

ORIGINAL ARTICLE

Diagnosis and treatment of pancreatic duct disruption or disconnection: an international expert survey and case vignette study

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Abstract

Background: Pancreatic duct disruption or disconnection is a potentially severe complication of necrotizing pancreatitis. With no existing treatment guidelines, it is unclear whether there is any consensus among experts in clinical practice. We evaluated current expert opinion regarding the diagnosis and treatment of pancreatic duct disruption and disconnection in an international case vignette study.

Methods: An online case vignette survey was sent to 110 international expert pancreatologists. Expert selection was based on publications in the last 5 years and/or participation in development of IAP/APA and ESGE guidelines on acute pancreatitis. Consensus was defined as agreement by at least 75% of the experts.

Results: The response rate was 51% ($n = 56$). Forty-four experts (79%) obtained a MRI/MRCP and 52 experts (93%) measured amylase levels in percutaneous drain fluid to evaluate pancreatic duct integrity. The majority of experts favored endoscopic transluminal drainage for infected (peri)pancreatic necrosis and pancreatic duct disruption (84%, $n = 45$) or disconnection (88%, $n = 43$). Consensus was lacking regarding the treatment of patients with persistent percutaneous drain production, and with persistent sterile necrosis.

Conclusion: This international survey of experts demonstrates that there are many areas for which no consensus existed, providing clear focus for future investigation.

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Introduction

Approximately 20% of patients with acute pancreatitis develop necrosis of the pancreatic parenchyma or extrapancreatic fat tissue.^{1–3} Necrosis of the pancreatic parenchyma is frequently accompanied by loss of pancreatic duct integrity. As a result, the

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main pancreatic duct no longer communicates with the gastrointestinal tract, leading to leakage of pancreatic fluid in the surrounding tissues.^{4,5} This phenomenon is also referred to as a disrupted or disconnected pancreatic duct and is thought to persist in approximately 10%–30% of patients with necrotizing pancreatitis.^{4,6,7} Leakage of pancreatic fluid due to a disrupted or disconnected pancreatic duct causes several problems, such as persistent pancreatic fistulae, recurrent pancreatic fluid collections, and pancreatic ascites, which generally impedes the patient's recovery. Despite the complexity of this condition, there are currently no standardized guidelines on the diagnostic work-up and treatment. It is also unclear whether there is consensus among expert pancreatologists in daily clinical practice. The aim of this study was to evaluate current expert opinion regarding the diagnosis and treatment of pancreatic duct disruption and disconnection following necrotizing pancreatitis to aid clinical decision making and to identify areas of future research.

Methods

Study design

An international case vignette survey study among a multidisciplinary expert group of pancreatologists was performed. Experts were selected based on publications on pancreatic duct disruption and disconnection following necrotizing pancreatitis in the last five years, and/or participation in the development of

the International Association of Pancreatology/American Pancreatic Association (IAP/APA) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines on acute pancreatitis.^{2,8} Invitations were sent through e-mail in August 2019, followed by four weekly reminders. Additionally, targeted email reminders were sent in December 2019. The survey was administered via Research Electronic Data Capture (REDCap) and data was collected anonymously.

Survey design

The survey consisted of several demographical questions, including the experts' specialty, type of hospital, and working experience. Moreover, 6 general questions and 3 case vignettes with regards to diagnosis and treatment of disrupted or disconnected pancreatic duct were included in the survey ([Supplementary Appendix](#)). The case vignettes addressed several clinical scenarios, but all concerned a 65-year old female patient, without significant co-morbidity, admitted with biliary necrotizing pancreatitis ([Fig. 1](#)). For each vignette, the experts were questioned on their preferred diagnostic modality and treatment strategy. The survey questions were developed by an international multidisciplinary writing committee, including gastroenterologists, surgeons and a radiologist. Questions were based on the results of two systematic reviews and the preliminary results of an (unpublished) prospective observational cohort study of the Dutch Pancreatitis Study Group.^{9–11}

