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Title:

Endoscopic management of pancreatic collections. Endoscopic Ultrasound Group, Spanish Society of Digestive Endoscopy (GSEED-USE) Clinical Guidelines

Authors:
Mariano González-Haba Ruiz, María Teresa Betés Ibáñez, Belén Martínez Moreno , Alejandro Repiso Ortega, Carlos de la Serna Higuera, Julio Iglesias García, Oriol Sendino García, María Moris Felgueroso, Belén Agudo Castillo, José Miguel Esteban López-Jamar, Mayra Dalila Lindo Ricce, María Teresa Soria San Teodoro, Eloísa Moya Valverde, Diego Muñoz López, Laura Uribarri González, Sergio Sevilla Ribota, José Lariño Noia, Manuel Pérez Miranda, José Ramón Aparicio Tormo, Juan José Vila Costas, Enrique Vázquez Sequeiros, José Carlos Subtil Íñigo, Enrique Pérez-Cuadrado-Robles, Andrés Sánchez Yagüe, Jorge Antonio Núñez Otero, José Ramón Foruny Olcina

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Endoscopic management of pancreatic collections. Endoscopic Ultrasound Group, Spanish Society of Digestive Endoscopy (GSEED-USE) Clinical Guidelines

Mariano González-Haba Ruiz[1], María Teresa Betés Ibáñez[2], Belén Martínez Moreno[3], Alejandro Repiso Ortega[4], Carlos de la Serna Higuera[5], Julio Iglesias García[6], Oriol Sendino García[7], María Moris Felgueroso[8], Belén Agudo Castillo[1], José Miguel Esteban López-Jamar[9], Mayra Dalila Lindo Ricce[4], María Teresa Soria San Teodoro[10], Eloísa Moya Valverde[11], Diego Muñoz López[4], Laura Uribarri González[12], Sergio Sevilla Ribota[13], José Lariño Noia[6], Manuel Pérez Miranda[5], José Ramón Aparicio Tormo[3], Juan José Vila Costas[12], Enrique Vázquez Sequeiros[14], José Carlos Subtil Íñigo[2], Enrique Pérez-Cuadrado-Robles[15], Andrés Sánchez Yagüe[16], Jorge Antonio Núñez Otero[11], José Ramón Foruny Olcina[14]

[1]Department of Digestive Diseases. Hospital Universitario Puerta de Hierro Majadahonda. Majadahonda, Madrid. Spain. [2]Clínica Universidad de Navarra. Pamplona, Spain. [3]Hospital General Universitario de Alicante. Alicante, Spain. [4]Complejo Hospitalario de Toledo. Toledo, Spain. [5]Hospital Universitario Río Hortega. Valladolid, Spain. [6]Hospital Clínico Universitario de Santiago. Santiago de Compostela, A Coruña. Spain. [7]Hospital Clínic Barcelona. Barcelona, Spain. [8]Hospital Universitario Marqués de Valdecilla. Santander, Spain. [9]Hospital Clínico San Carlos. Madrid, Spain. [10]Hospital Universitario Miguel Servet. Zaragoza, Spain. [11]Hospital Universitario del Sureste. Arganda del Rey, Madrid. Spain. [12]Hospital Universitario de Navarra. Pamplona, Spain. [13]Hospital Universitario Infanta Cristina. Parla, Madrid. Spain. [14]Hospital Universitario Ramón y Cajal. Madrid, Spain. [15]Hôpital Européen Georges-Pompidou. Paris, France. [16]Hospital Quirónsalud Marbella. Marbella, Málaga. Spain

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Correspondence: Mariano González-Haba Ruiz. Department of Digestive Diseases. Hospital Universitario Puerta de Hierro Majadahonda. C/ Manuel de Falla, 1. 28222

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Majadahonda, Madrid. Spain
e-mail: marianoghr@gmail.com

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ABSTRACT

Acute pancreatitis is associated with significant morbidity and mortality. It can develop complications such as fluid collections and necrosis. Infection of necrosis occurs in about 20-40 % of patients with severe acute pancreatitis, and is associated with organ failure and worse prognosis. In the past few years the treatment of pancreatic collections has shifted from open surgery to minimally invasive techniques such as endoscopic ultrasound-guided drainage. These guidelines from a selection of experts among the Endoscopic Ultrasound Group, Spanish Society of Gastrointestinal Endoscopy (GSEED-USE) are intended to provide advice on the management of pancreatic collections based on a thorough review of the available scientific evidence. It also reflects the experience and clinical practice of the authors, who are advanced endoscopists or clinical pancreatologists with extensive experience in managing patients with acute pancreatitis.

Keywords: Endoscopic ultrasound. Walled-off pancreatic necrosis. Necrotizing pancreatitis. Endoscopy. Surgery. Minimally invasive. Step-up approach. Pancreatic collections.

INTRODUCTION

Acute pancreatitis (AP) is one of the most frequent causes of hospital admission in our environment. Most of the patients will have a favorable outcome, but in 10-20 % of

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cases it may be associated with necrosis, organ failure and infection, with a mortality rate of up to 30 % (1). These clinical guidelines focus on the role of endoscopy in the management of pancreatic collections.

METHODOLOGY

The Endoscopic Ultrasound Group within the Spanish Society of Gastrointestinal Endoscopy (GSEED-USE), through its coordinator (MGH), elected a subgroup of experts in the field from among its members. The guideline was divided into topics and each topic was assigned to a team led by one or two experts. Each group developed a series of questions that were accepted by the rest of the authors.

