Optimizing the step-up approach for infected necrotizing pancreatitis

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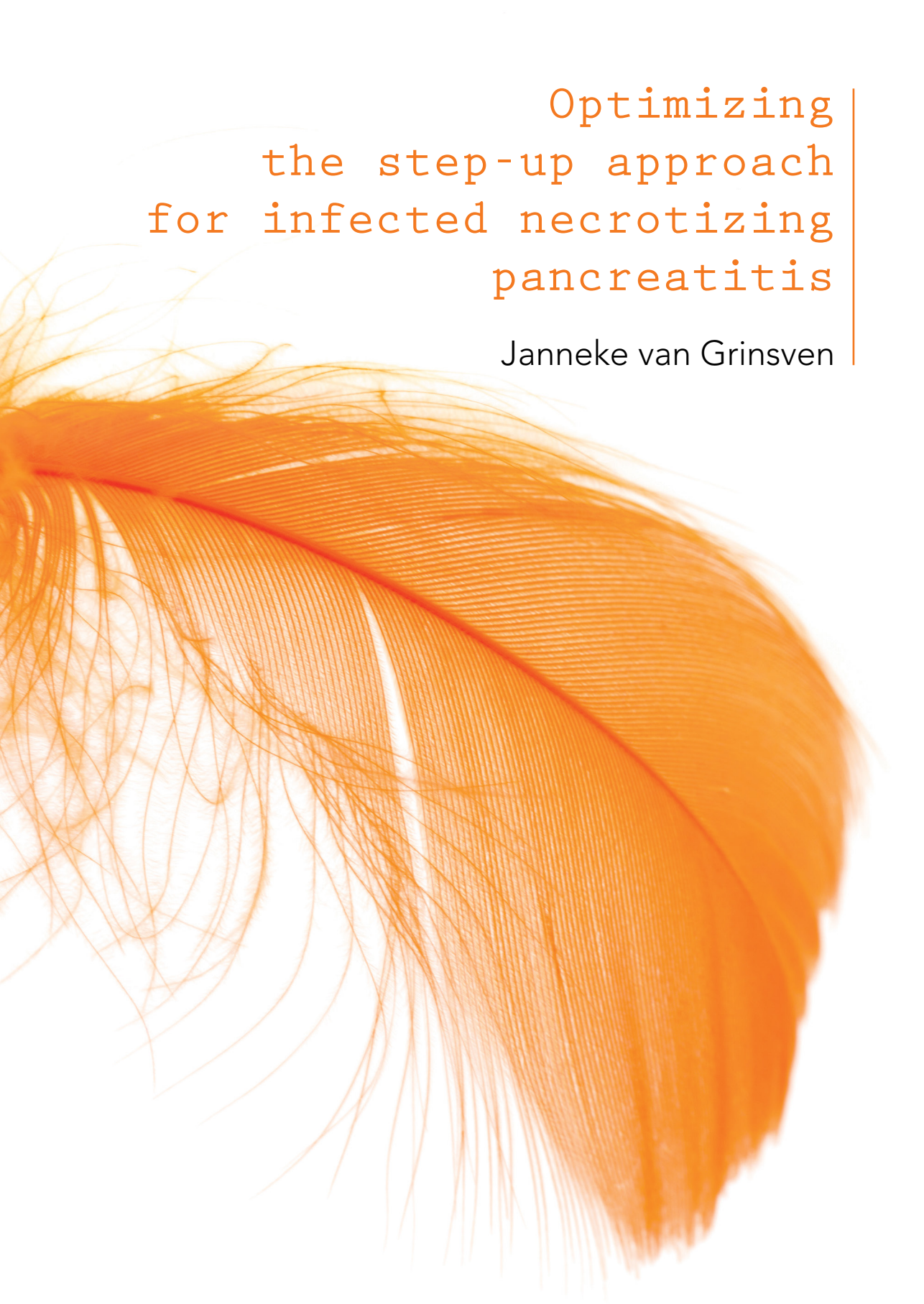

Optimizing the step-up approach for infected necrotizing pancreatitis

Janneke van Grinsven

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Optimizing the step-up approach for infected necrotizing pancreatitis

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CHAPTER 1

General introduction and thesis outline

This chapter is partly based on Chapter 15 of the textbook 'Prediction and management of severe acute pancreatitis', editors C.E. Forsmark and T.B. Gardner, written by Janneke van Grinsven, Marc G. Besselink, Olaf J. Bakker, Sandra van Brunschot, Marja A. Boermeester, Hjalmar C. van Santvoort

Background

Acute pancreatitis is usually a self-limiting disease of which most patients recover without serious complications. About 20% of patients, however, develop severe acute pancreatitis with (extra) pancreatic necrosis or collections [1]. When these collections become organized, usually around 3-4 weeks after onset of disease, they are called 'walled-off necrosis' (WON). Necrotizing pancreatitis is associated with a mortality of 15% [2]. In two-thirds of patients the disease can be treated conservatively, when necrosis remains sterile [3, 4]. Invasive intervention for sterile necrosis carries a serious risk of introducing infection, which necessitates additional interventions and increases mortality [5, 6]. In about one-third of patients with necrotizing pancreatitis, secondary infection of necrosis occurs [7]. Infected necrosis is one of the most severe complications of acute pancreatitis. It drives clinical deterioration and organ failure in the second phase of the disease, as it usually occurs in the second to the third week after disease onset [7]. It is generally accepted that infected necrosis is an indication for invasive intervention.

Management strategies for invasive intervention in infected necrotizing pancreatitis have evolved over the last decade. The preferred treatment used to be primary open necrosectomy with early and complete debridement of infected necrosis. The current standard is a minimally invasive step-up approach involving percutaneous or endoscopic catheter drainage as the first step [8, 9]. When catheter drainage does not lead to clinical improvement, necrosectomy should follow. In the Dutch randomized controlled PANTER trial, a step-up approach starting with catheter drainage, followed when needed by retroperitoneoscopic debridement, was superior to open necrosectomy in terms of major early and late complications [8]. This step-up approach is gaining widespread popularity. There are several forms of minimally invasive necrosectomy, e.g., laparoscopic transperitoneal necrosectomy, sinus tract endoscopy (STE), and video-assisted retroperitoneal debridement (VARD). Endoscopic transluminal treatment through the stomach or duodenum is an elegant alternative to surgery. It can also be performed according as a step-up approach, starting with endoscopic transluminal drainage and, if needed, proceeding tot endoscopic transluminal necrosectomy. This chapter provides an overview of techniques and outcomes of these different minimally invasive approaches in patients with necrotizing pancreatitis.

Transition to minimally invasive techniques

In recent years, there has been an increased interest in the development of minimally invasive techniques to treat gastrointestinal disorders. The treatment of infected necrotizing pancreatitis is also shifting toward minimally invasive laparoscopic (transperitoneal), radiological (retro- and transperitoneal), endoscopic (transgastric), and retroperitoneoscopic techniques [10]. Traditionally, open necrosectomy was the procedure of choice. Published mortality rates for open necrosectomy range from 6 [11] to 50% [12]. Minimally invasive techniques have several potential advantages in comparison with open necrosectomy. These include a reduced inflammatory response to intervention with a lower risk of inducing organ failure in these already critically ill patients, reduced extent of bacteremia, reduced rate of wound complications, shorter hospital and intensive care unit (ICU) stay, and faster convalescence [2]. Several minimally invasive necrosectomy techniques have been developed, all to facilitate the removal of solid debris. In 1996, Gagner et al. [13] described a laparoscopic debridement, which theoretically holds the risk of spreading the infection into the abdominal cavity and an enhanced risk of intestinal tract erosions. This is why a retroperitoneal approach appears to be a better alternative for open necrosectomy. The peritoneum is left intact and contamination of the peritoneal cavity is prevented.

Retroperitoneoscopic techniques

Historically, an open retroperitoneal approach via lumbotomy was performed. Three observational cohort studies have reported mortality rates of 20-33% with a complication rate of 20-50% [14-16]. Enteric fistulas were noted in 40% of cases, hemorrhage in 45%, and colonic necrosis in 15%. These complications of the open retroperitoneal approach could be the result of the narrow surgical entrance with a largely blind necrosectomy. To overcome these disadvantages different groups have developed alternative retroperitoneal interventions under direct endoscopic vision or video-assisted. In 1998, Gambiez et al. [17] were first to describe this retroperitoneoscopic approach in the management of infected necrotizing pancreatitis. They treated 20 patients with a short left or right lumbotomy (6 cm in length) centered on the 12th rib. Under direct vision of an endoscope (23-cm mediastinoscope) the peripancreatic necrosis was removed by blunt dissection with a suction metal tube. Afterwards a continuous irrigation tube drain was left in the retroperitoneal space. Later Castellanos et al. [18] used a flexible endoscope for visualization and manual necrosectomy of the necrotic cavity, with a left or right translumbar incision of approximately 15 cm in length. In these two studies, success

rate was respectively 75% and 73% and mortality 10% and 27%. Hereafter, several derivative retroperitoneoscopic techniques have been described in larger cohorts. Two of these techniques have gained widespread acceptance: STE and VARD. These techniques and their reported results are described in more detail below.

Sinus tract endoscopy

In 2000, Carter et al. [19] first described 4 patients undergoing STE after placement of a percutaneous drain. Under CT guidance an 8F pigtail nephrostomy catheter is placed in the infected cavity. The selected route on the left side, that will allow subsequent dilatation, is between the lower pole of the spleen and the splenic flexure. For right- sided necrosis, the route through the gastrocolic omentum anterior to the duodenum, is taken. Under general anesthesia on the operating room, this catheter tract is dilated up to 30F with graduated dilatators under radiologic guidance. A nephroscope is inserted through this dilated drain path under intermittent irrigation and suction and the solid debris is removed using grasping forceps. A continuous postoperative lavage system is placed, and continued until lavage fluid clears or until the next procedure. If an ongoing sepsis is suspected a second procedure may be performed, after additional CT-imaging. Both a flexible or rigid endoscopic system can be used for STE. Since only small fragments of necrosis can be removed piecemeal with a flexible endoscope, an operating nephroscope may be preferred for primary explorations. Others have reported STE results using different terminology. Conner et al. [20] described their experience with "minimally invasive retroperitoneal pancreatic necrosectomy" (or MIRPN). They reported the results of 88 procedures in 24 patients; in 21 patients 36 complications occurred (88%), 6 patients died (25%), and 5 patients (21%) required open surgery for or subsequent distant collections or bleeding. The same group later described an updated cohort of patients undergoing "minimal access retroperitoneal pancreatic necrosectomy" (or MARPN) [11]. They compared MARPN with open necrosectomy in a retrospective analysis of prospective data in 189 patients. Mortality was 19% compared to 38% in the open group; 31% and 56% of patients, respectively, had postoperative organ failure, 43% versus 77% required postoperative ICU support and 55% versus 81% had complications. Thus, this study showed significant benefits for this retroperitoneoscopic approach compared to open necrosectomy.

Percutaneous catheter drainage and video-assisted retroperitoneal debridement (surgical step-up approach)

VARD is another retroperitoneoscopic technique, and has proven to be safe and efficient [8, 21-23]. VARD is, in essence, a minimally invasive hybrid between the classic lumbotomy and STE, both mentioned above. STE obviates the need for an incision. VARD includes an incision of 5 cm in length, but can also be considered as minimally invasive, opposed to the 15 cm incision in an open translumbar approach. Therefore, larger pieces of necrosis can be removed and VARD seems to be easier to perform than STE, particularly in centers where interventions in this relatively rare condition are not performed routinely [23]. In 2001 Horvath et al. [21] first described the VARD procedure. In the Dutch PANTER trial [8] VARD was part of a minimally invasive step-up approach which was compared to primary open necrosectomy. In the surgical step-up group, first, a percutaneous catheter drainage (PCD) was placed by the radiologist under CT or ultrasound guidance. Preferable a large size drain (14 French or more) was placed through the left retroperitoneum, facilitating VARD at a later stage if needed. VARD was only performed in the case of no clinical improvement, and no possibilities for additional drainage on contrast-enhanced computed tomography (CECT). In more than 65% of patients with infected necrosis PCD through the left retroperitoneum was feasible [24]. The VARD procedure [25] is performed under general anesthesia and the patient is in supine position and 30° tilted towards the contralateral side. A VARD can be performed via a left-sided or right-sided approach, the latter being more challenging. The ipsilateral arm is positioned over the patient's head and the following landmarks can be marked; xiphoid, costal margin, anterior superior iliac spine, and mid-axillary line. A preoperatively placed retroperitoneal percutaneous drain is needed as a guideline for safe entry into the left-sided window between spleen, kidney, and colon. From the right side, a safe entry ventral to the inferior caval vein and dorsal to the colon is needed. Near the percutaneous drain, about two fingers below the left costal margin over the mid-axillary line, the planned incision site is also marked. Now the entire abdomen and flank are prepared and draped, to enable conversion to laparotomy. A subcostal 4-5 cm incision is performed over the previously marked site and the muscles are divided sequentially. With the palpating finger the drain is located and followed into the infected collection. The collection wall can be fibrotic. A clamp over the drain may facilitate opening the collection. Care has to be taken to stay close on the drain as from the left side the colon and spleen are nearby. Once the collection is opened, pus will drain spontaneously. The first necrosis can be removed blindly using finger fracture, suction, and a grasping forceps. Subsequently, a 0° laparoscope is introduced and a long gallbladder forceps is used

parallel to the video scope in order to remove the necrosis under direct vision. Extended collections, not approachable through one incision, are quite rare but sometimes require another incision in the left or right flank. Only pieces of loose necrosis should be removed to minimize the risk of bleeding. If there is an arterial bleeding that cannot be easily controlled surgically, the cavity should be packed with gauzes and the intervention radiologist is asked to perform an embolization. In case of venous bleeding, packing should suffice to stop the bleeding, followed by repeat necrosectomy after 24-48 h. In case of severe hemodynamic instability, not improving by packing, the procedure should be converted to laparotomy with opening of the omental sac. In general, the more complete the collection's encapsulation, the easier the necrosectomy can be performed. After completion of the procedure, two large bore surgical drains are placed, one deep in the collection and one more superficial. The fascia is closed over the drains and the skin can be closed or left open for healing by secondary intention. Postoperatively, the drains are continuously flushed with increasing amounts of saline or peritoneal dialysis fluid, building up from 100 mL per hour to 3-5 L per 24 h in the first 3 days. In 2010, a prospective multicenter study [26] reported outcomes on 40 patients with infected necrosis treated in six university medical centers in the USA and Canada. Percutaneous drain placement was the first intervention in all patients. Nine patients (23%) were treated with drains only. In 60% of the other 31 patients a successful VARD was performed. The most common reason for crossover from VARD to open surgery was a central collection extending into the mesenteric root and could not be accessed via the flank. Mortality was 5% and most common complications were pancreatic fistulae and bleeding requiring intervention in respectively 18% and 8% of patients. In most patients (81%) one VARD procedure was sufficient, and no patient required more than two VARD procedures. The overall mortality of VARD reported in literature is 13%, with a range of 0-33% [25].

Endoscopic transluminal drainage and endoscopic transluminal necrosectomy (endoscopic step-up approach)

If a necrotic collection is located close to stomach or duodenum, it can be treated endoscopically according the NOTES principle (natural orifice transluminal endoscopic surgery) [27]. Endoscopic treatment can be performed under conscious sedation, thus without the need for general anesthesia and therefore potentially reduces the proinflammatory response and risk of procedure-related complications (e.g. multiple organ failure) in these already ill patients [28-30]. Also, for endoscopic treatment no laparotomy or lumbotomy is needed, avoiding complications such as wound infection, pancreatic or intestinal fistula and incisional hernia. In 2000 the first cohort of necrotizing pancreatitis patients treated by endoscopic transluminal necrosectomy was published [31]. A systematic review in 2013 included a total of 14 similar studies, mostly retrospective observational cohorts [32]. In this systematic review endoscopic necrosectomy seemed a safe and effective minimally invasive treatment for necrotizing pancreatitis patients. In total 81% of patients were treated successfully with endoscopic necrosectomy alone. Endoscopic necrosectomy was associated with a mortality rate of 6% (28/460 patients) and complication rate of 36%, most often bleeding [32]. Only one small randomized controlled trial compared endoscopic necrosectomy to primary open surgical necrosectomy in patients with necrotizing pancreatitis [33]. In this study the endoscopic approach reduced major complications from 69% to 40% compared the surgery group. Similar to the percutaneous-surgical approach, the endoscopic approach can be performed step-up wise. Endoscopic ultrasound guided transluminal drainage of the necrotic collection is performed as the first step of treatment. Two 7 Fr double pigtail stents are inserted into the collection. Recently also fully-covered metal stents were introduced for this purpose, with which a larger diameter can be achieved [34, 35]. A nasocystic catheter is positioned in the fluid collection alongside the inserted stents which will be continuously flushed with 1 litre saline per 24 hours, with the intent to keep the drains open. In case of no clinical improvement, additional drainage can be considered. If re-drainage is clinically unsuccessful or impossible, endoscopic transluminal necrosectomy is needed. For the endoscopic necrosectomy, the cystogastrotomy is dilated up to 18 mm and the cavity is entered with a therapeutic gastroscope to perform necrosectomy under direct endoscopic vision. Multiple instruments can be used for the necrosectomy (e.g. a basket or snare). The procedure is completed when most necrotic tissue is removed. The procedure sometimes needs to be repeated several times until most necrotic tissue has been removed [36].

Thesis outline

The aim of the studies described in this thesis is to optimize the step-up approach in patients with infected necrotizing pancreatitis. To that end, studies focused on (I) decision-making on invasive interventions, (II) advancing strategies and techniques of catheter drainage and necrosectomy, and (III) assessing the optimal timing of primary catheter drainage in patients with infected necrotizing pancreatitis.

PART I Decision-making on invasive interventions - addresses the following questions:

- What is the value of a 24/7 online nationwide multidisciplinary expert panel for decision-making in necrotizing pancreatitis patients, both from clinicians' and experts' point of view? (Chapter 2)
- What is the natural history of gas configurations and encapsulation on computed tomography (CT) during the disease course of patients with necrotizing pancreatitis? (Chapter 3)
- What is the association between early CT-assessed body composition parameters and mortality in patients with necrotizing pancreatitis? (Chapter 4)

PART II Drainage and debridement techniques - addresses the following questions:

- What are the clinical outcomes of a proactive percutaneous catheter drainage strategy, including frequent and early drain revising and upsizing, compared to a standard percutaneous catheter drainage strategy in patients with infected necrotizing pancreatitis? (Chapter 5)
- Is the endoscopic step-up approach superior to a surgical step-up approach in patients with infected necrotizing pancreatitis? (Chapter 6)

PART III Timing of primary catheter drainage - addresses the following questions:

- What is the current evidence on timing of primary catheter drainage in patients with infected necrotizing pancreatitis? (Chapter 7)
- What is the current international expert opinion on (A) diagnosing infected necrosis in patients with necrotizing pancreatitis and (B) the ideal timing of invasive interventions in these patients? (Chapter 8)
- What is the study design of the randomized controlled multicenter POINTER trial; comparing immediate catheter drainage to postponed catheter drainage in patients with infected necrotizing pancreatitis? (Chapter 9)

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PART I

DECISION-MAKING ON INVASIVE INTERVENTIONS

2

CHAPTER 2

The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis

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Gastroenterology 2017 Mar;152(4):685-688.e6

The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis

Acute pancreatitis is the most common gastrointestinal reason for acute hospitalization [1]. Approximately 20% of patients with acute pancreatitis develop necrotizing pancreatitis [2,3]. In approximately 30% of these patients, secondary infection of the necrosis occurs, which almost always requires an invasive intervention [4,5]. Diagnosing infected necrosis on clinical grounds can be difficult. Furthermore, even if infected necrosis is proven, international guidelines advise to postpone invasive intervention to around 4 weeks after disease onset [6,7]. This allows for necrotic collections to encapsulate (i.e., walled-off necrosis), thereby technically facilitating intervention and reducing the risk of complications such as perforation and bleeding [6,7]. However, the clinical condition of some patients does not permit a delay in intervention. Clinical decision making regarding the indications or and timing of invasive intervention and preferred approach (percutaneous, surgical, or endoscopic) can, therefore, be challenging [8]. Moreover, the incidence of infected necrotizing pancreatitis is low and even tertiary referral centers may only treat 10-15 patients per year [9].

Several international, multidisciplinary, and multicenter approaches have been initiated to improve the care for patients with pancreatitis and facilitate clinical research. In recent years, multiple national study groups have been formed worldwide, for example, in the Netherlands, the United States, Germany, Switzerland, and Hungary [10-14]. Also evidence- and consensus-based guidelines were composed by international experts in the field [6, 7, 15, 16]. International scientific collaborations were initiated, for example, Pancreas2000 (www.pancreas2000.org) and PANCREA (Pancreatitis Across Nations Clinical Research and Education Alliance) [17, 18]. National and international multidisciplinary surveys were published in an attempt to identify differences and similarities in pancreatitis management strategies [8, 19-21]. Finally, several studies have been published that suggested clinical benefit of centralization of pancreatitis care in high-volume centers [22-26].

In 2006, the Dutch Pancreatitis Study Group (DPSG) introduced another approach to improve the outcome of patients with pancreatitis: We launched a 24/7, online, nationwide, multidisciplinary expert panel for clinicians treating patients with acute necrotizing pancreatitis [27].

This panel aimed to aid all Dutch clinicians in difficult clinical decisions concerning these patients, with treatment advice and assessment of eligibility for ongoing nationwide randomized trials. This report describes the rationale and design of this expert panel and the results of a prospective evaluation among the consulting clinicians and consulted experts.