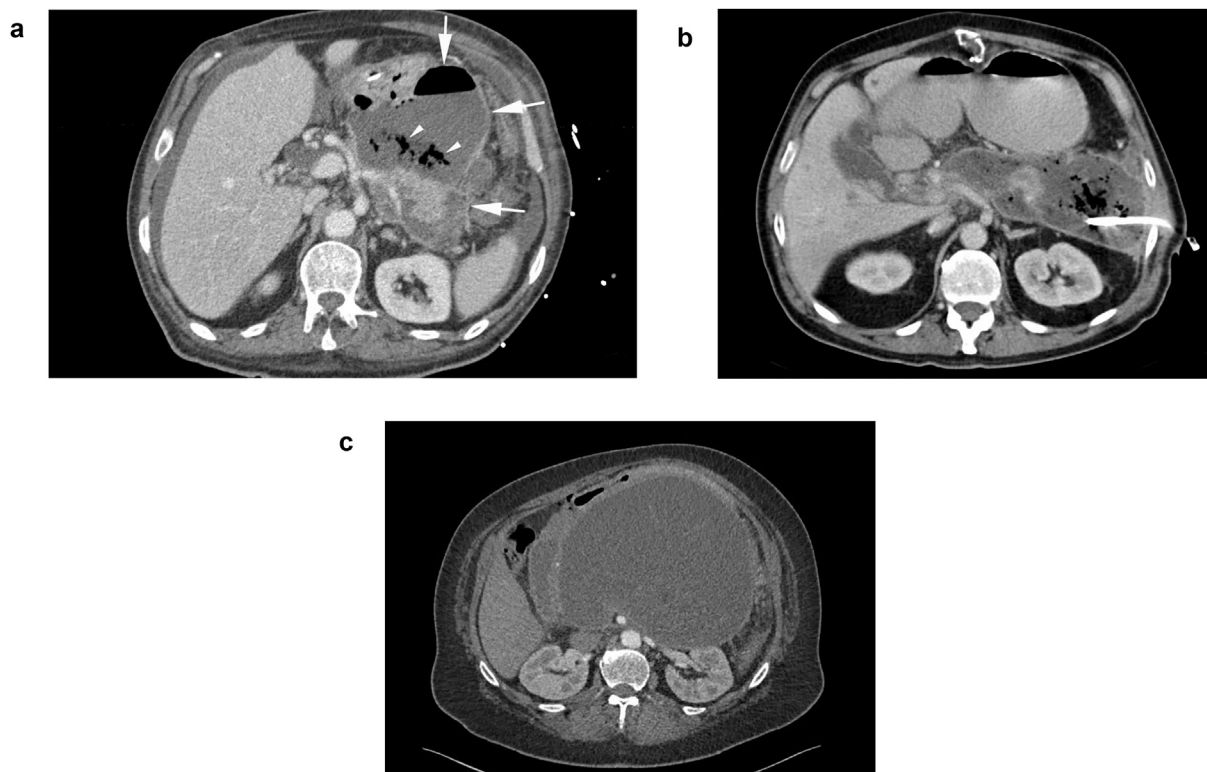


Figure 1 The case vignettes: clinical scenarios and imaging findings

Study definitions

Disruption of the pancreatic duct was predefined as a partial interruption of the pancreatic duct. Disconnection of the pancreatic duct was defined as a complete (circumferential) interruption of the pancreatic duct. Consensus was defined as agreement by at least 75% of the experts. Consensus statements were evaluated based on the Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (Table 4).^{12,13} Quality of evidence was categorized as high (level A), moderate (level B), low (level C), or very low (level D).

Statistical analysis

Descriptive data are presented as frequencies with percentages for categorical data. Continuous variables are summarized as mean with standard deviation (SD) or median with interquartile range (IQR) depending on normality of distribution. Subgroup analyses using Fisher's exact test for categorical variables were performed to compare treatment strategies of expert pancreatologists from different specialties. *P*-values <0.05 were considered statistically significant and all tests were two-sided. Statistical analysis was conducted using R version 3.5.1.

