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

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Bibliography
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Tables e1 – e16
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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. 

   **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.**

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.**

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**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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ANP</td>
<td>acute necrotizing pancreatitis</td>
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<tr>
<td>APA</td>
<td>American Pancreatic Association</td>
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<tr>
<td>AUC</td>
<td>area under the curve</td>
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<td>BISAP</td>
<td>bedside index of severity in acute pancreatitis</td>
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<td>BUN</td>
<td>blood urea nitrogen</td>
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<tr>
<td>CE-CT</td>
<td>contrast-enhanced computed tomography scan</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CTSI</td>
<td>CT severity index</td>
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<tr>
<td>DBC</td>
<td>determinant-based classification</td>
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<td>DEN</td>
<td>direct transluminal endoscopic necrosectomy</td>
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<td>DPDS</td>
<td>disconnected pancreatic duct syndrome</td>
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<tr>
<td>ERCP</td>
<td>endoscopic retrograde cholangiopancreatography</td>
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<td>ESGE</td>
<td>European Society of Gastrointestinal Endoscopy</td>
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<td>EUS</td>
<td>endoscopic ultrasound</td>
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<td>EXPN</td>
<td>extrapancreatic (peripancreatic) necrosis</td>
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<tr>
<td>FC-SEMS</td>
<td>fully covered self-expandable metal stent</td>
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<tr>
<td>FNA</td>
<td>fine needle aspiration</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development, and Evaluation</td>
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<tr>
<td>IAP</td>
<td>International Association of Pancreatologists</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<tr>
<td>IPN</td>
<td>infected pancreatic and/or peripancreatic necrosis</td>
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<tr>
<td>LAMS</td>
<td>lumen-apposing metal stent</td>
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<tr>
<td>MPD</td>
<td>main pancreatic duct</td>
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<tr>
<td>MRCP</td>
<td>magnetic resonance cholangiopancreatography</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MTGT</td>
<td>multiple transluminal gateway technique</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PCD</td>
<td>percutaneous catheter drainage</td>
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<td>PFC</td>
<td>pancreatic fluid collection</td>
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<tr>
<td>RAC</td>
<td>revised Atlanta classification</td>
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<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
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<td>VARD</td>
<td>video-assisted retroperitoneal debriement</td>
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<tr>
<td>WON</td>
<td>walled-off necrosis</td>
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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 peripancreatic necrosis and organ failure), (ii) moderate (presence of sterile peripancreatic necrosis and/or transient organ failure), (iii) severe (presence of either infected peripancreatic necrosis or persistent organ failure), and (iv) critical (presence of infected peripancreatic 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 peripancreatic 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. persist-
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, gas in the pancreatic and/or peripancreatic tissues (75% – 90% of cases), the pancreatic parenchyma and peripancreatic tissues (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-margined 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 (peri)pancreatic 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.

1.3 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].

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 (8.2 mmol/L) as a predictor of persistent organ failure after 48 hours of admission 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...
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.

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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, maintenance 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 3, 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 ima-
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 Pancreatologists (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.

**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 or 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)
Flushin 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 7, available online in Supplementary materials).

4.2.2 Is there a benefit of using a forward-viewing endoscope over 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 [147]. 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, maintenance 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). SEMSSs are either fully covered biliary metal stents (FCSEMSs), lumen-apposing metal stents (LAMSSs; Axios stent, Boston Scientific, Natick, Massachusetts, USA; Nagi stent or Spaxus stent, Taewoong, Seoul, South Korea), or esophageal SEMSSs. 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 SEMSSs (mix of LAMSS and FCSEMS; n=43), except for a shorter procedure time for SEMSSs (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 LAMSSs (n=72), showed a superior clinical success rate for LAMSSs (94% vs. 74%; *P*<0.05) [156] (Table 8, available online in Supplementary materials).

A US single-center RCT comparing LAMSSs 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 LAMSS group (6/12; 50%), consisting of bleeding and embedded LAMSSs [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 9, 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 irrigation through the working channel of the endoscope is also proposed during the necrosectomy session, occasionally with a large volume of warmed antibiotic (1–2L of bacitracin–saline, 25,000 Units/L) or with 100–300mL 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 9, available online in Supplementary materials).

Finally, nasocystic irrigation seems to be safe. With the exception of a peritoneal perforation during a forced irrigation with 1000mL 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?

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 CO2 vs. air for insufflation

**RECOMMENDATION**

ESGE recommends exclusive use of CO2 instead of air for insufflation during 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 that occurs when air enters the systemic venous circulation. The risk of gas embolism can be significantly reduced by insufflating CO2 instead of air, because of the higher capacity of blood to absorb CO2 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 CO2 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 10, 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 pseudoneurysm 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 \( \geq 20 \) 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?

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.

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 main pancreatic duct 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.

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 surgically accessible fluid collection). An increased fluid amylase concentration (≥ 3 times the serum value) is indicative of an external pancreatic fistula.

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 [221–223]. Initial management of pancreatic fistulas can be conservative unless sepsis is present because most will close spontaneously after a median interval of 70 days [220–222].

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 transpapillary 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, 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 (2016–2017) and from Boston Scientific (ongoing); his department is receiving research support from Olympus (ongoing). I. Hertz is a consultant (speaker/tutor) for Olympus Europe (ongoing). I. Papakonstantinou 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 Cook Scientific (2016–2017), and from Olympus and Cook Medical (ongoing). J. van Hooft received lecture fees from Medtronic (2014–2015) and a consulting 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. Ball, M. Besselink, M. Delhaye, J.-M. Dumonceau, A. Ferreira, T. Gyökeres, T. Huc, M. Milashka, H. van Santvoort, G. Vanbiervliet, and R. Voermans have no competing interests.

**References**


[38] Bollen TL, Singh VK, Maurer R et al. Comparative evaluation of the modified CT severity index and CT severity index in assessing severity of acute pancreatitis. AJR Am J Roentgenol 2011; 197: 386–392


cholangiopancreatography. AJR Am J Roentgenol 2006; 186: 499–506


[133] van Santvoort HC, Besselin MG, Bakker OJ et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. NEJM 2010; 362: 1491–1502


Arvanitakis Marianna et al. Endoscopic management of acute-necrotizing pancreatitis ... Endoscopy 2018; 50
Table e1: Individual studies regarding validation of classification systems for severity of acute pancreatitis

<table>
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<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Study design</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome / LOE</th>
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<tbody>
<tr>
<td>Nawaz [1]</td>
<td>2013</td>
<td>Prospective cohort Tertiary referral center USA</td>
<td>256 patients 52% males Median age: 51 y Biliary: 39% OH: 14% (Peri)pancreatic necrosis: 21% IN: 8% Persistent OF: 24% Overall mortality: 4%</td>
<td><strong>AC vs RAC vs DBC</strong> The peak severity category was selected during the entire FU period (12 months)</td>
<td></td>
<td>Mortality (AUC)</td>
</tr>
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<td>ICU LOS (SDC)</td>
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<td>Need for intervention (AUC) (surgical, endoscopic, percutaneous)</td>
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LOE: high
<table>
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<tr>
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<th>Study Type</th>
<th>Country</th>
<th>Number of Patients</th>
<th>Gender</th>
<th>Mean Age</th>
<th>Biliary (%)</th>
<th>OH (%)</th>
<th>Pancreatic necrosis (%)</th>
<th>IN (%)</th>
<th>Persistent OF (%)</th>
<th>Overall Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thandassery</td>
<td>2013</td>
<td>Observational study</td>
<td>India</td>
<td>151</td>
<td>67%</td>
<td>41 y</td>
<td>34%</td>
<td>48%</td>
<td>68%</td>
<td>11%</td>
<td>39%</td>
<td>19%</td>
</tr>
<tr>
<td>Acevedo-Piedra</td>
<td>2014</td>
<td>Prospective cohort</td>
<td>Spain</td>
<td>459</td>
<td>60%</td>
<td>61 y</td>
<td>59%</td>
<td>14%</td>
<td>29%</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
</tr>
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</table>

**Validation of the DBC**
No comparator

**Need for PCD insertion** (n=45)

- Severe vs critical
  - 47% vs 88%
  - \( p < 0.001 \)

**Need for surgery** (n=20)

- 19% vs 88%
  - \( p < 0.001 \)

**Mortality** (n=29)

- 34% vs 88%
  - \( p < 0.001 \)

**RAC vs DBC**

<table>
<thead>
<tr>
<th></th>
<th>RAC</th>
<th>DBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>67%</td>
<td>71%</td>
</tr>
<tr>
<td>Moderate</td>
<td>29%</td>
<td>24%</td>
</tr>
<tr>
<td>Severe</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Critical</td>
<td>--</td>
<td>0.6%</td>
</tr>
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</table>

**LOE**: moderate
<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Study Design</th>
<th>Country</th>
<th>Patients</th>
<th>Gender</th>
<th>Median Age</th>
<th>Biliary (%)</th>
<th>OH (%)</th>
<th>Pancreatic Necrosis (%)</th>
<th>IN (%)</th>
<th>Persistent OF (%)</th>
<th>Overall Mortality (%)</th>
<th>RAC</th>
<th>Validation of RAC</th>
<th>LOE</th>
</tr>
</thead>
</table>
| Choi [4]  | 2014 | Retrospective analysis of prospective cohort | Korea       | 553      | 62%    | --         | 30%         | 45%    | 20%                    | 8.7    | 11%                 | 2.7                   |      | Moderately severe AP with (n=14) or without (n=214) IN: mortality 7.1% vs 0.5%, p=0.119
|           |      | Tertiary referral center |             |          |        |            |             |        |                        |        |                     |                       |      | Severe AP with(n=34) or without (n=25) IN: mortality 32.3% vs 8%, p=0.026       |      |
| Talukdar [5] | 2014 | Prospective cohort | India       | 163      | 75%    | --         | 29%         | 40%    | 26%                    | 8      | 11%                 | 5%                    |      | Validation of RAC
|           |      | 2 academic hospitals   |             |          |        |            |             |        |                        |        |                     |                       |      | Moderately severe AP with IN (n=10) vs severe AP (n=18): mortality 10% vs 39%, p=0.11
|           |      |                       |             |          |        |            |             |        |                        |        |                     |                       |      | Similar outcomes (LOS, need for ICU, days in ICU, need for interventions, in-hospital mortality) for patients with moderately severe AP and IN compared to patients with severe AP according to the RAC
<p>|           |      |                       |             |          |        |            |             |        |                        |        |                     |                       |      | LOE: moderate                                                                   |      |</p>
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<th>Country</th>
<th>Patients</th>
<th>Gender</th>
<th>Age (Median)</th>
<th>Biliary (%)</th>
<th>OH (%)</th>
<th>(Peri)pancreatic necrosis (%)</th>
<th>IN (%)</th>
<th>Persistent OF (%)</th>
<th>Overall mortality (%)</th>
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<tr>
<td>2015</td>
<td>Retrospective</td>
<td>China</td>
<td>395</td>
<td>62%</td>
<td>--</td>
<td>54%</td>
<td>11%</td>
<td>61%</td>
<td>18%</td>
<td>17%</td>
<td>8.9%</td>
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<tr>
<td>2015</td>
<td>Prospective database</td>
<td>China</td>
<td>867</td>
<td>61%</td>
<td>49 y</td>
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<td>13%</td>
<td>15%</td>
<td>4%</td>
<td>7%</td>
<td>3%</td>
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### AC vs RAC vs DBC