The expert panel currently consists of 7 surgeons, 4 gastroenterologists, and 4 radiologists with vast experience in treating patients with necrotizing pancreatitis. Initially, the expert panel was instituted to assess eligibility for enrollment in the randomized PANTER trial [10]. During the subsequent PENGUIN trial, TENSION trial [ISRCTN09186711], and the ongoing POINTER trial [ISRCTN33682933], the expert panel proved to be of great value for assessing patient eligibility [28, 29]. Soon after implementation, the expert panel became a well-known and widely used consultation board for physicians in all Dutch hospitals regarding the management of necrotizing pancreatitis patients regardless of whether they participated in a trial. In 2009, the expert panel was runner-up for the Health-Safety-Prize of the Dutch Health Care Inspectorate.

The expert panel is consulted by filling out a form available on the DPSG website www.pancreatitis.nl (Supplementary Figure 1). The consulting clinician provides anonymous patient information, including medical history, clinical course, vital and inflammatory parameters, results from microbiologic cultures, previous interventions, and selected images from the most recent computed tomography (CT) scan. The expert form is e-mailed to the coordinating research fellow at the DPSG datacenter and then forwarded to the members of the expert panel who are alerted by a text message via mobile phone. The experts independently return their advice to the coordinating research fellow as soon as possible. Within 24 hours, the bundled expert advices are forwarded to the consulting clinician (Figure 1).

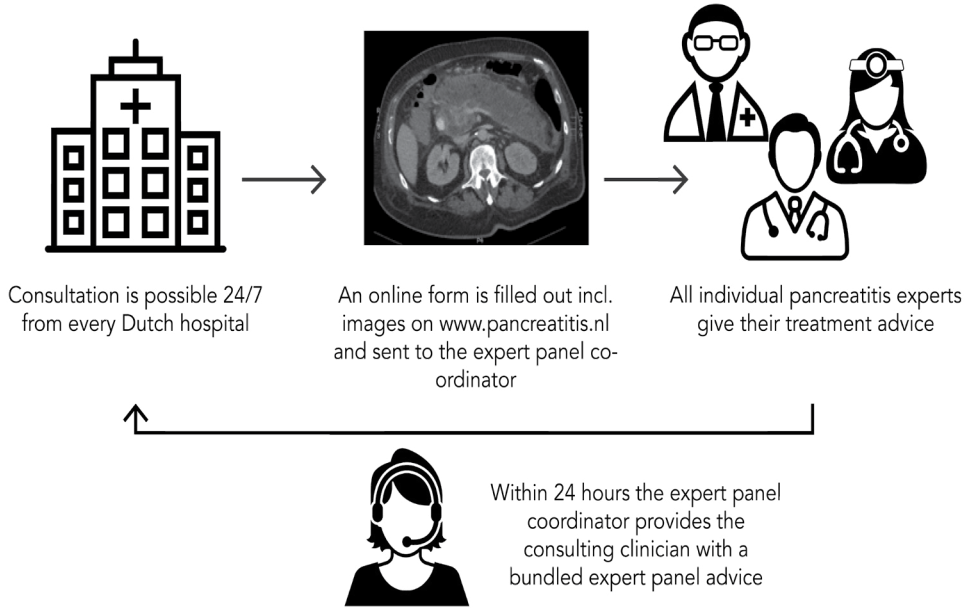
Between 2010 and 2014, a total of 397 patients with acute necrotizing pancreatitis were assessed by the expert panel (see Supplementary Materials and Methods). The number of consultations increased annually, from 30 consultations in 2010 to 111 consultations in 2014 (Supplementary Figure 2). The majority of requests were received from clinicians in nonacademic centers (327/397, 82%) and gastroenterology departments (217/397 [55%]; Table 1). Consultations were requested outside office hours in 191 cases (48%). In 299 cases (75%), the expert panel's advice was returned to the clinician within 24 hours. A median response rate of 7 of the 15 experts (47%) was seen. In most cases, the majority of experts agreed (i.e., 75% consensus) on the indication for invasive intervention and approach feasibility. Differing (50/50)

advice concerning the indication for invasive intervention was given in 42 cases (11%). Differing advice concerning the technical feasibility of a surgical, endoscopic, and percutaneous approach was given in 16 (4%), 26 (7%), and 10 (3%) cases, respectively.Clinicians completed a survey in 157 of the 397 consultations (40%; Supplementary Table 1). The expert panel was easily accessible according to 148 of 157 clinicians (94%) and 138 clinicians (88%) considered it a valuable tool. In total, 132 of 157 clinicians (84%) reported to have followed the expert advice. Among clinicians who answered the question, the expert advice was similar to their own opinion in 132 (84%) cases. In total, 132 clinicians (84%) valued the advice as support for their medical decision.

All 15 experts completed a survey, with a mean experience of 17 years (SD 8) of treating necrotizing pancreatitis patients (Supplementary Table 2). They reported a mean workload of 9 minutes (SD 3) per expert advice. According to 14 of the 15 experts (93%), the provided clinical information was usually sufficient to give a treatment advice. Moreover, 12 of the 15 experts (80%) suggested that the availability of a full CT study would be of additional value compared with receiving selected CT images.

To our knowledge, this is the first description of a 24/7, online, nationwide, multidisciplinary expert panel for any disease and undoubtedly for patients with necrotizing pancreatitis. The evaluation shows that our expert panel is feasible within the Dutch health care setting, and considered to be an accessible and valuable tool for treating clinicians. Despite the clinical heterogeneity of necrotizing pancreatitis and the inability of experts to evaluate these patients in person, there was an indifferent expert advice in only 3%-11% of cases. For most consultations, a clear expert advice was provided. Our evaluation has some limitations. First, no routine reminders were sent to experts asked for an opinion. This may explain the relatively low response rate of 40% (157 of 397 cases). Second, no clinical outcome data were available for patients evaluated by the expert panel. Therefore, no assessment of the additional clinical value of this expert panel on patients' outcome was performed. An important point of improvement that emerged from our evaluation was to increase the extent and quality of the imaging data (i.e., full CT study rather than selected images). Currently, we are piloting software to exchange complete CTs between participating hospitals.

Figure 1 Work flow expert panel consultation



In conclusion, the described expert panel is a successful example of an approach to coordinate care and research in the field of acute necrotizing pancreatitis. Based on our experience, the DPSG has also started an expert panel for chronic pancreatitis patients. Our example has also been followed by other nationwide study groups having set up similar expert panels, for example, the Dutch Pancreatic Cancer Group and the Dutch Initiative on Crohn's and Colitis diseases. A comparable system of an expert panel can be easily and inexpensively implemented in other national and international health care settings and for other diseases. In particular, a multidisciplinary and multicenter approach may lead to improved clinical outcomes and better quality control in clinical studies.

Table 1 Characteristics of expert panel consultations for necrotizing pancreatitis (2010-2014, n=397cases)

	n (%)
REQUESTS	
Non-academic centers	327 (82)
Request from Gastroenterologist Surgeon Intensive Care physician Other Unknown	 217 (54) 56 (14) 56 (14) 2 (1) 66 (17)
Request during office hours a	206 (52)
Initial admission to expert panel consultation, days (IQR)	26 (16-46)
PATIENTS	
Male patients	280 (71)
Age patient (SD)	57 (±14)
Disease etiology Biliary Alcoholic Unknown Other	 160 (40) 80 (20) 104 (26) 53 (14)
Patient admitted to ICU/MC Ward Pediatrics Outpatient clinic Unknown	 133 (33) 249 (62) 2 (1) 7 (2) 6 (2)
Organ failure Single organ Multiple organs	 51 (13) 55 (14)
Temperature ≥ 38.5	115 (29)
C-reactive protein (IQR)	200 (123-286)
Leucocytes (IQR)	15 (10-21)
Positive cultures None Blood Sputum Ascites Pancreatic drain Fine needle aspiration Urine Faeces Perineum Wound	 218 (55) 107 (27) 39 (10) 27 (7) 27 (7) 23 (6) 15 (4) 12 (3) 3 (1) 2 (1)
Antibiotics started	285 (72)

Diet	
Oral	109 (27)
Enteral tube	205 (52)
Trans parental	27 (7)
Nil per mouth	17 (4)
Combination	36 (9)
Unknown	3 (1)
Disease severity score b (IQR)	7 (5-8)
Number of imaging slices (IQR)	9 (5-11)
Imaging to expert panel consultation, days (IQR)	1 (0-3)
EXPERT PANEL ADVICE	
Expert advice returned within 24h	299 (75)
Number of expert responses within 24h c (SD)	6 (±2)
Number of expert responses total c (SD)	7 (±2)
Advice: indication for invasive intervention	
75-100% no	208 (52)
50-50%	42 (11)
75-100% yes	147 (37)
Advice: surgical step-up possible	
75-100% no	36 (9)
50-50%	16 (4)
75-100% yes	278 (70)
Not reported	67 (17)
Advice: endoscopic step-up possible	
75-100% no	51 (13)
50-50%	26 (7)
75-100% yes	252 (63)
Not reported	68 (17)
Advice: percutaneous catheter drainage possible	
75-100% no	11 (3)
50-50%	10 (3)
75-100% yes	347 (87)
Not reported	29 (7)

IQR, interquartile range; SD, standard deviation
a Office hours defined as Monday-Friday, 8am-5pm
b Score 0-10 reported by physician, 10=severe illness
c Total of 15 experts

2

Chapter 2

Supplementary

Supplementary Figure 1 Expert panel consultation form

PATIENT DESCRIPTION
Male / Female
Etiology:
ICU / Ward:
Age:
Total days of admission:
Start pancreatitis (date):
Previous interventions:
Medical history:

SUMMARY OF THE CLINICAL COURSE
Example:

Day 1 / 11 May 2016	*Admission with acute pancreatitis*
Day 3 / 13 May 2016	*ICU admission*
Day 5 / 15 May 2016	*CT: necrotizing pancreatitis*
Day .. / etc.	

CURRENT CONDITION

Cardiovascular
- Blood pressure:
- Hart rate:
- Inotropes:

Respiratory
- Need for oxygen:
- Saturation:
- Mechanical ventilation:

Renal
- Creatinine:
- Continuous venovenous hemodialysis:

Infectious
- Temperature:
- C-reactive protein:
- Leucocytes:

Cultures
Positive / Negative If positive (origin / date / organism):

Current antibiotics:

Current feeding method:

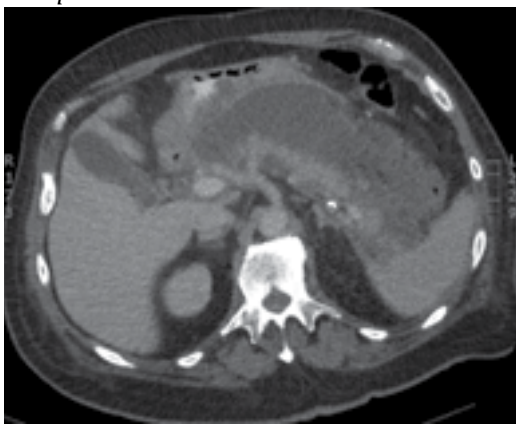
Degree of illness according to the physician (1 not ill - 10 very ill):

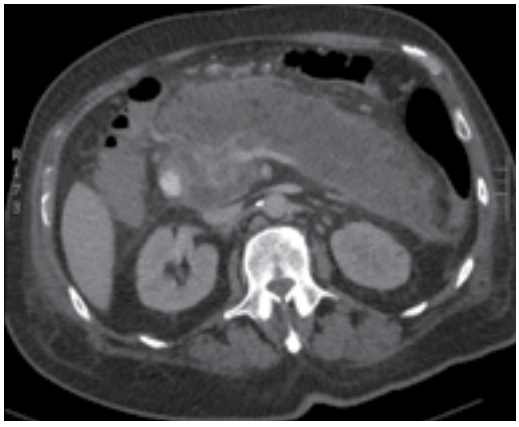
IMAGING DAY: DATE:

Paste here recent CT(s) and/or MRI(s) images.

At least 10 slices, including a slice with the maximum diameter of the collection, the cranial and caudal boundaries of the collection, as well as a few slices which show the relation with the stomach and flanks and thereby the best window for approach.

Example:





EXPERT ADVICE FORM

Expert's name:

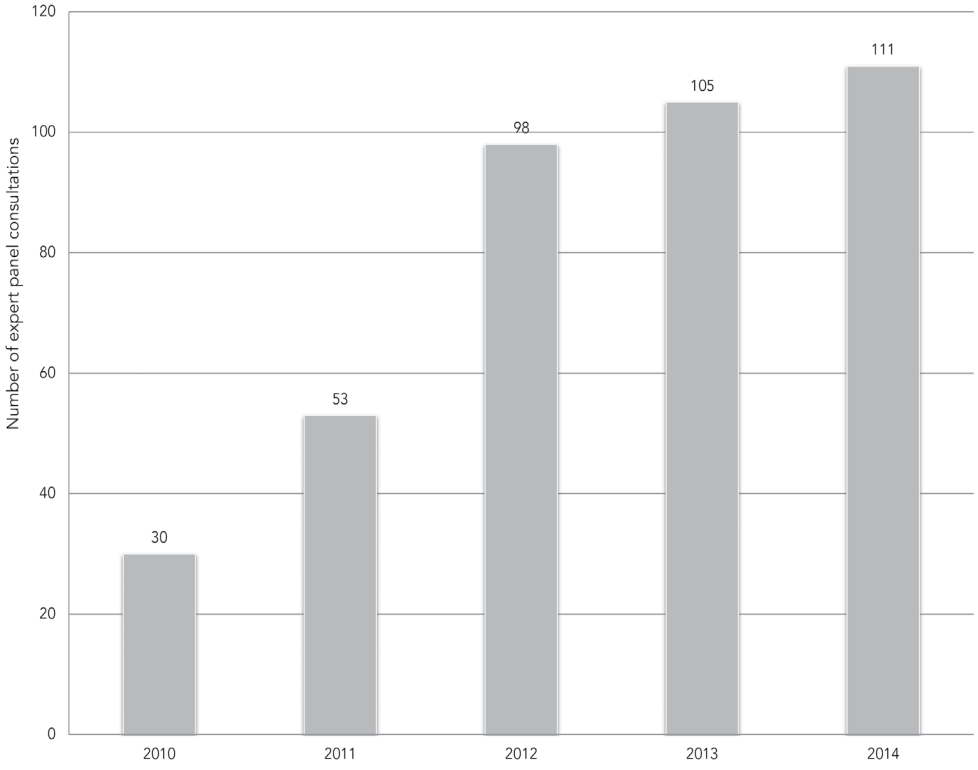
TO THE SURGEON / GASTROENTEROLOGIST
How urgent do you deem invasive intervention?

Not urgent at all — Urgent

Would you perform an intervention at this point in time?	Yes	No
Please write your comments:		
TO THE SURGEON		
If yes, is the surgical step-up approach possible?	Yes	No
TO THE GASTROENTEROLOGIST		
If yes, is the endoscopic transluminal step-up approach possible?	Yes	No
IN GENERAL		
Do you wish to receive additional information?	Yes	No
If yes, which information?		
TO THE RADIOLOGIST		
Is it possible to place a catheter drain in this collection?	Yes	No
If yes,		
Left retroperitoneal	Yes	No
Right retroperitoneal	Yes	No
Transabdominal	Yes	No
Endoscopic transluminal	Yes	No

Please write your comments:

Supplementary Figure 2 Number of expert panel consultations 2010-2014



Supplementary Table 1 Survey among clinicians using the online expert panel in the period 2010-2014 (n=157/397 cases)

	n (%)
Expert panel is easily accessible	148 (94)
Too much time to fill out consultation form	
Totally disagree	7 (5)
Disagree	76 (49)
Not agree or disagree	30 (19)
Agree	40 (26)
Fully agree	2 (1)
Advice too late	
Totally disagree	78 (50)
Disagree	62 (40)
Not agree or disagree	9 (6)
Agree	5 (3)
Fully agree	2 (1)
Advice followed	132 (84)
Advice similar to clinicians' initial opinion	132 (84)
Used to	
Convince colleagues	82 (52)
Convince surgeons	32 (20)
Convince gastroenterologists	38 (24)
Convince radiologists	17 (11)
Convince ICU physicians	21 (13)
Convince family	2 (1)
Support for medical decision	132 (84)
Valuable initiative	
Totally disagree	13 (9)
Disagree	3 (2)
Not agree or disagree	2 (1)
Agree	41 (26)
Fully agree	97 (62)
Valuable for other diseases	
Totally disagree	5 (3)
Disagree	5 (3)
Not agree or disagree	40 (26)
Agree	71 (46)
Fully agree	33 (22)

Supplementary Table 2 Overall expert evaluation (*n*=15 experts), SD, standard deviation

	n (%)
Specialism	
Surgeons	7 (46)
Gastroenterologists	4 (27)
Radiologists	4 (27)
Experience, years (SD)	17 (±8)
Time for expert mail evaluation, minutes (SD)	9 (±3)
How often information suffices	
Always	0 (0)
Often	14 (93)
Equal	1 (7)
Sometimes	0 (0)
Never	0 (0)
How satisfied with format	
Very satisfied	2 (13)
Satisfied	11 (73)
Not satisfied	1 (7)
No opinion	1 (7)
How often imaging suffices	
Always	0 (0)
Often	11 (73)
Equal	3 (20)
Sometimes	1 (7)
Never	0 (0)
How valuable would be complete imaging	
Very valuable	12 (80)
Valuable	3 (20)
Not valuable	0 (0)
What is your opinion on frequency	
Too often	2 (13)
Often	8 (53)
Not too often/not to little	5 (34)
Little	0 (0)
Too little	0 (0)
Receiving short text message	
Pleasant, only outside office hours	7 (47)
Pleasant, with every Expert mail	6 (40)
Not pleasant	2 (13)
Within how many hours should advice be returned	
< 6h	0 (0)
< 12h	5 (33)
< 24h	10 (67)
< 48h	0 (0)
> 48h	0 (0)
Valuable for other diseases	
No	4 (27)
Yes	11 (73)

Supplementary Text 1 Materials and methods

Design and setting

All patients with necrotizing pancreatitis evaluated by the Dutch 24/7 online nationwide pancreatitis expert panel between 2010 and 2014 were registered prospectively and analyzed. During that time, all consulting clinicians were sent a onetime request to fill out an evaluation about the expert panel consultation. In July 2014, all 15 members of the expert panel were asked to fill in an overall evaluation form.

Data extraction

All data were retrieved from the expert panel consultation forms and physician and expert evaluation forms.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Outcomes were reported as counts and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations or medians with interquartile ranges depending on normality distribution.

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3

CHAPTER 3

Natural history of gas configurations and encapsulation in necrotic collections during necrotizing pancreatitis

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Abstract

Background
Decision-making on invasive intervention in patients with clinical signs of infected necrotizing pancreatitis is often related to the presence of gas configurations and the degree of encapsulation in necrotic collections on imaging. Data on the natural history of gas configurations and encapsulation in necrotizing pancreatitis are, however, lacking.

Methods
A post-hoc analysis was performed of a previously described prospective cohort in 21 Dutch hospitals (2004-2008). All computed tomography scans (CTs) performed during hospitalization for necrotizing pancreatitis were categorized per week (1 to 8, and thereafter) and re-assessed by an abdominal radiologist.

Results
A total of 639 patients with necrotizing pancreatitis were included, with median 4 (IQR 2-7) CTs per patient. The incidence of first onset of gas configurations varied per week without a linear correlation: 2-3-13-11-10-19-12-21-12%, respectively. Overall, gas configurations were found in 113/639 (18%) patients and in 113/202 (56%) patients with infected necrosis. The incidence of walled-off necrosis increased per week: 0-3-12-39-62-76-93-97-100% for week 1-8 and thereafter, respectively. Clinically relevant walled-off necrosis (largely or fully encapsulated necrotic collections) was seen in 162/379 (43%) patients within the first 3 weeks.

Conclusions
Gas configurations occur in every phase of the disease and develop in half of the patients with infected necrotizing pancreatitis. Opposed to traditional views, clinically relevant walled-off necrosis occurs frequently within the first 3 weeks.

Introduction

Acute pancreatitis is the most common gastrointestinal disorder requiring hospital admission in the US and its incidence is rising [1]. Necrotizing pancreatitis, defined as necrosis of the pancreatic parenchyma and/or extrapancreatic fat tissue, occurs in around 20% of patients [2,3]. Associated collections in necrotizing pancreatitis (necrotic collections) are either called 'acute necrotic collections' (not fully encapsulated) or 'walled-off necrosis' (fully encapsulated) [4]. In case of infected necrosis, an invasive intervention is nearly always needed [5,6]. Current guidelines advise a step-up approach in patients with infected necrosis, starting with catheter drainage. If the patient does not recover with drainage alone, minimally invasive necrosectomy is performed [5,6]. Although overall outcome has improved over the last decade, mortality and morbidity in these patients are still 15% and 40%, respectively [7].

Decision-making on invasive intervention is influenced by clinical, biochemical, and imaging features, primarily on computed tomography (CT). Two CT features stand out in the decision-making process. First, the presence of gas configurations within necrotic collections is deemed important as this is regarded pathognomonic for infected necrosis. Second, the degree of encapsulation of necrotic collections is relevant because drainage is typically postponed until necrotic collections are largely or fully encapsulated. The timing of invasive intervention in patients with infected necrotizing pancreatitis, however, remains a topic of debate [8].

It is often assumed that gas configurations occur most often between the second and fourth week and that full encapsulation of necrotic collections occurs at least 4 weeks after symptom onset. Accurate data supporting these statements are, however, lacking [4]. Improved knowledge about the natural course of necrotic collections might support decision-making on timing of invasive intervention. Moreover, it can add to the interpretation and further standardization of clinical research in necrotizing pancreatitis.