Results

Expert profile

A total of 124 international expert pancreatologists were invited to participate in the survey (Fig. 2). Twelve experts were excluded because of incorrect contact details and 2 declined participation. A total of 56 international expert pancreatologists completed the survey. The response rate was 56/110 (51%): 27 surgeons (48%), 25 gastroenterologists (45%) and 4 radiologists (7%) participated (Table 1). Thirty-two (57%) were from Europe, 17 (30%) from North America, 3 (5%) from Asia, 3 (5%) from Oceania, and 1 (2%) from South America. The majority of experts (*n* = 49, 88%) worked in academic centers and 51 experts (91%) had over 10 years of experience in treating patients with necrotizing pancreatitis. Surgical experts had significantly longer

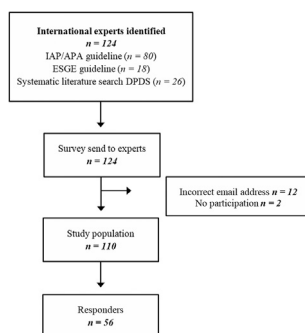


Figure 2 Identification and selection of international expert pancreatologists. ESGE European Society of Gastrointestinal Endoscopy; IAP/APA International Association of Pancreatology/American Pancreatic Association

Table 1 Details of experts

Demographics	<i>n</i> = 56 (%)
Specialty	
Surgeon	27 (48%)
Gastroenterologist	25 (45%)
Radiologist	4 (7%)
Continent	
Europe	32 (57%)
North America	17 (30%)
Asia	3 (5%)
Oceania	3 (5%)
South America	1 (2%)
Type of hospital	
Academic	49 (88%)
Non-academic	7 (12%)
Experience in treating patients with necrotizing pancreatitis	
5–10 years	5 (9%)
10–15 years	12 (21%)
15–20 years	14 (25%)
> 20 years	25 (45%)

experience treating patients with necrotizing pancreatitis (median > 20 years), as compared to the gastroenterologists (median 15–20 years) and radiologists (median 10–15 years; *p* = 0.047) (Supplementary Appendix Table 1).

Diagnosis

No consensus was reached on whether, in general, routine imaging should be performed to evaluate pancreatic duct integrity in patients with necrotizing pancreatitis. Imaging was obtained always by 20 (36%), usually by 15 (27%), sometimes by 17 (30%), and never by 4 experts (7%) (Table 2). There was also no agreement regarding the indication and best timing to assess a potential disrupted or disconnected pancreatic duct: 14 experts (25%) would evaluate pancreatic duct integrity before drainage of infected (peri)pancreatic necrosis; 36 experts (64%) in case of persistent percutaneous drain production; and 33 (59%) in case of persistent sterile (peri)pancreatic necrosis during follow-up. Once the decision was made to evaluate pancreatic duct integrity, 44 of 56 experts (79%) preferred magnetic resonance imaging (MRI) and/or magnetic resonance cholangiopancreatography (MRCP) (consensus statement 1, GRADE C; Table 4). Moreover, 26 of these 44 experts (59%) considered a secretin-enhanced MRI/MRCP (always *n* = 1, usually *n* = 9, or sometimes *n* = 16). Seventeen experts (30%) preferred to evaluate pancreatic duct integrity by contrast-enhanced CT (CECT), 11 (20%) by endoscopic retrograde cholangiopancreatography (ERCP), and 3 (5%) by endoscopic ultrasound (EUS). Differences in approach between specialties are outlined in Supplementary Appendix Table 1.

Table 2 Survey results: diagnostic approach

	Total (n = 56)
Do you evaluate pancreatic duct integrity in patients with necrotizing pancreatitis?	
Always	20 (36%)
Usually	15 (27%)
Sometimes	17 (30%)
Never	4 (7%)
Which diagnostic modality do you perform to evaluate disrupted or disconnected pancreatic duct in patients with necrotizing pancreatitis?	
CT	17 (30%)
MRI/MRCP	44 (79%)
EUS	3 (5%)
ERCP	11 (20%)
Do you perform a secretin-enhanced MRI? (n = 44)	
Always	1 (2%)
Usually	9 (21%)
Sometimes	16 (36%)
Never	18 (41%)
Do you measure amylase levels in percutaneous drain fluid in patients with necrotizing pancreatitis?	
Always	26 (46%)
Usually	12 (21%)
Sometimes	14 (25%)
Never	4 (7%)
When do you perform amylase measurements in percutaneous drain fluid? (n = 52)	
During the initial admission	15 (29%)
After the initial admission	13 (25%)
Both	24 (46%)

Fifty-two experts (93%) indicated that they measure amylase levels in percutaneous drain fluid to evaluate pancreatic duct integrity (consensus statement 2, GRADE C): 26 always (46%), 12 usually (21%), and 14 sometimes (25%). There was no consensus on the most appropriate timing of amylase measurements: 15 experts preferred measurement during admission after drainage (29%), 13 during follow-up (25%), and 24 preferred both (46%).