During the period between 2021 and 2022 the authors carried out a bibliographic search of PubMed/MEDLINE, the Cochrane Library, and Embase for publications in Spanish and English on this topic until December 2022, subsequently updated until November 2023. A cited reference search was also performed. The search was carried out with priority on randomized controlled trials (RCTs) and meta-analyses. Observational studies were also included if they addressed topics not covered in RCTs. The articles were individually evaluated using the Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) to rate the levels of evidence and recommendation (2). Clinical guidelines and expert opinions could also be taken into consideration to provide recommendations.

Each subgroup prepared draft proposals that were initially voted on using a Delphi system. Two rounds were held. Recommendations with less than 85 % agreement were reviewed considering expert comments and reformulated until > 90 % agreement was obtained at a meeting held in March 2023.

To adjust the recommendations to clinical practice, a survey was conducted among the authors, and extended to other national experts, about their personal approaches to situations with scarce clinical evidence, with the intention of giving an expert opinion in these cases.

After preparing a first consensus version of the manuscript, an external review was carried out by eight external experts, selected by the senior members, of these GSEED-USE guidelines, which was then sent to the rest of the authors. After agreement on a

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final version, the manuscript was sent to *The Spanish Journal of Digestive Diseases* (REED) for publication. All authors agreed on the final revised manuscript.

PRE-PROCEDURE ASPECTS

Nomenclature

What classification of acute pancreatitis should be used when considering an interventional treatment?

GSEED-USE suggests assessing the severity of the disease, taking into consideration the Revised Atlanta Classification (RAC) and also collection infection to establish an indication for treatment.

Low quality evidence. Weak recommendation

The most accepted classifications to define complications and establish the severity of AP are the Revised Atlanta Classification (RAC) and the Determinant-Based Classification (DBC) (3,4).

The RAC describes the initial clinical severity and defines in a clear and accepted manner the local complications of AP, distinguishing between those derived from interstitial or necrotizing pancreatitis and in accordance with their degree of development. According to this classification, there are acute (peri)pancreatic fluid collections (PFC), acute necrotic collections (ANC), pancreatic pseudocysts (PP), and walled-off pancreatic necrosis (WOPN). The DBC best describes severity on the subsequent weeks, as it includes infection of necrosis, which develops in most patients after 7-10 days of admission (5). Several studies conclude that DBC better defines the need for intervention (6,7), and is suggested to differentiate, in the severe pancreatitis group, cases with infected necrosis, as it is an independent predictor of mortality (8).

Indications for intervention (Table 1)

When is intervention indicated for non-infected necrosis?

GSEED-USE recommends drainage of non-infected necrosis in patients with persistent organ failure or progressive clinical deterioration when there is no other proven cause, as well as in cases of compression of adjacent structures (bile duct, gastric outlet

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obstruction).

Low quality evidence. Strong recommendation

GSEED-USE suggests considering drainage in case of clear acute compression of the splenoportal axis, especially when there is evidence of acute thrombosis.

Low quality evidence. Weak recommendation

More than 90 % of patients with necrotizing pancreatitis (NP) will develop acute collections (9,10). These necrotic collections can resolve with conservative treatment, and 50 % will progress to WOPN (9,10). Some studies have shown that the evolution to WOPN is more frequent and requires more intervention if necrosis is extensive and if it includes the pancreatic parenchyma (11,12). Up to 40 % of patients with NP will require intervention (13). Conservative management is reasonable in asymptomatic WOPN because in 50 % of cases they resolve or decrease in size during follow-up. Furthermore, various studies have shown that the complications that may arise during this conservative management are treatable without implying increased mortality (14,15).

Given that the two factors that define the prognosis of NP are organ failure and necrosis infection, drainage may be indicated in patients with sterile necrosis who present organ failure or clinical deterioration despite adequate treatment in the absence of other proven cause, because mortality in these cases is significantly higher (32 % vs 12 %) (5).

Drainage is also recommended for patients with symptoms derived from mechanical compression of adjacent structures, especially jaundice or gastric outlet obstruction (16,17).

In asymptomatic patients who present progressive growth in the size of the collection, it is recommended to assess drainage individually. In pancreatic collections associated with chronic pancreatitis, some authors only recommend drainage of these collections when growth is rapidly progressive (18).

Splanchnic vascular thrombosis is a common complication of AP (15 % of patients) (19). There are no data to support a need for anticoagulation in these patients, since

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the risk of developing complications in this setting is not clearly established. Although development of venous collaterals on CT has been described in 25-86 % of patients, and development of varices in 27-29 % (20,21), serious complications such as hemorrhage due to portal hypertension, intestinal ischemia or ascites seem to be very rare (19). Despite not being a clear indication in most studies, in practice acute thrombosis is considered an indication for treatment by most authors of this guideline, so it is suggested that drainage be considered under this circumstance.

When is intervention indicated for infected necrosis?

GSEED-USE recommends intervention for infected necrosis when it is suspected or confirmed based on clinical and radiological criteria, and there is no response to antibiotic therapy.

High quality evidence. Strong recommendation

Infection of pancreatic necrosis can lead to further deterioration with ongoing or new-onset organ failure, and increases mortality as an independent factor (8,22). There is broad consensus regarding invasive treatment when infection is confirmed or suspected (new-onset or persistent sepsis, clinical deterioration despite adequate support or presence of gas inside collections (16,17,23). To detect infection in the setting of pancreatic necrosis, magnetic resonance (MRI) seems to offer greater sensitivity than computed tomography (CT), although the supportive evidence is very scarce (24,25).