The main purpose of this study was to evaluate the natural history of gas configurations in and encapsulation of necrotic collections on CT during the disease course of necrotizing pancreatitis. In addition, clinical, and radiological factors associated with occurrence of gas and (early) encapsulation in necrotic collections were studied.

Methods

Study design and patients

This study is a post-hoc analysis of a prospective cohort of patients with necrotizing pancreatitis, collected from 2004 to 2008 in 21 Dutch hospitals of the Dutch Pancreatitis Study Group [9]. All contrast-enhanced CTs performed during the index admission and before any kind of invasive (surgical, endoscopic, or percutaneous) intervention were re-assessed by an experienced abdominal radiologist (TLB). Patients with at least one CT confirming the diagnosis of necrotizing pancreatitis were included. Follow-up CTs were performed in case of lack of clinical improvement according to current standard practice. CTs after any intervention were excluded. CTs were collected from all participating hospitals (including referral hospitals in transferred patients). Different brands of CT scanners were used and CT protocols varied widely among hospitals, varying from a monophasic to 4-phasic CT protocol. All CTs, however, were executed with a multislice technique (at least 16-slice multidetector CT scanner or higher) with 3 mm reconstructions and were contrast-enhanced in the pancreatic and/or portal venous phase. Also, in most cases reformatted images were available for review. Non-invasive treatment consisted of intravenous fluid therapy, oral or enteral feeding, and adequate pain management. Invasive interventions were performed in cases of (suspected) infected necrosis based on gas configurations on CT, positive culture after fine needle aspiration, or clinical deterioration with no other cause than infected necrosis [10].

Data-extraction

All CTs were categorized into groups according to duration since onset of disease, i.e. week 1 to 8, and further. If more than 1 CT was performed in a week, the last CT was used for assessment. In all CTs, the presence of first onset of gas configurations was evaluated (see Figure 1A-B for CT examples). Gas configurations depicted on every follow-up CT in patients undergoing a non-invasive treatment were not scored in the incidence assessment. The degree of encapsulation was scored as none (0%), moderately (less than 50%), largely (between 50 and 99%), or fully (100%) encapsulated (see CT examples in Figure 2A-D). Walled-off necrosis was defined according to the Revised Atlanta Classification as fully encapsulated necrotic collections [4]. In clinical practice, however, invasive intervention is contemplated and deemed feasible when infected necrotic collections are largely or fully encapsulated. Hence, besides the original definition of walled-off necrosis we also assessed a more clinically relevant definition of 'walled-off necrosis', defined as necrotic collections that are largely or fully encapsulated. In this line of reasoning, we defined 'early walled-off necrosis' as largely or fully encapsulated

Figure 1A

CT with gas configurations in acute necrotic collection

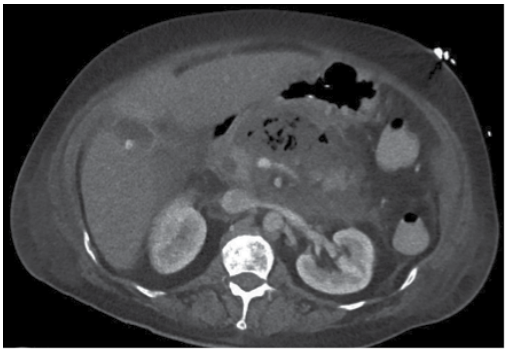


Figure 1B

CT with gas configurations in walled-off necrosis

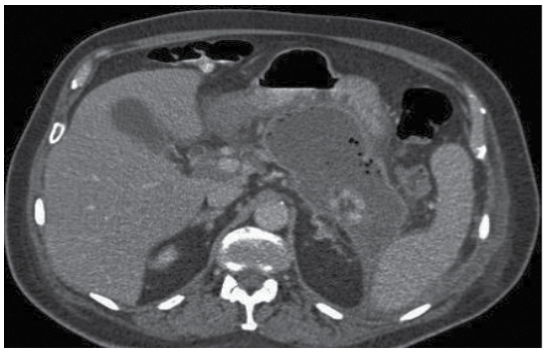


Figure 2A

CT 1 not encapsulated (0%)

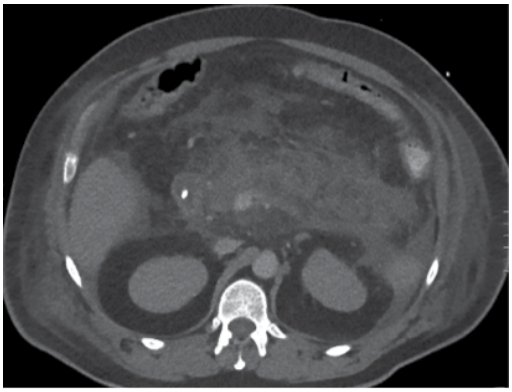


Figure 2B

CT 2 moderately encapsulated (<50%)

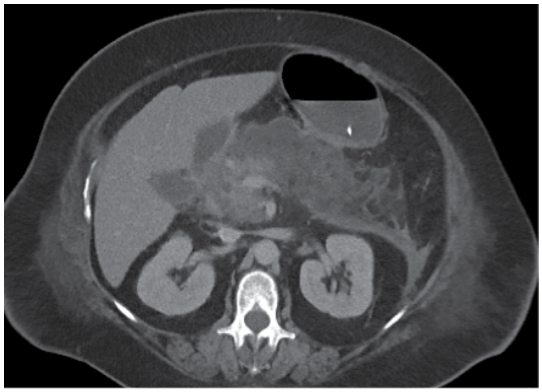


Figure 2C

CT 3 largely encapsulated (50-99%)

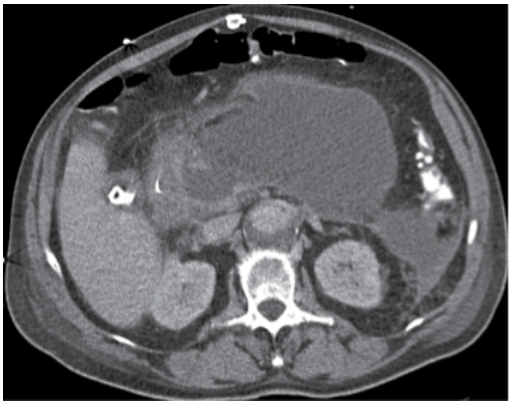
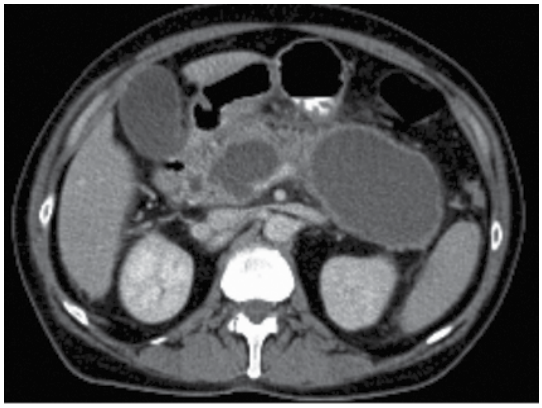


Figure 2D

CT 4 fully encapsulated /walled-off necrosis (100%)



collections occurring within 3 weeks after symptom onset, i.e. before the traditional 4 weeks mentioned in the Revised Atlanta Classification [4]. The following clinical baseline data were available: age, sex, disease etiology, and American Society of Anesthesiologists (ASA) classification. Data on type and timing of intervention and clinical outcome in patients with suspected infected necrosis have been published previously [9, 10].

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Outcomes were reported as absolute numbers and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations (SD) or medians with interquartile ranges (IQR) depending on normality of distribution. Univariable logistic regression was performed to identify factors associated with the occurrence of gas configurations and for 'early walled-off necrosis'. Factors associated in the univariable analysis ($P<0.1$) were entered into a multivariable logistic regressions analysis (backward stepwise elimination method). A two-sided P-value below 0.05 was considered statistically significant for all statistical tests.

Results

The study cohort consisted of 639 patients with necrotizing pancreatitis. Median age was 58 years (IQR 45-70) and 62% (398) of patients were male. A median of 4 (IQR 2-7, range 1-23) CTs were performed per patient (Table 1). The median CT severity index was 4 (IQR 4-8). In 324 (51%) patients, pancreatic parenchymal necrosis was present, in the remainder of 315 (49%) patients there was extrapancreatic necrosis only. A median of 3 (IQR 2-5) necrotic collections were observed per patient, mostly centrally located (i.e. predominantly in the lesser sac and/or transverse mesocolon) or left-sided (i.e. predominantly at the left side of the retroperitoneum), in 235 (37%) and 188 (29%) of patients, respectively. Figure 3 depicts the frequency per location of the (extra)pancreatic necrotic collections.

Table 1 Clinical and radiological characteristics of 639 patients with necrotizing pancreatitis

	All patients (n=639)
Age (years)	58 (45-70)
Male sex (%)	398 (62)
Etiology (%)	
Biliary	304 (48)
Alcohol	150 (23)
Other	63 (10)
Unknown	122 (19)
ASA classification on admission (%)	
I (healthy status)	202 (32)
II (mild systemic disease)	347 (54)
III (severe systemic disease)	90 (14)
No. of CTs per patient	
Total	4 (2-7)
Before intervention	3 (2-4)
CT severity index^	4 (4-8)
Pancreatic necrosis (%)	324 (51)
Extrapancreatic necrosis alone (%)#	315 (49)
Extent of pancreatic necrosis (%) n=324	
<30%	132 (40)
30-50%	83 (26)
>50%	109 (34)
No. of necrotic collections	3 (2-5)
Location of necrotic collections (%)	
Left	188 (29)
Right	55 (9)
Central	235 (37)
Bilateral	161 (25)
Gas configurations on CT (%)	
Total	113 (18)
Among 202 patients with infected necrosis	113 (56)

Abbreviations; ASA: American Society of Anesthesiologists; CT: computed tomography; ^CT severity index (score 1-10); #No pancreatic necrosis present; Continuous variables; are provided as mean (±SD) or median (IQR) depending on normality of distribution.

Table 2A Univariable and multivariable logistic regression analysis for factors associated with gas configurations (113 of 639 patients, 18%)

	Univariable OR (95% CI)	P	Multivariable OR (95% CI)	P
Age	1.019 (1.005-1.033)	0.006	1.032 (1.016-1.048)	<0.001
Sex (male)	1.301 (0.846-2.001)	0.230		
ASA classification (ASA 3)	1.195 (0.681-2.095)	0.535		
CT severity index	1.309 (1.205-1.422)	<0.001	0.986 (0.852-1.141)	0.852
Presence of pancreatic parenchymal necrosis	4.883 (2.994-7.964)	<0.001	4.046 (2.398-6.826)	<0.001
No. of necrotic collections	1.275 (1.152-1.410)	<0.001	1.160 (1.026-1.312)	0.018
Location of necrotic collection (left vs. non-left)	3.499 (2.225-5.501)	<0.001	2.780 (1.692-4.569)	<0.001

Table 2B Univariable and multivariable logistic regression analysis for factors associated with early walled-off necrosis (i.e. within 3 weeks; 162 of 379 patients, 43%)

	Univariable OR (95% CI)	P	Multivariable OR (95% CI)	P
Age	1.004 (0.991-1.018)	0.522		
Sex (male)	0.655 (0.427-1.005)	0.053	0.625 (0.403-0.967)	0.035
ASA classification (ASA 3)	0.957 (0.536-1.707)	0.881		
CT severity index	1.062 (0.974-1.159)	0.173		
Presence of pancreatic parenchymal necrosis	1.852 (1.190-2.881)	0.006	1.761 (1.119-2.772)	0.014
No. of necrotic collections	1.019 (0.917-1.132)	0.730		
Location of necrotic collection (left vs. non-left)	1.233 (0.782-1.944)	0.368		
Gas configurations	1.762 (1.118-2.778)	0.015	1.617 (1.014-2.580)	0.044

Abbreviations; ASA: American Society of Anesthesiologists; CT: computed tomography; OR: odds ratio; CI: confidence interval.

Gas configurations

In 18% of patients (113 of 639 patients) and in 56% of patients with proven infected necrosis (113 of 202 patients), gas configurations were seen at some point in time. Figure 4 shows the number of patients (in %) in whom first onset of gas configurations were seen on CT per week: w1: 2%; w2: 3%; w3: 13%; w4: 11%; w5: 10%; w6: 19%; w7: 12%; w8: 21%; and >w8: 12%. There was no linear correlation. In a multivariable analysis, age (P<0.001), presence of pancreatic necrosis (*P*<0.001), number of necrotic collections (P=0.018), and left-sided collections (P<0.001) were independently associated with the occurrence of gas configurations (see Table 2A). As described previously, in 184 patients infected necrosis was confirmed by culture taken at the first intervention [10]. In 114 of these 184 patients (62%), the infection was monomicrobial, whereas in 70 patients (38%), two or more bacteria/fungi were cultured. Escherichia coli was most frequently found in patients with gas bubbles on CT (42 patients), whereas in patients without gas bubbles staphylococcus aureus was most frequently found (34 patients). No single micro-organism was found to be solely responsible for the formation of gas bubbles in necrotic collections.

Encapsulation

Figure 4 shows the degree of encapsulation related to the number of patients. The incidence of fully encapsulated necrotic collections (walled-off necrosis according to the Revised Atlanta Classification) increased per week: w1: 0%; w2: 3%; w3: 12%; w4: 39%; w5: 62%; w6: 76%; w7: 93%; w8: 97%; and >w8: 100%. Likewise, the incidence of largely or fully encapsulated necrotic collections (i.e., clinically relevant walled-off necrosis) increased per week: w1: 1%, w2: 17%, w3: 61%, w4: 88%, w5: 100%, w6: 99%, w7:100%, w8: 100%, >w8: 100%. Early clinically relevant walled-off necrosis (i.e. within the first 3 weeks) was seen in 162 of 379 (43%) patients. Male sex (*P*=0.035), pancreatic necrosis (*P*=0.014), and the presence of gas configurations (*P*=0.044) were independently associated with the occurrence of early clinically relevant walled-off necrosis in a multivariable analysis (see Table 2B).

Discussion

This study provides novel information on the natural history of imaging features of first onset of gas configurations and encapsulation in necrotizing pancreatitis. The main findings are that first onset of gas configurations and walled-off necrosis occur in nearly every phase of the disease, well before as after 4 weeks of symptom onset. Although walled-off necrosis becomes more prevalent with time, over 40% of patients already develop clinically relevant walled-off necrosis within the first 3 weeks of disease.

Figure 3 Location of (extra)pancreatic necrotic collections in 639 patients, with a median of 3 (IQR 2-5) collections per patient

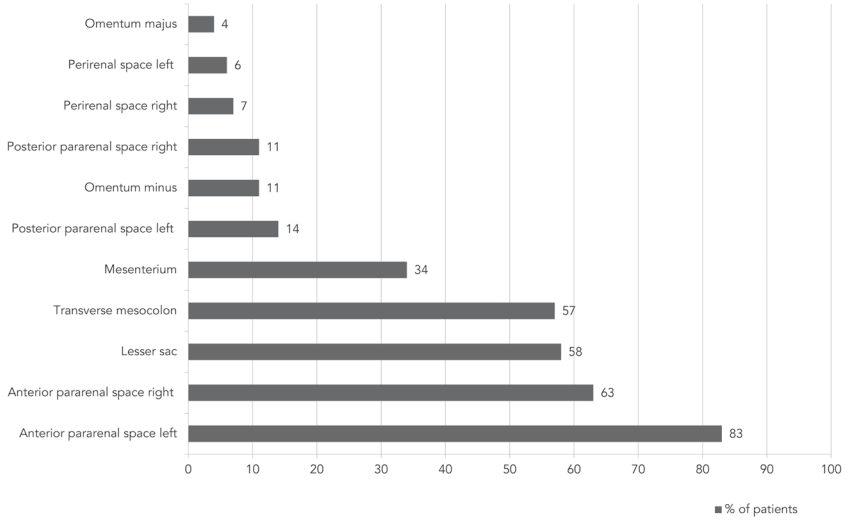
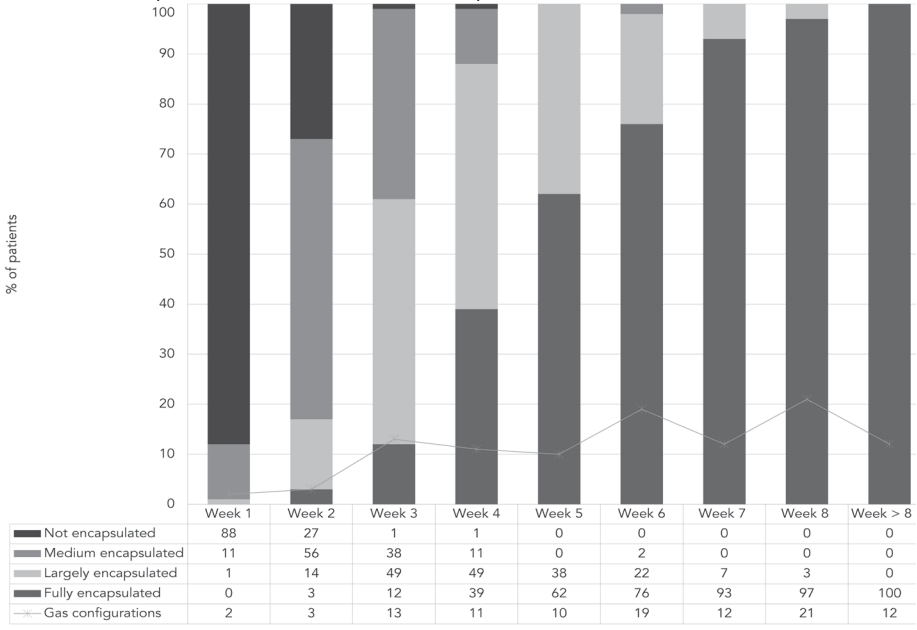


Figure 4 The degree of encapsulation and presence of gas configurations in (extra) pancreatic necrotic collection per week



	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week > 8
Not encapsulated	88	27	1	1	0	0	0	0	0
Medium encapsulated	11	56	38	11	0	2	0	0	0
Largely encapsulated	1	14	49	49	38	22	7	3	0
Fully encapsulated	0	3	12	39	62	76	93	97	100
Gas configurations	2	3	13	11	10	19	12	21	12

NB. Only patients in whom CT was performed AND (extra)pancreatic necrotic collections were seen (total n=639 patients); 1st week n=540 (85%); 2nd week n=329 (51%); 3rd week n=195 (31%); 4th week n=142 (22%); 5th week n=87 (14%); 6th week n=59 (9%); 7th week n=43 (7%); 8th week n=34 (5%); beyond 8 weeks n=138 (22%).

Gas in necrotic collections is thought to be caused by gas-forming bacteria or loss of integrity of the gastrointestinal tract [5]. Both are considered pathognomonic for infected necrosis. Infected necrosis is almost always an indication for invasive intervention since only a small subset (<5%) of patients recover with antibiotic treatment only [9]. Little is known about risk factors for gas configurations at imaging or timing of its occurrence. According to our study, gas configurations are seen in every phase of the disease, i.e. very early as well as late in the disease course. Gas configurations were more often seen in patients with higher age, parenchymal necrosis, multiple collections, and left-sided collections. The association between these factors and gas configurations remains speculative. It is conceivable that the translocation of bacteria is facilitated in the elderly and in cases where necrotic collections are in direct contact over a longer segment of the intestine. This latter phenomenon may be more pronounced in patients with parenchymal necrosis (i.e. more extensive collections) and in those with multiple collections. Furthermore, the greater part of the pancreas is located left of the midline, which likely contributes to the preferential spread of necrotic collections to the left retroperitoneal compartment. More research on this topic is, however, required for verification of this association. In the current study, different micro-organisms were responsible for the occurrence of gas in necrotic collections, including Gram-positive and Gram-negative bacteria as well as yeasts. Also, in a significant number of patients culture was polymicrobial. This justifies the institution of broad-spectrum antibiotics in patients with infected necrosis based on gas in necrotic collections, as routine narrowing of antibiotic treatment is not supported by our data.

The 2012 Revised Atlanta Classification classifies early pancreatic collections into acute peripancreatic fluid collections and acute necrotic collections, that after 4 weeks develop into pancreatic pseudocysts and walled-off necrosis, respectively, when completely encapsulated [4]. Necrotic collections may involve the pancreatic parenchyma and/or extrapancreatic tissues and are considered a different clinical entity with a worse clinical outcome as compared with interstitial edematous pancreatitis [4, 11]. Little is known about the natural history of imaging features of necrotic collections. Previous studies have evaluated the natural clinical history of (extra)pancreatic collections, but did not analyze their imaging characteristics or timing of encapsulation [12-15].

Some have studied the clinical course (i.e. resolution) of pancreatic fluid collections and risk factors associated with the presence of pancreatic collections [12, 13], analyzed clinical and biochemical factors associated with formation of encapsulation (or 'pseudocyst formation') [12, 14], or evaluated resolution of necrotic collections in the later phase of disease by means of endoscopic ultrasound or transabdominal ultrasonography (i.e. not by CT) at different time points (i.e. after 4-6 weeks up to 6 months) [13, 15].