<table>
<thead>
<tr>
<th>Category</th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>15%</td>
<td>30%</td>
<td>35%</td>
</tr>
<tr>
<td>Moderate</td>
<td>--</td>
<td>53%</td>
<td>42%</td>
</tr>
<tr>
<td>Severe</td>
<td>85%</td>
<td>17%</td>
<td>11%</td>
</tr>
<tr>
<td>Critical</td>
<td>--</td>
<td>--</td>
<td>12%</td>
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</table>

### Mortality (AUC)

<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
</tr>
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<tbody>
<tr>
<td>AC</td>
<td>0.59</td>
<td>0.90</td>
<td>0.96</td>
</tr>
<tr>
<td>RAC</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>DBC</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
</tr>
</tbody>
</table>

**LOE**: moderate

### Need for surgery (AUC)

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<tr>
<th></th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>0.61</td>
<td>0.90</td>
<td>0.85</td>
</tr>
<tr>
<td>RAC</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>DBC</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
</tr>
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</table>

**LOE**: moderate

### RAC vs DBC

<table>
<thead>
<tr>
<th>Category</th>
<th>RAC</th>
<th>DBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>66%</td>
<td>83%</td>
</tr>
<tr>
<td>Moderate</td>
<td>27%</td>
<td>7%</td>
</tr>
<tr>
<td>Severe</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Critical</td>
<td>--</td>
<td>2%</td>
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### DBC severe category

<table>
<thead>
<tr>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POF without IN</td>
</tr>
<tr>
<td>No POF with IN</td>
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**LOE**: high
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Country</th>
<th>Patients</th>
<th>Gender</th>
<th>Age</th>
<th>Biliary</th>
<th>OH</th>
<th>Pancreatic Necrosis</th>
<th>IN</th>
<th>Persistent OF</th>
<th>Mortality (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bansal [8]</td>
<td>2016</td>
<td>Observational study</td>
<td>Prospective database</td>
<td>UK</td>
<td>228 patients</td>
<td>52% males</td>
<td>Median age: 56 y</td>
<td>Biliary: 61%</td>
<td>OH: 26%</td>
<td>Pancreatic necrosis: 25%</td>
<td>IN: 8%</td>
<td>Persistent OF: 13%</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Severity</th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>56%</td>
<td>57%</td>
<td>68%</td>
</tr>
<tr>
<td>Moderate</td>
<td>--</td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td>Severe</td>
<td>44%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>Critical</td>
<td>--</td>
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<td>4%</td>
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**AC vs RAC vs DBC**

<table>
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<tr>
<th>Procedure</th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
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</thead>
<tbody>
<tr>
<td>Mortality (AUC)</td>
<td>0.80</td>
<td>0.96</td>
<td>0.93</td>
</tr>
<tr>
<td>ICU admission (AUC)</td>
<td>0.82</td>
<td>0.93</td>
<td>0.92</td>
</tr>
<tr>
<td>ICU LOS (Spearman's ρ)</td>
<td>0.49</td>
<td>0.64</td>
<td>0.67</td>
</tr>
<tr>
<td>Open necrosectomy (AUC)</td>
<td>0.70</td>
<td>0.83</td>
<td>0.85</td>
</tr>
<tr>
<td>Percutaneous drainage (AUC)</td>
<td>0.83</td>
<td>0.88</td>
<td>0.89</td>
</tr>
<tr>
<td>LOS (Spearman's ρ)</td>
<td>0.55</td>
<td>0.65</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**LOE**: high
Fernandes [9] 2016 Retrospective Portugal 525 patients 59% males Median age: 63 y Biliary: 39% OH: 26% (Peri)pancreatic necrosis: 17% IN: 3.4% Persistent OF: 11% Overall mortality: 6%

<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
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<tbody>
<tr>
<td>Mild</td>
<td>39%</td>
<td>48%</td>
<td>68%</td>
</tr>
<tr>
<td>Moderate</td>
<td>--</td>
<td>42%</td>
<td>18%</td>
</tr>
<tr>
<td>Severe</td>
<td>61%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Critical</td>
<td>--</td>
<td>--</td>
<td>2%</td>
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**AC vs RAC vs DBC**

<table>
<thead>
<tr>
<th>Mortality (AUC)</th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
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<tbody>
<tr>
<td></td>
<td>0.69</td>
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<td>0.91</td>
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<th>ICU admission (AUC)</th>
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<th>DBC</th>
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<tr>
<td></td>
<td>0.75</td>
<td>0.80</td>
<td>0.81</td>
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**ICU LOS (Spearman’s p)**

<table>
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<th>RAC</th>
<th>DBC</th>
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<tbody>
<tr>
<td></td>
<td>0.13</td>
<td>0.18</td>
<td>0.24</td>
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**Need for intervention (AUC)**

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<th></th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
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<tbody>
<tr>
<td>Surgical, endoscopic, percutaneous</td>
<td>0.70</td>
<td>0.78</td>
<td>0.88</td>
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**Hospital LOS (Spearman’s p)**

<table>
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<tr>
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<th>RAC</th>
<th>DBC</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0.39</td>
<td>0.38</td>
<td>0.37</td>
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</table>

LOE: moderate
### Retrospective analysis of a prospective database

Referral center: USA

| 338 patients | 49% males | Median age: 52 y | Biliary: 30% | OH: 21% | Pancreatic necrosis: 11% | IN: 2% | Persistent OF: 13% | Overall mortality: 4% |

<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>RAC</th>
<th>DBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>60%</td>
<td>60%</td>
<td>71%</td>
</tr>
<tr>
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<td>27%</td>
<td>14%</td>
</tr>
<tr>
<td>Severe</td>
<td>40%</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Critical</td>
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<td>0.6%</td>
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### AC vs RAC vs DBC

<table>
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<tr>
<th>Mortality (AUC)</th>
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</thead>
<tbody>
<tr>
<td>AC</td>
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<td>0.81</td>
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<th>ICU admission (AUC)</th>
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<tbody>
<tr>
<td>AC</td>
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<td>0.79</td>
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<table>
<thead>
<tr>
<th>ICU LOS (cut-off 11d) (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
</tr>
<tr>
<td>0.57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital LOS (cut-off 7d) (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
</tr>
<tr>
<td>0.76</td>
</tr>
</tbody>
</table>

