into account walled-off necrosis location and local expertise (weak recommendation, low quality evidence).

Endoscopic necrosectomy was examined in three meta-analyses 153,195,196; 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 between early (during initial access) and delayed DEN. Possible clinical improvement with WON drainage alone (in a recent RCT, drainage was sufficient in 41%) 185 support delayed DEN a few days after endoscopic drainage 91, 196.

Endoscopic necrosectomy was compared with various interventions:
- Compared with VARD, endoscopic necrosectomy was associated with a better outcome in a small RCT including 22 patients with IN, 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 OF 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 regarding major complications and death but there were fewer occurrences of fistulas and a shorter length of stay\(^{185}\) (Table 8).

- PCD (matched cohort study, n=24): endoscopic necrosectomy was associated with more frequent clinical resolution (92% vs. 25%), shorter length of stay and lower health care utilization\(^{152}\).

- Minimally invasive retroperitoneal necrosectomy (retrospective study, n=32): endoscopic necrosectomy was associated with similar success but fewer interventions and shorter length of stay (21 vs. 63 days)\(^{197}\) (Table 9).

- Compared with open necrosectomy, endoscopic necrosectomy was associated with similar success but fewer complications (27% vs 86% and 44% vs 90%) and shorter length of stay (32 vs. 74 days and 21 vs 52 days)\(^{197, 198}\). In both studies, mortality was also lower with endoscopic necrosectomy (0 vs 14% and 6% vs 63%)\(^{197, 198}\).

**Step-up approaches**

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

- ESGE suggests delaying the first intervention by 4 weeks if tolerated by the patient (weak recommendation, low quality evidence).

A. How do step-up and open necrosectomy compare in terms of death or major morbidity, new onset multiple OF, 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 overall as well as serious adverse events and of mean costs and that (ii), compared with video-assisted minimally invasive step-up approach (VARD), endoscopic-assisted minimally invasive step-up approach (DEN) was better in terms of adverse events but required more procedures (median difference, 2) \(^{199}\). 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 MOF (12\% vs. 40\%) and long term morbidity (new onset pancreatic insufficiency) but not in 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 step-up approach using transmural endoscopic drainage followed by DEN if necessary was comparable to the PCD/VARD step-up approach regarding major complications and death. However, the rate of pancreatic fistula (5\% vs 32\%), length of stay and costs were significantly reduced in the endoscopic group \(^{185}\).

**Complications**

What are the adverse effects related to endoscopic necrosectomy and what is their incidence?

Based on a systematic review including 13 retrospective cohort series (n=455) and the aforementioned RCT (n=98), overall complication rate was 36\% \(^{153}\). Bleeding was the most common complication with an incidence of 18\%. Perforation (excluding gastric/duodenal perforations) occurred in 4\%, and a pancreatic fistula in 5\%.
6. Late outcome of invasive interventions

A. When and how to perform follow-up imaging after invasive procedures for WON?

- ESGE suggests deciding on follow-up imaging based on clinical findings or when invasive treatment is contemplated whereby contrast-enhanced CT is the imaging method of choice *(weak recommendation, low quality evidence)*. Though evidence for a 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 routine follow-up. Relevant clinical findings include sudden-onset or increase of abdominal pain, OF, signs of sepsis, other signs of local complications (e.g., sudden drop of hemoglobin).

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

B. When should percutaneous drains be removed?

- ESGE suggests removing percutaneous drains when the effluent is clear and production is less than 50 cc per 24 hours, without evidence of a pancreaticocutaneous fistula *(weak recommendation, very low quality evidence)*. There are no studies available regarding this subject.

C. When should transluminal stents be removed?

- ESGE recommends lumen-apposing metal stent retrieval within 4 weeks to prevent stent-related adverse effects and long-term indwelling of double pig-tail plastic stents in the case of a disconnected pancreatic duct syndrome *(strong recommendation, low quality evidence)*.
Regarding drainage of WON with plastic stents and long term indwelling in patients with disconnected pancreatic duct syndrome (DPDS), data from retrospective series indicated a low rate of recurrence, as well as a low rate of spontaneous stent migration. 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. 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), whereby a MPD rupture seemed to predispose for a recurrent pseudocyst in case the stent was removed. Infectious complications due to permanent stent indwelling did not occur in any of the aforementioned series.

Regarding LAMS, although a study reported that stents were removed after a median of 32 days (range 2–178) with no LAMS-related adverse effects, an interim analysis of an ongoing RCT revealed a worrisome rate of LAMS-related adverse effects (50%, 6/12), in the group of patients having undergone LAMS insertion; this incited investigators to modify the protocol and retrieve the LAMS within 4 weeks. That would consequently signify that, in case of suspected DPTS, LAMS should be replaced by plastic stents at that time.

D. Is imaging of the pancreatic duct necessary before retrieving the transluminal stents?

- ESGE suggests performing imaging (preferably a 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 level evidence).

A MPD rupture could lead to a recurrent collection after removal of the transluminal stents. Some centers therefore perform imaging of the MPD by CECT, MRCP with...
secretin and/or ERCP prior to drainage and/or stent removal of WON. No studies investigated if management based on standard imaging of the MPD prior to removal of the transluminal stents decrease the number of recurrent PFCs \(^{204}\).