While some patients with infected necrosis respond to antibiotic treatment at the time of suspected diagnosis, the percentage is low (26) and very close follow-up is required to escalate therapy, as most of these patients will require intervention.

Appropriate timing for intervention

What is the most appropriate timing for intervention?

GSEED-USE recommends postponing drainage until there is a mature collection, with a defined wall in imaging techniques, provided that the patient's clinical condition allows it.

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Low quality evidence. Strong recommendation

The timing of endoscopic intervention is crucial in the management of these patients. Since the inflammatory process does not improve significantly with drainage, the necessary time should be allowed for the collection to become organized, generally 4 weeks after AP onset. An estimation of the extent to which the liquefaction and organization process has progressed can be obtained using CT, MRI, ultrasound, or endoscopic ultrasound (EUS).

Endoscopic treatment in the absence of a defined wall is theoretically associated with a higher risk of complications (27). In patients with clinical deterioration despite adequate support, who do not show a defined wall in their collections, percutaneous drainage is the most widely accepted approach (13). Recently, some studies have shown that endoscopic transmural drainage can be used effectively in the early stages of the disease without higher complication rates (28,29). However, the evidence supporting early intervention is still limited. The POINTER study and its subsequent update compared catheter drainage within the first 24 hours of infection diagnosis with postponed endoscopic drainage, and showed that early drainage did not exhibit any superiority in terms of complications, and that the group in which drainage was postponed required fewer invasive interventions (30,31). Therefore, there is a possible role for early endoscopic drainage in critically ill patients with infected pancreatic collections and organ failure, although it should be performed in highly experienced centers with multidisciplinary teams.

Imaging studies

What is the best imaging technique for the evaluation of pancreatic collections and necrosis in order to propose a possible endoscopic therapy?

GSEED-USE suggests performing pancreatic MRI (with secretin if available) to assess the solid component of necrosis and the potential disruption of the main pancreatic duct for eventful therapeutic procedures.

Low quality evidence. Weak recommendation

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MRI exhibits the highest sensitivity and specificity in comparison to CT and EUS for detecting pancreatic necrosis. Additionally, it surpasses CT in accuracy for characterizing the proportion of solid components, particularly after the fourth week (32). MRI -preferably with secretin- is recommended for the anatomical evaluation of the pancreatic duct and its possible communication or disruption (33,34). However, in routine clinical practice CT is the most widely used technique due to its wider availability, as secretin is not available in most centers.

EUS is useful for diagnosis and characterization prior to drainage (size, distance from the lumen of the digestive tract, solid component, vascular structures) (17,18,32,35), although diagnostic usefulness is limited by its being more invasive than MRI.

Indication for fine-needle aspiration (FNA)

In which cases would it be necessary to perform FNA in patients with pancreatic necrosis or collections?

GSEED-USE recommends against a systematic use of FNA prior to endoscopic drainage of pancreatic collections for the diagnosis of infected necrosis. However, it may be considered if its findings would be essential for making therapeutic decisions (initiation or adjustment of targeted antibiotic treatment, in selected cases of non-accessible infected collections and poor clinical outcome).

Low quality evidence. Strong recommendation

The use of FNA to obtain samples for culture in patients undergoing endoscopic drainage for suspected infection is not recommended (1,16,17). The added value provided by FNA is limited when clinical symptoms or radiological signs highly suggestive of infection are already present (36). In the PANTER study (22), patients were treated based on suspicion of necrosis infection without prior FNA and a diagnostic accuracy of > 90 % was shown.

Culture samples obtained by FNA present a high rate of false positives and negatives (28). In exceptional cases where patients exhibit infected collections non-accessible to drainage, and experience poor clinical progress despite broad-spectrum antibiotic therapy, fine-needle aspiration (FNA) may facilitate microbiological culture, enabling a

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precise adjustment and guidance of treatment. (37).

Periprocedural antibiotic prophylaxis

Is antibiotic prophylaxis necessary in patients with pancreatic collections or necrosis in order to prevent the potential risk of infection associated with invasive therapeutic procedures?

GSEED-USE suggests against systematic administration of antibiotics prior to therapy in patients with pancreatic collections when there is no clear evidence or high suspicion of infection.

Low quality evidence. Weak recommendation

The systematic use of antibiotics to prevent infection of collections after drainage has not shown a decrease in morbidity and mortality (38,39). Its use may only be recommended in case of multi-organ failure in the course of severe pancreatic necrosis when infection from another source cannot be ruled out.

PROCEDURE

Significant advances have been made in the interventional management of infected necrosis in recent decades, particularly in procedures such as video-assisted retroperitoneal debridement (VARD), transgastric drainage, and endoscopic necrosectomy. Available evidence has positioned the "step-up" approach (surgical or endoscopic) as the standard approach (13,26,40,41). This approach consists of an endoscopic transluminal or image-guided percutaneous drainage procedure as first step, followed by minimally invasive necrosectomy when there is no clinical improvement.

Necrosectomy can be endoscopic, minimally invasive surgical (laparoscopic or VARD), or open surgical. The latter is reserved for cases where other modalities of necrosectomy have failed or are not feasible, given its association with higher morbidity and increased healthcare costs.

General measures

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There's a general consensus in recommending the use of CO_2 to reduce the risk of embolism (0.9 %-2 %) (42).

In large collections, because of the risk for bronchoaspiration after drainage, the procedure should be performed under general anesthesia with orotracheal intubation.