| LOE: high |

---

**AC**: Atlanta classification 1992; **AP**: acute pancreatitis; **AUC**: area under the ROC curve (predictive accuracy for binary outcomes); **d**: days; **DBC**: Determinant-based classification; **FU**: follow-up; **ICU**: intensive care unit; **IN**: infected necrosis, **LOE**: level of evidence; **LOS**: length of stay; **n.c.**: not calculable; **NS**: not significant; **OF**: organ failure; **OH**: alcoholic; **PCD**: percutaneous drainage; **POF**: persistent organ failure; **RAC**: Revised Atlanta Classification 2012; **SDC**: Somer’s D coefficient (predictive accuracy for continuous outcomes); **y**: year
<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Study design</th>
<th>Score/marker cut-off</th>
<th>Outcome</th>
<th>Conclusion / LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mofidi [11]</td>
<td>2006</td>
<td>Retrospective analysis of a prospective database 759 AP Overall mortality: 5.9%</td>
<td>Persistent SIRS at 48h n = 138 (18.2%)</td>
<td>• Mortality</td>
<td>Persistent SIRS / Transient SIRS / No SIRS 25.4% vs 8% vs 0.7% p &lt; 0.001 LOE: moderate</td>
</tr>
<tr>
<td>Singh [12]</td>
<td>2009</td>
<td>Prospective cohort study 252 AP</td>
<td>Persistent SIRS at 48h n = 71 (28.2%)</td>
<td>• POF</td>
<td>Persistent SIRS / Transient SIRS / No SIRS 17% 1% 0% p&lt;0.0001 11% 1% 0% p&lt;0.0001 LOE: moderate</td>
</tr>
<tr>
<td>Singh [13]</td>
<td>2009</td>
<td>Prospective cohort study 397 AP Overall mortality: 3.5%</td>
<td>BISAP ≥ 3 (within 24h of admission)</td>
<td>• Prediction of mortality • Prediction of OF OR: 7.4 • Prediction of POF OR: 12.7 • Prediction of PN OR: 3.8</td>
<td>BISAP  Apache II AUC: 0.82 0.88 BISAP ≥ 3: sens 71%, spec : 83%, PPV : 17.5%, NPV : 99% LOE: moderate</td>
</tr>
<tr>
<td>Papachristou [14]</td>
<td>2010</td>
<td>Prospective cohort 185 AP 40 SAP (POF) (22%) Overall mortality: 3.8%</td>
<td>BISAP ≥ 3 (within 24h of admission) Ranson ≥ 3 Apache II ≥ 8 (within 24h of admission)</td>
<td>• Prediction of SAP (POF) • Prediction of mortality</td>
<td>BISAP  Ranson  Apache II AUC: 0.81 0.94 0.78 +LR: 4.62 8.40 2.50 AUC : 0.82 0.95 0.94 LOE: moderate</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Analysis Period</td>
<td>Prediction of SAP</td>
<td>Prediction of Mortality</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>------------------------------------</td>
<td>-----------------</td>
<td>-------------------</td>
<td>------------------------</td>
</tr>
</tbody>
</table>
BISAP ≥ 3  
Apache II ≥ 17  
BISAP ≥ 3 | • Prediction of SAP (one or more of mortality, POF, local complications that require intervention)  
• Prediction of mortality |                   | Apache II  
BISAP (AUC)  
0.77 0.71 | Moderate |
| Mounzer [16] | 2012 | 2 prospective cohort studies  
Training cohort  
n = 256 AP  
Overall mortality: 3.9%  
Validation cohort  
n = 397 AP  
Overall mortality: 3.5% | At admission / at 48h | Apache II ≥ 7  
BISAP ≥ 2  
Glasgow ≥ 2  
HAPS ≥ 1  
Ranson ≥ 2  
SIRS ≥ 2  
BUN ≥ 23 mg/dl  
JSS ≥ 2  
Creatinine ≥ 1 mg/dl  
Panc 3 ≥ 1  
POP ≥ 9 | • Prediction of SAP  
• Prediction of mortality | Results for validation cohort  
AUC at admission  
0.71 0.69 0.67 0.66 0.63 0.64 0.73 0.66 0.70 0.73 0.57 0.64 0.71 | 0.74 0.66 0.63 0.64 0.73 0.66 0.70 0.73 0.57 0.64 0.71 | High |
| Khanna [17] | 2013 | Prospective cohort  
72 AP  
Overall mortality: 12.5% | Within the first 24h of admission | SIRS ≥ 2  
Apache II ≥ 8  
BISAP ≥ 2  
CRP ≥ 150 mg/l  
Ranson ≥ 3  
Glasgow ≥ 3 | • Prediction of SAP (based on AC 1992)  
• Prediction of mortality |                   | AUC prediction of SAP  
of mortality  
0.73 0.88 0.80 0.91 0.85 0.75 | 0.76 0.86 0.83 0.75 0.84 0.83 | Low |
| Park [18] | 2013 | Retrospective analysis 303 patients Overall mortality: 2% | **Within the first 24h of admission**  
BISAP $\geq 2$  
Ranson $\geq 3$  
Apache II $\geq 8$ | • **Prediction of SAP** (based on AC 1992)  
AUC: 0.80  
Ranson: 0.74  
Apache II: 0.80 | BISAP | Ranson | Apache II | AUC: 0.80 | 0.74 | 0.80 | NS |
| Yang [19] | 2014 | Systematic review 7 studies 11 predictors 1589 patients POF : 17% | Apache II $\geq 7$  
Ranson $\geq 2$  
BISAP  
JSS $\geq 1$  
POP $\geq 9$  
SIRS  
BUN $\geq 23$ mg/dl  
Creatinine  
Glasgow  
HAPS $\geq 1$  
Panc 3 | • **Prediction of POF**  
< 48h from admission  
best sensitivity: Apache II (0.84)  
best specificity: JSS (0.90)  
best + LR: JSS (5.19)  
best – LR: POP (0.61)  
best DOR: Apache II (13.71)  
≥ 48h from admission  
best sensitivity: Apache II (0.84)  
best specificity: Ranson (0.93)  
best + LR: BUN (8.45)  
best – LR: HAPS (0.52)  
best DOR: JSS (26.08) | < 48h from admission  
best sensitivity: Apache II (0.84)  
best specificity: JSS (0.90)  
best + LR: JSS (5.19)  
best – LR: POP (0.61)  
best DOR: Apache II (13.71)  
≥ 48h from admission  
best sensitivity: Apache II (0.84)  
best specificity: Ranson (0.93)  
best + LR: BUN (8.45)  
best – LR: HAPS (0.52)  
best DOR: JSS (26.08) | LOE: low |
Koutroumpakis [20] 2015  Post-hoc retrospective analysis of 3 prospectively enrolled cohort of patients with AP 1612 patients Overall mortality: 4.9%

<table>
<thead>
<tr>
<th>Admission values</th>
<th>Prediction of POF</th>
<th>At admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN ≥ 20 mg/dl</td>
<td>BUN Hct Creat Apache II</td>
<td>AUC: 0.65 0.67 0.59 0.66</td>
</tr>
<tr>
<td>Hct ≥ 44%</td>
<td>Hct Creat Apache II</td>
<td>At 24h rise in:</td>
</tr>
<tr>
<td>Creat ≥ 1.8 mg/dl</td>
<td></td>
<td>BUN Hct Creat</td>
</tr>
<tr>
<td>Apache II ≥ 8</td>
<td></td>
<td>AUC: 0.71 0.57 0.66</td>
</tr>
</tbody>
</table>

**At 24h rise in:**
- BUN
- Hct
- Creatinine

- Hct ≥ 44% on admission and rise in BUN at 24h
- predicted severity of AP defined as risk of POF
- revealed the highest accuracy (0.67 and 0.71 respectively)

