

ORIGINAL ARTICLE

Diagnostic strategy and timing of intervention in infected necrotizing pancreatitis: an international expert survey and case vignette study

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Abstract

Background: The optimal diagnostic strategy and timing of intervention in infected necrotizing pancreatitis is subject to debate. We performed a survey on these topics amongst a group of international expert pancreatologists.

Methods: An online survey including case vignettes was sent to 118 international pancreatologists. We evaluated the use and timing of fine needle aspiration (FNA), antibiotics, catheter drainage and (minimally invasive) necrosectomy.

Results: The response rate was 74% (N = 87). None of the respondents use FNA routinely, 85% selectively and 15% never. Most respondents (87%) use a step-up approach in patients with infected necrosis. Walled-off necrosis (WON) is considered a prerequisite for endoscopic drainage and percutaneous drainage by 66% and 12%, respectively. After diagnosing infected necrosis, 55% routinely postpone invasive interventions, whereas 45% proceed immediately to intervention. Lack of consensus about timing of intervention was apparent on day 14 with proven infected necrosis (58% intervention vs. 42% non-invasive) as well as on day 20 with only clinically suspected infected necrosis (59% intervention vs. 41% non-invasive).

Discussion: The step-up approach is the preferred treatment strategy in infected necrotizing pancreatitis amongst expert pancreatologists. There is no uniformity regarding the use of FNA and timing of intervention in the first 2–3 weeks of infected necrotizing pancreatitis.

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Introduction

Acute pancreatitis is the most common benign gastrointestinal condition requiring acute hospital admission¹ with annual costs exceeding \$2 billion in the US.² Approximately 20% of patients develop necrotizing pancreatitis defined by necrosis of the pancreatic parenchyma or extrapancreatic fat tissue.³ Infected necrotizing pancreatitis occurs in one third of these patients and is one of the most severe complications of acute pancreatitis.³ It is associated with the need for invasive interventions in 90–95% of patients, prolonged hospital and intensive care stay, and a 15–30% mortality rate.^{4,5}

Diagnosing infected (extra)pancreatic necrosis can be challenging. Several diagnostic strategies have been reported, including the presence of gas on contrast-enhanced computed tomography (CECT), microbiological culture from fine needle aspiration (FNA), and clinical suspicion based on clinical and biochemical signs of infection. Consensus regarding the optimal diagnostic strategy in these patients seems to be lacking, especially about diagnosing infected necrosis in the absence of gas on CECT.^{6,7} In daily practice, clinical parameters such as fever and increased serum inflammatory markers are frequently used to decide on invasive intervention for suspected infected necrosis.

Current international guidelines on acute pancreatitis^{6,7} advise to postpone all forms of invasive intervention preferably until the stage of walled-off necrosis (WON) has been reached, which occurs typically about four weeks after disease onset. Antibiotics are often used at this stage and may even obviate the need for intervention in a small subset of patients with infected necrosis.⁴ The majority of patients however will undergo invasive treatment, which according to the guidelines, should entail a step-up approach.⁸ This approach consists of catheter drainage (percutaneous or endoscopic), followed, if necessary, by surgical or endoscopic necrosectomy.^{4,8,9} The rationale to postpone intervention stems mainly from the era where primary open necrosectomy was the treatment of choice. Performing necrosectomy in WON probably lowers the risk of bleeding and perforation compared with an early necrosectomy.^{4,10–13} Since the introduction of the step-up approach, timing of catheter drainage remains controversial. In daily practice and current literature, timing of the initial catheter drainage after disease onset varies greatly.^{8,14–16}

The present study was designed to explore the current opinion of international expert pancreatologists regarding management of suspected or documented infected necrotizing pancreatitis in order to help design future prospective studies.