Drainage technique

What is the preferred drainage technique for pancreatic pseudocysts?

GSEED-USE recommends endoscopic management of pancreatic pseudocysts over percutaneous or surgical drainage.

High quality evidence. Strong recommendation

Pancreatic pseudocysts (PPs) are exceptional in the course of AP, since the majority of acute collections resolve. Transmural endoscopic management of PPs is considered the initial method of choice over percutaneous drainage (41). Studies that have compared EUS-guided drainage with surgical intervention found that, with similar technical success and complication rates, EUS-guided drainage was a more cost-effective procedure associated with shorter hospital stay (43,44).

What is the preferred drainage technique for walled-off pancreatic necrosis?

SEED-USE recommends endoscopic drainage for WOPN over the surgical step-up approach (laparoscopic or video-assisted retroperitoneal debridement (VARD))

Moderate quality evidence. Strong recommendation

Three RCTs have confirmed that EUS-guided drainage is linked to shorter hospital stay, reduced healthcare costs, and fewer complications compared to surgical step-up treatment (laparoscopic or VARD), with at least comparable mortality rates (26,40,41). The five-year follow-up of one of these trials shows comparable results in terms of collection resolution, although fewer pancreatic fistulae were observed with the endoscopic approach (45).

Transmural drainage technique

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Which is the most appropriate endoscopic method of transmural drainage, conventional endoscopic drainage or EUS-guided drainage?

GSEED-USE recommends EUS-guided transmural drainage over conventional endoscopic drainage.

Moderate quality evidence. Strong recommendation

Endoscopic drainage of pancreatic collections has evolved over time. EUS allows drainage of PPs and WOPN located adjacent to the wall, without the need for extrinsic compression. It also allows the best puncture point to be identified for drainage, identifying the presence of vascular structures of significant caliber or other organs, which increases the safety of the procedure. Two RCTs demonstrated greater technical success of EUS-guided drainage compared to pure endoscopic drainage (100 % vs 33 % and 94 % vs 72 %) (46,47).

Type of STENT

What type of stent should be used to perform transmural drainage of pancreatic collections (plastic or metallic)?

GSEED-USE recommends performing drainage of pancreatic pseudocysts either with double “pig-tail” plastic stents or luminal apposing metal stents.

Low quality evidence. Strong recommendation

GSEED-USE suggests performing drainage of walled-off necrosis with a lumen-apposing metal stent as the first option, as long as its early removal can be ensured once the collection has resolved.

Low quality evidence. Weak recommendation

Currently there are three types of stents for transmural drainage of pancreatic collections. Plastic stents (PS, among which the double “pig-tail” type (DPS) is the most commonly used), straight fully covered self-expandable metal stents (FCSEMS) (biliary or esophageal), and lumen-apposing metal stents (LAMS). The latter can incorporate electrocautery, allowing their placement in a single step and thus reducing the time of

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the intervention. There is a lot of heterogeneity between studies that evaluate endoscopic drainage of pancreatic collections, and most encompass pseudocysts and WOPN together, as well as different types of stents.

Drainage of pseudocysts with a PS has clinical success rates greater than 85 %, with adverse events at 10-20 % (48,49). Although some studies favor FCSEMS or LAMS over PS, most publications generally find no significant differences in clinical success and complications rates (46,48-52). PS are cost effective (53) but can make the procedure longer and more complex.

Regarding WOPN, FCSEMS and LAMS enable larger caliber drains, theoretically reducing obstruction rate, aiding in solid necrotic material drainage, and facilitating subsequent access for necrosectomy. However, literature analysis on the most suitable stents for WOPN drainage presents conflicting results (54-56).

Two recent studies suggest similar results in terms of efficacy and need for necrosectomy between LAMS and PS (57,58). In the first RCT published that compared LAMS vs PS for drainage of WOPN, a bleeding rate of 50 % was observed in the LAMS group if they were maintained for more than 3 weeks, which made it necessary to modify the trial protocol with early withdrawal of the LAMS (59), a strategy that has become widespread.

Although earlier publications show a favorable tendency towards LAMS in terms of clinical success and fewer complications (49,51,60-62), other publications do not evidence such differences (48,49,63). Two recent meta-analyses analyzing 22 studies and 2,953 patients (64,65) found no significant differences in clinical success. However, LAMS showed a lower tendency for adverse events. Lastly, a recent meta-analysis only found significant differences in procedure duration in favor of LAMS (66).

In efforts to enhance WOPN drainage rates, studies have been published achieving good results by draining at various points of the collection with both PS and LAMS (67-69).

In summary, based on the analyzed data, we suggest draining WOPN with either PS or LAMS, considering the latter as the primary choice since it decreases procedure duration and complexity despite higher costs. Removal should not be delayed (3-4 weeks) after collection resolution. Drainage of pancreatic pseudocysts can be

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performed with both PS or LAMS.

Coaxial STENT

Is it advisable to place a coaxial double-pigtail plastic stent when using SEMS/LAMS for drainage of pancreatic collections?

GSEED-USE suggests against systematic placement of a coaxial "double-pig-tail" stent (DPS) inside SEMS or LAMS, although certain groups of patients could benefit from this strategy.

Low quality evidence. Weak recommendation

The safety of metallic stents in the drainage of PFC is a major concern for endoscopists. Side effects such as bleeding, obstruction, infection, buried stent or migration have been described with rates ranging from 13 % to 53 % (48,51).

Regarding SEMS, due to its morphology, coaxial DPS placement has been shown to reduce migration rate in patients with biliary stents (70-72) and in pseudocysts (73).