Treatment

Thirty experts (54%) pointed out that the presence of a (suspected) disrupted or disconnected pancreatic duct influences their preferred method of intervention for necrotizing pancreatitis, especially regarding the type of intervention, transluminal stent type and duration of stenting.

The results of the case vignettes are summarized in Table 3. For the first case vignette (patient A: infected necrosis and indication for drainage), the majority of experts preferred endoscopic transluminal drainage if duct disruption (84%, n = 47) or duct disconnection (88%, n = 49) is confirmed on imaging

(consensus statement 3, GRADE C). The minority of experts simultaneously administered somatostatin analogues (5% in case of duct disruption, and 7% in case of disconnection). Only a few experts would combine endoscopic transluminal drainage with endoscopic transpapillary drainage for duct disruption (13%, n = 7) or duct disconnection (4%, n = 2).

There was no consensus on the preferred type of transluminal stent used for endoscopic transluminal drainage among the gastroenterologists: 56% of the gastroenterologists (n = 14) favored double pigtail plastic stents and 44% (n = 11) lumen-apposing metal stents (LAMS). Most gastroenterologists (84%, n = 21) would retrieve transluminal stent(s) during follow-up, but 16 (76%) of them would first perform imaging to rule out a disrupted or disconnected pancreatic duct (consensus statement 4, GRADE D). Ten of 14 gastroenterologists (71%) that opted for double pigtail plastic stents would retrieve the stents during follow-up, in contrast to 4 gastroenterologists (29%) who would leave the stents in place. The gastroenterologists that preferred LAMS (44%, n = 11), would all remove the LAMS within 8 weeks after initial drainage.

For the second case vignette (patient B: infected necrosis with persistent drain output), 42 experts (75%) would perform an intervention if pancreatic duct disruption was located in the pancreatic head. Fourteen experts (25%) would treat such patient conservatively. There was also no consensus on the type of intervention: 20 experts (36%) preferred endoscopic transpapillary drainage, 19 experts (34%) preferred endoscopic transluminal drainage to internalize the external drain, and 3 experts (5%) surgical resection. If duct disruption was located in the pancreatic tail, 19 experts (34%) would treat the patient conservatively, and 37 experts (66%) would proceed to intervention. Nine experts (16%) favored endoscopic transpapillary drainage, 25 experts (45%) endoscopic transluminal drainage to internalize the external drain, and 3 experts (5%) distal pancreatectomy. Additionally, 5 experts (9%) would consider surgery at an earlier stage in younger and surgical fit patients, whereas 25 experts (45%) would consider surgery later in the disease course.

There was no consensus on the therapeutic approach presented in the third case vignette (patient C: asymptomatic patient with persistent sterile (peri)pancreatic necrosis during follow-up): 19 experts (34%) preferred conservative treatment whereas 37 experts (66%) would perform an intervention. Thirty-three experts (59%) preferred endoscopic transluminal drainage over other therapeutic options, for both pancreatic duct disruption and disconnection. Six of these experts (11%) would combine the procedure with endoscopic transpapillary stenting for pancreatic duct disruption and 3 experts (5%) for pancreatic duct disconnection.