Methods

We developed an online survey to assess the opinion of a panel of 130 international expert pancreatologists regarding diagnosis and invasive treatment of infected necrotizing pancreatitis. The selection was based on recent participation in collaborative

publications on invasive interventions in necrotizing pancreatitis cohorts,^{17,18} collaborative projects such as participation in an Individual Patient Data Meta-Analysis about necrosectomy in severe acute pancreatitis (unpublished data), the development of recent evidenced-based guidelines⁶ and the Dutch Online Pancreatitis Expert Panel¹⁹ (excluding members of the writing committee of the present study).

Of the 130 international expert pancreatologists, 118 e-mail addresses were obtained (72 surgeons, 37 gastroenterologists and 9 radiologists) from 79 different centers in 23 countries covering 6 continents. In December 2013, the participants were invited via an e-mail link to an online survey program (www.surveymonkey.com), followed by a total of four weekly reminders.

The survey consisted of 18 opinion-probing questions and 10 short clinical cases ([Appendix I and II](#)). The clinical cases (case vignettes) were all similar except for duration of disease, which varied from 7, 10, 14, 20 and 30 days after onset of acute pancreatitis symptoms, with patients having clinical signs of infection with or without gas in the necrotic collection on CECT.

Data were collected anonymously and analysed using IBM SPSS Statistics 22. Answers were described as counts and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations (SD) or interquartile ranges (IQR) depending on normality distribution. Additionally, we compared the group of respondents who preferred a surgical step-up approach with the group preferring an endoscopic step-up approach using a chi-squared test. A McNemar's test was used to compare the results of the different case vignettes reciprocally (e.g. with versus without presence of gas on imaging and disease duration 7 vs. 10 days; 10 vs. 14 days; 14 vs. 20 days and 20 vs. 30 days). A p-value below 0.05 was considered statistically significant for all statistical tests.

Results

Characteristics of respondents

The response rate was 74% (87/118); 60% (N = 52) of the respondents were surgeons, 32% (N = 28) gastroenterologists, and 8% (N = 7) radiologists ([Fig. 1](#)). Fifty-six percent (N = 49) of the respondents were from Europe, 28% (N = 24) from North-America, and 16% (N = 14) from other continents. The majority of respondents (85%, N = 74) worked in academic centers. Respondents had a median of 20 (IQR 10–26) years of experience in treating patients with necrotizing pancreatitis. Most respondents (87%, N = 76) preferred using a step-up approach, consisting of primary catheter drainage, followed, if necessary, by necrosectomy.

Diagnosing infected necrosis: use of FNA

None of the respondents routinely use FNA for diagnosing infected necrosis and 15% (N = 13) never use FNA ([Table 1a](#)). Eighty-five percent (N = 74) use FNA selectively: 18% (N = 16)