**LOE**: high

AC: Atlanta classification 1992; AP: acute pancreatitis; **Apache II**: Acute Physiology and Chronic Health Examination; AUC: area under the ROC curve; BISAP: Bedside Index for Severity in Acute Pancreatitis; BUN: blood urea nitrogen; Creat: creatinine; DOR: diagnostic Odds ratio; HAPS: Harmless Acute Pancreatitis score; Hct: hematocrit; JSS: Japanese Severity Scale; LOE: level of evidence; + LR: positive likelihood ratio; - LR: negative likelihood ratio; NPV: negative predictive value; OF: organ failure; OR: Odds ratio; PN: pancreatic necrosis; POF: persistent organ failure; POP: Pancreatitis Outcome Prediction; PPV: positive predictive value; SAP: Severe acute pancreatitis; sens: sensitivity; spec: specificity; SIRS: Systemic Inflammatory Response Syndrome
<table>
<thead>
<tr>
<th>Author, year [ref]</th>
<th>Study design</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baillargeon, 1998 [21]</td>
<td>Prospective</td>
<td>N=64, AP</td>
<td>Serial Hct measurements</td>
<td>Pancreatic necrosis development</td>
<td>Admission Hct&gt;47% or failure to decrease at 24 h were strong risk factors for the development of pancreatic necrosis</td>
<td>Low</td>
</tr>
<tr>
<td>Eckerwall, 2006 [22]</td>
<td>Retrospective</td>
<td>N=99, AP</td>
<td>Initial fluid resuscitation and nutritional support</td>
<td>Various clinical outcomes</td>
<td>4000 ml or more of fluids during the first 24 h associated with more respiratory complications and more ICU admissions (p&lt;0.001 for both).</td>
<td>Low</td>
</tr>
<tr>
<td>Mao, 2007 [23]</td>
<td>Prospective</td>
<td>N=83, severe AP</td>
<td>Early fluid expansion (Group 1, within 24 h after admission) vs. middle fluid expansion (Group 2, within 25 - 48 h) vs. late fluid expansion (Group 3, within 49 - 72 h)</td>
<td>Parameters of treatment with fluids within 4 d after admission. Serum lactic level, APACHEII scores, operation rate within 2 weeks, rate of mechanical ventilation, rate of ACS and survival rate</td>
<td>- Time interval for fluid expansion criteria in Group 1&lt;Group 2&lt;Group 3 (P &lt; 0.05). - Fluid sequestration in Group 2 was lower than those of Group 1 and Group 3 (P &lt; 0.05); non-significant between Group 1 and Group 3 (P &gt; 0.05). - At the 1st to the 3rd day APACHEII scores in Group 1 were higher than those of Group 2 and Group 3 (P &lt; 0.05); and at the 2nd and 3rd day, APACHEII scores in Group 3 were higher than those of Group 2 (P &lt; 0.05). - Rate of mechanical ventilation in Group 1 was higher than in Group 2 and 3 (P &lt; 0.05) - Rate of ACS was lowest in Group 2 (P &lt; 0.05). - Survival rate in Group 1 was lower than in Group 2 and Group 3 (P &lt; 0.05)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Huber, 2008 [24]</td>
<td>Prospective</td>
<td>N=24, severe AP</td>
<td>Hemodynamic measurements using the PiCCO system</td>
<td>to evaluate the predictive value of CVP and Hct with regard to intrathoracic blood volume index (ITBI) and to correlate them to CI</td>
<td>ITBI appears to be more appropriate for volume management than CVP or Hct.</td>
<td>Low</td>
</tr>
<tr>
<td>-----------------</td>
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<td>---------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Mao, 2009 [25]</td>
<td>RCT</td>
<td>N=76, severe AP</td>
<td>Rapid fluid expansion (Group 1) vs. controlled fluid expansion (Group 2)</td>
<td>Parameters of fluid expansion, blood lactate concentration were obtained when meeting the criteria for fluid expansion. APACHE II scores were obtained serially for 72 hours. Rate of mechanical ventilation, incidence of abdominal compartment syndrome (ACS), sepsis, and survival rate were obtained</td>
<td>Group 1 had lower intervals to meet fluid expansion criteria ($P &lt; 0.05$). Blood Lac concentrations were lower as compared to the level upon admission ($P &lt; 0.05$) and reached the normal level in both groups upon treatment. Only at d1 Hct was lower in Group 1 ($P &lt; 0.01$). Fluid sequestration within 4 d was higher in Group 1 ($P &lt; 0.05$). APACHE II scores were higher in Group 1 on d 1, 2, and 3 ($P &lt; 0.05$). Rate of mechanical ventilation was higher in group 1 ($P &lt; 0.05$). The incidences of abdominal compartment syndrome (ACS) and sepsis were lower in Group 2 ($P &lt; 0.05$). Survival was lower in Group 1 ($P &lt; 0.05$).</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mao, 2010 [26]</td>
<td>RCT</td>
<td>N=115, severe AP</td>
<td>Rapid (HCT &lt;35%) vs. slow (HCT ≥35%) hemodilution within 48 h of onset</td>
<td>Incidence of sepsis, interval to sepsis, mortality</td>
<td>There were significant differences in the time interval to sepsis in rapid hemodilution compared with the slow hemodilution group and the incidence of sepsis was higher in the rapid group compared to the slow in the first 28 days. The survival rate of the slow hemodilution group was better than the rapid hemodilution ($P &lt;0.05$)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>AP</td>
<td>Of concern</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td>-----------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Madaria, 2011 [27]</td>
<td>Prospective</td>
<td>247, AP</td>
<td>group A: &lt;3.1 l vs. group B: 3.1-4.1 l vs. group C: &gt;4.1 l (during the initial 24 h)</td>
<td>incidence of OF, local complications, and mortality</td>
<td>Group C was significantly and independently associated with persistent OF, acute collections, respiratory insufficiency, and renal insufficiency. Group A was not associated with OF, local complications, or mortality. Group B had an excellent outcome.</td>
<td></td>
</tr>
<tr>
<td>Kuwabara, 2011 [28]</td>
<td>Retrospective</td>
<td>9489, AP</td>
<td>4 groups (ventilation, hemodialysis, combination of ventilation and hemodialysis, and neither ventilation nor hemodialysis)</td>
<td>mortality, complications, AP severity, need for surgery and fluid volume (FV) during the initial 48 h (FV48) and during hospitalization (FVH) and FV ratio (FVR) as FV48/FVH</td>
<td>A high FV48 increased mortality and a high FVR decreased mortality in patients with severe AP. A high FV48 required ventilation in patients with severe AP, which was independently associated with mortality</td>
<td></td>
</tr>
<tr>
<td>Mole, 2011 [29]</td>
<td>Retrospective</td>
<td>30, severe AP</td>
<td>Vital signs, clinical course and fluid administered during the first 72 h were tabulated against urine output, CVP and inotrope/vasopressor therapy.</td>
<td>Fluid volume, CVP, inotropes/vasopressors, urine output</td>
<td>The volume of crystalloid given was significantly less at 48 h in patients who died in hospital (P &lt; 0.001). Non-survivors had a higher CVP (P &lt; 0.001), received more inotropes/vasopressors (P &lt; 0.001) and had lower urine output (P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Mounzer, 2012 [16]</td>
<td>Prospective</td>
<td>553, AP</td>
<td>Clinical scoring systems comparison</td>
<td>Persistent OF prediction</td>
<td>BUN and creatinine similar to complex systems</td>
<td></td>
</tr>
<tr>
<td>Wall, 2011</td>
<td>Retrospective</td>
<td>286, AP</td>
<td>Early (initial 48 h from admission) aggressive vs.</td>
<td>Mortality, development of</td>
<td>Early aggressive hydration associated with less mortality (p=0.03) and less necrosis</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Setting</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Level</td>
</tr>
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</tr>
<tr>
<td>Wu, 2011 [31]</td>
<td>RCT</td>
<td>40, AP</td>
<td>RL vs. NS</td>
<td>Systemic inflammation (SIRS+CRP levels)</td>
<td>Higher reduction in SIRS with RL (P=0.035). Higher reduction in CRP with RL (P=0.02)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Wu, 2011 [32]</td>
<td>Meta-analysis</td>
<td>1043, AP</td>
<td>serial blood urea nitrogen (BUN) measurement</td>
<td>prediction of mortality</td>
<td>BUN of 20 mg/dL or higher was associated with an OR=4.6 (95% CI, 2.5-8.3) for mortality. Any rise in BUN at 24 hours was associated with an OR of 4.3 (95% CI, 2.3-7.9) for death</td>
<td>High</td>
</tr>
<tr>
<td>Buxbaum, 2014 [33]</td>
<td>RCT</td>
<td>62, ERCP patients</td>
<td>Aggressive RL vs. standard RL</td>
<td>PEP, hyperamylasemia, pain</td>
<td>Less PEP with aggressive hydration (P=0.016). Other differences non-significant</td>
<td>Moderate</td>
</tr>
<tr>
<td>Weitz, 2014 [34]</td>
<td>Retrospective</td>
<td>391, AP</td>
<td>Aggressive early (within 24h) hydration</td>
<td>Disease severity, local complications, max. CRP</td>
<td>Aggressive hydration leads to higher severity, max. CRP and more complications</td>
<td>Low</td>
</tr>
<tr>
<td>Zeng, 2014 [35]</td>
<td>Retrospective</td>
<td>163, severe AP</td>
<td>Early (within 24 h) to achieve central venous pressure &gt;8 cmH2O, urine output &gt;0.5 mL/kg/h and Hct&lt;44 vs. late hydration</td>
<td>Pancreatic infection</td>
<td>Early hydration associated with lower incidence of pancreatic infection (&lt;0.0001)</td>
<td>Low</td>
</tr>
<tr>
<td>Shaygan-Nejad, 2015</td>
<td>RCT</td>
<td>150, ERCP patients</td>
<td>Aggressive RL vs. standard RL</td>
<td>PEP, hyperamylasemia, pain</td>
<td>Less PEP, hyperamylasemia and pain with aggressive hydration (P=0.002, 0.006 and ≤ 0.005, respectively).</td>
<td>Moderate</td>
</tr>
<tr>
<td>[36]</td>
<td>Sun, 2015 [37]</td>
<td>Retrospective</td>
<td>N=43, severe AP</td>
<td>fluid resuscitation under the guidance of PiCCO vs. no PiCCO</td>
<td>1) Fluid volume, 2) SIRS duration, 3) APACHE II score, 4) ICU stay, 5) incidence of mechanical ventilation, 6) abdominal infection, 7) mortality</td>
<td>PiCCO group better in parameters 1-4 (p&lt;0.05). Other differences non-significant</td>
</tr>
<tr>
<td></td>
<td>Yang, 2015 [38]</td>
<td>Retrospective</td>
<td>N=116, severe AP</td>
<td>IAP and CVP measurement</td>
<td>Correlation between IAP and CVP</td>
<td>CVP and IAP have an inverted U-shaped relationship. Results may have crucial implications for fluid resuscitation</td>
</tr>
<tr>
<td></td>
<td>Sharma, 2016 [39]</td>
<td>RCT</td>
<td>N=49, predicted severe AP</td>
<td>IV RL vs. NJ hydration</td>
<td>Mortality, persistent organ failure, pancreatic necrosis, local complications, intra-abdominal pressure, need for interventions, adverse effects</td>
<td>No differences</td>
</tr>
<tr>
<td></td>
<td>Choi, 2017 [40]</td>
<td>RCT</td>
<td>N=510, ERCP patients</td>
<td>Aggressive RL vs. standard RL</td>
<td>PEP, hyperamylasemia, PEP severity, fluid overload</td>
<td>Less PEP and PEP severity with aggressive hydration (P=0.016 and 0.04, respectively). No difference in fluid overload</td>
</tr>
</tbody>
</table>

**ACS**: abdominal compartment syndrome; **AP**: acute pancreatitis; **BUN**: blood urea nitrogen; **CI**: cardiac index; **CVP**: central venous pressure; **HCT**: hematocrit; **IAP**: intra-abdominal pressure; **ICU**: intensive care unit; **LOE**: level of evidence; **NJ**: nasojejunal; **NS**: normal saline; **OF**: organ failure; **PEP**: post ERCP pancreatitis; **PiCCO**: pulse indicator continuous cardiac output; **RL**: Ringer’s Lactate; **SIRS**: systemic inflammatory response syndrome.
<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Comparison</th>
<th>Number of patients (NG/NJ)</th>
<th>End points</th>
<th>Results</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eatock [41]</td>
<td>2005</td>
<td>NG vs NJ</td>
<td>27/23</td>
<td>-APACHE-II -CRP levels - Pain (VAS)</td>
<td>No difference</td>
<td>Moderate (small sample)</td>
</tr>
<tr>
<td>Kumar [42]</td>
<td>2006</td>
<td>NG vs NJ</td>
<td>15/16</td>
<td>- Pain recurrence - Tolerance</td>
<td>No difference</td>
<td>Moderate (small sample)</td>
</tr>
<tr>
<td>Singh [43]</td>
<td>2012</td>
<td>NG vs NJ</td>
<td>39/39</td>
<td>- Infectious complications - LoS - Pain in refeeding</td>
<td>No difference</td>
<td>Moderate (small sample)</td>
</tr>
</tbody>
</table>

CRP: C-Reactive protein; LoS: Length of stay; NG: nasogastric; NJ: Nasojejunal; VAS: Visual analogue score
Table e5: Individual studies regarding the role of early ERCP in acute biliary pancreatitis

<table>
<thead>
<tr>
<th>First author, year [ref]</th>
<th>Study design</th>
<th>n</th>
<th>Population</th>
<th>Mortality</th>
<th>OR (95%CI), p</th>
<th>Complications</th>
<th>OR (95%CI), p</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoptolemos, 1988 [44]</td>
<td>Single center RCT</td>
<td>131 (121 reported)</td>
<td>Suspected biliary acute pancreatitis (US and laboratory data)</td>
<td>1/59</td>
<td>0.197 (0.022-1.735), 0.143*</td>
<td>7/59</td>
<td>0.422 (0.158-1.124), 0.084*</td>
<td>ERCP within 72 hours (of admission); ES if CBD stone;</td>
</tr>
<tr>
<td>Fan, 1993 [45]</td>
<td>Single center RCT</td>
<td>195</td>
<td>Acute pancreatitis (including non-biliary)</td>
<td>17/97</td>
<td>0.531 (0.268-1.052), 0.069*</td>
<td>5/97</td>
<td>0.537 (0.173-1.666), 0.282*</td>
<td>ERCP within 24 hours; ES if CBD stone; subgroup analyses for mortality in severe AP and complications in biliary AP were performed and favored ERCP.</td>
</tr>
<tr>
<td>Folsch, 1997 [46]</td>
<td>Multi-center RCT</td>
<td>238</td>
<td>Acute biliary pancreatitis with bilirubin &lt; 90 μmol/L (&lt; 5 mg/dL)</td>
<td>14/126</td>
<td>2.62 (0.83-8.32), 0.10</td>
<td>58/126</td>
<td>0.823 (0.494-1.370), 0.454*</td>
<td>The trial was stopped at the second interim analysis, due to excess mortality in the ERCP group. The calculated sample size was 380. ERCP within 72 hours (of onset). Complication incidence was similar but severe complications were more frequent in ERCP group.</td>
</tr>
<tr>
<td>Oria, 2007 [47]</td>
<td>Single center RCT</td>
<td>103</td>
<td>Acute biliary pancreatitis without cholangitis</td>
<td>3/51</td>
<td>2.04 (0.17-23.24), 1.0</td>
<td>11/51</td>
<td>1.28 (0.48-3.42), 0.80</td>
<td>ERCP within 72 hours from admission; 1 patient excluded from analysis due to misdiagnosis - pancreatic cancer</td>
</tr>
<tr>
<td>Chen, 2010 [48]</td>
<td>Single center RCT</td>
<td>53</td>
<td>Severe acute biliary pancreatitis without cholangitis</td>
<td>0/21</td>
<td>0.284 (0.013-6.212), 0.424*</td>
<td>n/a</td>
<td>n/a</td>
<td>ERCP (without fluoroscopy) within 72 hours of admission; lack of outcome data; unclear if patients were removed from the analysis</td>
</tr>
<tr>
<td>Tang, 2010 [49]</td>
<td>Single center RCT</td>
<td>90</td>
<td>Severe acute biliary pancreatitis (patients with cholangitis or biliary obstruction were included)</td>
<td>0/30</td>
<td>n/a</td>
<td>n/a</td>
<td>2/30</td>
<td>0.286 (0.053-1.549), 0.146</td>
</tr>
</tbody>
</table>