Discussion

This international expert survey identifies a lack of expert consensus regarding the optimal diagnostic and treatment

Table 3 Case vignettes results: treatment approach

	Conservative treatment	Somatostatin analogue	Endoscopic transpapillary drainage	Endoscopic transluminal drainage	Percutaneous catheter drainage	Surgical cystogastro- or jejunostomy	Surgical resection
Infected (peri)pancreatic necrosis and need for drainage^a							
Disrupted pancreatic duct	–	3 (5%)	9 (16%)	47 (84%)	10 (18%)	1 (2%)	0 (0%)
Disconnected pancreatic duct	–	4 (7%)	3 (5%)	49 (88%)	9 (16%)	2 (5%)	0 (0%)
Infected (peri)pancreatic necrosis and persistent drain production							
Duct disruption in pancreatic head	14 (25%)	–	20 (36%)	19 (43%)	–	0 (0%)	3 (5%)
Duct disruption in pancreatic tail	19 (34%)	–	9 (16%)	25 (45%)	–	0 (0%)	3 (5%)
Persistent sterile (peri)pancreatic necrosis during follow-up^a							
Disrupted pancreatic duct	19 (34%)	1 (2%)	8 (14%)	33 (59%)	2 (4%)	1 (2%)	0 (0%)
Disconnected pancreatic duct	19 (34%)	1 (2%)	4 (11%)	33 (59%)	3 (5%)	2 (4%)	0 (0%)

^a Combined treatment was possible, % percentage of experts (n = 56).

approach for patients with disrupted or disconnected pancreatic duct following necrotizing pancreatitis. The experts reached agreement in two important areas: 1) MRI/MRCP as the preferred diagnostic modality to evaluate pancreatic duct integrity; and 2) endoscopic transluminal drainage as the preferred intervention for patients with infected (peri)pancreatic necrosis and pancreatic duct disruption or disconnection.

In line with the survey results, (secretin-enhanced) MRI/MRCP is advised in current guidelines (Table 4).⁸ The sensitivity of MRI/MRCP to evaluate pancreatic duct integrity is lower than the current reference standard ERCP, but with less risks of procedure-related complications.^{14–17} Secretin stimulates the secretion of pancreatic juice, which dilates the pancreatic duct, and improves the diagnostic capabilities of MRCP.^{14–16} Interestingly, in this survey, almost half of experts who preferred MRI/MRCP, never performed secretin-enhanced MRI/MRCP. Presumably, limited access to secretin and/or high(er) costs compared with ‘standard’ MRI/MRCP could have contributed to the experts’ responses.

CECT and EUS were chosen by the minority of experts. Disrupted or disconnected pancreatic duct can be suspected on CECT, but has a wide reported sensitivity range (0–80%).^{18,19} The role of EUS as diagnostic modality is unclear, and only evaluated in one prospective study in which pancreatic duct integrity was assessed during initial endoscopic transluminal drainage of walled-off necrosis.²⁰ Nevertheless, adequate visualization of the pancreatic duct by EUS depends on the endoscopists experience.

The majority of experts considered measuring amylase levels in percutaneous drain fluid for evaluation of pancreatic duct integrity. Overall, diagnostic accuracy of amylase-measurement in drain fluids is 65% (Table 4).^{18,21–25} The combination of drain output and amylase level contributes to early recognition and treatment of pancreaticocutaneous fistula. Based on the volume of amylase in percutaneous drain fluid, one cannot differentiate between partial disruption or complete disconnection of the

pancreatic duct. In this survey, the most appropriate time of measuring amylase levels remained unclear. Also, there is no clearly defined cutoff level of drain output. A recent retrospective study, however, demonstrated that patients with ‘low output’ pancreaticocutaneous fistula (<200 ml/day) were successfully treated conservatively, with spontaneous closure of the fistula within 3 months.²⁶

According to the survey, endoscopic transluminal drainage was the experts’ first preferred treatment strategy for patients with infected (peri)pancreatic necrosis and a confirmed disrupted or disconnected pancreatic duct. A consistency in preference over disease stage, as presented in the different cases in the survey, was nevertheless not found. To the extent that expert preference is aligned with treatment success, the survey results are in line with a recent systematic review, which reported that endoscopic transluminal drainage had the highest pooled success rate of 92%.^{9,20,27–29} In these studies, double plastic pigtailed were used and left in situ for a long or even indefinite period of time.^{20,28,29} Previous research demonstrated a decreased recurrence rate of pancreatic fluid collections when double plastic pigtailed are either left in situ, or exchanged in case of LAMS.³⁰ Surprisingly, the majority of experts indicated to remove transluminal stents, but only after they evaluated pancreatic duct integrity on imaging.