Migration does not seem to be a significant problem with LAMS. Coaxial placement of DPS in LAMS for drainage of pancreatic collections has been analyzed in some retrospective studies with conflicting results. Some studies find a lower incidence of infection particularly in pseudocysts (74-76), while others do not show significant differences, either in resolution rate or in adverse effects (71). A recent RCT showed a significantly lower global rate of adverse events and stent occlusion rate in EUS-guided drainage of WON when a coaxial DPS was placed (77).

The placement of a coaxial DPS could be more beneficial in patients at high risk of bleeding (patients under anticoagulant therapies, collateral vessels, coagulation disorders), or infection (immune compromise). When there is a rapid collapse of the cavity (predominant liquid component) or LAMS obstruction is anticipated, placement of a coaxial DPS could also be considered.

Use of fluoroscopy

Is it essential to perform endoscopic drainage under fluoroscopic control?

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GSEED-USE suggests that EUS-guided drainage of pancreatic collections can be safely and effectively performed without fluoroscopy, especially when LAMS are used. This approach would be recommended for critically ill patients who have difficulty being transported to a fluoroscopy-equipped room.

Low quality evidence. Weak recommendation

Most of pancreatic collection drainage procedures have been traditionally performed using a combination of EUS and fluoroscopic imaging. However, drainage guided exclusively by EUS shows a high technical success rate, a good safety profile, and a low complication rate (78-80). The use of LAMS facilitates treatment without fluoroscopy by reducing the number of instrument exchanges via guidance, significantly shortening procedure duration (78,79). This approach could be particularly useful for critically ill patients with transportation challenges or when avoiding radiological exposure, such as in pregnant patients.

Naso-cystic catheter

When is the placement of a naso-cystic catheter indicated for irrigation of a collection?

GSEED-USE suggests against placement of a naso-cystic catheter for irrigation of pancreatic collections. It can be considered in cases predominantly containing solid material to facilitate debridement of necrotic tissue.

Low quality evidence. Weak recommendation

Available data on the placement of a naso-cystic catheter for lavage or irrigation of a collection through LAMS or in parallel with PS are limited (81-84). There are no prospective RCTs establishing the most suitable duration or volume of irrigation. The most common protocol involves constant instillation of saline through a 7-8.5 F catheter at a daily volume of 500-1000 ml.

Some authors recommend antibiotic irrigation based on the culture analysis obtained during drainage (85,86). Results have also been published using lavage with diluted hydrogen peroxide (0.1-3 %) or streptokinase to facilitate debridement (87-89),

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although evidence in this aspect is lacking.

Percutaneous drainage associated with transmural drainage

When should transmural endoscopic drainage be combined with percutaneous drainage?

GSEED-USE suggests considering combined endoscopic and percutaneous drainage in patients with large-sized pancreatic necrosis extending towards the pelvis or paracolic gutters.

Low quality evidence. Weak recommendation

Percutaneous drainage (PCD) remains a therapeutic option in patients with unformed pancreatic collections and poor response to medical treatment in the early stages of pancreatitis (usually less than 4 weeks). Additionally, it is an option when endoscopic transmural drainage is unavailable, ineffective, or technically infeasible.

Isolated PCD can resolve pancreatic necrosis in up to 35-51 % of cases (13,26). Combined endoscopic-percutaneous drainage may be necessary under specific circumstances and can facilitate necrosis resolution by creating an irrigation circuit through the drainage system (90).

The combination of percutaneous and endoscopic drainage can be considered in patients in whom a PCD has been placed in the early stages of AP with persistence of the collection, once the endoscopic approach is possible and safe, and also simultaneously in cases in which the necrosis extends into one or both parietocolic spaces or towards the pelvis.

PCD can be placed after endoscopic drainage when the latter may be insufficient to drain the most sloping portions of the necrosis. Published studies of combined drainage show a trend towards decreased hospitalization time, resolution of necrosis, exposure to ionizing radiation, lower rates of pseudoaneurysm-related bleeding, and reduced need for surgical rescue (90--92). Similarly, in patients with isolated PCD showing no favorable progress, combining endoscopic transmural drainage may be considered (91).

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It is worth highlighting that the percutaneous access tract can serve as a later access point for a "step-up" surgical approach. This access tract can also be used for direct percutaneous endoscopic necrosectomy through an esophageal FCSEMS, leveraging the flexibility of an endoscope (93).

Pancreaticocutaneous fistulae are a primary disadvantage of isolated PCD. The combination of endoscopic transmural drainage significantly reduces their development (90-92).

Combined endoscopic drainage (transmural-transpapillary)

Is it advisable to combine transpapillary drainage with transmural drainage?

GSEED-USE recommends against routine combination of transpapillary drainage with transmural drainage.

Low quality evidence. Strong recommendation

There is limited evidence regarding the combination of transpapillary drainage with endoscopic transmural drainage. A meta-analysis incorporating 9 studies, comprising 2 prospective observational and 7 retrospective observational studies, concluded that transpapillary drainage does not confer additional benefits to transmural drainage of pancreatic collections. The results showed equivalent outcomes in terms of technical and clinical success, recurrence, and complication rates (94). These findings should be interpreted with caution as they are not from RCTs, and there might be indications for specific patients with partial disruption of the main pancreatic duct.

POST-PROCEDURE

Antibiotic therapy

Which antibiotics are recommended after endoscopic drainage of an infected pancreatic collection?

GSEED-USE recommends using broad-spectrum antibiotic therapy with pancreatic penetration.