*Odds ratio were calculated as they were not provided in the original published manuscript.
Table e6  Summary of studies regarding the outcome of conservative management for infected necrosis.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baril, 2000 [50]</td>
<td>Retrospec</td>
<td>n = 42 with IPN (subgroup)</td>
<td>PCD (n = 25), primary surgery (n = 11), antibiotics only (n = 6)</td>
<td>Subsequent surgery, mortality, length of stay</td>
<td>Subsequent surgery (6/25, 5/11, 0/6); death (2/25, 1/11, 2/6); length of stay (32, 60, 38)</td>
<td>Low</td>
</tr>
<tr>
<td>Ramesh, 2003 [51]</td>
<td>Retrospec</td>
<td>n = 4 with IPN</td>
<td>Antibiotics</td>
<td>Clinical outcome</td>
<td>Improvement with no intervention 100%</td>
<td>Low</td>
</tr>
<tr>
<td>Runzi, 2005 [52]</td>
<td>Prospec</td>
<td>n = 28 with IPN (n = 16)</td>
<td>No surgery throughout</td>
<td>Complications, organ failure, death</td>
<td>6/16, 10/16, 2/16, respectively</td>
<td>Low</td>
</tr>
<tr>
<td>Garg, 2010 [53]</td>
<td>Retrospec + prospec</td>
<td>n = 80 with IPN (subgroup)</td>
<td>Conservative treatment vs. surgery</td>
<td>Mortality, survival rates</td>
<td>Survival rates: primary conservative vs. surgery (76.9% vs 46.4%; ( P = 0.005 ))</td>
<td>Mod</td>
</tr>
<tr>
<td>Mouli, 2013 [54]</td>
<td>Meta-analysis</td>
<td>12 studies</td>
<td>Primary conservative treatment (antibiotics +/- drainage; 8 studies), primary PCD (4 studies)</td>
<td>Clinical success, mortality, need for surgery</td>
<td>Conservative management successful in 64%; mortality 12% + 26% of patients required necrosectomy or additional surgery for complications</td>
<td>Mod</td>
</tr>
</tbody>
</table>
Babu, 2013 [55]

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prospec</td>
<td>n = 70 with severe acute pancreatitis</td>
<td>Only antibiotics (n = 14), PCD (n = 29), PCD + surgery (n = 27)</td>
<td>Identification of factors that led to surgery after initial PCD, and identification of a subgroup of patients where PCD alone would be effective</td>
</tr>
</tbody>
</table>

IPN, infected pancreatic and/or peripancreatic necrosis; Mod, moderate; PCD, percutaneous catheter drainage; Prospec, prospective; Retrospec, retrospective.
<table>
<thead>
<tr>
<th>First author, year, study design</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Conclusion</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahaleh, 2006 Prospec</td>
<td>99 patients with PFCs</td>
<td>EUS-guided (n = 46) vs. conventional (n = 53)</td>
<td>PFC resolution</td>
<td>84% vs. 91% (NS)</td>
<td>No difference</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
<td>19% vs. 18% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varadarajulu, 2008 RCT</td>
<td>29 patients with PFCs</td>
<td>EUS-guided (n = 14) vs. conventional (n = 15)</td>
<td>Technical success</td>
<td>14 (100%) vs. 5 (33%) (P &lt; 0.001)</td>
<td>Favors EUS-guided in technical success</td>
<td>Mod</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
<td>0% vs. 13% (NS)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical success</td>
<td>100% vs. 87% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park, 2009 RCT</td>
<td>60 patients with PFCs</td>
<td>EUS-guided (n = 31) vs. conventional (n = 29)</td>
<td>Technical success</td>
<td>29 (94%) vs. 21 (72%) (P = 0.039)</td>
<td>Favors EUS-guided in technical success</td>
<td>Mod</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
<td>7% vs. 10% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical success</td>
<td>89% vs. 86% (NS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EUS, endoscopic ultrasound; Mod, moderate; NS, non-significant; PFC, pancreatic fluid collection; Prospec, prospective; RCT, randomized controlled trial.
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Conclusion</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bang, 2015 [59]</td>
<td>Systematic review</td>
<td>17 studies; 881 patients with PFCs: pseudocyst (n = 514); WON (n = 183)</td>
<td>PPS (n = 702) vs. metal stents (SEMS, LAMS) (n = 124)</td>
<td>Clinical success</td>
<td>Overall 81% vs. 81% (NS)</td>
<td>No difference (overall and for WON)</td>
<td>Mod</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
<td>Pseudocyst 85% vs. 83% (NS)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFC recurrence</td>
<td>WON 70% vs. 78% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
<td>16% vs. 23% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost</td>
<td>10% vs. 9% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mukai, 2015 [60]</td>
<td>Retrospec</td>
<td>70 patients with WON</td>
<td>PPS (n = 27) vs. metal stents (FC-SEMS, LAMS) (n = 43)</td>
<td>Technical success</td>
<td>100% vs. 100% (NS)</td>
<td>No difference in outcomes. Procedure time shorter for SEMS</td>
<td>Mod</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical success</td>
<td>92.6% vs. 97.7% (NS)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
<td>18.5% vs. 7% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost</td>
<td>No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bapaye, 2017 [61]</td>
<td>Retrospec</td>
<td>133 patients with WON</td>
<td>PPS (n = 61) vs. metal stents (LAMS) (n = 72)</td>
<td>Technical success</td>
<td>100% vs. 100% (NS)</td>
<td>Better clinical outcome and shorter hospital stay with LAMS</td>
<td>Mod</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical success</td>
<td>73.7% vs. 94% (P &lt; 0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complications</td>
<td>36.1% vs. 5.6% (P &lt; 0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality</td>
<td>6.5% vs. 4.1% (NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DEN requirement</td>
<td>48% vs. 33.3% (NS)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospital stay</td>
<td>8 vs. 4.1 days (P &lt; 0.05)</td>
<td></td>
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</tr>
</tbody>
</table>