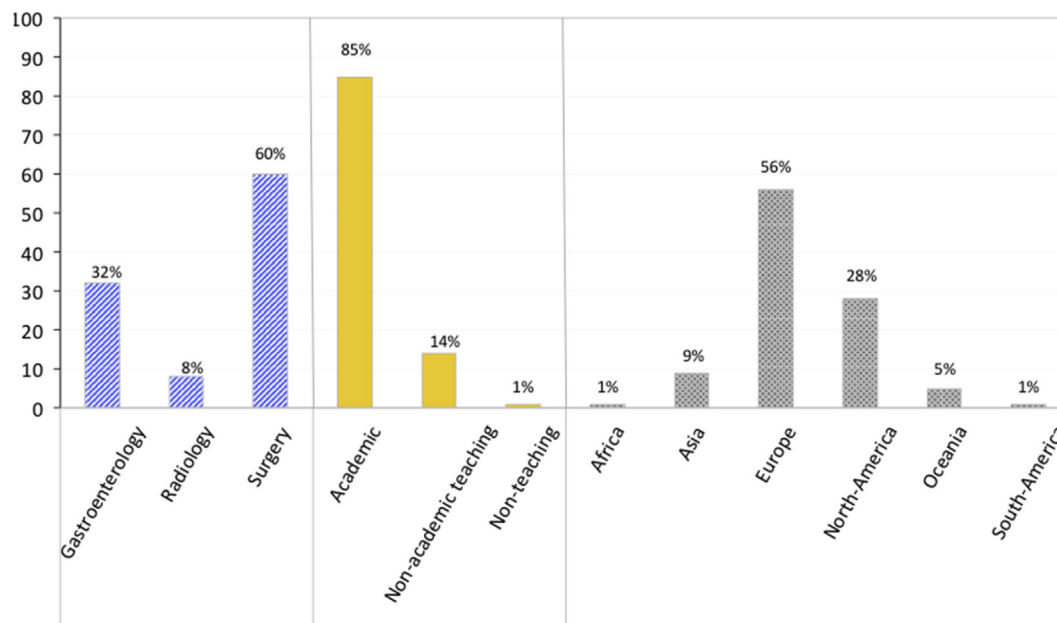


Figure 1 Baseline characteristics of respondents

use FNA in case of clinical signs of infected necrosis *without* gas on CECT, 22% (N = 19) use FNA with clinical signs *regardless* of CECT findings, and 45% (N = 39) rarely use it.

In case of a negative culture after FNA but persistent clinical suspicion of infected necrosis (i.e. other sources of infection excluded), 48% (N = 42) of respondents adopt a wait and see policy, 25% (N = 22) proceed to intervention, 8% (N = 7) repeat FNA once, and 4% (N = 3) repeat FNA as often as needed to confirm infected necrosis.

There is no difference seen in FNA strategies comparing the group of respondents who preferred a surgical step-up approach with the endoscopic step-up approach group ($p = .192$) (Table 2).

Timing of invasive interventions

Evidence for performing percutaneous catheter drainage as first intervention step is considered moderate or strong according to 40% (N = 35) and 36% (N = 31), respectively. For postponing catheter drainage until walled-off necrosis the evidence is rated moderate or strong by 34% (N = 30) and 14% (N = 12) of respondents, respectively (Table 1b). In patients with confirmed infected necrosis, 55% (N = 48) of respondents postpone an intervention and await the effect of antibiotics, whereas 45% (N = 39) immediately perform an intervention. Twelve percent (N = 11) always await the stage of WON, 44% (N = 38) sometimes perform a percutaneous catheter drainage (PCD) before WON is reached, and the remaining 44% (N = 38) perform PCD whenever there is a drainable fluid collection on imaging, thus not necessarily in WON. Furthermore, 72% (N = 63) proclaim that a PCD can be performed any time during the disease, whereas others regard a specific time period during which PCD

should not be performed with a median of 13 (IQR 7-15) days after onset of disease. Furthermore 67% (N = 58) agree that PCD upsizing (for instance from 14 to 22 Fr) is a potentially useful strategy in patients with infected necrosis who do not improve after initial PCD placement. Completely walled-off collections are a prerequisite for surgical necrosectomy, endoscopic transluminal drainage, and endoscopic transluminal necrosectomy, according to two thirds of the respondents (Table 1c).

Seventy-eight percent (N = 46) of the surgical step-up approach users and 61% (N = 17) of the endoscopic step-up approach users do not report a specific time window during which PCD should not be performed ($p = .093$) (Table 2). Some 58% (N = 34) of respondents favouring the surgical step-up approach perform a PCD before WON has developed compared with 14% (N = 4) of those favouring the endoscopic step-up approach ($p < .001$). PCD upsizing was considered potentially useful according to the surgical and endoscopic step-up users in 75% (N = 44) and 50% (N = 14), respectively ($p = .023$).

Case vignettes

At day 7 after onset of disease, 35% (N = 30) of respondents proceed to intervention when both gas in necrotic collections on CECT and clinical signs are present, versus 2% (N = 2) in case of clinical signs of infected necrosis alone. At 10, 14, 20, and 30 days after disease onset, either *with* gas on CECT versus *without* gas and clinical signs alone, 60% vs. 18% (10 days), 58% vs. 25% (14 days), 77% vs. 59% (20 days), and 89% vs. 72% (30 days) of respondents, respectively, proceed to intervention (Fig. 2).