The pathophysiology and rate of encapsulation of necrotic collections is as of yet incompletely understood. It is generally assumed that in necrotizing pancreatitis, the premature release of activated pancreatic enzymes and resultant acinar cell injury incites an extensive local and systemic inflammatory response. Locally this might be regarded as a natural defense mechanism in which the body attempts to contain the area of inflammation. Over time, a capsule of granulation tissue is formed at the periphery to separate the inflamed tissue from healthy tissue to mitigate further spread of toxic enzymes and thus to wall off necrotic collections. This natural process of walling off an inflammatory process is likely analogous to an abscess wall formation. It is often stated (but not studied) that the timing of encapsulation takes about 4 weeks and this timescale is incorporated by the Revised Atlanta Classification. In the current study, however, there was a wide temporal range in which necrotic collections eventually became walled-off. In 85% of patients, it took well over 4 weeks for necrotic collections to become completely walled off, whereas in 3% and 12% complete encapsulation was already noted during the second and third week, respectively. Moreover, early clinically relevant walled-off necrosis (within the first 3 weeks) occurred in 43% and was more seen in male patients, patients with parenchymal necrosis, and patients with gas configurations (i.e. parameters associated with poorer clinical outcome [16, 17]). The reason for the wide temporal range and observed associations with early encapsulation remain speculative. Possibly, the magnitude of inflammatory response incited locally together with immune-mediated and patient factors could result in necrotic collections becoming walled-off early or late. More research on this topic is, however, needed.

Our study has several limitations. First, for this study, CTs were assessed by one abdominal radiologist. Therefore, no interobserver agreement could be calculated. Since other studies show good agreement for type of necrotic collection, presence of intraluminal gas in necrotic collections, and presence of a wall among experienced radiologists [18], we expect our results to be reproducible. Second, full blinding of CTs was unfortunately not feasible. The radiologist was aware of the date and the presence of prior CTs, but was blinded to date of symptom onset and the clinical

course. Third, follow-up CTs were not routinely (for example, weekly) performed but rather on the discretion of treating physicians, often based on change in a patient's condition. This is in line with standard practice as routinely performing CT is not justifiable out of costs and radiation burden perspectives. Fourth, CTs were executed with varying CT protocols. All CTs, however, were performed with a multislice technique with 3 mm reconstructions and were contrast-enhanced in the pancreatic and/or portal venous phase. Also, in most cases reformatted images were available for review. Therefore, we feel that the finding of gas within collections was easily visible whenever present. Fifth, we defined 'clinically (relevant) walled-off necrosis' as necrotic collections that are largely or fully encapsulated. We feel that in clinical practice the distinction between collections that are not or only moderately encapsulated are treated different (non-invasive therapy) compared with those that are largely or fully encapsulated (invasive therapy possible). More data are needed to determine whether this definition more closely relates to clinical management than the original definition.

Results of this study could have therapeutic implications because the knowledge of gas configurations and early encapsulation might influence the timing to proceed to an earlier invasive intervention in a subset of patients with infected necrosis. Current international guidelines, however, advice to postpone invasive intervention for at least 4 weeks in patients with (suspected) infected necrotizing pancreatitis until walled-off necrosis is present because intervention is believed to be safer in walled-off necrosis (e.g. less bleeding) [5,6]. This advice is primarily based on studies in which patients underwent early primary open necrosectomy (within first 2 weeks) which was associated with worse outcome [19-21]. Nowadays, standard treatment of infected necrosis is primary catheter drainage. At least 35-50% of patients do not need additional necrosectomy after catheter drainage and this is associated with a lower risk for complications [7, 22]. Since catheter drainage is the first step of treatment which does not require fully encapsulated necrotic collections, some suggest that early and proactive drainage could prevent clinical deterioration, improve outcome, and shorten hospital stay [23, 24]. This hypothesis is currently being studied in the Dutch multicenter randomized controlled POINTER trial (ISRCTN33682933). This study compares immediate catheter drainage with postponed catheter drainage in patients with proven or suspected infected necrotizing pancreatitis.

In conclusion, opposed to common views, gas configurations and walled-off necrosis are seen in every phase of the disease in patients with necrotizing pancreatitis. This may have therapeutic implications in a subset of patients with infected necrosis and early walled-off necrosis.

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4

CHAPTER 4

The association of computed tomography-assessed body composition with mortality in patients with necrotizing pancreatitis

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Abstract

Background
Identification of patients with necrotizing pancreatitis at high risk for a complicated course could facilitate clinical decision-making. In multiple diseases, several parameters of body composition are associated with impaired outcome, but studies in necrotizing pancreatitis are lacking.

Methods
A post hoc analysis was performed in a national prospective cohort of 639 patients with necrotizing pancreatitis. Skeletal muscle mass, skeletal muscle density, and visceral adipose tissue were measured at the third lumbar vertebra level (L3) on contrast-enhanced computed tomography (CT) within 10 days after initial admission and 1 month thereafter.

Results
In total, 496 of 639 patients (78%) were included. Overall mortality rate was 14.5%. Skeletal muscle mass and density and visceral adipose tissue on first CT were not independently associated with in-hospital mortality. However, low skeletal muscle density was independently associated with increased mortality in patients ≥65 years (OR 2.54 (95%CI 1.12–5.84, P = 0.028). Skeletal muscle mass and density significantly decreased within 1 month, for both males and females, with a median relative loss of muscle mass of 12.9 and 10.2% (both P < 0.001), respectively. Skeletal muscle density decreased with 7.2 and 7.5% (both P < 0.001) for males and females, respectively. A skeletal muscle density decrease of ≥10% in 1 month was independently associated with in-hospital mortality: OR 5.87 (95%CI 2.09–16.50, P = 0.001).

Conclusion
First CT-assessed body composition parameters do not correlate with in-hospital mortality in patients with necrotizing pancreatitis. Loss of skeletal muscle density ≥10% within the first month after initial admission, however, is significantly associated with increased mortality in these patients.

Introduction

Acute pancreatitis is the most common reason for acute gastrointestinal hospital admission [1]. Necrotizing pancreatitis develops in around 20% of patients [2,3]. Depending on the presence of organ failure, necrotizing pancreatitis is classified as moderate severe or severe pancreatitis [4]. Mortality increases, and severe morbidity rates exceed 40%, particularly when the necrosis is infected [5]. Infected necrosis occurs in around 30% of patients with necrotizing pancreatitis and is in general an indication for invasive intervention (i.e., catheter drainage, if necessary followed by a necrosectomy) [6,7]. Necrotizing pancreatitis is characterized by a variable clinical course. To further improve outcome of patients with necrotizing pancreatitis, identification of determinants associated with high risk of mortality is needed in these patients. Several scoring systems, both radiological and clinical, have been developed to predict the severity of acute pancreatitis at hospital admission with comparable moderate accuracy for predicting mortality [8]. All radiologic scoring systems focus on pancreatitis-associated findings (such as necrosis, pancreatic collections, and inflammatory changes), but factors associated with body composition are not part of any of these systems. Body composition parameters that can easily and reliably be assessed on computed tomography (CT), such as skeletal muscle mass and skeletal muscle density (i.e., a measure for skeletal muscle quality and intramuscular fat infiltration), are predictive factors for poor outcome in various populations, particularly within surgical oncology, [9, 10] but also in liver transplant, vascular surgery, intensive care, and trauma patients [11-14]. Furthermore, the loss of skeletal muscle mass, for example during chemotherapy, is associated with poor outcome [15]. Visceral adipose tissue, the metabolically active component of total body adipose tissue, is another body composition measure that can be assessed on CT. Visceral obesity is associated with impaired outcome after surgery for various malignancies, such as colorectal, adrenorenal, and hepatocellular carcinoma [16-18] Moreover, a recent study suggests that android fat distribution may predict the severity of acute pancreatitis [19]. Therefore, the aim of this study was to investigate the association between parameters of body composition (i.e., skeletal muscle mass, skeletal muscle density, and visceral adipose tissue) at onset of disease with in hospital mortality in patients with necrotizing pancreatitis and to analyze whether skeletal muscle loss during the course of disease is associated with mortality in these patients.

Methods

Patients

A post hoc analysis of a prospective, observational cohort consisting of 639 necrotizing pancreatitis patients was performed. This cohort was collected in 21 Dutch hospitals (eight Dutch university medical centers and 13 teaching hospitals) from 2004 to 2008 [3]. All patients who had an abdominal CT examination performed of sufficient quality (i.e., complete images, no artifacts, and contrast-enhanced) within the first 10 days after initial admission were included. Patients with unknown body height were excluded from analyses including skeletal muscle mass, because skeletal muscle mass is expressed in the L3 muscle index (cm2/m2) [23]. Furthermore, CTs performed 30 days (±15 days) thereafter were also collected (i.e., 1-month CT). Skeletal muscle depletion was defined as a decrease exceeding 10% percent, as this was considered clinically relevant. Severe skeletal muscle depletion was defined as a decrease exceeding 25%.

Skeletal muscle and adipose tissue measurements

Body composition measurements were performed on routinely performed contrast-enhanced abdominal CTs using FatSeg. This software program was developed at the Erasmus MC University Medical Center to perform cross-sectional soft tissue (i.e., skeletal muscle and adipose tissue) measurements on CT using the MeVisLab development environment for medical image processing and visualization version 2.4 (available from http://www.mevislab.de), as previously described.20 In short, the cross-sectional skeletal muscle mass area was measured with manually tracing inner and outer contours using a preset Hounsfield unit (HU) range of -30 to +150 on the level of the third lumbar vertebra (L3) on which both transversal processes were visible. The following muscles were included: psoas, paraspinal, transverse abdominal, external oblique, internal oblique, and rectus abdominis. The cross-sectional skeletal muscle area was corrected for height squared (m2), resulting in the L3 muscle index (cm2/m2) [21]. Mean skeletal muscle attenuation (in HU) was used as a measure of skeletal muscle density, with low skeletal muscle density reflecting high intramuscular adipose tissue infiltration and poor skeletal muscle quality [22,23]. Visceral adipose tissue measurements were performed on the same slice with a preset HU range of -190 to -30. Selected intraluminal bowel content expressing the same radio density as adipose tissue was manually erased. Sex-specific tertiles for the body composition parameters were created. Data of our research group showed high inter- and intra-observer agreement for skeletal muscle and adipose tissue measurements on CT [24].

Baseline characteristics

Baseline characteristics collected at admission at onset of disease were age, sex, body mass index (BMI, kg/m2), disease etiology, American Society of Anesthesiologists (ASA) classification, and the presence of organ failure at admission. Furthermore, the following clinical scores to predict the severity of pancreatitis were calculated: Acute Physiologic and Chronic Health Evaluation (APACHE) II score and Modified Glasgow score (i.e., Imrie score), with parameters collected within 24 and 48 h after admission, respectively. Additionally, the highest C-reactive protein (CRP) level in the first 48 h of admission was collected. APACHE II score (≥8), Modified Glasgow score (≥3), and CRP levels (≥150 mg/L) are previously described predictors for disease severity in acute pancreatitis [25-28]. Necrotizing pancreatitis was defined according to the 2012 revised Atlanta classification [4]. The presence of necrotizing pancreatitis was assessed on all baseline CTs by an experienced abdominal radiologist (TLB).

Study outcomes

The primary outcome was mortality during initial admission. Furthermore, the changes in skeletal muscle mass and skeletal muscle density between the baseline CT and CT after 1 month were calculated. Since there is great inter-slice variability in visceral adipose tissue due to the position of visceral organs and the potential development of (peri)pancreatic necrosis over time, this measurement was only performed on baseline CTs at onset of disease.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Outcomes were reported as absolute numbers and percentages for categorical variables. Continuous variables were summarized as either means with corresponding standard deviations (SD) or interquartile ranges (IQR) depending on normality of distribution. The chi-square test was used to compare categorical variables. T tests were used for normally distributed continuous variables and the Mann–Whitney U test for non-normally distributed continuous variables. The change in skeletal muscle mass was assessed using the non-parametric paired Wilcoxon test. Univariable logistic regression analysis was performed to identify parameters that were associated with the outcome measures. Parameters that were associated in univariable analysis ($P < 0.100$) were entered into a multivariable logistics regressions analysis (backward stepwise elimination method). A two-sided P value below 0.05 was considered statistically significant for all statistical tests. First, the association between the body composition measures and in-hospital mortality was evaluated, followed by the association between the loss in skeletal muscle mass and density and mortality. Parameters representing disease severity (e.g., APACHE

II and Modified Glasgow score) were excluded from this analysis, because these were assessed within the first 48 h of admission. Receiver Operation Characteristic (ROC) curves with corresponding areas under the curve (AUC) were created to test the predictive accuracy of known predictive scores (i.e., APACHE II score, Modified Glasgow score, and highest CRP level in the first 48 h of admission) and the CT-assessed body composition parameters. An AUC of 0.91-1.00 was considered excellent, 0.81-0.90 good, 0.71-0.80 fair, 0.61-0.70 poor, and 0.51-0.60 very poor.

Results

Patients and baseline characteristics

Of 639 patients, 143 patients (22%) were excluded either because the baseline CT was performed later than 10 days after initial admission, no sufficient (assessable) CT was available, or no contrast enhanced CT was performed (Fig. 1). The final study cohort consisted of 496 patients (62% males) with a median age of 58 (IQR 45–70) and BMI of 26.7 (IQR 25.0–30.2) kg/m2.

Figure 1 Inclusion flowchart

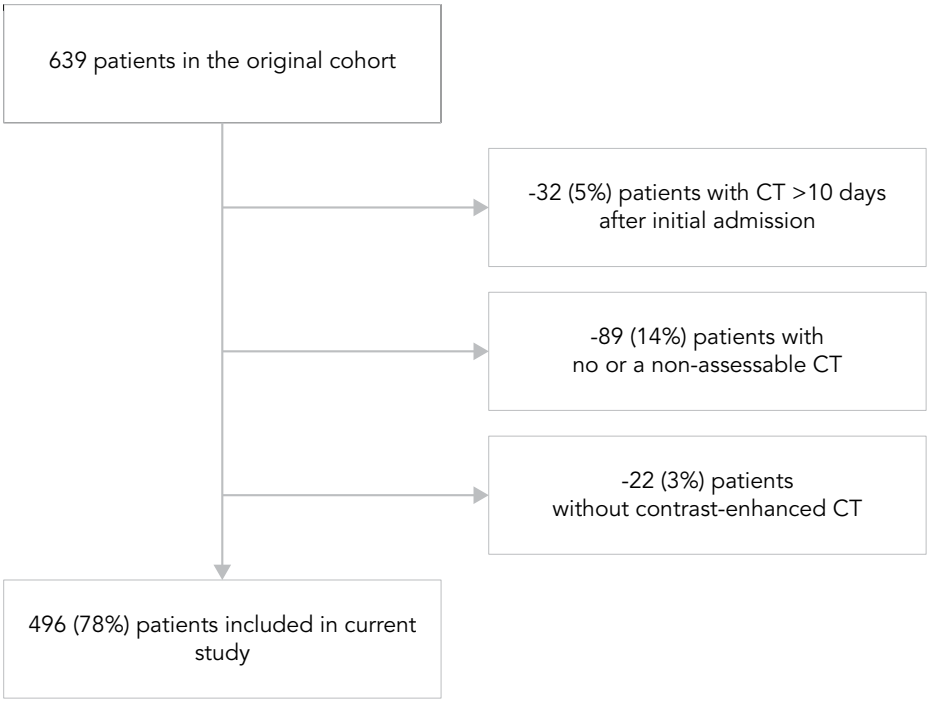


Table 1 Baseline characteristics of 496 patients with necrotizing pancreatitis

Characteristic	All patients (n=496)
Age, years (IQR)	58 (45-70)
Males (%)	308 (62)
BMI, kg/m² (IQR)*	26.7 (25.0-30.2)
<18.5 (%)	3 (1)
18.5-24.9 (%)	61 (25)
25-29.9 (%)	120 (48)
≥30 (%)	64 (26)
Etiology (%)	
Biliary	240 (48)
Alcohol	114 (23)
Other	51 (10)
Unknown	91 (18)
ASA classification on admission (%)	
I (healthy status)	149 (30)
II (mild systemic disease)	272 (55)
III (severe systemic disease)	75 (15)
Organ failure at admission (%)	52 (11)
Predicted severity of pancreatitis	
APACHE II score on admission (IQR)	8 (5-11)
APACHE II score ≥ 8 on admission (%)	254 (51)
Modified Glasgow score within first 48 hours of admission (IQR)	3 (2-5)
Modified Glasgow score ≥3 (%)	320 (65)
Highest CRP level in first 48 hours of admission, mg/L (IQR)	291 (213-381)
CRP level ≥150 mg/L (%)#	397 (86)
Pancreatic necrosis (%)	240 (48)
Time between admission and 1-month CT, days (IQR)	2 (0-5)

Abbreviations: BMI, Body Mass Index (*available for 248 patients); ASA, American Society of Anesthesiologists; APACHE-II, Acute Physiologic and Chronic Health Evaluation (APACHE)-II; CRP; C-Reactive Protein (# available for 463 patients); CT, Computed Tomography. Continuous variables are provided as mean (± Standard Deviation [SD]) or median (Interquartile Range [IQR]) depending on normality of distribution.

Baseline characteristics of the included patients are shown in Table 1. Baseline characteristics and study outcome (in-hospital mortality) did not significantly differ between included and excludedpatients, except the presence of pancreatic necrosis (included patients 48.4% versus excluded patients 58.7%, P = 0.029) and BMI (included patients median BMI 26.7 kg/m2 versus excluded patients median BMI 28.9 kg/m2, P = 0.044). Body height was unknown for 94 (19.0%) patients.

Body composition measurements
For males, the median L3 muscle index and muscle density were 53.7 (IQR 47.5-59.4) cm2/m2 and 34 (28-40) HU, respectively, and for females 44.6 (IQR 38.6-50.2) cm2/m2 and 28 (IQR 20-35) HU, respectively. The median visceral adipose tissue area was 234.3 (IQR 172.2-308.1) cm2 for males and 156.8 (IQR 104.1-220.0) cm2 for females.

Association of body composition with mortality
The median time interval between initial admission and the first abdominal CT was 2 days (IQR 0-5). The mortality rate was 14.5% (72/496) and did not significantly differ between included and excluded (14.7%) patients (P = 0.960). A non-significant association between the lowest L3 muscle index tertile and mortality was found (OR 0.976 (95%CI 0.507-1.878), P = 0.942). Significant univariable associations between the lowest HU tertile and highest VAT tertile and the highest VAT tertile were not independently associated with mortality in multivariable analysis after correcting for age, ASA classification, the presence of pancreatic necrosis, and the presence of organ failure at admission: adjusted OR 1.132 (95%CI 0.617-2.078), P = 0.688 and 1.311 (95%CI 0.732-2.349), P = 0.363 (Table 2). As skeletal muscle mass and density are strongly associated with age,29 subgroup analyses were performed in patients aged <65 and ≥65 years. Patients aged ≥65 in the lowest skeletal muscle density tertile showed an increase mortality rate (29.3%) compared with patients in the mid and highest tertile (13.5%), P = 0.008. Skeletal muscle density in the lowest tertile was associated with an increased risk of in-hospital mortality (adjusted OR 2.54 (95%CI 1.12-5.84), P = 0.025) in patients ≥65 years, independently of ASA classification, organ failure at admission, and pancreatic necrosis. An incremental increase in skeletal muscle density showed a protective effect on mortality (adjusted OR 0.94 (95%CI 0.90-0.99), P = 0.010).

Table 2 Univariable and multivariable logistic regression analysis for risk factors for in-hospital mortality (n=496, 72 patients deceased)

	Univariable		Multivariable	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Sex (male)	0.78 (0.47-1.29)	0.331		
Age (years)	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	<0.001
BMI (kg/m^2)*				
20.0-24.9 (normal)	1 (ref)			
<18.5 vs normal	2.55 (0.21-30.89)			
>25.0-29.9 vs normal	0.62 (0.26-1.51)			
≥30 vs normal	0.73 (0.27-1.99)	0.553		
ASA I-II	1 (ref)			
ASA III	4.33 (2.46-7.62)	<0.001	4.026 (2.17-7.49)	<0.001
Organ failure at admission	5.22 (2.79-9.76)	<0.001	5.49 (2.74-10.99)	<0.001
Pancreatic necrosis	2.42 (1.43-4.09)	0.001	2.98 (1.65-5.38)	<0.001
L3 index (cm^2/m^2)				
Highest and mid tertile	1 (ref)			
Lowest tertile	0.98 (0.51-1.88)	0.942		
Skeletal muscle density (HU)				
Highest and mid tertile	1 (ref)			
Lowest tertile	2.37 (1.43-3.92)	0.001	1.13 (0.62-2.08)	0.688
VAT (cm^2)				
Highest and mid tertile	1 (ref)			
Lowest tertile	1.88 (1.130-3.13)	0.015	1.31 (0.73-2.35)	0.363

Abbreviations: BMI, Body Mass Index (*available for 248 patients); ASA, American Society of Anesthesiologists; VAT, Visceral Adipose Tissue area; OR, Odds Ratio; CI; Confidence Interval.

Predictive accuracy of established risk parameters and body composition parameter

The ROC curves are depicted in Fig. 2, for males and females, separately. In males (Fig. 2a), APACHE II and Modified Glasgow scores showed a poor predictive value (AUC 0.62 and 0.62, respectively) and all body composition parameters a very poor predictive value (AUC ranging from 0.53 to 0.59). In females (Fig. 2b), APACHE II and Modified Glasgow score showed a fair predictive value with AUCs of 0.72 and 0.80, respectively. Skeletal muscle and visceral adipose tissue mass showed a very poor predictive value (AUC 0.52 and 0.59, respectively), whereas skeletal muscle density showed a fair predictive value with an AUC of 0.71.