Based on the available literature and the survey results, several steps for patient care and topics for future research were identified (Fig. 3). Because the presence of a disrupted or disconnected pancreatic could influence the route of drainage and type of stent, evaluation of pancreatic duct integrity before drainage may be considered. MRI/MRCP, if CECT cannot provide a definite answer, seems justified as the first step. Regarding interventions, endoscopic transluminal drainage in the case of (suspected) pancreatic duct disruption or disconnection in a patient with infected (peri)pancreatic necrosis seems to be preferred. If (peri)pancreatic necrosis cannot be reached endoscopically, or already has been drained percutaneously, it is recommended to measure drain output and amylase levels to

Table 4 Consensus statements on diagnosis and treatment

STATEMENT	AGREEMENT	GRADE
<i>Diagnostics</i>		
1. MRI/MRCP for evaluation of pancreatic duct integrity in patients with necrotizing pancreatitis.	79%	C
2. Amylase measurements in percutaneous drain fluid for evaluation of pancreatic duct integrity.	93%	C
<i>Treatment</i>		
1. Endoscopic transluminal drainage for infected (peri)pancreatic necrosis and pancreatic duct disruption or disconnection.	88%	C
2. Evaluation of pancreatic duct integrity prior transluminal stent removal.	76%	D

GRADE; Grades of Recommendations, Assessment, Development, and Evaluation MRI; magnetic resonance imaging, MRCP; magnetic resonance cholangiopancreatography.

monitor the development of pancreaticocutaneous fistula. Conservative treatment of patients with low output pancreaticocutaneous fistula seems indicated. Long-term indwelling of transluminal double pigtailed stents is suggested in the case of a proven disrupted or disconnected pancreatic duct.

This study has several limitations. First, the 51% response rate is limited, compared to previous similar expert surveys.^{31,32} The topic of this survey represents a niche and limited studied aspect of acute pancreatitis, which might explain the lower response rate.

Second, while we could assert the experts' preferences over the different disease stages as presented in the case vignettes, our survey design did not allow us to evaluate the experts' preference for cases without documented pancreatic duct disruption or disconnection. The survey findings only allowed us to draw conclusions on treatment preferences for (peri)pancreatic

necrosis in the presence of documented pancreatic duct disruption or disconnection. Therefore, it is unknown whether experts would have adjusted initial treatment for (peri)pancreatic necrosis based on pancreatic duct integrity. Because endoscopic transluminal drainage has become increasingly popular in recent years as the first step for (peri)pancreatic necrosis, it may be possible that endoscopic transluminal drainage is also the preferred choice regardless of pancreatic duct integrity.^{33,34}

Additionally, it was difficult to address all clinical scenarios concerning a disrupted or disconnected pancreatic duct in a short survey and the case vignettes. It is a heterogeneous disease, clinically characterized by different manifestations (e.g. recurrent pancreatic fluid collections, pancreaticocutaneous, gastro-intestinal or pleural fistula). As a result, the clinical situations that were considered most relevant, in particular pancreatic duct