The presence of gas in necrotic collections on CECT leads to earlier interventions for all five time periods ($p < .001$) compared

Table 1 Results survey: questions and answers of respondents

Survey questions	Survey answers	N = 87	%
1a. General management of infected necrotizing pancreatitis			
What is your routine interventional approach?	Surgical step-up	53	61
	Direct surgery	6	7
	Endoscopic step-up	23	26
	Direct endoscopy	5	6
Which techniques are available in your hospital? (More answers possible)	Image-guided percutaneous catheter drainage	86	99
	Minimally invasive percutaneous necrosectomy	70	80
	Endoscopic transluminal drainage	78	90
	Endoscopic transluminal necrosectomy	62	71
	Open surgical necrosectomy	85	98
	Diagnostic fine needle aspiration	82	94
Do you use FNA for diagnosing infected necrosis?	Routinely	0	0
	Selectively		
	Clinical signs, without gas on CT	16	18
	Clinical signs, regardless gas on CT	19	22
	Rarely	39	45
	Never	13	15
Which strategy in case of negative FNA?	Repeat FNA maximum once	7	8
	Repeat FNA as often as needed to confirm infection	3	4
	Proceed to intervention	22	25
	Carefully watch over clinical course	42	48
	Never	13	15
Await effect of antibiotics first?	No	39	45
	Yes	48	55
1b. Percutaneous catheter drainage			
How strong do you rate the evidence supporting percutaneous catheter drainage as first step?	No evidence	2	2
	Weak	19	22
	Moderate	35	40
	Strong	31	36
How strong do you rate the evidence regarding postponing percutaneous catheter drainage until walled-off necrosis?	No evidence	12	14
	Weak	33	38
	Moderate	30	34
	Strong	12	14
Is there a time window for percutaneous catheter drainage?	No	63	72
	Yes	24	28
	<days no PCD (median, IQR)	13	7–15
Do you place a percutaneous drain before walled-off necrosis?	No	11	12
	Sometimes	38	44
	Yes, if drainable fluid	38	44
Is upsizing a percutaneous catheter drain a potentially useful measure?	No	29	33
	Yes	58	67

Table 1 (continued)

Survey questions	Survey answers	N = 87	%
1c. Other interventions			
What is the ideal moment for surgical necrosectomy?	Early as possible in infected necrosis	29	33
	In case of walled-off necrosis	58	67
Is walled-off necrosis a prerequisite for endoscopic drainage?	No	19	22
	Yes	57	66
	Do not know	11	12
Is walled-off necrosis a prerequisite for endoscopic necrosectomy?	No	12	14
	Yes	61	70
	Do not know	14	16

to clinical signs of infection alone. Significantly more respondents proceed to an invasive intervention in case of clinical signs of infection at day 10 compared with day 7 ($p < .001$), day 20 with day 14 ($p < .001$), and day 30 with day 20 ($p = .002$), regardless of the presence of gas on imaging. In contrast, no difference was seen in the decision to proceed to intervention comparing the cases at day 14 compared with day 10, either with gas ($p = .180$) or without gas and clinical signs alone ($p = .774$) on CECT.

No significant differences were found comparing surgical and endoscopic approach users in proceeding to intervention for all ten case vignettes.

Discussion

This survey identified areas of (lack of) consensus amongst international expert pancreatologists regarding the optimal diagnostic strategy and timing of intervention in patients with infected necrotizing pancreatitis. Although the 'step-up approach' is now established as the routine management strategy in these patients, there is a clear lack of consensus on the use of FNA to diagnose infected necrotizing pancreatitis. Although most respondents agreed that early PCD in the first 2–3 weeks would be technically feasible, there is a clear lack of consensus on whether this would be clinically useful.