Skeletal muscle mass and density loss during the disease course

In total, 189 patients (66.7% male, median age 58 years) had a baseline CT and a CT 1 month thereafter with a median time interval of 29 (IQR 25-33) days. In-hospital mortality in these patients was 14.3% (27/189). For males, the median skeletal muscle mass (i.e., cross-sectional skeletal muscle area) decreased from 169.7 (IQR 153.2-193.9) cm2 to 147.9 (IQR 131.5-166.7) cm2 and for females from 125.2 (IQR 112.1-137.3) cm2 to 111.9 (98.9-121.6) cm2 (both $P < 0.001$). This resulted in a median relative difference of 12.9% (IQR 5.8-20.9) and 10.2% (IQR 1.4-18.8), respectively. For males, the median skeletal muscle density decreased from 33 (IQR 27-39) HU to 31 (IQR 23-38) HU and for females from 27 (IQR 20-33) HU to 23 (IQR 15-35) HU (both $P < 0.001$), with median relative differences of 7.2% (IQR −9.1-22.7) for males and 7.5% (IQR −15.0-32.3) for females. Corrected for the time interval between the baseline CT and the followup CT, significant decreases in cross sectional skeletal muscle area of 0.43% (IQR 0.15-0.72) and in skeletal muscle density of 0.28% (IQR −0.41-0.97) per day were observed ($P < 0.001$ and $P = 0.035$, respectively). In total, 110 (58.2%) patients lost ≥10% of cross-sectional skeletal muscle area. Eighty-nine (47.1%) patients experienced ≥10% decrease in skeletal muscle density.

Figure 2
Receiver Operating Curves (ROC) for severity scores (i.e. APACHE II and Modified Glasgow scores) and CT-assessed body composition parameters. Skeletal muscle density (HU) and mass (cm^2/m^2) values have been inverted because lower values represent higher risk.

Figure 2a Males

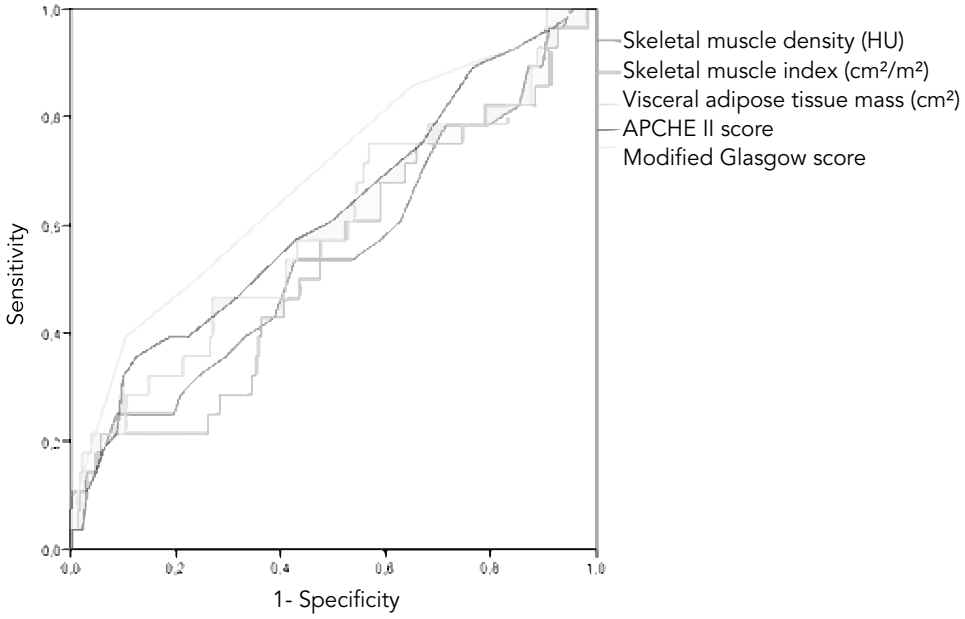
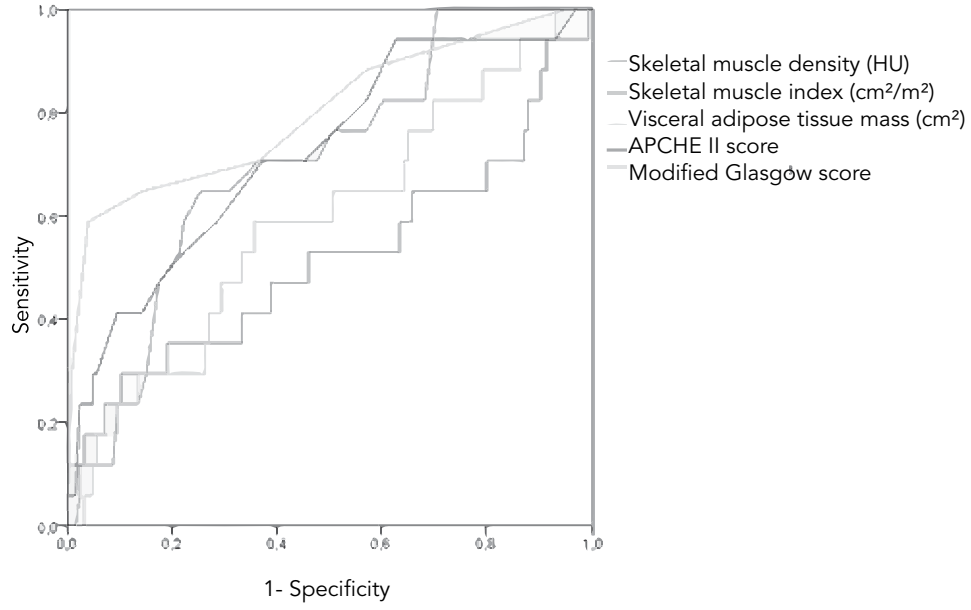


Figure 2b Females



Mortality rate was not significantly different between patients with compared to patients without ≥10% skeletal muscle mass loss (14.5 versus 13.9%, P = 0.904), whereas patients with ≥10% decrease in skeletal muscle density showed an increased risk of mortality (24.7 versus 5.0%, P < 0.001). More than 10% skeletal muscle density loss (adjusted OR 5.87 (95%CI 2.09-16.50), P = 0.001) was an independent risk factor for in-hospital mortality, after correcting for sex and age (Table 3). These patients had a significantly longer hospital (median 70 (IQR 45-106) versus 45 (IQR 23-71) days, P < 0.001) and intensive care unit (median 0 (IQR 0-11) versus 14 (IQR 2-38) days, P < 0.001) stay compared with patients <10% skeletal muscle density loss. Twenty-eight (14.8%) and 48 (25.4%) patients experienced decreases in skeletal muscle mass and density that exceeded 25%. More than 25% skeletal muscle mass loss was not independently associated with increased in-hospital mortality (adjusted OR 2.72 (95%CI 0.98-7.56), P = 0.055) after correcting for age, while a decrease of ≥25% skeletal muscle density was associated with increased in-hospital mortality (adjusted OR 5.4 (95%CI 2.25-13.04), P < 0.001).

Table 3 Association between skeletal muscle mass and skeletal muscle density loss within one month and mortality (n=189, 27 patients deceased)

	Univariable OR (95% CI)	**P**	**Multivariable OR (95% CI)**	**P**
Sex (male)	0.688 (0.30-1.59)	0.380	0.82 (0.33-2.04)	0.669
Age (years)	1.045 (1.01-1.08)	0.007	1.04 (1.01-1.08)	0.016
≥ 10% Skeletal muscle mass loss (cm^2)	1.05 (0.46-2.41)	0.904	0.75 (0.29-1.93)	0.556
≥ 10% Skeletal muscle density loss (HU)	6.24 (2.25-17.30)	<0.001	5.87 (2.09-16.50)	0.001

Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Discussion

This is the first, multicenter study to analyze the association between CT-assessed body composition parameters and mortality in patients with necrotizing pancreatitis. None of the early body composition parameters chosen was associated with in-hospital mortality overall. Nevertheless, low skeletal muscle density was independently associated with mortality in patients aged ≥65. Furthermore, our data suggest that skeletal muscle depletion of ≥10% after 1 month in patients with necrotizing pancreatitis may identify patients at risk for mortality. We hypothesized that CT assessed skeletal muscle mass corrected for body height (low L3 muscle index) was associated with impaired outcome in patients with necrotizing pancreatitis. Although the association between body composition (i.e., skeletal muscle and visceral adipose tissue mass) and outcome has been investigated extensively in cancer populations, [9, 10] some studies have shown its association in benign diseases [11–14]. Low skeletal muscle density was shown to be of prognostic value in patients with renal cell carcinoma [30], lymphoma [31], melanoma [32], and various other malignancies [22]. Moreover, a previous study reported lower mean values of the cross-sectional muscle area, as well as a lower mean BMI in patients with chronic pancreatitis compared with the current study cohort [33]. In the current study among patients with necrotizing pancreatitis, however, neither skeletal muscle mass nor density was related to mortality in the overall population. There are two possible explanations for the differing findings. First, the acute onset of the disease in these a priori relatively healthy patients (85% ASA classification 1–2) could explain the higher index values in our cohort as there was no underlying disease or catabolic state before. Previous studies on this topic primarily investigated patients with metabolically active diseases (e.g., cancer patients) or those with chronic illnesses (e.g., patients awaiting liver transplantation for cirrhosis, patients with chronic pancreatitis). Second, higher age is a significant determinant for sarcopenia (i.e., the involuntary loss of skeletal muscle mass and strength). Prior studies predominantly included older patients (e.g., patients with cancer or abdominal aortic aneurysm), whereas the age of patients with necrotizing pancreatitis is usually considerably lower (median age of 58 years in our study). Our finding in older patients is in line with a previous study on short-term outcomes in colorectal cancer patients. Especially in patients ≥65 years of age, an association was found with increased infectious complication rates, inpatient rehabilitation care, and consequently prolonged hospital stay [29]. Besides skeletal muscle mass and density, the amount of visceral adipose tissue was also not associated with mortality in patients with necrotizing pancreatitis in the current study. This is in line with a previous study, which found no relationship between adipose tissue distribution and pancreatitis

severity [34]. In this particular study, obese patients showed worse predicted severity scores (e.g., by the Ranson score), but abdominal fat distribution was not independently associated with the actual acute pancreatitis severity and mortality. Another recent study found no difference in clinical outcome in ICU-admitted acute pancreatitis patients with or without a decrease in visceral adipose tissue mass [35]. Future studies should further address whether routine assessment of these body composition parameters could be of added value in current (CT) severity index models. Although necrotizing pancreatitis is innately a benign disease, it is characterized by a striking hypercatabolic metabolic state. Based on results of this study, this leads to considerable skeletal muscle loss within 1 month in some patients, which is comparable with or even larger than the loss in palliative cancer patients in 3 to 6 months [36]. Previous studies showed that both prolonged hospital stay and inflammatory processes (such as acute pancreatitis) are known to be associated with skeletal muscle depletion [37, 38]. Also, a significant decrease in skeletal muscle mass has previously been described in various cancer patients undergoing (neo)adjuvant chemotherapy or chemo-radiation therapy. This was associated with increased incidence of postoperative complications in esophageal cancer patients [37]. Furthermore, a decreased survival has been reported in colorectal cancer patients who experienced skeletal muscle depletion [39, 40], but not in esophagogastric cancer patients [41, 42]. Interestingly, in patients with necrotizing pancreatitis, we found that substantial loss of skeletal muscle density (7.2 and 7.5% for males and females, respectively) in the first month after initial admission significantly correlated with mortality. The differing and positive effect of the decline of skeletal muscle mass on mortality in necrotizing pancreatitis compared with other diseases likely relates to the intensity and degree of its loss within a shorter period of time. As such, considerable loss of skeletal muscle mass and density during the course of acute pancreatitis correlates with disease severity and can identify those at high risk of mortality. Furthermore, it is conceivable that considerable alterations in body composition may prolong the period of convalescence in those who survive. A previous study among acute pancreatitis patients who were admitted at the ICU found no skeletal muscle mass loss, whereas a significant decrease in visceral adipose tissue mass was observed [35]. However, this study cohort consisted of only 21 patients and the time interval between CTs was not described. Furthermore, inter-slice variability in visceral adipose tissue due to the position of visceral organs and the potential development of (peri)pancreatic necrosis over time may have contributed to the significant detected decrease in visceral adipose tissue mass, whereas skeletal muscle mass has been measured more reliably. Our findings support the potential beneficial effects of nutritional support in acute pancreatitis. In the early phase, nutrition is essential as it maintains

gut function, prevents ileus, and reduces bacterial overgrowth [43]. Both in the early and late phases of the disease, active nutrient repletion helps tissue repair and healing and may potentially minimize alterations in body composition. However, nutritional support only, as any other monotherapy, will probably not be sufficient [44]. Therefore, future research should focus on nutritional support and other pharmacological agents to counterbalance the detrimental effects of skeletal muscle depletion in patients with necrotizing pancreatitis [44]. Alternative treatment options, such as myostatin inhibition, which reduces skeletal muscle wasting [45], are currently being investigated in phase II clinical trials in cancer patients [46] and might prove useful in acute pancreatitis. Future studies on this topic are highly warranted. This study has some limitations. First, patients were divided in sex-specific tertiles rather than using dichotomous cutoff values, since commonly used cut-off values to classify patients as (non)sarcopenic have been derived only in cancer patients [20-22]. Using optimal stratification to find cut-off values, as has been performed in previous studies [20, 21], was not possible due to the dichotomous character of our primary study end-point (i.e., in-hospital mortality). Another limitation is that our results apply only to patients who eventually develop necrotizing pancreatitis. We feel, however, that inclusion of patients with interstitial disease would not have altered our results in a meaningful way, as mortality is rare in patients with interstitial pancreatitis, who in general recover fast and uneventfully. Finally, as described previously, CTs were not performed routinely or at regular time intervals, but only in patients who showed predicted severe pancreatitis, deteriorated or did not improve clinically [3]. This explains the short median time interval of 2 days between admission and the first CT. Furthermore, the comparable mortality rates between the entire cohort (14.5%) and the cohort of patients who had a CT after 1 month (14.3%) suggest that patients who had no CT after 1 month either had deceased or experienced an uneventful recovery and that early body composition was not associated with mortality. Consequently, this may have led to selection bias and results should therefore be interpreted with caution. In conclusion, neither early skeletal muscle mass and density nor visceral adipose tissue mass are associated with in-hospital mortality in patients with necrotizing pancreatitis. However, low skeletal muscle density was independently associated with in hospital mortality in patients ≥65 years. Furthermore, significant decreases in skeletal muscle mass and density were observed in the first month after initial admission. A decrease of ≥10%in skeletal muscle density within the first month after admission may identify patients at increased risk for mortality. Future prospective studies should investigate the true value of CT-assessed skeletal muscle mass and density, visceral adipose tissue, and its losses, to predict patient outcome in acute (necrotizing) pancreatitis and determine whether (prophylactic) treatment allows counteracting the deleterious effects of body composition alterations.

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PART II

DRAINAGE AND DEBRIDEMENT TECHNIQUES

5

CHAPTER 5

Proactive versus standard percutaneous catheter drainage for infected necrotizing pancreatitis

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Abstract

Objectives
Percutaneous catheter drainage (PCD) is often the first invasive treatment step for infected necrotizing pancreatitis. A proactive PCD strategy, including frequent and early drain revising and upsizing, may reduce the need for surgical necrosectomy and could improve outcomes, but data are lacking.

Methods
Necrotizing pancreatitis patientswere identified from in-hospital databases (2004–2014). Patients with primary PCD for infected necrotizing pancreatitis were included. Outcomes of patients from 1 center using a proactive PCD strategy were compared with 3 standard strategy centers.

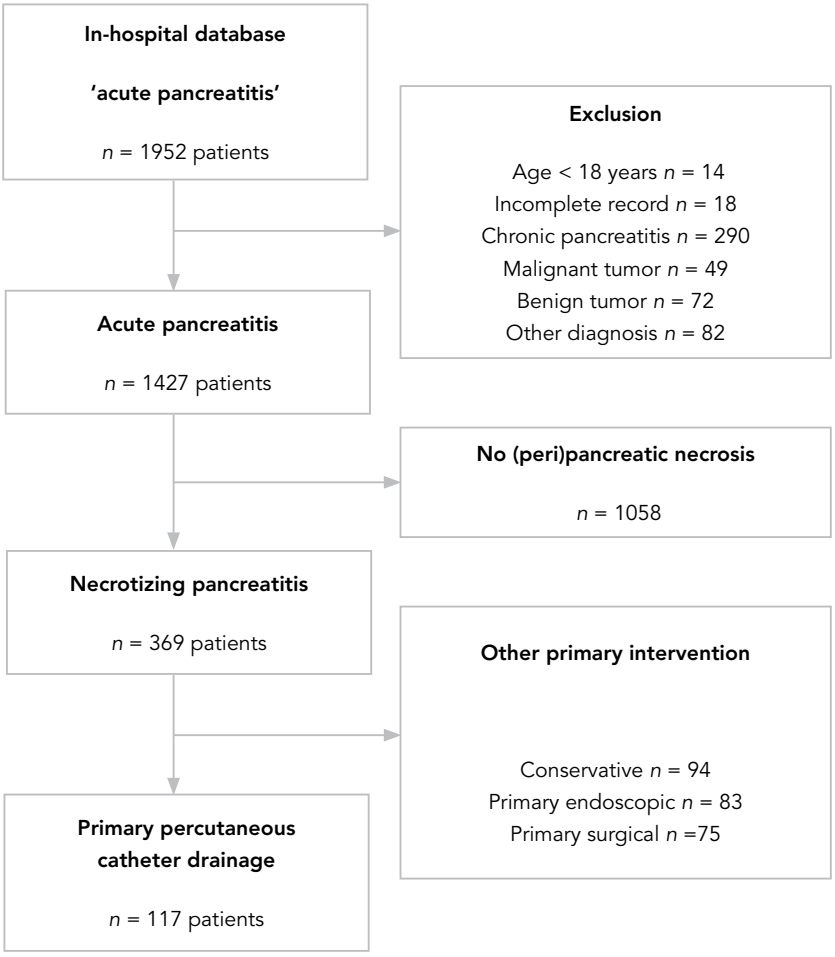
Results
In total, 369 (25.9%) of 1427 patients received a diagnosis of necrotizing pancreatitis, and 117 (31.7%) of 369 patients underwent primary PCD for infected necrosis: 42 in the proactive group versus 75 in the standard group. Patients in the proactive group had more drain-related procedures (median, 3; interquartile range [IQR], 2–4; versus 2; IQR, 1–2; $P < 0.001$) and larger final drain sizes (median, 16F; IQR, 14F–20F; versus 14F; IQR, 12F–14F; $P < 0.001$). Fewer patients underwent additional necrosectomy in the proactive group, 12 (28.6%) versus 39 (52.0%) (adjusted odds ratio, 0.349; 95% confidence interval, 0.137–0.889; $P = 0.027$), with similar hospital stay and mortality.

Conclusions
A proactive PCD strategy is associated with reduced need for necrosectomy in infected necrotizing pancreatitis, compared with standard PCD, with similar clinical outcomes.

Introduction

Necrotizing pancreatitis complicates 20% of all acute pancreatitis episodes [1, 2]. In 30% of these patients, secondary infection of the (peri)pancreatic necrosis occurs, which is almost always an indication for invasive intervention [1, 2]. Recent evidence- and consensus-based international guidelines advice a step-up approach, starting with (either percutaneous or endoscopic) catheter drainage, followed by, if necessary, a (surgical or endoscopic) necrosectomy [3, 4]. The step-up approach reduces the rate of major morbidity, albeit not mortality, and is now accepted by international experts as the strategy of first choice [5, 6]. Percutaneous catheter drainage (PCD) is the first step of the step-up approach. An additional necrosectomy is indicated only in patients who do not clinically improve after catheter drainage [7]. Percutaneous catheter drainage is technically feasible in 95% of patients and is the only invasive treatment required in at least one third of patients [5, 8]. Consensus on the technical details of PCD is lacking, and varying strategies exist [6]. Outcomes after primary PCD for infected necrosis vary greatly with mortality rates ranging from 4% to 29% [5, 9-19]. These differences might be explained by differences in PCD strategy, for example, number of drainage procedure, drain size, and timing of first and additional drainage, but these variables are only rarely reported. The aim of this study was to compare a proactive PCD strategy, including frequent and early drain revisions and upsizing to larger drains, with a standard PCD strategy in terms of need for necrosectomy and overall outcome in the step-up approach toward patients with (suspected) infected necrotizing pancreatitis.

Figure 1 Flowchart of in- and excluded patients



Materials and methods

Design and setting

This retrospective observational cohort study was performed according the recommendations of the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [20]. Patients were included in 4 pancreatitis tertiary referral centers of the Dutch Pancreatitis Study Group. One center (Academic Medical Center, Amsterdam, the Netherlands) used a proactive PCD strategy in patients with infected necrotizing pancreatitis, whereas the other 3 centers (Erasmus Medical Center Rotterdam, St Antonius Hospital Nieuwegein, and University Medical Center Groningen) used a standard PCD strategy. The proactive PCD strategy consisted of frequent and early drain revision and upsizing of drains in case of lack of clinical improvement. The standard PCD strategy consisted of a maximum of 1 to 2 drainage procedures without routine upsizing of drains, but an early "step-up" with minimally invasive necrosectomy (ie, video-assisted retroperitoneal debridement) in case of lack of clinical improvement. Based on the previous PANTER trial, all 4 centers used a standard drain flushing protocol of at least 50 mL saline 3 times daily [5].

Patients

The administrative code for acute pancreatitis was used to identify all patients admitted from January 2004 until May 2014. After screening electronic patient records, all patients with necrotizing pancreatitis primary treated with PCD for suspected or documented infected (peri)pancreatic necrosis were included. Patients younger than 18 years, with incomplete admission records and conservative or primary endoscopic or surgical treatment for infected necrosis, were excluded.

Baseline characteristics

The following baseline characteristics were collected; sex, age, American Society of Anesthesiologists classification, disease etiology, and hospital transfer. Also, clinical parameters indicating disease severity, maximal 48 hours prior to first PCD, were collected: presence of (multi)organ failure, body temperature, leukocyte count, and C-reactive protein. Acute Physiologic and Chronic Health Evaluation II scores and modified Glasgow Coma Scale scores were calculated, if sufficient clinical parameters were available [21,22].