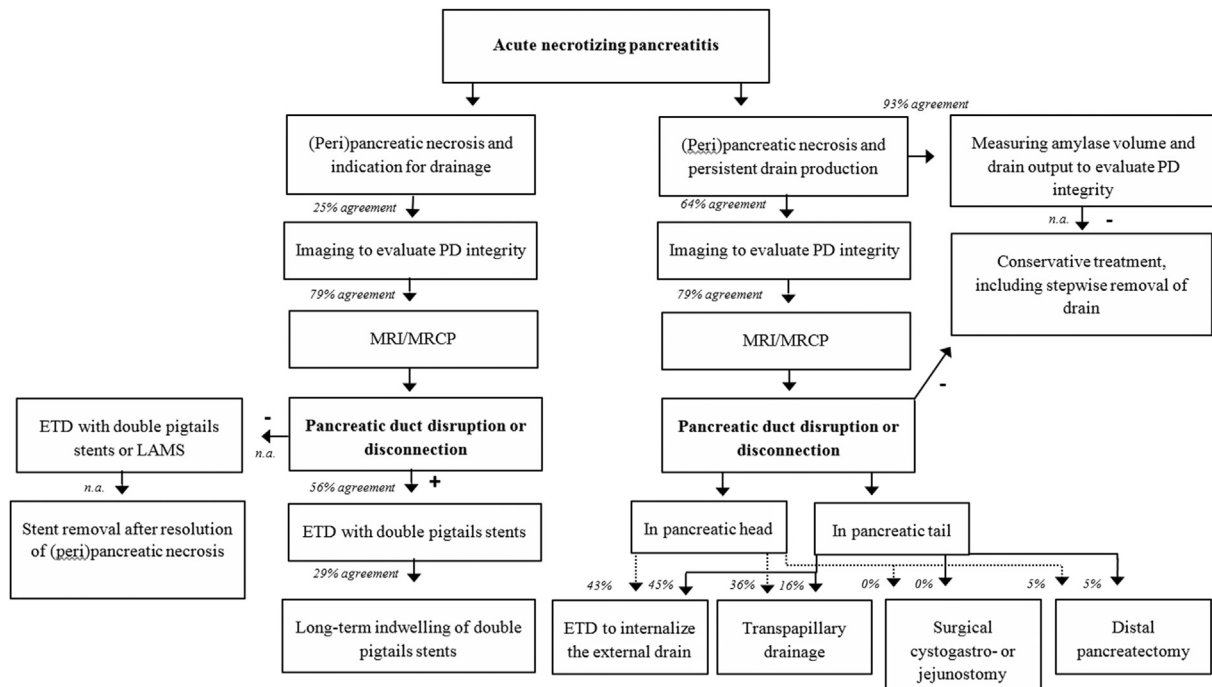


Figure 3 Summary of potential steps for patient care and topics for future research. ETD endoscopic transluminal drainage; LAMS lumen-apposing metal stents; n.a. data not analyzed in the survey; % percentage of expert agreement (n = 56)

disruption or disconnection in the presence of (peri)pancreatic necrosis, were evaluated in the survey. Also, the survey results did not indicate a clear difference in treatment approach between management for a partial disrupted and complete disconnected pancreatic duct. Moreover, the survey did not evaluate the treatment of patients with persistent, treatment refractory disrupted or disconnected pancreatic duct and the role of surgery in such cases. Last, treatment of patients with gastro-intestinal or pleural fistulas was not addressed in the survey. Consequently, expert opinion on less common, but not less important, clinical manifestations of a disrupted or disconnected pancreatic duct remained unclear. To investigate the incidence and clinical consequences of disrupted or disconnected pancreatic duct and pancreatic fistula, the POLAR study, a prospective multicenter study (Netherlands Trial Register, NL8123), was recently initiated. In the study, patients with parenchymal necrosis will undergo a standardized diagnostic work-up according to the current guidelines, including a secretin-enhanced MRCP. The aim of the POLAR study is to develop a personalized best-practice algorithm for patients with pancreatic disruption or disconnection following necrotizing pancreatitis. Other areas of future research should include the optimal management of patients with persistent drain production or with persistent sterile necrosis, the choice of transluminal stent (metal or plastic) in cases of a disrupted or disconnected pancreatic duct, and less common complications such as gastro-intestinal or pleural fistulas.

In conclusion, this international survey identified a clinically relevant lack of expert consensus on diagnosing and treating pancreatic duct disruption or disconnection in patients with necrotizing pancreatitis. Nonetheless, MRI/MRCP was the preferred diagnostic, and endoscopic transluminal drainage the preferred intervention for patients with infected necrotizing pancreatitis and pancreatic duct disruption or disconnection.

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Author contributions

LB, HT, RCV, HCvS and RPV designed the study protocol. All co-authors critically edited the survey questions and case vignettes. LB and HT collected and analyzed the data. LB and HT drafted the manuscript. All co-authors read, edited and approved the final manuscript.

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Conflicts of interest

Lotte Boxhoorn, Hester C. Timmerhuis, Robert C. Verdonk, Marc G. Besselink and Thomas L. Bollen, Karen D. Horvath, and Hjalmar C. van Santvoort do not have potential conflicts of interest or disclosures to report.

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- Appendix A. Supplementary data**
Supplementary data to this article can be found online at <https://doi.org/10.1016/j.hpb.2020.11.1148>.