Diagnosing infected necrosis is important, since it typically requires invasive intervention. Gas in a necrotic collection demonstrated on imaging investigations is considered proof of infection and occurs in around 40% of patients with infected necrosis.²⁰ The case vignettes in this study showed that the presence of gas in necrotic collections inclined respondents to intervene earlier than when only clinical signs of infection were present. Earlier guidelines advised to use FNA in all patients with (extra)pancreatic necrosis on imaging who deteriorate after a week.³ In the current era of postponed interventions, even in case of documented infection, FNA-culture results will not lead to earlier intervention. Moreover, there is an alleged 12–25% risk of false negative FNA-culture results.^{21,22} According to more recent

guidelines,^{6,7} FNA should be used selectively, which is in line with the response of the majority of pancreatologists in this study.

Consensus regarding the timing of intervention is lacking as shown by an almost equal division between respondents awaiting the full effect of antibiotics or those immediately proceeding to intervention in infected necrosis. This discrepancy in timing of intervention was most apparent in the early case vignettes, before the stage of walled-off necrosis (day 7–20). This implies that some pancreatologists feel that a non-invasive approach with antibiotics alone is an effective treatment for infected necrosis. According to the current literature antibiotic treatment alone will only be successful in a small subset of patients with infected necrosis.^{4,23} Pancreatologists who prefer to intervene only once WON is present can have technical or safety motives and therefore postpone intervention. Other pancreatologists are inclined to intervene immediately in suspected or proven infected necrosis, either because they believe that an invasive intervention is inevitable or to prevent patients from further clinical deterioration.

Alternatively, the lack of consensus on timing of invasive intervention could be caused by interobserver differences in assessing degree of encapsulation and liquefaction in the case vignettes. Despite the well accepted revised Atlanta criteria to describe (peri)pancreatic collections, poor interobserver agreement on encapsulation of collections remains.²⁴ Therefore, validated morphologic terms should be used preferably,²⁵ but are impossible to apply in one CECT image.

With respect to the different interventional approaches, two-thirds of respondents stated that WON is a prerequisite for surgical necrosectomy, endoscopic transluminal drainage, and endoscopic transluminal necrosectomy. However, according to the majority of respondents WON is not a prerequisite for PCD. Accordingly, respondents using the surgical step-up approach tend to be less reluctant in proceeding to catheter drainage in infected necrosis than the respondents using the endoscopic step-up approach. Little evidence exists on the optimal timing of catheter drainage as the first step of the step-up approach. Additionally, the updated evidence-based guidelines^{6,7} consider

Table 2 Results subgroup analysis: survey answers based on type of step-up approach routinely used

Survey questions	Survey answers	Routinely using a surgical approach N = 59 (%)	Routinely using an endoscopic approach N = 28 (%)	p-value
Speciality	Gastroenterology	4 (7)	24 (86)	<.001*
	Surgery	48 (81)	4 (14)	
	Radiology	7 (12)	0 (0)	
Do you use FNA for diagnosing infected necrosis?	Routinely	0 (0)	0 (0)	.192
	Clinical signs no gas	13 (22)	3 (11)	
	Clinical signs regardless gas	15 (26)	4 (14)	
	Rarely	22 (37)	17 (61)	
	Never	9 (15)	4 (14)	
Await effect of antibiotics first?	No	28 (47)	11 (39)	.474
	Yes	31 (53)	17 (61)	
Is there a time window for percutaneous catheter drainage?	No	46 (78)	17 (61)	.093
	Yes	13 (22)	11 (39)	
Do you place a percutaneous drain before walled-off necrosis?	No	6 (10)	5 (18)	<.001*
	Sometimes	19 (32)	19 (68)	
	Yes, if drainable fluid	34 (58)	4 (14)	
Is upsizing a percutaneous catheter drain a potentially useful measure?	No	15 (25)	14 (50)	.023*
	Yes	44 (75)	14 (50)	
What is the ideal moment for surgical necrosectomy?	Early as possible	22 (37)	7 (25)	.256
	In walled-off necrosis	37 (63)	21 (75)	
Is walled-off necrosis a prerequisite for endoscopic drainage?	No	12 (20)	7 (25)	.213
	Yes	37 (63)	20 (71)	
	Do not know	10 (17)	1 (4)	
Is walled-off necrosis a prerequisite for endoscopic necrosectomy?	No	7 (12)	5 (18)	.261
	Yes	40 (68)	21 (75)	
	Do not know	12 (20)	2 (7)	

this scant evidence to be of low quality (grade 1C). The recommendation to postpone intervention until WON has occurred is based on studies pertaining to the timing of necrosectomy (second step of the step-up approach), showing lower mortality and complication rates for postponed necrosectomy.^{4,10–13}