DEN, direct transluminal endoscopic necrosectomy; FC-SEMS, fully covered self-expandable metal stents; LAMS, lumen-apposing metal stents; NS, non-significant; PFC, pancreatic fluid collection; PPS, plastic pigtail stent; Retrospec, retrospective; WON, walled-off necrosis.
Table e9  Summary of selected studies regarding technical modalities applied during endoscopic necrosectomy.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design; objective</th>
<th>Intervention</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Procedures and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seifert, 2009 [62]</td>
<td>Multicenter retrospective study (1999–2005) To describe the first long-term results of a large multicenter series on DEN</td>
<td>DEN</td>
<td>93 patients with WON</td>
<td>Clinical success: 81% (75/93) Necrosectomy sessions: mean 6.2 (range 1–35); 18% of patients had one session; remaining patients mean 7.5 sessions (range 2–35)</td>
<td>Nasocystic irrigation placed during access phase; no details on volume, time, or caliber for instillation</td>
</tr>
<tr>
<td>Gardner, 2011 [63]</td>
<td>Multicenter retrospective study (2003–2011) To highlight the outcomes of DEN for the treatment of WON</td>
<td>DEN Access phase with EUS or under direct video endoscopy + PPS + drainage</td>
<td>104 patients with WON Irrigation for 37/104 (35.6%)</td>
<td>Clinical success: 91% (95/104) Number of sessions: median 2; mean 2.5; range 1–13</td>
<td>Nasocystic drainage during access phase; no technical details on volume, time, or caliber for instillation</td>
</tr>
<tr>
<td>Bakker, 2012 [64]</td>
<td>RCT</td>
<td>DEN or surgical necrosectomy Access phase with EUS + PPS+ drainage</td>
<td>22 patients (10 treated by DEN)</td>
<td>Death and major complications for DEN vs. surgery: 20% vs. 80% (P = 0.03)</td>
<td>6-Fr nasocystic catheter with irrigation of 1 L of normal saline daily placed during access phase (but not between each necrosectomy procedure)</td>
</tr>
<tr>
<td>Author</td>
<td>Study Type</td>
<td>Setting</td>
<td>DEN Access Phase</td>
<td>Drainage</td>
<td>Necrosectomy Sessions</td>
</tr>
<tr>
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</tr>
<tr>
<td>Jürgensen, 2012 [65]</td>
<td>Retrospective, multicenter (no dates given)</td>
<td>To compare DEN with or without multisession irrigation</td>
<td>DEN Access phase with EUS + PPS + drainage Debridement with tripod polyp-grasping forceps</td>
<td>35 patients with WON</td>
<td>Average necrosectomy sessions per patient = 2.9 Average endoscopy sessions per patient = 6.2 Clinical resolution = 94%</td>
</tr>
<tr>
<td>Seewald, 2012 [66]</td>
<td>Retrospective, monocentric (1997–2008)</td>
<td>To determine the immediate and long-term results of endoscopic drainage and DEN in the management of PFC</td>
<td>DEN Access phase with EUS + PPS + drainage</td>
<td>49 patients with WON</td>
<td>Technical success = 97.5% Clinical resolution = 83.8% Necrosectomy sessions: mean 8.2 (range 1–33)</td>
</tr>
<tr>
<td>Abdelhafez, 2013 [67]</td>
<td>Retrospective, monocentric (2010–2011)</td>
<td>To evaluate safety and efficacy of hydrogen peroxide use to facilitate the debridement process during DEN</td>
<td>DEN Access phase with side-viewing endoscope + PPS</td>
<td>10 patients with WON</td>
<td>Necrosectomy sessions per patient: mean 1.4 Clinical success: 100%</td>
</tr>
<tr>
<td>Rische, 2013</td>
<td>Retrospective,</td>
<td>DEN</td>
<td>27 patients with</td>
<td>Technical and clinical</td>
<td>Standard gastroscope after dilation up to 20 mm (CRE</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Intervention</td>
<td>Patients</td>
<td>Outcomes</td>
<td>Technical Details</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>[68]</td>
<td>monocentric (2006–2011) To analyze the long-term outcome of 40 patients with complicated acute pancreatitis treated by EUS-guided transgastric drainage or necrosectomy</td>
<td>Access phase with EUS + PPS + drainage</td>
<td>WON (irrigation for 23 patients [85%])</td>
<td>success</td>
<td>Necrosectomy with forceps, Dormia baskets, and saline flushing Nasocystic suction catheters for daily flushing of the cavity; flushing volume 50–500 mL three times per day The period of peri-interventional flushing was longer in the group with pancreatic necrosis (5.6 days vs. 14.4 days)</td>
</tr>
<tr>
<td>Yasuda, 2013 [69]</td>
<td>Prospective, multicenter (2005–2011) To evaluate the efficacy and safety of DEN</td>
<td>Access phase using EUS with PPS + nasocystic catheter</td>
<td>57 patients with WON</td>
<td>Successful resolution achieved in 43 patients (75%) following a median of 5 sessions (range 1–20)</td>
<td>Conventional forward-viewing endoscope Water-jet function was used in 37 patients (65%), and carbon dioxide gas in 39 patients (68%) Endoscopic accessories to remove necrotic tissue (pentapod forceps, rat-tooth forceps, and polypectomy snares) with forceful irrigation of normal saline [500–1500 mL]) Nasocystic catheter with daily irrigation using 500–1000 mL of normal saline during initial phase and between necrosectomy sessions; no detail on caliber Irrigation was not a predictive factor of success/failure</td>
</tr>
<tr>
<td>Kumar, 2014 [70]</td>
<td>Matched cohort retrospective study</td>
<td>Access phase EUS</td>
<td>12 patients with WON</td>
<td>Clinical resolution of symptomatic WON after</td>
<td>Large single-channel or a double-channel endoscope (GIF XTQ-160 or GIF 2T-160; Olympus)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Study Description</td>
<td>Drainage Method</td>
<td>Clinical Success</td>
<td>Complications</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
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</tr>
<tr>
<td>Mukai, 2015 [60]</td>
<td>Retrospective, monocentric (2006–2013) To evaluate the safety, efficacy, and cost performance of drainage of WON using metal stents (FC-SEMS/LAMS) vs. PPSs</td>
<td>DEN LAMS/FC-SEMS or PPS</td>
<td>70 patients with WON (irrigation for 36/70 patients [51.4%])</td>
<td>Clinical success = 95.7%</td>
<td>Nasocystic tube drainage; 5-Fr to 6-Fr during access phase; irrigation by 500–1000 mL of normal saline solution/day</td>
</tr>
<tr>
<td>Mukai, 2015 [71]</td>
<td>Retrospective, monocentric (2006–2013) To evaluate the efficacy of endotherapy for the treatment of PFC</td>
<td>Drainage and DEN PPS or FC-SEMS for access under EUS guidance</td>
<td>89 patients and 75 WON</td>
<td>Clinical success = 96.6%</td>
<td>5-Fr or 6-Fr nasocystic catheters were simultaneously placed during access phase; no details on modalities of instillation</td>
</tr>
<tr>
<td>Schmidt, 2015 [72]</td>
<td>Retrospective, monocentric</td>
<td>DEN Access phase</td>
<td>81 patients with WON</td>
<td>Technical and clinical success</td>
<td>Therapeutic gastroscope (Olympus; GIF-1TQ160/XTQ160)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Time Period</td>
<td>Objective</td>
<td>Intervention Details</td>
<td>Technical Success</td>
</tr>
<tr>
<td>-------</td>
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<td>----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Gornals, 2016 [73]</td>
<td>Prospective, monocentric (2011–2014)</td>
<td>(2005–2011)</td>
<td>To assess the outcome and safety profile of DEN</td>
<td>DEN Access phase using EUS with LAMS Irrigation session with endoscopic flushing powerful pump (OFP, Olympus) and 500–1500 mL</td>
<td>Technical success = 99% Clinical success = 89% (72/81) Number of procedures: median 4 (range 1–8)</td>
</tr>
<tr>
<td>Mathers, 2016 [74]</td>
<td>Retrospective, monocentric (2007–2014)</td>
<td>(2005–2011)</td>
<td>To evaluate efficacy</td>
<td>DEN Percutaneous drains upsized to 24- to 28-Fr</td>
<td>Complete removal of all percutaneous drains without recurrence of clinical symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Description</th>
<th>Patients</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siddiqui, 2016 [75]</td>
<td>Multicenter retrospective study (2012–2014)</td>
<td>To evaluate the overall clinical outcomes of the LAMS for EUS-guided transmural drainage of patients with PFC</td>
<td>Drainage and DEN LAMS</td>
<td>Success rate: 92% (11/12) Time from onset of symptoms until the first necrosectomy: median 85 days (range 21–248) Number of necrosectomies: median 2.3</td>
<td>solid debris</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82 patients and 68 with WON (22/68 patients with nasocystic instillation)</td>
<td>Clinical success: 88.2% (60/68) Success with nasocystic tube vs. no nasocystic tube: 90.9% vs. 95.6% (P = 0.59) Mean of endoscopic sessions = 2.8</td>
<td>Nasocystic tube placement in 22 patients during access phase; irrigation with normal saline solution for 48–72 hours; no details on caliber or volume for instillation No significant difference in terms of clinical success with or without nasocystic tube</td>
</tr>
<tr>
<td>Thompson, 2016 [76]</td>
<td>Monocentric prospective study (no date given)</td>
<td>To describe the clinical outcomes of a standardized DEN Access phase with EUS + PPS + drainage Debridement during the initial</td>
<td>60 patients with WON</td>
<td>Clinical resolution = 86.7% 39/60 (65%) with only one session</td>
<td>No nasocystic tube placed; large volume warmed antibiotic lavage (1–2 L of bacitracin–saline 25 000 Units/L) during the debridement</td>
</tr>
<tr>
<td>method for direct endoscopic necrosectomy</td>
<td>procedure in 98.3%</td>
<td></td>
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<td>-----------------------------------------</td>
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</tbody>
</table>

CRE balloon, controlled radial expansion balloon; DEN, Direct endoscopic necrosectomy; EUS, endoscopic ultrasound; FC SEMS, fully covered self-expandable metal stent; LAMS, lumen-apposing metal stent; PCD, percutaneous catheter drainage; PFC, pancreatic fluid collection; PPS, plastic pigtail stent; RCT, randomized controlled trial; WON, walled-off necrosis.
Table e10  Selected retrospective series comparing combined (transmural plus transpapillary) vs. transmural only drainage of pancreatic fluid collections.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Number of patients</th>
<th>Combined</th>
<th>Transmural only</th>
<th>Outcome</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trevino, 2010 [77]</td>
<td>110 (WON 20%)</td>
<td>40 (36%); (WON, n = 1)</td>
<td>70 (74%); (WON, n = 21)</td>
<td>Treatment success: better with combined than transmural only (97.5% vs. 80%; ( P = 0.01 ))</td>
<td>Low</td>
</tr>
<tr>
<td>Varadarajulu, 2011 [78]</td>
<td>211 (WON 27%)</td>
<td>72 (34%); (WON, n = 10)</td>
<td>139 (66%); (WON, n = 47)</td>
<td>Treatment success: 85%, with no significant difference between combined and transmural treatment</td>
<td>Low</td>
</tr>
<tr>
<td>Yang, 2016 [79]</td>
<td>174 (pseudocyst 100%)</td>
<td>79 (45%)</td>
<td>95 (55%)</td>
<td>Long-term symptomatic resolution: 62% vs. 69% (NS)</td>
<td>Low</td>
</tr>
</tbody>
</table>

NS, nonsignificant; WON, walled-off necrosis.
Table e11  Retrospective series comparing single vs. multiple transluminal gateway technique for endoscopic drainage of WON.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Population</th>
<th>Multiple transluminal gateway technique, n</th>
<th>Single transluminal gateway technique, n</th>
<th>Clinical success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varadarajulu, 2011 [80]</td>
<td>60 patients with WON</td>
<td>12</td>
<td>48</td>
<td>91.7% vs. 52.1%; $P = 0.02$</td>
</tr>
<tr>
<td>Bang, 2013 [81]</td>
<td>76 patients with WON</td>
<td>18</td>
<td>58</td>
<td>94.4% vs. 62.1%; $P = 0.009$</td>
</tr>
<tr>
<td>Mukai, 2015 [71]</td>
<td>75 patients with WON</td>
<td>11</td>
<td>64</td>
<td>Overall, 97.8%</td>
</tr>
</tbody>
</table>

WON, walled-off necrosis.
Table e12  Summary of studies focused on factors predictive of the need for necrosectomy (surgical or endoscopic).