Low quality evidence. Strong recommendation

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GSEED-USE suggests obtaining a sample from the necrotic collection for microbiological analysis and adjustment of antibiotic therapy in cases of multi-resistant pathogens.

Low quality evidence. Weak recommendation

Empirical antibiotic treatment should cover gram-negative, aerobic gram-positive, and anaerobic microorganisms. Priority should be given to broad-spectrum antibiotics with adequate pancreatic penetration, such as carbapenems, quinolones, metronidazole, or 3rd-5th generation cephalosporins (95).

Aspiration of fluid for microbiological analysis during endoscopic drainage is a strategy that can help to adjust antimicrobial treatment in cases of infection by resistant bacteria or colonization by *Candida* spp (83,96,97).

For how long is antibiotic therapy recommended after endoscopic drainage of an infected pancreatic collection?

GSEED-USE suggests discontinuation of antibiotic therapy after drainage of an infected pancreatic collection upon resolution of signs and symptoms of infection and normalization of laboratory parameters.

GSEED USE suggests maintaining antibiotic therapy until complete resolution of the collection, and stent removal in case of reinfection secondary to stent obstruction.

Low quality evidence. Weak recommendation

Antibiotic treatment should be limited to what is necessary in terms of use and duration since development of infection by multi-resistant bacteria is an independent predictor of mortality (98). Once a collection has been drained, it seems reasonable to discontinue antibiotic therapy when the patient shows clinical and laboratory improvements indicative of infection resolution, and no recent positive cultures are present (5).

In the event of reinfection caused by stent obstruction by necrotic material, it is suggested that antibiotic therapy be maintained until the cavity is completely cleaned through necrosectomy and stents have been removed.

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Nutrition

What type of nutrition is considered most appropriate after endoscopic drainage of a pancreatic collection?

GSEED-USE recommends resuming oral diet within the first 24 hours after endoscopic drainage if the patient's clinical status allows it. If oral tolerance is not possible, enteral nutrition via the nasogastric or nasojejunal route is recommended.

Low quality evidence. Strong recommendation

There are no specific published data on nutritional support after endoscopic drainage of pancreatic collections; however, there is evidence to support the feasible and safe resumption of oral intake at 24-48 hours after the procedure (99-101).

In cases where oral tolerance is not possible, enteral nutrition via the nasogastric (NG) or nasojejunal (NJ) routes is recommended. There is insufficient evidence to recommend one type of tube over another in the absence of duodenal obstruction. Therefore, considering ease of placement, a NG tube may be preferred and, in case of intolerance, switching to a NJ tube should be considered (102).

Direct endoscopic necrosectomy (DEN)

In which cases is direct endoscopic necrosectomy (DEN) indicated?

GSEED-USE suggests that DEN should be reserved for patients with WOPN who do not respond adequately to endoscopic transmural drainage or in those with factors indicating a poor response to drainage, such as the presence of an abundant solid component in the necrotic cavity.

GSEED-USE suggests against routine use of DEN at the time of drainage, but it may be considered in large necrotic collections and in cases where there is a low output due to abundant solid debris.

Low quality evidence. Weak recommendation

The clinical success of endoscopic drainage in patients with WOPN is significantly lower than in pseudocysts because the spontaneous elimination of solid necrotic debris may

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be incomplete and often requires additional treatment (103). Multiple studies have demonstrated the advantages of a step-up strategy to avoid unnecessary procedures, as between 20 % and 90 % of patients with pancreatic collections can be treated exclusively with endoscopic drainage without the need for necrosectomy or other treatments (104).

The need for additional techniques such as DEN will depend primarily on the amount of solid material present within the necrotic cavity and its extension (105-107). DEN through transmural drainage has proven to be a safe and effective technique and has quickly become the method of choice over surgical debridement (26,41).

Some publications suggest that performing DEN in the same procedure as transmural drainage could expedite the resolution of necrosis compared to deferring DEN (108-110). A recent multicentric RCT showed that in patients with large necrotic collections performing upfront necrosectomy at the index intervention rather than as a step-up measure could safely reduce the number of reinterventions required to achieve treatment success (111).

Regarding the use of DEN on a scheduled basis or on demand based on clinical and radiological evolution, there is no consensus (112,113). DEN is generally delayed to a few days after drainage, to allow for the maturation of the fistulous tract and to reduce the risk of stent displacement.

Concomitant treatments

Is antiplatelet and anticoagulation treatment contraindicated in the peri-procedural setting of endoscopic drainage of a pancreatic collection?

GSEED-USE recommends holding anticoagulation and antiplatelet therapy before performing endoscopic drainage and necrosectomy, with the option to maintain low-dose aspirin treatment.

Low quality evidence. Strong recommendation

Endoscopic drainage is a procedure with a high risk of bleeding, with a rate of 5-15 % (114-116). Therefore, it is recommended to discontinue anticoagulants and antiplatelets according to the currently accepted recommendations in clinical

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guidelines (117).

Is it advisable to discontinue treatment with proton-pump inhibitors (PPIs) after endoscopic drainage of a pancreatic collection?

GSSED-USE suggests suspending PPI treatment in patients undergoing endoscopic drainage of a pancreatic collection in cases where there is no strong indication to continue use.

Low quality evidence. Weak recommendation

Although evidence is limited, maintaining a low gastric pH could facilitate liquefaction of necrosis, minimize bacterial overgrowth, facilitate necrosectomy, and improve stent patency (118).

Follow-up after drainage

When should follow-up be performed after endoscopic drainage and by what technique?