CECT has been described to adequately visualize the MPD in 75-100% of patients. Probably this is an overestimation due to the low quality of the studies \(^{205}, 206\). Imaging with MRCP provides a noninvasive and precise evaluation of the pancreatic parenchyma and MPD morphology. Secretin injection increases the sensitivity of MPD integrity assessment from 47.1% to 66.4% \(^{45}, 207, 208\).

E. What is the proportion of patients with recurrence after treatment?

Recurrence in the form of necrotic cavity or pseudocyst has been reported in approximately 10% of patients after any type of endoscopic treatment; for WON: 9.4% after endoscopic transmural drainage (single or multiple transmural gateway technique) in 53 patients \(^{182}\), 7.8% after combined percutaneous and endoscopic drainage in 103 patients \(^{189}\), and 10.9% (7%-15%) after endoscopic necrosectomy in a meta-analysis (8 studies, 233 patients) \(^{195}\).

F. How to manage DPDS?

- ESGE recommends long term indwelling of transluminal plastic stents after transluminal walled-off necrosis drainage in case of a proven disconnected pancreatic duct syndrome (strong recommendation, low quality evidence).

- ESGE suggests against combining transluminal drainage with routine stenting of the pancreatic duct in case of a disconnected pancreatic duct syndrome. In case of a partial main pancreatic duct disruption, 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\textsuperscript{182,202}. One retrospective study that included only a small number of patients with WON suggested that combining transpapillary and transluminal drainage would improve outcome\textsuperscript{179}.

If drainage of WON has not been performed yet or is not indicated, there is no indication for transpapillary stenting. In the case of a partial MPD disruption one could consider transpapillary stenting, preferably with the stent would bridging the MPD disruption\textsuperscript{209,210}. In the case transpapillary stenting of a partial disruption fails or in case of complete disruption, EUS guided MPD drainage can be considered\textsuperscript{211,212,213}. However, high quality data are scarce at the moment.

In case endoscopy fails and a recurrent PFC occurs, surgery (distal pancreatectomy or Roux-en-Y drainage) could offer an alternative with success rates over 90% but diabetes ensues in the vast majority of patients\textsuperscript{214,215,216}. (Table 6 on line)

A recent retrospective study showed that DPDS occurred more frequently in patients with WON compared to other PFCs (68.3% vs 31.7%) and was associated with more need for hybrid treatment (31.1% vs 4.8%, p<0.01), re-interventions (30% vs 18.5%, p=0.03), rescue surgery (13.2% vs 4.8%, p=0.02) and longer length of stay\textsuperscript{217}.

G. How to manage external pancreatic fistulae?

- ESGE suggests that the initial management for external pancreatic fistulae should be conservative; intervention can be considered for patients who develop associated complications and in patients with persistent external pancreatic fistulae (weak recommendation, low quality evidence).

- ESGE suggests considering endoscopic transluminal drainage (possibly in the setting of hybrid procedures) in the case of 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 percutaneous drain, or from a surgical wound), with an increased fluid amylase concentration ($\geq 3$ times the serum value)\textsuperscript{218,219,220}. Initial management of pancreatic fistulae could be conservative unless sepsis is present because most of these will close spontaneously after a median interval of 70 days\textsuperscript{218,219}.

In the case of an external pancreatic fistula associated with a partial MPD disruption and no PFC larger than 5cm, a transpapillary stenting can be considered. However, bridging the site of leakage with a pancreatic stent is successful in only 27% (9%-69%) of patients\textsuperscript{219,220,221}. In the only study comparing endoscopic transpapillary stenting and conservative management, the rate of external pancreatic fistulae closure was not significantly different, 84% after stenting vs 75% after conservative management (p=0.175)\textsuperscript{219}. The median time to closure was 71 days after stenting and 120 days after conservative management, which were not significantly different (p=0.13)\textsuperscript{219}.

Dual modality (percutaneous and endoscopic) drainage is aimed to reduce the incidence of external pancreatic fistula after PCD or surgical necrosectomy (incidence of external pancreatic fistulae of about 30%, ranging from 7% to 79%)\textsuperscript{91,185,218,219,220,221,222,223,224}. In a retrospective review of 103 patients who completed dual modality drainage, the rate of external pancreatic fistula was 0%\textsuperscript{189}.

Endoscopic transluminal drainage can also be considered in the case of an established external pancreatic fistula associated with a partial or complete MPD disruption, with or without PFC. By this procedure, an external pancreatic fistula can be transformed to an internal fistula with consequently closure of the cutaneous orifice\textsuperscript{225}. If a PFC is present,
it can be drained under EUS guidance and, if not possible, a transient collection can be created through injection into the external fistula, which is thereafter punctured for internalization of the pancreatic juice’s tract. In case of persistent or recurrent external pancreatic fistula or failure of conservative and less-invasive treatment, surgery (e.g. tail resection or ultimately a pancreaticojejunostomy) is still indicated as a last resort treatment. (Table 7 on line)

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.
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