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Population</th>
<th>Intervention/comparator</th>
<th>Conclusions</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Size of WON: 18 cm (12–21) vs. 14 cm (3–46)</td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extension of WON to paracolic gutter</td>
<td>8.5 (1.4–52.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pre-existing diabetes</td>
<td>4.1 (1.0–19.9)</td>
</tr>
<tr>
<td>Bakker, 2013 [83]</td>
<td>Prospective post-hoc analysis</td>
<td>639 patients with ANP</td>
<td>EXPN (n = 315) vs parenchymal pancreatic necrosis (n = 324)</td>
<td>Patients with EXPN had fewer complications</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Persistent organ failure: 21% vs. 45% (P &lt; 0.001)</td>
<td>OR 0.25 (CI 0.13–0.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IPN: 16% vs. 47% (P &lt; 0.001)</td>
<td>OR 0.25 (CI 0.13–0.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention: 18% vs. 57% (P &lt; 0.001)</td>
<td>OR 0.25 (CI 0.13–0.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mortality: 9% vs. 20% (P &lt; 0.001)</td>
<td>OR 0.25 (CI 0.13–0.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference in outcomes when EXPN was infected</td>
<td>OR 0.25 (CI 0.13–0.38)</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Study Type</td>
<td>Patients</td>
<td>Imaging Details</td>
<td>Treatment Details</td>
<td>Analysis Details</td>
</tr>
<tr>
<td>-------------</td>
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<td>------------------</td>
</tr>
<tr>
<td>Rana, 2014 [84]</td>
<td>Retrospective cohort</td>
<td>43 patients with WON. Solid debris: &lt;10%: 6 10%–40%: 33 &gt;40%: 4</td>
<td>ETD (n = 39) ETN or surgical necrosectomy (n = 4)</td>
<td>Correlation between type of treatment (ETD vs. ETN/surgical necrosectomy) and extent of necrosis ($r = 0.703; P &lt; 0.001$) Correlation between number of endoscopic procedures required for success and larger size of WON ($r = 0.320; P = 0.047$) and amount of solid debris ($r = 0.800; P &lt; 0.001$)</td>
<td></td>
</tr>
</tbody>
</table>
| Sarathi Patra, 2014 [85] | Prospective cohort | 109 patients: (80 ANP, 39 WON) | CE-CT within 5–7 days of onset | Prediction of ANC evolving into WON (multivariate analysis) (n = 39) | Mod
<p>|                       |                 |          |                 | Prediction of need for drainage (n = 13) or persistence of ANC (n = 7) (multivariate analysis) |
|                        |                 |          |                 | Admission BUN $\geq 20$ mg/dL | OR | P |
|                        |                 |          |                 | 10.96 (2.57–46.73) | 0.001 |
|                        |                 |          |                 | Baseline necrotic collection $&gt;6$ cm | OR | P |
|                        |                 |          |                 | 14.57 (1.60–132.35) | 0.017 |
|                        |                 |          |                 | Baseline ANC $&gt;6$ cm | OR | P |
|                        |                 |          |                 | 6.61 (1.77–24.59) | 0.005 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>CE-CT before PCD/ETD</th>
<th>Prediction of success of PCD/ETD in IPN (multivariate analysis)</th>
<th>Predictive High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hollemans, 2016 [86]</td>
<td>Prospective post-hoc analysis</td>
<td>130 patients with suspected infected necrosis (116 IPN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male sex</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male sex</td>
<td>0.21 (0.08–0.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple-organ failure</td>
<td>0.16 (0.04–0.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ percentage necrosis</td>
<td>0.44 (0.23–0.83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneous collection</td>
<td>0.19 (0.06–0.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left-sided necrosis*</td>
<td>12.83 (1.05–157)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUC of the prediction model = 0.76</td>
<td></td>
</tr>
</tbody>
</table>

ANC, acute necrotic collection; ANP, acute necrotizing pancreatitis; AUC, area under the ROC curve; BUN, blood urea nitrogen; CE-CT, contrast-enhanced CT scan; CI, confidence interval; ETD, endoscopic transmural drainage; ETN, endoscopic transmural necrosectomy; EXPN, extrapancreatic (peripancreatic) necrosis; HR, hazard ratio; IPN, infected pancreatic necrosis; Mod, moderate; OR, odds ratio; PCD, percutaneous catheter drainage; WON, walled-off necrosis.
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Type</th>
<th>Number of patients</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Santvoort, 2010 [87]</td>
<td>RCT</td>
<td>88 patients with IPN</td>
<td>Open necrosectomy (n = 45) vs. step-up approach (percutaneous drainage followed by VARD) (n = 43)</td>
<td>Major complication Mortality</td>
<td>69% vs. 40% (P = 0.006) 19% vs. 16% (P = 0.7)</td>
<td>High</td>
</tr>
<tr>
<td>Bakker, 2012 [64]</td>
<td>RCT</td>
<td>22 patients with IPN</td>
<td>ETN (n = 10) vs. surgical necrosectomy (VARD or open) (n = 12)</td>
<td>Post-procedure proinflammatory response (IL-6 levels) Major complication Mortality</td>
<td>Lower IL-6 levels in ETN (P = 0.004) 20% vs. 80% (P = 0.03) 10% vs. 40% (P = 0.3)</td>
<td>Mod</td>
</tr>
<tr>
<td>Cirocchi, 2013 [88]</td>
<td>Meta-analysis</td>
<td>4 studies (1 RCT); 336 patients</td>
<td>Minimally invasive necrosectomy (n = 215) vs. open necrosectomy (n = 121)</td>
<td>OR</td>
<td>Multiple-organ failure Incisional hernias New-onset diabetes Use of pancreatic enzymes 0.16 (0.06–0.39) 0.23 (0.06–0.90) 0.32 (0.12–0.88) 0.005 (0.04–0.57)</td>
<td>Mod</td>
</tr>
<tr>
<td>Gurusamy, 2016 [89]</td>
<td>Meta-analysis</td>
<td>8 RCTs, 306 patients with acute necrotizing pancreatitis</td>
<td>Open necrosectomy (n = 121) Minimally invasive step up approach (n = 80) Endoscopic minimally invasive approach (n = 10) Peritoneal lavage (n = 39)</td>
<td>Adverse effects</td>
<td>Minimally invasive step-up approach results in fewer adverse effects compared to open necrosectomy</td>
<td>Mod</td>
</tr>
<tr>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Van Brunschot, 2016 [90]</td>
<td>RCT</td>
<td>98 patients with IPN</td>
<td>Endoscopic step-up approach (ETD and DEN if necessary) (n = 51) vs. surgical step-up approach (PCD and VARD if necessary) (n = 47)</td>
<td>Major complications Death Need for necrosectomy Pancreatic fistula Length of stay, days Costs</td>
<td>20% vs. 28% (P = 0.35) 18% vs. 13% (P = 0.35) 41% vs. 49% (P = 0.43) 5% vs. 32% (P = 0.001) 36 vs. 69 (P = 0.03) Costs in favor of endoscopy</td>
<td>High</td>
</tr>
</tbody>
</table>

DEN, direct endoscopic necrosectomy; ETD, endoscopic transgastric drainage; ETN, endoscopic transgastric necrosectomy; IL-6, interleukin-6; IPN, infected pancreatic necrosis; Mod, moderate; OR, odds ratio; PCD, percutaneous catheter drainage; RCT, randomized controlled trial; VARD, video-assisted retroperitoneal debridement.
Table e14  Retrospective series reporting on endoscopic necrosectomy as primary intervention for acute necrotizing pancreatitis.

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Number of patients</th>
<th>Proven infection</th>
<th>Follow-up, months</th>
<th>Mortality</th>
<th>Non-endoscopic interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charnley, 2006 [91]</td>
<td>13</td>
<td>11 (85%)</td>
<td>16</td>
<td>2 (15%)</td>
<td>4 (31%): 2 PCD, 2 surgery</td>
</tr>
<tr>
<td>Escourrou, 2008 [92]</td>
<td>13</td>
<td>NA</td>
<td>20</td>
<td>0</td>
<td>2 (15%): PCD</td>
</tr>
<tr>
<td>Gardner, 2011 [63]</td>
<td>104</td>
<td>40 (38%)</td>
<td>19</td>
<td>6 (6%)</td>
<td>3 (3%): surgery</td>
</tr>
<tr>
<td>Bausch, 2012 [93]</td>
<td>18</td>
<td>13 (72%)</td>
<td>NA</td>
<td>1 (6%)</td>
<td>8 (44%): 7 surgery, 1 PCD</td>
</tr>
<tr>
<td>Ang, 2013 [94]</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NA, not available; PCD, percutaneous catheter drainage.
Table e15: Summary of studies focusing on endoscopic and surgical treatment of disconnected pancreatic duct syndrome (DPDS)

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Year</th>
<th>Study design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard [95]</td>
<td>2001</td>
<td>Retrospective cohort study</td>
<td>DPDS, n=27</td>
<td>RNY, n=13 Distal pancreatectomy, n=14</td>
<td>None</td>
<td>Treatment success 92% Treatment success 93%</td>
</tr>
<tr>
<td>Telford [96]</td>
<td>2002</td>
<td>Retrospective</td>
<td>PD disruption (n=43) - Acute pancreatitis (n=24) - Chronic pancreatitis (n=9) - Trauma (n=10)</td>
<td>PD stent</td>
<td>None</td>
<td>Treatment success 25 (58%) On multivariate analysis, only the bridging stent position remained correlated to improved outcome</td>
</tr>
<tr>
<td>Tann [97]</td>
<td>2003</td>
<td>Retrospective cohort study</td>
<td>DPDS, n=26</td>
<td>RNY, n=15 Distal pancreatectomy, n=11</td>
<td>None</td>
<td>Treatment success 92%</td>
</tr>
<tr>
<td>Varadarajulu [98]</td>
<td>2005</td>
<td>Retrospective study</td>
<td>Patients with a PD disruption proven by ERCP (n=97) - Acute pancreatitis (n=44) - Chronic pancreatitis (n=47) - Trauma (n=6)</td>
<td>PD stent</td>
<td>None</td>
<td>Pancreatographic and clinical response - Overall 51% (49/97) - Not specified for acute pancreatitis patients - A partial (instead of a complete) disruption and bridging of the disruption with the stent were predictors of successful outcome</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Study Type</td>
<td>Condition Description</td>
<td>Procedures (n)</td>
<td>Treatment Success</td>
<td>Notes</td>
</tr>
<tr>
<td>------------------</td>
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<td>-----------------------</td>
<td>------------------------------------------------------</td>
<td>-------------------</td>
<td>-------</td>
</tr>
</tbody>
</table>
| Lawrence [99]    | 2008 | Retrospective      | PD disruption and acute pancreatitis (n=29) | -Transluminal and PD stent, n=20  
- PD stent, n=9 | None | Treatment success (not specified for PD stent only)  
- Overall 76%  
- Recurrence 50% |
| Pelaez-Luna [100] | 2008 | Retrospective cohort study | PD disruption and acute pancreatitis (n=31) | -PD stent, n=4  
-Transluminal drainage, n=22  
-Surgery, n=5 | None | Treatment success  
-Endoscopy 73% (19/26), not specified in transluminal or PD stent |
| Trevino [77]     | 2010 | Retrospective cohort study | EUS guided transmural drainage (n=110) | Simultaneous PD stent  
 n=40  
WON n=1 | No PD stent, n=70  
WON n=21 | Treatment success  
-Overall 97.5% vs 80% (p=0.01)  
-WON: N/A |
| Pearson [101]    | 2012 | Retrospective cohort study | DPDS due to acute pancreatitis, n=7 | RNY, n=7 | None | Treatment success 100% |
| Shrode [102]     | 2013 | Retrospective cohort study | DPDS managed endoscopically (n=113) | -PD stent only, n=8  
-PD stent and transmural drainage, n=14  
-Transmural stent only, n=33 | None | Resolution of DPDS and leakage.  
-PD stent only: 6 (75%)  
- PD stent and transmural drainage 8 (57%)  
-Transmural stent only 24 (73%) |