An experienced radiologist (K.P.v.L.) assessed all computed tomography (CT) scans made before primary PCD for; number and location of necrotic collections, extent of pancreatic necrosis, CT severity index, and the presence of gas configurations in the collections. In addition, information about the first PCD procedure was collected: timing of first PCD procedure (days from admission), size of the first drain used (in French), number of drains placed at first procedure, drain location, and positive microbiological cultures from the first PCD.

Outcomes

Patients were analyzed in 2 groups: proactive PCD strategy versus standard PCD strategy. The groups were compared for (re) interventions; recovery after 1 PCD procedure, total number of PCD procedures, time between first and second drainage (in days), maximal final drain size (in French), total duration of PCD (in days), need for necrosectomy, and number of necrosectomies. Length of index hospital admission (days from first drainage to discharge), need for new intensive care unit (ICU) admission, and readmission were analyzed in both groups. A readmission within 10 days was considered 1 primary hospital admission. Severe complications, that is, bleeding requiring invasive intervention or blood transfusion, new-onset (multi) organ failure, and mortality, were also reported.

Statistical analysis

Data were analyzed using IBMSPSS Statistics forWindows, version 22.0 (IBM Corp, Armonk, NY). Outcomes were reported as counts and percentages for categorical variables. Continuous variables were summarized as either means with corresponding SD or medians with interquartile ranges (IQRs), depending on normality distribution. For analyzing the differences between the 2 strategy groups, a ×2 test was used for categorical variables, a Student t test was used for continuous normally distributed variables, and a Mann-Whitney U test was used for non–normally distributed continuous variables. $P < 0.050$ was considered statistically significant. Significant univariable associations between PCD strategy and outcomes were adjusted for confounding factors and baseline differences ($P < 0.050$) using multivariable regression analyses.

Results

Patients

In the 4 participating centers, 1952 unique patients were identified from January 2004 to May 2014. Next, patient files were screened, and patients were excluded for various reasons as shown in Figure 1. In total, 1427 patients (73.1%) were confirmed to have acute pancreatitis. After further excluding 1058 patients (74.1%) without necrosis, 369 patients with necrotizing pancreatitis remained. Of these 369 patients, 252 patients (68.3%) were excluded because they either were treated conservatively (e.g., sterile necrosis, n = 94) or had a primary endoscopic (n = 83) or primary surgical intervention (n = 75). In total, 117 patients were initially treated with PCD and included in this study.

Baseline characteristics

In total, 42 patients (35.9%) were treated in the proactive PCD strategy center versus 75 patients (64.1%) in the standard PCD strategy centers (Table 1). Patients in the proactive PCD group were younger than those in the standard PCD group (59 [SD, 15)years vs 64 [SD, 14] years; P = 0.043). The proportion of patients with (multi)organ failure was comparable between groups. The first PCD procedure in both groups was similar concerning start drain size and number and location of first drains placed (Table 2). Only the timing of first PCD was different (median, 27 days after admission [IQR, 17-48 days] in the proactive PCD group vs 21 days [IQR, 11-31 days] in the standard PCD group; P = 0.011). The majority of patients had a positive culture of the first drain fluid, 27 patients (73.0%) versus 55 patients (84.6%), respectively, P = 0.154

Table 1 Baseline characteristics: proactive vs. standard PCD strategy

Data are presented as number (%), mean (SD), or median (IQR). *Data based on clinical parameters maximal 48 hours prior primary drainage. †Ranges from 0 to 8. ‡Data were derived from the CT closest to primary drainage. §Score ranges from 0 to 10. APACHE II indicates Acute Physiologic and Chronic Health Evaluation II (score ranges from 0 to 71); ASA, American Society of Anesthesiologists.

	Proactive PCD strategy n=42	Standard PCD strategy n=75	P-value
Sex, male, n (%)	29 (69.0)	49 (65.3)	0.683
Age, mean (SD), y	59 (15)	64 (14)	0.043
ASA classification, n (%) (n = 113)			0.817
I Healthy status	9 (23.7)	22 (29.3)	
II Mild systemic disease	23 (60.5)	42 (56.0)	
III Severe systemic disease	6 (15.8)	11 (14.7)	
Cause of pancreatitis, n (%) (n = 97)			0.798
Biliary	13 (35.1)	21 (35.0)	
Alcohol	6 (16.2)	7 (11.7)	
Other	18 (48.6)	32 (53.3)	
Transferred from another center, n (%)	37 (88.1)	57 (76.0)	0.114
Clinical parameters*			
Organ failure, n (%) (n = 116)			0.422
No organ failure	21 (51.2)	32 (42.7)	
Single organ failure	8 (19.5)	23 (30.7)	
Multi organ failure	12 (29.3)	20 (26.7)	
Temperature, median (IQR), °C (n = 83)	38.4 (37.3-39.2)	38.2 (37.3-38.8)	0.747
Leukocyte count, median (IQR), 10-9/L (n = 103)	17.4 (11.2-23.7)	16.4 (11.8-22.0)	0.633
C-reactive protein, median (IQR), mg/L (n = 101)	157 (87-244)	210 (122-301)	0.136
APACHE II score ≥8, n (%) (n = 104)	30 (81.1)	53 (79.1)	0.810
Modified Glasgow Coma Scale score ≥3,† n (%) (n = 94)	18 (48.6)	37 (64.9)	0.118
Imaging‡ (n = 110)			
No. of necrotic collections, median (IQR)	2 (1-3)	2 (1-3)	0.301
Location of necrotic collections, n (%)			0.062
Left	14 (34.1)	39 (56.5)	
Right	1 (2.4)	0 (0.0)	
Central	15 (36.6)	21 (30.4)	
Diffuse	11 (26.9)	9 (13.1)	
Extent of pancreatic necrosis, n (%)			0.494
< 30%	4 (9.8)	8 (11.6)	
30-50%	5 (12.2)	14 (20.3)	
> 50%	32 (78.0)	47 (68.1)	
CT severity index, § median (IQR)	10 (9-10)	10 (8-10)	0.179
Gas in necrotic collection, n (%)	20 (47.6)	34 (50.0)	0.808

Outcomes

The total number of PCD procedures was higher in the proactive PCD group (median, 3 procedures [IQR, 2-4 procedures] vs 2 procedures [IQR, 1-2 procedures]; P < 0.001; Table 3). Time between the first and second PCD procedures was shorter in the proactive PCD group (median, 7 days [IQR, 4-18 days] vs 14 days [IQR, 8-23 days]; P = 0.092). Patients in the proactive PCD group had larger final drain sizes (median, 16F [IQR, 14F-20F] vs 14F [IQR, 12F-14F; P < 0.001]; and 17 patients [42.5%] vs 6 patients [8.8%; P < 0.001] with a final drain of 20F or larger). Fewer patients underwent an additional necrosectomy in the proactive PCD group, 12 patients (28.6%) versus 39 patients (52.0%), P = 0.014. Both groups did not differ in length of hospital stay after primary PCD, new-onset ICU admission, or need for readmission. Bleeding complications and mortality were comparable in both groups, 7 patients (17.1%) versus 14 patients (19.4%), respectively (P = 0.755), and 7 (16.7%) versus 14 (18.7%) patients (P = 0.787), respectively. Fewer patients had new-onset (multi)organ failure in the proactive PCD group, 4 patients (10.0%) versus 22 patients (30.1%), P = 0.015. After adjusting for potential confounding factors, that is, sex, age, and timing of first drainage with multivariable regression, treatment in a proactive drainage strategy center was independently associated with a reduced need for necrosectomy (adjusted odds ratio, 0.349 [95% confidence interval, 0.137-0.889]; P = 0.027), but not independently associated with less new (multi)organ failure (adjusted odds ratio, 0.325 [95% confidence interval, 0.083-1.273]; P = 0.107).

Table 2 Characteristics of the first catheter drainage procedure: proactive vs. standard PCD strategy

	Proactive PCD strategy n=42	Standard PCD strategy n=75	P-value
Days from admission to drainage, median (IQR) (n = 103)	27 (17-48)	21 (11-31)	0.011
Drain size, median (IQR) (n = 106)	14F (12F-15F)	14F (10F-14F)	0.134
No. of drains, median (IQR) (n = 111)	1 (1-2)	1 (1-1)	0.129
Drain location, n (%) (n = 103)			0.687
Left retroperitoneal	23 (65.7)	52 (76.5)	
Right retroperitoneal	2 (5.7)	2 (2.9)	
Trans abdominal	6 (17.1)	8 (11.8)	
Combination	4 (11.4)	6 (8.8)	
Positive culture of drain fluid, n (%) (n = 102)	27 (73.0)	55 (84.6)	0.154

Data are presented as number (%) or median (IQR).

Table 3 Outcomes: proactive vs. standard PCD strategy

	Proactive PCD strategy n=42	Standard PCD strategy n=75	P-value
Re-interventions			
Recovery after 1 PCD procedure, n (%) (n = 114)	2 (4.9)	8 (11.0)	0.271
Total no. of drainage procedures, median (IQR)	3 (2-4)	2 (1-2)	< 0.001
Time between PCD 1 and 2, median (IQR), d (n = 73)	7 (4-18)	14 (8-23)	0.092
Maximal final drain size, median (IQR) (n = 108)	16 (14-20)	14 (12-14)	< 0.001
Final drain size ≥20F, n (%) (n = 108)	17 (42.5)	6 (8.8)	< 0.001
Total drainage duration, median (IQR), d (n = 89)	42 (16-92)	52 (31-86)	0.254
Need for necrosectomy, n (%)	12 (28.6)	39 (52.0)	0.014
No. of necrosectomies, median (IQR)	0 (0-1)	1 (0-1)	0.013
Admission			
Length of hospital stay after drainage,* median (IQR), d (n = 109)	42 (21-92)	46 (25-81)	0.835
Need for new ICU admission, n (%) (n = 109)	4 (10.5)	16 (22.5)	0.123
Need for readmission, n (%) (n = 116)	8 (19.0)	24 (32.4)	0.121
Complications			
Bleeding requiring intervention,† n (%) (n = 113)	7 (17.1)	14 (19.4)	0.755
New-onset (multi)organ failure,‡ n (%) (n = 113)	4 (10.0)	22 (30.1)	0.015
Mortality, n (%)	7 (16.7)	14 (18.7)	0.787

Data are presented as number (%) or median (IQR). *From first drainage to discharge. †Bleeding after primary drainage requiring invasive intervention or blood transfusion. ‡New multiorgan failure after primary drainage.

Discussion

This first multicenter study on technical details of PCD in the step-up approach to infected necrotizing pancreatitis suggests that multiple drainage procedures are nearly always required, and a "proactive" PCD strategy reduces the need for further necrosectomy without differences in clinical outcomes.

With 117 patients, this is the largest cohort of patients treated with primary PCD for infected necrosis. To our knowledge, there are no other studies known comparing different PCD strategies in this patient category. Current international guidelines provide no specific details on the PCD strategy in the step-up approach to infected necrotizing pancreatitis [3, 4]. In a recent survey, 58 of 87 international expert pancreatologists (67%) felt that upsizing of drains was a potential useful measure [6]. In a randomized controlled trial comparing the surgical step-up approach with primary open necrosectomy, 15 (35%) of 43 patients were successfully treated with PCD alone (median drain size, 14F, with median of 1 drain procedure) without additional necrosectomy [5]. A systematic review, including mostly retrospective studies, reported a success rate of 56% for PCD treatment alone (214 of 384 patients) [8]. Drain sizes varied from 8F to 28F. No accurate mean number of procedures could be calculated because most reports did not provide these data. The results of the systematic review correspond with our standard PCD group success rate of 48% for treatment with PCD alone. However, in the current study, 71% of patients treated with a proactive PCD strategy did not undergo necrosectomy. Besides a reduced need for necrosectomy, no differences in clinically relevant outcomes (e.g., new-onset organ failure, mortality) were found, although a type II error cannot be excluded.

A previous study of our group did not identify drain size and upsizing as independent predictors for success of catheter drainage [23]. This study, however, included patients up to 2008, whereas the current study included patients until 2014, the period wherein the proactive PCD strategy was introduced. Furthermore, in the previous study, the median number of drainage procedures was 1 versus 3 in the proactive PCD strategy in this study. These factors might explain the higher success rate of treatment with PCD alone in the current study (71%). Probably not only the absolute drain size, but also the complete strategy including frequent and early drain revision, is of additional value. This is also suggested in a recently published study of patients in whom a proactive PCD protocol (including frequent drain revising and upsizing) appeared to improve outcome, although the majority of these patients had sterile necrosis (27/39 patients [69%]) [24].

Because of the multiple PCD procedures, one might expect a longer hospital stay and longer duration of drainage in the proactive PCD group. However, we did not find any differences. Whether to prefer less necrosectomies or less PCD procedures is debatable and cannot be determined from these data. A video-assisted retroperitoneal debridement procedure and other minimally invasive necrosectomy techniques are known to be relatively safe and effective in 1 to 2 procedures [5, 25]. However, these procedures require general anesthesia and surgical expertise. On the other hand, PCD procedures are performed under local anesthesia and often easily available in many hospitals. Nevertheless, drain revising and upsizing also require dedicated and experienced interventional radiologists.

Time between admission and first PCD was different in both groups, with a median of 27 days in the proactive PCD group versus median 21 days in the standard PCD group (P = 0.011; Table 2). This might be caused by the referral pattern to the proactive PCD center. The number of transferred patients was, however, high in both groups and not significantly different, 37 (88.1%) versus 57 patients (76.0%), P = 0.114. When excluding the transferred patients in both groups, timing of first drainage was comparable (median, 20 days [IQR, 4-29 days] in the proactive PCD group vs 16 days [IQR, 11-24 days] in the standard PCD group; P = 0.865).

The current study has its limitations. First, we performed a retrospective study, which explains our missing data on some baseline characteristics and outcomes. Second, in an attempt to minimize selection bias, we compared centers routinely using different PCD strategies, rather than comparing individual patients. This choice may have introduced some center-specific treatment bias, for example, additional noninvasive treatment, and the expertise of local physicians. Because all 4 hospitals are tertiary referral centers and longstanding participants in the Dutch Pancreatitis Study Group, these differences are expected to be small. Third, there were no detailed data available on the flushing of drains. As mentioned, however, the general drain management was similar and based on the previous PANTER trial, in which all 4 centers participated [5]. Nevertheless, differences between centers (e.g., continuous flushing system on percutaneous drains) cannot be excluded. Fourth, our primary end point, additional necrosectomy, is a rather subjective measure, because proceeding to necrosectomy is a decision of the treating physician in the end.

In addition to a surgical approach toward infected necrotizing pancreatitis, the endoscopic treatment of patients with infected necrotizing pancreatitis has gained popularity [26-28]. Endoscopic treatment can also be conducted in a step-up fashion, starting with endoscopic transluminal drainage via stomach or duodenum [29]. In this study, patients with primary endoscopic drainage were excluded, because endoscopic drain management differs from PCD. Although beyond the scope of this study, it would be interesting to compare different endoscopic drainage strategies. Regarding the optimal PCD strategy, future prospective studies should focus on adequate start size, maximum number of drain procedures before proceeding to necrosectomy, flushing management, and timing of primary and additional drainage. The latter is done in the ongoing POINTER trial (ISRCTN33682933), comparing a direct primary drainage strategy with a postponed primary drainage strategy. Besides in-hospital complications for different PCD strategies, long-term outcomes such as pancreatic fistula, pancreas insufficiency, quality of life, and medical costs also should be taken into account. Unfortunately, following our retrospective data, a treatment algorithm of when to proceed to a re-intervention (i.e., drain revising or upsizing or minimally invasive necrosectomy) cannot be made. Therefore, a prospective study, including standardized decision making for re-intervention, is needed.

In conclusion, a proactive PCD strategy is associated with a reduced need for additional necrosectomy in patients with (suspected) infected necrotizing pancreatitis. A proactive PCD strategy seems to be safe and effective with similar outcomes as a standard PCD strategy center. Further (preferably randomized) studies should assess the true value and the ideal content of the proactive PCD strategy.

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CHAPTER 6

Endoscopic or surgical step-up approach for infected necrotising pancreatitis (TENSION trial): a multicentre randomised trial

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Abstract

Background
Infected necrotising pancreatitis is a potentially lethal disease and an indication for invasive intervention. The surgical step-up approach is the standard treatment. A promising alternative is the endoscopic step-up approach. We compared both approaches to see whether the endoscopic step-up approach was superior to the surgical step-up approach in terms of clinical and economic outcomes.

Methods
In this multicentre, randomised, superiority trial, we recruited adult patients with infected necrotising pancreatitis and an indication for invasive intervention from 19 hospitals in the Netherlands. Patients were randomly assigned to either the endoscopic or the surgical step-up approach. The endoscopic approach consisted of endoscopic ultrasound-guided transluminal drainage followed, if necessary, by endoscopic necrosectomy. The surgical approach consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement. The primary endpoint was a composite of major complications or death during 6-month follow-up. Analyses were by intention to treat. This trial is registered with the ISRCTN registry, number ISRCTN09186711.

Findings
Between Sept 20, 2011, and Jan 29, 2015, we screened 418 patients with pancreatic or extrapancreatic necrosis, of which 98 patients were enrolled and randomly assigned to the endoscopic step-up approach (n=51) or the surgical step-up approach (n=47). The primary endpoint occurred in 22 (43%) of 51 patients in the endoscopy group and in 21 (45%) of 47 patients in the surgery group (risk ratio [RR] 0·97, 95% CI 0·62–1·51; p=0·88). Mortality did not differ between groups (nine [18%] patients in the endoscopy group vs six [13%] patients in the surgery group; RR 1·38, 95% CI 0·53–3·59, p=0·50), nor did any of the major complications included in the primary endpoint.

Interpretation
In patients with infected necrotising pancreatitis, the endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group. The outcome of this trial will probably result in a shift to the endoscopic step-up approach as treatment preference.

Introduction

Acute pancreatitis is a potentially lethal disease with increasing incidence. Approximately 10-20% of patients develop necrosis of pancreatic parenchyma or extrapancreatic tissues [1, 2]. Moreover, about one third of these patients develop infection of the necrotic tissue, which generally requires an invasive intervention [3].

In the past 10 years, the surgical step-up approach, consisting of percutaneous catheter drainage followed, if necessary, by minimally invasive necrosectomy, has replaced open surgery as the standard treatment [4, 5]. A randomised trial of the surgical step-up approach versus primary open necrosectomy showed that catheter drainage as a first step obviates the need for necrosectomy in 35-50% of patients [4, 6].

An endoscopic step-up approach is a potentially less invasive alternative. Endoscopic necrosectomy has shown promising results in reducing complications in several observational studies and one small pilot randomised trial [7, 8]. These favourable results were explained by the absence of general anaesthesia and surgical exploration with a reduction of surgical stress and surgeryassociated complications such as pancreatic fistulas. The endoscopic approach can also be performed in a step-up fashion, starting with endoscopic transluminal drainage, only to be followed by endoscopic necrosectomy if drainage does not result in clinical improvement.

We did a multicentre randomised trial to investigate whether the endoscopic step-up approach is superior to the surgical step-up approach in patients with infected necrotising pancreatitis.

Methods

Study design and participants

In this multicentre, randomised, superiority trial, we recruited adult (≥18 years of age) patients from seven university medical centres and 12 teaching hospitals of the Dutch Pancreatitis Study Group with a high suspicion or evidence of infection of pancreatic or extrapancreatic necrotic tissues (ie, infected necrosis) with an indication for invasive intervention, for whom both the endoscopic and surgical step-up approach were deemed feasible by a multidisciplinary expert panel. We defined infected necrosis as a positive culture obtained by fine-needle aspiration or the presence of gas within necrotic collections on contrast-enhanced CT. Infected necrosis was suspected in necrotising pancreatitis patients with clinical signs of persistent sepsis or progressive clinical deterioration despite maximal support on the intensive care unit (ICU) without other causes for infection. Key exclusion criteria were previous invasive interventions for necrotising pancreatitis, chronic pancreatitis, and recurrent acute pancreatitis. Further exclusion criteria are given in the Appendix.

All patients or their legal representatives provided written informed consent before randomisation. The study protocol [9] was approved by the institutional review board of the Academic Medical Centre Amsterdam and all other participating centres, and the study was conducted according to this protocol. All authors vouched for the accuracy and completeness of the data and analyses.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to either the endoscopic step-up approach or the surgical step-up approach. Block randomisation with a concealed, fixed block size and stratified by treatment centres was performed centrally by the study coordinators (SvB and JvG) using a web-based randomisation program. Owing to the unfeasibility of masking, all participants and physicians were aware of treatment allocation.

Procedures

An expert panel consisting of 17 experts (nine gastrointestinal surgeons, four gastrointestinal endoscopists, and four radiologists [including MAB, TLB, MJB, VCC, CHD, CHvE, HvG, J-WH, SHH, JSL, KPvL, VBN, J-WP, RT, HGG, and PF]) assessed the indication, timing, and feasibility of both the endoscopic and surgical step-up approaches for all patients [4]. Whenever possible, randomisation and intervention were postponed until 4 weeks after onset of pancreatitis in line with international guidelines [5].

Treatment strategies were standardised across sites. Patients assigned to the endoscopy group underwent endoscopic ultrasound-guided transluminal (ie, transgastric or transduodenal) drainage with placement of two 7 Fr (2·3 mm diameter) double pigtail stents and one 8·5 Fr (2·8 mm) nasocystic catheter as the first step. If drainage alone did not lead to considerable clinical improvement, endoscopic transluminal necrosectomy was performed [9].