With a high response rate of 74% of pancreatologists experienced in treating and researching this relatively rare group of patients, we believe our results reliably reflect current clinical practice amongst expert pancreatologists. The majority of respondents were from Europe and North-America, mostly

affiliated to academic or tertiary referral centers. Consensus on the topics under study in other continents and non-expert centers remains unclear. However, this is not necessarily a limitation since this is an expert opinion study on a complex problem likely best cared for in such centers. The study would be strengthened by greater variety of location which might capture more variation in approach that would help understand true expert opinion. Second, although infected necrotizing pancreatitis is a heterogeneous disease, for study purposes case descriptions needed to be concise and highlight those clinical items that are currently considered most relevant to the

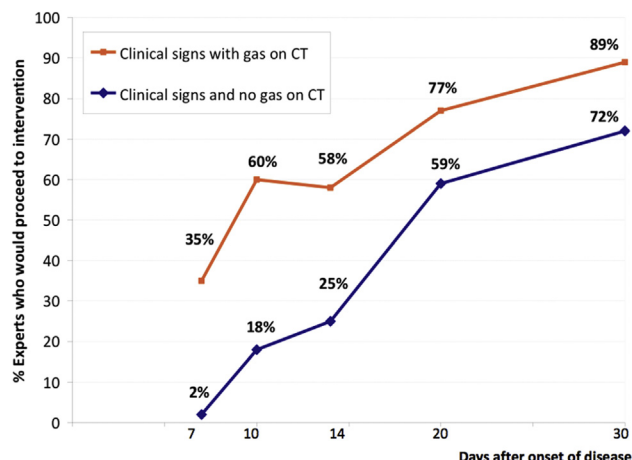


Figure 2 Results case vignettes: percentage of respondents answered to proceed to invasive intervention of the (peri)pancreatic necrotic collections at day 7, 10, 14, 20 and 30 days after onset of disease

question at hand. For the same reasons, imaging illustration was limited to one CECT image per case. How this limitation affected our results is speculative.

In conclusion, this study showed that the step-up approach is now the preferred treatment strategy in patients with infected necrotizing pancreatitis. Consensus is lacking regarding the use of FNA and the timing of catheter drainage in patients with (suspected) infected necrotizing pancreatitis. Future (preferably randomized) studies should address these issues and especially determine whether routine use of early FNA and early catheter drainage compared to postponed catheter drainage could improve outcomes in patients with infected necrotizing pancreatitis.

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JvG, SvB, TLB, HvS and MGB designed the study protocol and questionnaire. All co-authors critically edited the survey questions and case vignettes. JvG collected and analyzed the data and drafted the manuscript under supervision of MGB, where after the complete writing committee co-authored, read, and approved the final version.

Conflict of interest

None to declare.

Collaborators

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Löhr, J Mayerle, T Mayumi, A Mittal, J Moessner, D Morgan, K Mortele, W Nealon, J Neoptolemos, V Nieuwenhuijs, I Nordback, A Olah, K Oppong, R Padbury, G Papachristou, R Parks, J Poley, D Radenkovic, M Raraty, B Rau, V Rebours, S Rische, M Runzi, N Sainani, M Sarr, S Schaapherder, S Seewald, H Seifert, T Shimosegawa, S Silverman, V Singh, A Siriwardena, W Steinberg, R Sutton, K Takeda, R Timmer, S Vege, R Voermans, J de Waele, Ch Wang, A Warsaw, J Werner, B Weusten, D Whitcomb, J Wig, J Windsor, N Zyromski.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.hpb.2015.07.003>.