**DPDS**: disconnected pancreatic duct syndrome; **EUS**: Endoscopic ultrasound; **N/A**: not available; **PD**: pancreatic duct; **PFC**: pancreatic fluid collection; **ref**: references; **RNY**: Roux-en-Y drainage; **WON**: Walled-off necrosis
Table e16: Summary of studies focusing on management of external pancreatic fistula (EPF)

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Year</th>
<th>Study design</th>
<th>Population</th>
<th>Intervention / Comparator</th>
<th>Outcome / LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boerma [103]</td>
<td>2000</td>
<td>Observational study</td>
<td>48 patients operative necrosectomy 16 ERP for EPF Median FU: 24m</td>
<td>EPF 21/48 = 44% MPD disruption (n=15) (head: 5, body: 4, tail: 4, body + tail: 2) Fistula output: 125 ml/d (50 – 800) Time from operative necrosectomy to ETS: 35 d (13 – 189) <strong>Endoscopic Transpapillary Stenting (ETS)</strong> - Beyond the site of leakage (n=9) - Short stent (5 or 7 cm) for leakage from the tail (n=4) No comparator</td>
<td>Median time to EPF closure: 10 d (2 – 64) Stent removal after 6 w Recurrent pseudocysts in the tail (n=3) → distal pancreatectomy (n=3) LOE: low</td>
</tr>
<tr>
<td>Connor [104]</td>
<td>2005</td>
<td>Retrospective analysis of prospective database</td>
<td>88 patients  - 47 minimally invasive necrosectomy  - 41 open necrosectomy 63 surviving patients Median FU: 29 m IN: 78%</td>
<td>EPF: 8/63 = 13% 7/8 <strong>conservative management</strong> 1/8 ETS No comparator</td>
<td>EPF closure: 8/8 LOE: low</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Study Design</td>
<td>Study Details</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>------------</td>
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<td>-----------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Sikora [105]</td>
<td>2006</td>
<td>Retrospective analysis of prospective database</td>
<td>156 patients Surgical necrosectomy and/or PCD 119 necrosis 37 abscess 81 surviving patients IN: 76%</td>
<td>EPF: 43/81 = 53% Fistula output: &lt; 200 ml/d: 67% 200 – 500 ml/d: 26% &gt; 500 ml/d: 7% Conservative management: n=38 Intervention: 5/43 = 12%</td>
<td></td>
</tr>
<tr>
<td>Arvanitakis [106]</td>
<td>2007</td>
<td>Observational study</td>
<td>4 patients Surgical necrosectomy Complete MPD rupture: 4 Median FU: 11 m</td>
<td>EPF (n=4) Fistula output Median 200 ml/d (60 – 400) Transpapillary ductal drainage: n=3 Transmural PFC drainage: n=3 Pancreaticobulbostomy: n=1</td>
<td></td>
</tr>
</tbody>
</table>

Sikora 2006: Retrospective analysis of prospective database
- 156 patients
- Surgical necrosectomy and/or PCD
- 119 necrosis
- 37 abscess
- 81 surviving patients
- IN: 76%

EPF: 43/81 = 53%
Fistula output:
- < 200 ml/d: 67%
- 200 – 500 ml/d: 26%
- > 500 ml/d: 7%
Conservative management: n=38 Intervention: 5/43 = 12%
- EPS: n=2
- Fistulojejunostomy: n=1
- Downsizing/gradual withdrawal of PCD: n=2

Arvanitakis 2007: Observational study
- 4 patients
- Surgical necrosectomy
- Complete MPD rupture: 4 Median FU: 11 m

EPF (n=4) Fistula output Median 200 ml/d (60 – 400) Transpapillary ductal drainage: n=3 Transmural PFC drainage: n=3 Pancreaticobulbostomy: n=1

Papachristou 2007: Retrospective analysis of a prospective endoscopy database
- 53 patients
- 2 patients with CP on imaging studies
- ETD/ETN (22): 28
- Endoscopy + PCD: 13
- Endoscopy + surgery: 5
- Endoscopy + PCD + surgery: 7
- IN: 49%
- Mean FU: 6 m

EPF: 2/53 = 4%
Surgery:
- Repair of fistula by surgery: n=1
- Distal pancreatectomy: n=1

Spontaneous EPF closure: 38/43 = 88%
Recurrent pseudocyst: 9/38 → surgery: n=7 (cyst gastrostomy: 3, cyst jejunostomy: 4)
Median time to EPF closure: 70 d (28-424)
LOE: moderate

EPF closure: 4/4
EPF recurrence: 0/4
LOE: low

LOE: low
| Bakker [107] | 2011 | Retrospective analysis of a prospective database 15 centers | 115 patients 64 percutaneous drainage/necrosectomy/both 51 surgery IN: 71% | EPF: 35/115 = 30%  
**Comparator ETS (n=19) vs conservative (n=16)**  
*Time from initial treatment to ERP (ETS group): 34 d*
**ETS vs conservative**  
*Fistula output: 150 ml/d vs 250 ml/d, p=0.35*  
- Bridging disruption: 4/19 = 21%  
- Internal stent (in the collection): 6/19  
Short TP stent: 9/19  
**ETS vs conservative**  
*Fistula closure: 16/19 (84%) vs 8/12 (75%) p=0.175*  
*Median time to closure: 71 d vs 120 d, p=0.13*  
*Failed EPF closure:*  
- surgery (PJ): 1 vs 3  
- ETD: 0 vs 1  
- death: 2 vs 0  
No predictive factor of fistula closure  
*LOE: high*

10 studies including reference 10 | 360 pancreatic fistula  
281 endoscopic treatment for EPF  
131 acute necrotizing pancreatitis | EPF  
**Endoscopic transpapillary stenting (ETS): n=281**  
No comparator  
**EPF closure: 200/281 = 71%**  
*Time to EPF closure: 2 – 122 d*  
*LOE: moderate*

| Bakker [64] | 2012 | RCT PENGUIN trial 4 centers | 20 patients  
Surgical necrosectomy (VARD or open, n=10)  
Endoscopic necrosectomy (ETN, n=10)  
FU: 6 m  
IN: 95% | EPF: 8/20 = 40%  
(7/10 in SN vs 1/10 in ETN, p=0.02)  
No data on management  
No clear if EPF was an early or late complication  
*LOE: not assessed despite of RCT*
| Beck [108] | 2012 | Retrospective review of a prospective database | 135 patients Operative necrosectomy Minimally invasive: n=20 Open: n=115 DPDS: n=66 | EPF: 85/135 = 63% 82% in DPDS Fistula output > 200 ml/d **Surgery** (n=71) • Drainage of the fistula track: n=16 • Drainage of the pancreatic duct PJ: n=22 • Resection: n=12 | Mixed results for EPF and recurrent collection Success of management by surgery: 68/71 = 96% | **LOE**: low |
| Karjula [109] | 2014 | Observational study Consecutive patients | 29 patients Open surgical necrosectomy 24 surviving patients IN: 66% FU: 21 m | EPF documented by ERCP: 19/24 = 79% **Endoscopic Transpapillary Stenting (ETS)** Site of leakage: head (3), body (14), tail (4), both head and tail (1) • Bridging stent: 2/23 = 9% • Internal draining stent into the cavity: 12/23 • Transpapillary stent: 9/23 | Technical success: 23/24 = 96% Fistula closure: 23/23 Median time to EPF closure: 82 d (2 – 210) Recurrent pseudocyst: n=7 (stent clogging: 3, stent migration: 4) → repeated ETS No separate results for EPF and IPF | **LOE**: low |
| Gomatos [110] | 2016 | Prospective database | 394 patients 274 minimally invasive necrosectomy (MARPN) 120 open necrosectomy IN: 78% | EPF: 14/274 = 5% 14/120 = 12% 28/394 = 7% p=0.032 No data on management of EPF | No data | **LOE**: not assessed despite large population |

**CP**: chronic pancreatitis; **DPDS**: Disconnected pancreatic duct syndrome; **EPF**: External Pancreatic Fistula; **EPS**: Endoscopic pancreatic sphincterotomy; **ERP**: Endoscopic Retrograde Pancreatography; **ETD**: Endoscopic Transmural Drainage; **ETN**: Endoscopic Transmural Necrosectomy; **ETS**: Endoscopic Transpapillary Stenting; **FU**: follow-up; **IN**: infected necrosis; **IPF**: internal pancreatic fistula; **LOE**: level of evidence; **MPD**: main pancreatic duct; **PCD**: percutaneous drainage; **PFC**: pancreatic fluid collection; **PJ**: pancreaticojejunostomy; **SN**: Surgical necrosectomy
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