Patients assigned to the surgery group underwent radiological CT-guided or ultrasound-guided percutaneous catheter drainage as first step. The preferred route was through the left retroperitoneum with the catheter as guidance for video-assisted retroperitoneal debridement (VARD), if needed. For most collections, this route is the shortest and thereby often the safest. Furthermore, the drain remains retroperitoneal and does not infect the intraabdominal space [4, 10]. If drainage was clinically unsuccessful a VARD procedure was performed [11].

In both treatment groups, additional endoscopic as well as percutaneous drainage and endoscopic or surgical necrosectomies were allowed. All interventions were done by experienced endoscopists, surgeons, and interventional radiologists. Details on both treatment groups, interventions, postoperative management, and criteria for clinical improvement are in the Appendix. Routine laboratory tests were done at randomisation and for the 7 consecutive days after, as per daily clinical practice. Follow-up visits were 3 and 6 months after randomisation. Patients were asked to complete a questionnaire, a CT was performed, and exocrine and endocrine pancreatic function were measured (Appendix).

Data were collected by local physicians using a standardised case record form (CRF). An independent monitor, unaware of the treatment assignments, checked all endpoints and CRFs with on-site source data. Discrepancies were resolved through consensus among two investigators who were unaware of treatment allocation and not involved in patient care. All CTs were reviewed by an experienced abdominal radiologist (TLB) unaware of the treatment group and outcomes.

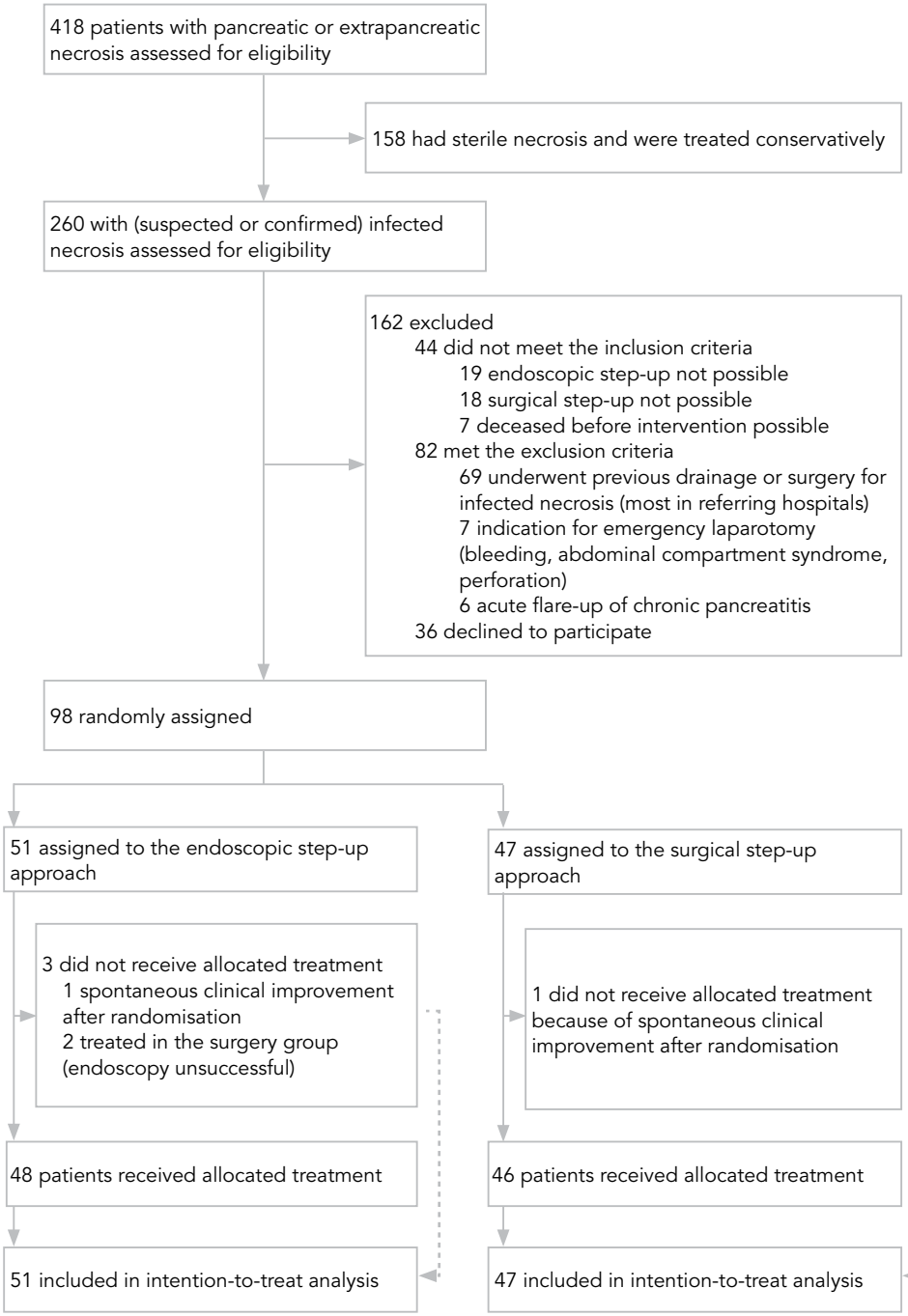
Outcomes

The primary endpoint was a composite of major complications or death within 6 months after randomisation. Major complications were defined as new-onset organ failure (ie, cardiovascular, pulmonary, or renal), bleeding requiring intervention, perforation of a visceral organ requiring intervention (except for the intentionally made perforation during endopscopic treatment), enterocutaneous fistula requiring intervention, and incisional hernia (including burst abdomen). Predefined secondary endpoints included the individual components of the primary endpoint, pancreatic fistula, exocrine and endocrine pancreatic insufficiency, biliary strictures, wound infections, need for necrosectomy, total number of interventions, length of hospital and ICU stay, costs (eg, costs per patient with poor outcome, costs per qualityadjusted life-year [QALY], and total direct and indirect medical costs), quality of life, and the total number of crossovers between groups (for definitions of these primary and secondary endpoints see the Appendix).

An adjudication committee composed of five surgeons, three endoscopists, and one radiologist performed a blinded outcome assessment. They individually evaluated each patient for the occurrence of the primary endpoint. Disagreements were resolved during a plenary consensus meeting before data analysis started.

After enrolment of each consecutive group of 25 patients, an independent data safety and monitoring committee evaluated the progress of inclusion and safety endpoints for each patient with unblinded data. Patient reports and a list of potential adverse events were presented to the data safety and monitoring committee (see Appendix).

Figure Trial profile



Statistical analysis

Based on an expected absolute reduction in the primary composite endpoint of 26% (from 43% to 17%) with a twosided α of 5%, power of 80%, and 2% loss to follow-up, we calculated a total sample size of 98 patients. The expected reduction in the primary endpoint in favour of the endoscopic step-up approach was based on the results of various cohort studies, systematic reviews, and a small randomised controlled pilot trial [7, 12-23].

We present results as relative risks with corresponding 95% CIs. We compared dichotomous data with Fisher's exact test, continuous data with the Mann-Whitney U test, and categorical data with the linear-by-linear association test.

All primary analyses were by intention to treat. We also did per-protocol analyses. We did a formal test of interaction using logistic regression to assess whether treatment effects differed significantly between predefined subgroups (ie, patients with singular or multiple organ failure at randomisation, academic or non-academic institutions, and time between onset of symptoms and randomisation [<28 vs ≥28 days]).

We did no interim analyses. We considered a two-sided p value of less than 0·05 to be statistically significant, and did not adjust p values for multiple testing. Additional details on the statistical analyses are in the Appendix.

We calculated costs as the product sum of the number of resources used and their respective unit costs. Qualityadjusted life-years (QALYs) were calculated as the product sum of EQ-5D-3L-based health utilities at successive measurements during follow-up (3 and 6 months after randomisation) and the lengths of times in between measurements and baseline. We calculated confidence intervals for between-group differences using biascorrected and accelerated (BCa) bootstrapping, stratified by treatment group and drawing 1000 samples of the same size as the original sample separately for each group and with replacement. Lastly, we did several non-specified posthoc analyses of the primary endpoints, which are presented in the Appendix.

This trial is registered with the ISRCTN registry, number ISRCTN09186711.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 20, 2011, and Jan 29, 2015, 418 patients with pancreatic or extrapancreatic necrosis in 19 Dutch hospitals were screened, of which 98 were eligible (figure). 51 patients were randomly assigned to the endoscopic step-up approach and 47 to the surgical stepup approach. In each treatment group, one patient did not undergo any intervention because of spontaneous clinical improvement shortly after randomisation. In two other patients in the endoscopy group, owing to the technical difficulty of the drainage procedure, the endoscopist was not able to successfully puncture the collection. These two patients underwent treatment within the surgical step-up approach and were analysed according to the intention-to-treat principle in the endoscopy group. Baseline characteristics were equally distributed between groups (table 1).

The primary composite endpoint occurred in 22 (43%) patients in the endoscopy group and in 21 (45%) in the surgery group (relative risk 0·97, 95% CI 0·62–1·51; p=0·88; table 2). We observed no significant difference in new-onset single organ failure between groups (table 2); however, new-onset cardiovascular organ failure and persistent cardiovascular organ failure occurred more frequently in the surgery group (table 2). We observed no differences in major complications including bleeding, perforation of a visceral organ, enterocutaneous fistula, and incisional hernia. Mortality was similar in both groups (table 2). The causes of death between both groups did not differ, with most patients dying because of progressive sepsis (two [22%] of nine patients in the endoscopy group, two [33%] of six in the surgery group) and multiple organ failure (four [44%] in the endoscopy group, two [33%] in the surgery group).

The incidence of pancreatic fistulas was lower in the endoscopy group than in the surgery group (table 2). All patients with pancreatic fistulas required persistent drainage during follow-up and nine (60%) of these patients (one patient in the endoscopy group and eight in the surgery group) underwent an additional endoscopic retrograde cholangiopancreatography with pancreatic sphincterotomy or stent placement. At 6-month followup, we observed no differences regarding exocrine and endocrine insufficiency, biliary strictures, and wound infections (table 2).

Mean length of hospital stay was 16 days shorter in the endoscopy group compared with the surgery group (table 2). 22 (43%) patients in the endoscopy group and 24 (51%) patients in the surgery group were treated with catheter drainage only (table 2). The remaining patients underwent necrosectomy, occurring sooner in the endoscopy group compared with the surgery group (table 2). More necrosectomy procedures were done in the endoscopy group compared with the surgery group. We observed no difference in the median number of interventions (drainage or necrosectomy) between groups (table 2).

The most common adverse events were pneumonia (16 [31%] patients in the endoscopy group vs nine [19%] in the surgery group), bacteraemia (11 [22%] vs six [13%]), ascites (seven [14%] vs eight [17%]), urinary tract infection (six [12%] vs four [9%]), cholecystitis or cholangitis (four [8%] vs three [6%]), and atrial fibrillation (three [6%] vs two [4%]). All adverse events are listed in the Appendix.

Table 1 Baseline characteristics

	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)
Age, years	63 (14)	60 (11)
Female	17 (33%)	18 (38%)
Male	34 (67%)	29 (62%)
Cause of pancreatitis		
Gallstones	26 (51%)	30 (64%)
Alcohol abuse	7 (14%)	7 (15%)
Other*	18 (35%)	10 (21%)
Body-mass index†	29 (25-32)	28 (25-30)
Coexisting condition		
Cardiovascular disease	26 (51%)	18 (38%)
Pulmonary disease	8 (16%)	6 (13%)
Chronic renal insufficiency	4 (8%)	0
Diabetes	11 (22%)	7 (15%)
ASA class on admission		
I: healthy status	17 (33%)	18 (38%)
II: mild systemic disease	29 (57%)	27 (57%)
III: severe systemic disease	5 (10%)	2 (4%)
CT severity index‡	6 (6-8)	8 (6-10)
Extent of pancreatic necrosis		
<30%	26 (51%)	22 (47%)
30-50%	15 (29%)	10 (21%)
>50%	10 (20%)	15 (32%)
Necrosis extending >5cm down the retrocolic gutters	20 (39%)	22 (47%)
Encapsulation of the necrotic collection		
Partial	15 (29%)	14 (30%)
Complete	36 (71%)	33 (70%)
Gas configurations within the necrotic collection	23 (45%)	27 (57%)
Disease severity§		
Admitted to the ICU at randomisation	21 (41%)	25 (53%)
SIRS¶	33 (65%)	38 (81%)
APACHE II score ‖	9 (5-13)	10 (6-13)
APACHE II score ≥ 20‖	3 (6%)	4 (9%)
Modified Glasgow score**	2 (1-3)	2 (1-3)
Modified MODS score††	0 (0-1)	0 (0-2)

SOFA score††	0 (0-4)	1 (0-3)
C-reactive protein mg/L/‡‡	168 (105-258)	189 (136-301)
White cell count $x10^{-9}$ per L§§	14.4 (9.4-18.0)	13.1 (10.5-17.4)
Single organ failure	13 (25%)	14 (30%)
Respiratory	11 (22%)	13 (28%)
Cardiovascular	11 (22%)	7 (15%)
Renal	3 (6%)	1 (2%)
Multiple organ failure	9 (18%)	7 (15%)
Time since onset of symptoms, days	39 (28-54)	41 (28-52)
Antibiotic treatment at randomisation	10 (20%)	9 (19%)
Tertiary referral	35 (69%)	35 (74%)
Confirmed infected necrosis¶¶	46 (90%)	46 (98%)

Data are mean (SD), median (IQR), or n (%). ASA=American Society of Anesthesiologists. ICU=intensive care unit. SIRS=systemic inflammatory response syndrome. APACHE=Acute Physiology and Chronic Health Evaluation. MODS=multiple organ dysfunction syndrome. SOFA=Sequential Organ Failure Assessment. *Includes, among others, medication, anatomic abnormalities, and unknown aetiology. †Data missing in 34 patients. ‡Data were derived from the CT performed just before randomisation. Scores range from 0 to 10, with higher scores indicating more extensive pancreatic necrosis and extrapancreatic collections. §Data were based on maximum values during the 24 h before randomisation unless stated otherwise. ¶SIRS was defined according to the consensus-conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine. ||Scores range from 0 to 71, with higher scores indicating more severe disease.**Scores range from 0 to 8, with higher scores indicating more severe disease. ††Scores range from 0 to 24, with higher scores reflecting more severe organ dysfunction. ‡‡Data missing in 10 patients. §§Data missing in two patients. ¶¶Confirmed infected necrosis was defined as a positive culture of pancreatic or extrapancreatic necrotic tissue obtained by fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the collection on contrast-enhanced CT.

Table 2 Primary and secondary endpoints according to the intention-to-treat analysis

	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)	Relative risk (95% CI)	p value
Primary endpoint				
Major complications or death*	22 (43%)	21 (45%)	0.97 (0.62-1.51)	0.88
Secondary endpoints				
New-onset organ failure†				
Pulmonary	4 (8%)	7 (15%)	0.53 (0.16-1.68)	0.27
Persistent pulmonary	4 (8%)	5 (11%)	0.74 (0.21-2.58)	0.63
Cardiovascular	3 (6%)	9 (19%)	0.31 (0.09-1.07)	0.045
Persistent cardiovascular	2 (4%)	8 (17%)	0.23 (0.05-1.03)	0.032
Renal	2 (4)%	6 (13%)	0.31 (0.07-1.45)	0.11
Persistent renal	2 (4%)	6 (13%)	0.31 (0.07-1.45)	0.11
Single organ failure	7 (14%)	13 (28%)	0.50 (0.22-1.14)	0.087
Persistent single organ failure	6 (12%)	11 (23%)	0.50 (0.20-1.25)	0.13
Multiple organ failure	2 (4%)	6 (13%)	0.31 (0.07-1.45)	0.11
Persistent multiple organ failure	2 (4%)	5 (11%)	0.37 (0.08-1.81)	0.20
Bleeding (requiring interventions)	11 (22%)	10 (21%)	1.01 (0.47-2.17)	0.97
Perforation of a visceral organ or enterocutaneous fistula (requiring intervention)	4 (8%)	8 (175)	0.46 (0.15-1.43)	0.17
Incisional hernia	0	1 (2%)		0.30
Death	9 (18%)	6 (13%)	1.38 (0.53-3.59)	0.50
Other endpoints‡				
Pancreaticocutaneous fistula	2/42 (5%)	13/41 (32%)	0.15 (0.04-0.62)	0.0011
Exocrine insufficiency				
Use of enzymes	16/42 (38%)	13/41 (32%)	1.20 (0.66-2.17)	0.54
Fecal elastase <200 mg/g	22/42 (52%)	19/41 (46%)	1.13 (0.73-1.75)	0.58
Steatorrhoea	6/42 (14%)	7/41 (17%)	0.84 (0.31-2.28)	0.73
Endocrine insufficiency	10/42 (24%)	9/41 (22%)	1.08 (0.49-2.39)	0.84
Biliary strictures	3 (6%)	3 (6%)	0.92 (0.20-4.34)	0.92
Wound infections	2 (4%)	3 (6%)	0.61 (0.11-3.52)	0.58
Health-care use				
Median number of interventions§	3 (2-6)	4 (2-6)	..	0.35
Drainage procedures¶	1 (1-3)	3 (1-5)	..	0.0041
Necrosectomies‖	2 (1-4)	1 (1-1)	..	0.0004
Number of necrosectomies	..	..	..	0.0062

0	22 (43%)	24 (51%)	0.84 (0.55-1.29)	..
1	9 (18%)	18 (38%)	0.46 (0.23-0.92)	..
2	8 (16%)	3 (6%)	2.46 (0.69-8.72)	..
≥3	12 (24%)	2 (4%)	5.53 (1.31-23.42)	..
Additional percutaneous drainage in the endoscopy group	14 (27%)	..	..	..
Additional VARD procedure in the endoscopy group	2 (4%)	..	..	..
Additional endoscopic drainage in the surgical group	..	2 (4%)	..	..
Additional endoscopic necrosectomy in the surgical group	..	0	..	..
Days between first drainage and first necrosectomy				
Median (range)	10 (5-16)	23 (9-62)	..	0.013
Mean (SD)	14 (14)	33 (30)	..	..
Days in ICU within 6 months of randomisation**				
Median (IOR)	0 (0-3)	2 (0-11)	..	..
Mean (SD)	13 (31)	13 (21)	..	0.31
Days in hospital within 6 months of randomisation				
Median (IOR)	35 (19-85)	65 (40-90)	..	..
Mean (SD)	53 (47)	69 (38)	..	0.014

Data are n (%), mean (SD), or median (IQR) unless otherwise stated. Relative risk is reported for dichotomous variables for the endoscopic step-up approach as compared with the surgical step-up approach. ICU=intensive care unit. VARD=video-assisted retroperitoneal debridement. *Multiple events in the same patient were considered as one endpoint. †Organ failure occurring after randomisation and not present 24 h before randomisation. ‡Patients were assessed 6 months after randomisation; patient deaths were excluded. §This category included all drainage procedures (endoscopic or percutaneous) and necrosectomies (endoscopic or VARD) as part of the endoscopic or surgical step-up approach. ¶This category included primary drainage procedures (endoscopic or percutaneous) as part of the endoscopic or surgical step-up approach and additional drainage procedures before and after necrosectomy in both treatment groups. ||This category included all necrosectomies (endoscopic or VARD procedure) as part of the endoscopic or surgical step-up approach. **For patients not present in ICU 24 h before randomisation.

Correction for trends in baseline characteristics (ie, chronic renal insufficiency, systemic inflammatory response syndrome, and modified multiple organ dysfunction syndrome) with multivariable regression analyses did not affect the results (Appendix). Predefined subgroup analyses for time of randomisation and institution showed no significant differences in the primary endpoint (Appendix). We found no differences in outcome in the subgroup of patients with organ failure at randomisation or after correction for imbalances in baseline in this subgroup. Additional perprotocol analyses did not affect the results, except that persistent cardiovascular organ failure no longer differed between groups (Appendix).

The mean costs of the index interventions (ie, all drainage and necrosectomy procedures) were €3785 in the endoscopy group and €2851 in the surgery group, with a mean difference of €934 (BCa 95% CI −€82 to €2097). The mean total costs per patient from randomisation until 6-month follow-up were €60 228 for the endoscopic step-up approach and €73 883 for the surgical step-up approach. The resulting mean difference of −€13 655 (−€35 782 to €10 836) per patient was not significant.

The number of QALYs gained for the endoscopy group was 0·2788 (BCa 95% CI 0·2458 to 0·3110) compared with 0·2988 (0·2524 to 0·3398) for the surgery group. The mean difference was −0·0199 (−0·0732 to 0·0395). The savings per loss of a single QALY were €684 455. The probability of the endoscopic step-up approach being cost-effective is 0·896 at a societal willingness-to-pay level of €50 000 per QALY (see Appendix for details of the cost analysis).

Discussion

This randomised superiority trial showed that the endoscopic step-up approach was not superior to the surgical step-up approach in reduction of major complications or death in patients with infected necrosis. However, our results showed a benefit in secondary endpoints of endoscopic treatment.

Our results are not in line with a previous small randomised controlled trial [7], a systematic review [8], and observational studies [24,25] suggesting clinical superiority of endoscopy. Several possible explanations exist for the differing outcome.

First, observational studies have a risk of confounding by indication and most of these studies did not have a well defined study protocol or clearly described treatment algorithms. Furthermore, patients with sterile collections were also included in some of these studies, which could have led to comparisons of less severe cases with patients with infected necrosis. In our trial, inclusion criteria were strict and were confirmed by an expert panel.