GSEED-USE suggests determining the timing of imaging follow-up after endoscopic drain placement based on clinical findings, particularly when contemplating invasive treatment or before considering the removal of LAMS. It is recommended to perform this follow-up using CT.

Low quality evidence. Weak recommendation

There is a lack of studies evaluating the optimal imaging test for follow-up after endoscopic drainage and the ideal timing for its performance (119). No studies certify the safety of MRI in patients with LAMS, and it may also generate image artifacts. Therefore, follow-up after drainage using CT is recommended. Traditionally, follow-up has been recommended based on pertinent clinical findings or when considering invasive treatments, rather than offering routine follow-up (120,121). Some studies that have assessed an imaging test protocol a week after drainage observed a decrease in early adverse events (121).

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Timing for STENT removal

When should stents used for endoscopic drainage be removed?

GSEED-USE recommends early removal (3-4 weeks) of LAMS in case of predominantly fluid collections or after confirming the resolution of the collection, while maintaining a plastic stent in the long-term in case of disconnected pancreatic duct syndrome (DPDS).

Low quality evidence. Strong recommendation

GSEED-USE suggests individualizing the decision to maintain LAMS for longer or replace it with plastic stents in cases of WOPN with persistent solid content that have not developed complications after 4 weeks.

Low quality evidence. Weak recommendation

An increase in adverse events has been observed if LAMS are not removed early, with bleeding being most concerning (114). Both a RCT and a recent meta-analysis observed a significantly increased risk of bleeding after 3-4 weeks of LAMS placement (59,65). A radiological follow-up study observed that the majority of LAMS-drained collections resolved at least significantly in less than 4 weeks (119).

Follow-up after STENT removal

How should follow-up be carried out after stents used for endoscopic drainage have been removed?

GSEED-USE suggests performing a control CT scan at 3-6 months and subsequently depending on symptoms. Closer follow-up is suggested in patients with suspected DPDS.

Low quality evidence. Weak recommendation

The risk of recurrence after resolution of a pancreatic collection is low (1.25-4.4 %) in patients who do not present DPDS (59,122). For this reason, after removal of the drain, systematic radiological follow-up tests are not indicated in asymptomatic patients. However, in patients with DPDS this risk can reach 28 %, even with a permanent PS left

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in place after LAMS removal (123). Another study observed that recurrence occurred on average within 6 months (124), so we suggest a first CT at 3-6 months. New studies are required to evaluate the optimal long-term follow-up.

COMPLICATIONS

Disconnected pancreatic duct syndrome (DPDS)

When must DPDS be confirmed and by what technique?

GSEED-USE recommends suspecting DPDS in patients with extensive necrosis and intraglandular collections. MRI with secretin should be used when available.

GSEED-USE recommends attempting to diagnose DPDS before drain removal.

Low quality evidence. Strong recommendation

Scientific evidence regarding DPDS is scarce. A recent meta-analysis concludes that ERCP and MRI have similar diagnostic accuracy when diagnosing DPDS (125). MRI should be the first test to be performed when DPDS is suspected due to its non-invasive nature (34,125). It is advisable to perform MRI once the acute episode of AP has passed, as inflammatory changes and acute collections may hinder the assessment of the pancreatic ductal system. The addition of a dynamic study with secretin can help identify communication between the main duct and the collection.

What is the preferred treatment of choice for DPDS?

GSEED-USE recommends EUS-guided transmural drainage when DPDS is associated with a pancreatic collection.

GSEED-USE recommends to consider other options such as transpapillary drainage, EUS-guided pancreatogastrostomy or (additional) surgery in DPDS without associated a collection.

GSEED-USE recommends leaving permanent plastic stents after removing LAMS if DPDS is strongly suspected or confirmed.

Low quality evidence. Strong recommendation

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In DPDS with an associated collection the treatment of choice is endoscopic drainage since it has similar efficacy to surgical treatment but less morbidity. Transpapillary drainage is not used as monotherapy, nor has it been shown to improve results in combination with transmural endoscopic treatment, even when the disruption is overcome. A recent systematic review and meta-analysis demonstrated a success rate of 81 % for transpapillary drainage, 92 % for transmural drainage, 80 % for distal pancreatectomy, and 84 % for surgical cysto-jejunostomy (126). In a prospective study, the surgical alternative was related to a morbidity rate of 46 %, a mortality rate of 2 %, and a high rate of readmission (19 %) and reintervention (11 %) (127).

In the absence of an associated collection, transpapillary drainage is not recommended due to its limited success in reconnecting the pancreatic segment in patients with DPDS (9-30 %) (128). It may only be useful in cases with partial DPDS (128,129). Other studies have demonstrated that in cases of complete DPDS, adding transpapillary drainage to transmural drainage does not improve clinical outcome and may increase adverse events such as pancreatitis or infection (94,121,129,130).

There are no specific studies evaluating different types of stents in DPDS patients, so the recommendation is based on studies about draining pancreatic collections in general. There appear to be no differences between PS or LAMS; however, the latter has a higher rate of long-term complications (bleeding, burying, migration), so it should be replaced with a PS (131,132).

Multiple studies agree that in total DPDS, early stent removal is associated with a higher risk of recurrence (128,133,134). On the other hand, a recent multicenter trial demonstrated that disruptions located in the body and tail had a higher risk of treatment failure (123).

Several studies have shown a higher recurrence rate in patients with DPDS after removal of transgastric drainage (135-137). Therefore, it is recommended to maintain the stents, creating a permanent internal fistula and replacing LAMS with PS (59), which have a low profile of long-term complications (120,138).

Despite the ongoing evolution of endoscopic treatment for DPDS, in some cases it is not successful, and a multidisciplinary approach is required, either combining endoscopic and percutaneous methods or using a surgical approach. Surgery for DPDS

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includes both resection and drainage of the pancreatic tissue proximal to the pancreatic duct disruption, considering the high risk of endocrine and exocrine insufficiency that it entails (126,127).

Pancreatic fistulae

What is the preferred treatment for pancreatic fistulae?

GSEED-USE recommends using an individualized approach to pancreatic fistulae. Endoscopic treatment (combined or not with the percutaneous route) should be specially considered in cases with associated collections.

Low quality evidence. Strong recommendation

The initial management of a pancreatic fistula may be conservative unless sepsis is present, as a high percentage of fistulae resolve spontaneously within approximately 70 days (139). When a pancreatic fistula is associated with partial DPDS and small collections, transpapillary drainage may be considered, although success rate is often low (140). A dual modality (percutaneous and endoscopic) is frequently used to reduce the number of external pancreatic fistulae that may occur after percutaneous drainage or surgical necrosectomy (139-143). In patients with persistent or recurrent percutaneous fistula and failure of more conservative treatments, surgery should be considered (125,144).

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Table 1. Main recommendations

1	GSEED-USE recommends drainage of non-infected necrosis in patients with persistent organ failure or progressive clinical deterioration, when there is no other proven cause, as well as compression of adjacent structures (bile duct, gastric outlet obstruction)

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	Low quality evidence. Strong recommendation
2	GSEED-USE suggests considering drainage in case of clear acute compression of the splenoportal axis, especially in cases of acute thrombosis *Low quality evidence. Weak recommendation*
3	GSEED-USE recommends intervention for infected necrosis, when it is suspected or confirmed based on clinical and radiological criteria, and that does not respond to antibiotic therapy *High quality evidence. Strong recommendation*
4	GSEED-USE recommends postponing drainage until there is a mature collection, with a defined wall in imaging techniques, provided that the patient's clinical condition allows it *Low quality evidence. Strong recommendation*
5	GSEED-USE recommends against routine administration of antibiotics prior to therapy in patients with pancreatic collections when there is no clear evidence or high suspicion of infection. *Low quality evidence. Weak recommendation*
6	GSEED-USE recommends endoscopic management of pancreatic pseudocysts over percutaneous or surgical drainage. *High quality evidence. Strong recommendation* GSEED-USE recommends endoscopic-based drainage for WOPN over the surgical step-up approach (laparoscopic or video-assisted retroperitoneal debridement (VARD)) *Moderate quality evidence. Strong recommendation*
7	GSEED-USE recommends performing drainage of pancreatic pseudocysts either with double “pig-tail” plastic stents or luminal apposing metal stents *Low quality evidence. Strong recommendation* GSEED-USE suggests performing drainage of walled-off necrosis with a lumen apposing metal stent as the first option, as long as its early removal can be ensured once the collection has resolved. *Low quality evidence. Weak recommendation*
8	GSEED-USE suggests against systematic placement of a coaxial “double-pig-tail”

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	stent (DPS) inside SEMS or LAMS, although certain groups of patients could benefit from this strategy. *Low quality evidence. Weak recommendation*
9	GSEED-USE suggests considering combined endoscopic and percutaneous drainage in patients with large-sized pancreatic necrosis extending towards the pelvis or paracolic gutters. *Low quality evidence. Weak recommendation*
10	GSEED-USE suggests discontinuation of antibiotic therapy after drainage of an infected pancreatic collection upon resolution of signs and symptoms of infection and normalization of analytical parameters. GSEED USE suggests maintaining antibiotic therapy until complete resolution of the collection and stent removal in case of reinfection secondary to stent obstruction *Low quality evidence. Weak recommendation*
11	GSEED-USE suggests that DEN should be reserved for patients with WOPN who do not respond adequately to endoscopic transmural drainage or in those with factors indicating a poor response to drainage, such as the presence of an abundant solid component in the necrotic cavity. GSEED-USE suggests against routine use of DEN at the time of drainage, but it may be considered in large necrotic collections and in cases where there is low output due to abundant solid debris. *Low quality evidence. Weak recommendation*
12	GSEED-USE recommends early removal (3-4 weeks) of LAMS in case of predominantly fluid collections or after confirming the resolution of the collection, while maintaining a plastic stent in the long-term in case of disconnected pancreatic duct syndrome (DPPS) *Low quality evidence. Strong recommendation*

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	GSEED-USE suggests individualizing the decision to maintain LAMS for longer or replace it with plastic stents in cases of WOPN with persistent solid content that have not developed complications after 4 weeks, *Low quality evidence. Weak recommendation*
13	GSEED-USE recommends suspecting DPDS in patients with extensive necrosis and intraglandular collections. MRCP with secretin (s-MRCP) should be used when available. GSEED-USE recommends attempting to diagnose DPDS before drain removal. *Low quality evidence. Strong recommendation*
14	GSEED-USE recommends EUS-guided transmural drainage when DPDS is associated with a pancreatic collection. GSEED-USE recommends to consider other options such as transpapillary drainage, EUS-guided pancreatogastrostomy or (additional) surgery in DPDS without an associated collection. GSEED-USE recommends leaving permanent plastic stents after removing LAMS if the presence of DPDS is confirmed/known. *Low quality evidence. Strong recommendation*

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