Second, in line with a previously proposed hypothesis, the previous small trial [7] showed that endoscopic treatment led to a less severe pro-inflammatory response and, subsequently, fewer occurrences of new organ failure compared with surgery. These results were also not confirmed in our trial. Although we did not measure the pro-inflammatory response, new-onset single organ failure as a clinical manifestation of immune response did not differ between groups. However, both cardiovascular and persistent cardiovascular organ failure were lower in the endoscopy group. This difference could be the result of the differing designs of both studies. The previous trial [7] compared an endoscopic necrosectomy with a surgical necrosectomy instead of two step-up approaches as in our trial. This trial design also explains the inclusion of more severely ill patients (ie, patients in whom percutaneous drainage failed) in the previous trial [7]. Moreover, 40% of the surgical patients in the previous study [7] received open necrosectomy as opposed to VARD, whereas in our trial no patients underwent an open necrosectomy. This difference is important because open necrosectomy is thought to be associated with more complications than is VARD.

Third, patients in our trial were more severely ill than those included in the previous trial [7] in terms of ICU stay, presence of systemic inflammatory response syndrome, single or multiple organ failure at randomisation, and the high percentage of patients with confirmed infected necrosis compared with the patients included in previous observational studies.

Finally, our sample size could still have been too small. The number of patients needed was based on the results of small, mostly observational studies. A small sample size might therefore have overestimated the effect of endoscopic treatment.

51% of surgical patients were successfully treated with catheter drainage only. This result is higher than the 35% successfully treated in a previous randomised trial [4], but comparable with a published systematic review [6]. We found that more than 40% of patients in the endoscopy group were also successfully treated with endoscopic drainage only without additional necrosectomy. Previous research has

identified male sex, multiple organ failure, increasing percentage of pancreatic necrosis, and heterogeneity of the collection as negative predictors for success of percutaneous catheter drainage in infected necrotising pancreatitis [26]. The total number of necrosectomy procedures in both treatment groups are in line with published data [4, 7].

During the inclusion period, 37 (14%) of 260 patients were excluded because either the endoscopic or surgical approach was deemed not possible. As with percutaneous drainage, endoscopic drainage was feasible in almost all patients included (96%). 14 (27%) of 51 patients in the endoscopy group needed additional percutaneous catheter drainage mostly when necrosis was extending down retroperitoneally into the pelvis. Despite the need for additional percutaneous drainage, the incidence of pancreatic fistulas was significantly lower in the endoscopy group. All recorded pancreatic fistulas were external (ie, pancreaticocutaneous fistulas). These fistulas might account for serious morbidity (ie, pain, loss of pancreatic juices), additional interventions, extended hospital stay, and intensified follow-up. Socalled internal pancreatic fistulas probably also occurred in the endoscopy group. These internal fistulas, however, are deemed less clinically relevant than external pancreatic fistulas.

The interval between the first drainage and first necrosectomy was notably shorter in the endoscopy group than in the surgery group. This result could be due to a potentially higher threshold in the surgery group to proceed to VARD after catheter drainage compared with the threshold in the endoscopy group to proceed to endoscopic necrosectomy. Additional necrosectomy after endocopic drainage is a relatively small step, done by the same specialist via the same route. The step from catheter drainage to VARD in the surgery group was larger, with the surgeon performing the minimally invasive surgical necrosectomy after previous drainage done by the radiologist. Furthermore, compared with the endoscopy group, drains in the surgery group were more often repositioned and upsized, and multiple drains were placed more often [27]. This argument is supported by the difference in patients treated with solely catheter drainage in the surgery group between a previous trial [4] (35%) and our current study (50%), indicating more extensive and better drainage in our study. Moreover, percutaneous drains have a larger diameter and potentially clog less frequently than do endoscopic catheters. These aspects of the surgical step-up approach might have resulted in a prolonged effect of percutaneous drainage, delay of necrosectomy, and, subsequently, prolonged hospital stay.

During the course of the trial, short lumen-apposing fully-covered metal stents were introduced into the medical armatorium, which are gaining popularity in endoscopic treatment. The larger diameter compared with the plastic pigtail stents that were used in this trial potentially leads to better drainage and, hypothetically, fewer necrosectomies. Disadvantages might be migration of the stent, bleeding, perforation, and stent overgrowth [28-31]. In view of insufficient evidence of significant benefit of metal stents over plastic pigtail stents, we decided to use the well studied pigtail stents during the entire study.

Our study has some limitations. First, as mentioned, our sample size was still relatively small. However, because no trends for differences in mortality were seen, a larger trial is unlikely to find a significant difference in mortality. Second, almost one third of patients in the endoscopy group underwent additional percutaneous drainage. Because this was a pragmatic trial, percutaneous drainage was allowed, as would be done in clinical practice in these patients. Third, follow-up was 6 months after randomisation. This length could be too short to detect further benefits or complications of the endoscopic stepup approach on the long term.

Treatment of infected necrosis is complex and mortality remains high despite treatment techniques becoming progressively less invasive and more tailored. In clinical practice, the endoscopic step-up approach is gaining popularity alongside the surgical step-up approach. Our study has shown that both approaches are valid treatment options, although an important clinical advantage of the endoscopic approach is the reduction in external pancreatic fistulas and hospital stay. In our view, patients with infected necrosis should be treated in tertiary referral centres by multidisciplinary teams where both the endoscopic and surgical step-up approach are available, because a combined approach might be required in some patients. Based on current findings, the first step of step-up treatment will most likely be endoscopic, if several options are available. In the future, a tailored approach based on patient characteristics, location of collections, and degree of encapsulation will probably become the new standard.

In conclusion, this multicentre randomised trial did not show the hypothesised superiority of the endoscopic stepup approach in reducing major complications or death in patients with infected necrosis, although the number of pancreatic fistulas and total hospital stay were lower in the endoscopy group.

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6

CHAPTER 6

Appendix

Study participants

Acute pancreatitis was defined as having at least 2 of the 3 following features: 1) upper abdominal pain, 2) serum lipase or amylse levels above 3 times the upper level of normal and 3) characteristic findings of acute pancreatitis on cross-sectional abdominal imaging.

Exclusion criteria

Exclusion criteria were previous invasive interventions for necrotising pancreatitis, an acute flare up of chronic pancreatitis, recurrent acute pancreatitis, and an indication for emergency laparotomy (i.e. abdominal compartment syndrome, perforation of a visceral organ, bleeding and bowel ischaemia).

Treatment groups

The first step of treatment (step 1) was catheter drainage. This was performed ultrasound guided transluminal in the endoscopic step-up approach and percutaneously in the surgical step-up approach. Criteria similar to the PANTER trial were used to define clinical improvement, failure of drainage and to decide to go to the next step, endoscopic transluminal necrosectomy or surgical necrosectomy (step 2) [1, 2]. Criteria were similar in both groups. Each step was only considered successful in case of clinical improvement. 'Clinical improvement'was defined as: improved function of at least two organ systems (i.e. circulatory, pulmonary, renal) or at least 10% improvement of two out of three parameters of infection (i.e. C-reactive protein, leucocyte count or temperature) within 72 hours. Deterioration of these parameters by other infectious causes (e.g. an urinary tract infection) was excluded. Clinical failure was defined as the absence of clinical improvement or clinical deterioration.

If there was no clinical improvement 72 hours after drain placement, a CT scan was made to check the position of the drain. If the position of the drain was adequate and no additional drainable collections were seen, the patient proceeded to the next step (step 2). If the position of the drain was inadequate or an additional drainable collection was seen, a second drain was placed. 72 hours after a second drainage-procedure the patient was again evaluated. In case of improvement, treatment was conservative; otherwise the patient was taken to the next step (step 2). If after drainage, at any moment in time, a deterioration of at least two organ systems (i.e. circulatory, pulmonary, renal), or at least 10% deterioration of two out

of three parameters (i.e. C-reactive protein, leucocyte count or temperature), the next step (step 2) was taken. Deterioration of these parameters by other infectious causes (i.e. an urinary tract infection or pneumonia) was excluded.

Group A: Endoscopic transluminal step-up approach
Both approaches were performed, according to a strict protocol, in selected centres with documented expertise (i.e. more than ten EUS-guided transluminal (i.e. transgastric or transduodenal) drainage procedures and five endoscopic necrosectomy procedures performed for infected necrosis in the endoscopy group and at least ten VARD procedures performed in the surgery group) and, if necessary, under supervision of a more experienced endoscopist. All EUS procedures were performed with large channel linear echoendoscopes.

Step 1: endoscopic transluminal drainage
Under sedation, endoscopic ultrasound guided transluminal (i.e. transgastric or transduodenal) drainage of the necrotic collection was performed as the first step of treatment. Two 7 Fr double pigtail stents were inserted into the collection. A naso-cystic catheter was positioned in the fluid collection alongside the inserted stents which was continuously flushed with 1 liter saline/24 hours. This with the intent to keep the drains open and not for removing necrosis. In case of clinical improvement, no necrosectomy was performed and the results were awaited. If necessary, renewed or additional drainage (e.g. endoscopically or percutaneous) was performed after 72 hours. If re-drainage was clinically unsuccessful (according to the criteria for 'clinical improvement') or impossible, endoscopic transluminal necrosectomy was performed (step 2).

Step 2: endoscopic transluminal necrosectomy
The cystogastrotomy was dilated up to 18 mm and the cavity was entered with a therapeutic gastroscope to perform a necrosectomy under direct endoscopic vision. The procedure was completed when most necrotic tissue was removed. Again two 7 Fr plastic double pigtail stents and a naso-cystic catheter were inserted into the collection.

Group B: Surgical step-up approach
This approach was similar to the step-up approach used in the PANTER trial [2].

Step 1: percutaneous catheter drainage (PCD)
A percutaneous 14 French drain was placed in the (extra-)pancreatic collection under guidance of CT or ultrasound (step 1). Multiple drains were allowed. The preferred

route was through the left retroperitoneum, thereby facilitating VARD at a later stage if needed. Furthermore, for most collections this is also the shortest and often safest route, and like this you stay retroperitoneal and do not infect the intraabdominal space. If through the left retroperitoneum was not possible, transperitoneal drainage was performed. Drains were kept open by flushing with 50 ml saline once every 8-hours, with the intent to keep the drains open and not for removing necrosis. In case of clinical improvement, results were awaited. If a collection was inadequately drained after 72 hours, additional drainage (i.e. percutaneous or endoscopically) was performed. If drainage was clinically unsuccessful (i.e. according to the criteria for 'clinical improvement'), or in case of clinical deterioration, the patient underwent a surgical necrosectomy (step 2).

Step 2: VARD (if not possible laparotomy)
VARD is a drain-guided, minimally invasive retroperitoneal procedure, requiring a small incision. Using the retroperitoneal drain for guidance, only loosely adherent necrosis was removed from the collection with video-assistance after which two large bore surgical drains were inserted. A continuous post-operative lavage system (building up to 10 litres saline per 24 hours) was installed. In case of absence of clinical improvement (or deterioration), a CT scan was performed and VARD was repeated. If initial VARD was not possible, for whatever reason, debridement by laparotomy was performed.

If drainage (step 1) fails (clinically or technically) in one of both groups, the next step for the endoscopy group was cross-over to the surgery group and the next step for the surgery group was step 2 (i.e. VARD, if not possible laparotomy). In case of (per) acute clinical deterioration (e.g. bleeding with shock) the decision on therapy was left to the clinician in charge.

Patients were assigned to the endoscopic or surgical step-up approach as the initial and preferred technique. However, all clinically indicated procedures, whether endoscopic or percutaneous, were allowed throughout the course of their disease.

General supportive treatment

All patients received oral nutrition, if tolerated. If this was not tolerated, a nasojejunal feeding tube was introduced and enteral feeding was started. If gastrointestinal feeding was contra-indicated, the patient received parenteral nutrition. No antibiotic prophylaxis was used. In intensive care units selective decontamination of the digestive tract was allowed as this was the standard of care for all patients.

Antibiotics were used in case of suspected infected necrosis in order to postpone intervention. Intervention was postponed until (extra)pancreatic collections were demarcated as shown on CT, which usually occurs around 28 days after onset of symptoms.

Data collection and endpoint assessment

Patients were scored having a primary endpoint yes or no. So, if one of the components of the primary endpoint occurred within 6 months after randomisation this was accounted as having a primary endpoint. Outpatient follow-up visits took place according to the discretion of the responsible physician, but in any case 3 and 6 months after randomisation. All patients underwent a routine contrast enhanced CT 3 and 6 months after randomisation and received a questionnaire (SF-36 [3], EQ-5D [4], Health and Labour [5]) 3 and 6 months after randomisation. Exocrine and endocrine pancreatic function were measured in every patient, 3 and 6 months after randomisation with blood glucose measurements and fecal elastase tests.

Patient safety

To optimize patient safety an independent Data Safety and Monitoring Committee (DSMC) evaluated the progress of the trial and examined safety endpoints after inclusion of each consecutive group of 20 patients. All involved physicians were repetitively asked to report any potential adverse events. These events were listed and presented to the DSMC in an unblinded fashion. The DSMC discussed the implications of the data presented. In addition, all deceased patients were extensively evaluated by the DSMC for cause of death and possible intervention related serious adverse events. The outcome of the meeting of the DSMC was discussed with the trial steering committee and was reported to the responsible investigational review board. All adverse events were reported to the Dutch Central Committee on Research involving Human Subjects and the investigational review board.

Sample size, statistical analysis and economic evaluation

Sample size

Combined results of recently performed non-randomised studies showed that endoscopic transluminal necrosectomy resulted in a combined mortality and major morbidity rate of 17%. Data from the PANTER trial showed a combined mortality and major morbidity rate of 40%. Furthermore, in the VARD group an incisional

hernia rate of 7% was seen. Incisional hernia cause pain and patient discomfort. Furthermore, intensified follow-up and additional surgery is required to perform a correction. Assuming that some patients will develop an incisional hernia in the VARD group without having another primary endpoint, the prevalence of mortality and major morbidity in the VARD group, including incisional hernias was estimated to amount to 43%.

Therefore, sample size calculations were based on the assumption that the endoscopy group could reduce the cumulative primary endpoint by 26% (43% to 17%) in comparison with the surgery group. With a 2-sided significance level of 5% and power of 80%, taking into account a 2% drop-out rate, the inclusion of a total of 98 (2x49) patients was required to demonstrate this effect.

Statistical analysis
Variables are summarized as frequencies and percentages, means with standard deviations and in case of skewed distributions as medians with ranges. Results are presented as relative risks with corresponding 95% confidence intervals. Comparison of the primary endpoint is expressed in terms of a relative risk and corresponding 95% confidence intervals. Dichotomous data were compared with the use of Fisher's exact test, continuous data with Mann-Whitney U test, and categorical data with the linear-by-linear association test. A two-tailed $p<0.05$ was considered statistically significant. p-Values were not adjusted for multiple testing. Both, intention-to-treat and per-protocol analyses were performed. Predefined subgroup analysis were performed for patients with and without (multiple) organ failure, institution and time between onset of symptoms and randomisation (<28 or ≥28 days). To this end, formal tests for interaction using logistic regression were performed. In the event of imbalance between groups at baseline, logistic regression analysis were used to correct for the effect of the covariates.

Economic evaluation
Set up from a societal perspective, the economic evaluation was performed as a cost-effectiveness as well as cost-utility analysis with, respectively, the costs per alive patient without major complications and the costs per quality adjusted life year as primary economic outcomes. We included the direct and indirect medical and non-medical costs of care. The medical costs included costs of ICU-care, admission at the general ward, visits to the emergency department, ambulance transfers and all diagnostic and therapeutic procedures during the index admission and re-admissions within 6 months after randomisation. Furthermore, all outpatient clinic consultations and out-of-hospital costs (rehabilitation centre admissions, general

practitioner consultations and home care use) during follow-up were included. Direct non-medical costs reflect the non-reimbursable out-of-pocket expenses by patients related to the disease, for example travel to and from health care providers, private household assistance, etc. Data on the use of health care resources were gathered by case record forms, patient questionnaires and hospital information systems. Unit costing was based on the 2015 Dutch manual for costing in health care research [6, 7]. Endoscopic drainage and necrosectomy are relatively new intervention modalities for which no standardized costs were available. Therefore, after consulting the financial department of different (academic) centres, a unit cost was composed for these interventions. A top-down cost calculation was performed for the different types of surgery, including VARD. All unit costs are reported in Table A4. The base year for costs was 2014 and all costs are displayed in Euros.

Health utilities were derived from the EQ-5D-3L health status profiles using existing health valuation algorithms from the literature [8, 9]. The algorithms were based on the time trade-off elicitation techniques applied to representative samples of the general population in the Netherlands and the United Kingdom (UK).

Analyses were performed based on intention-to-treat. Differences between groups were assessed using accelerated non-parametric bootstrapping to account for sampling variability. Incremental cost-effectiveness ratios were calculated reflecting the extra costs per additional patient alive without major morbidity and the extra costs per additional QALY. Results are graphically shown by a cost-effectiveness plane of 1,000 bootstraps (Figure A1) and the corresponding cost-effectiveness acceptability curve (Figure A2).

Box A1 Definitions of the primary and secondary endpoints

Endpoint	Definition
Primary Endpoint	
New onset organ failure	Organ failure occurring after randomisation and not present 24 hours before randomisation: - Pulmonary: a PaO2 < 60 mmHg despite FiO2 30%, or the need for mechanical ventilation - Cardiovascular: a systolic blood pressure < 90 mmHg despite adequate fluid resuscitation or need for vasopressor support - Renal: a serum creatinine > 177 mmol/L after rehydration or need for hemofiltration or hemodialysis (in case patients already suffered from renal insufficiency before this episode of AP [creatinine > 177 umol/L] this does not count as renal failure)
Multiple organ failure	Failure of 2 or more organ systems (respiratory, cardiovascular or renal) at the same moment

Persistent organ failure	Failure of one or more organ systems for at least 48 hours
Bleeding requiring intervention	Requiring surgical, radiologic, or endoscopic intervention
Perforation of a visceral organ requiring intervention	Requiring surgical, radiologic, or endoscopic intervention
Enterocutaneous fistula requiring intervention	Secretion of fecal material from a percutaneous drain or drainage canal after removal of drains or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery
Incisional hernia (including burst abdomen)	Full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction
Secondary Endpoints	
Pancreaticocutaneous fistula	Output, through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level
Exocrine pancreatic insufficiency	Oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea 6 months after randomisation; this requirement was not present before onset of pancreatitis
Endocrine pancreatic insufficiency	Insulin or oral antidiabetic drugs required 6 months after randomisation; this requirement was not present before onset of pancreatitis
Wound infections	A superficial incisional SSI (surgical site infection) and must meet the following criterion: infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least 1 of the following: - Purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site - Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision - At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured, a culture-negative finding does not meet this criterion - An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination - Diagnosis of superficial/deep incisional SSI by the surgeon or attending physician

Table A1 Additional analysis - post hoc endpoints

	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)	Relative risk (95% CI)	p-value
Organ failure or death†	15 (29%)	13 (28%)	1.06 (0.57-1.99)	0.85
Primary endpoint including pancreatic fistula‡	23 (45%)	28 (60%)	0.76 (0.52-1.11)	0.15
New-onset organ failure§				
Pulmonary organ failure duration - median (range)	3 (2-89) (n=4)	10 (1-36) (n=7)		0.85
Persistent pulmonary organ failure duration - median (range)ø	3 (3-89) (n=4)	17 (2-36) (n=5)		0.65
Cardiovascular organ failure duration - median (range)	2 (1-2) (n=3)	4 (1-14) (n=9)		0.06
Persistent cardiovascularorgan failure duration - median (range)ø	2 (2-2) (n=2)	6 (2-14) (n=8)		0.06
Renal organ failure duration - median (range)	24 (21-26) (n=2)	7 (2-29) (n=6)		0.18
Persistent renal organ failure duration - median (range)ø	24 (21-26) (n=2)	7 (2-29) (n=6)		0.18
Organ failure duration - median (range)	3 (1-89) (n=7)	10 (1-39) (n=13)		0.72
Persistent organ failure duration - median (range)ø	11 (2-89) (n=6)	12 (2-39) (n=11)		0.61
Multiple organ failure duration - median (range)	44 (2-85) (n=2)	6 (1-17) (n=6)		0.62
Persistent multiple organ failure duration - median (range)ø	44 (2-85) (n=2)	7 (2-17) (n=5)		0.85
Days in hospital after first necrosectomy¤ - median (range)	29 (3-456)	34 (2-150)		0.93

This table includes additional endpoints which were not predefined within our study protocol. These analyses were performed post hoc. †New-onset organ failure or death within 6 months after randomisation. ‡The originally defined composite primary endpoint supplemented with pancreatic fistula within 6 months after randomisation. §New organ failure occurring after randomisation and not present 24 hours before randomisation, duration was presented in days. øPersistent organ failure was defined as new onset organ failure that lasted for at least 48 hours. ¤Total number of days a patient was admitted in the hospital after the first necrosectomy was performed, and within 6 months following randomisation (mean and SD were 62 (±91) and 45 (±35) respectively).

Table A2 Results of subgroup analyses for the primary endpoint

Predefined subgroup	Endoscopic step-up approach	Surgical step-up approach	Relative risk (95% CI)	p-value
Patients with (multiple) organ failure	6/13 (46%)	5/14 (36%)	3.80 (0.26-55.13)	0.33
Patients admitted at academic centre	12/29 (41%)	15/29 (52%)	0.80 (0.46-1.40%)	0.43
Patients with time between onset of symptoms and randomisation of <28 days (vs ≥28 days)	14/39 (36%)	16/37 (43%)	0.83 (0.47-1.45)	0.51

This was a logistic regression analysis for the primary endpoint in the subgroup of patients with (multiple) organ failure, institution, and time between onset of symptoms and randomisation (<28 or ≥28 days). Data are numbers and percentages and, if applicable, data are corrected for imbalances in baseline in the respective subgroup.

Table A3 Results of the predefined per-protocol analysis

	Endoscopic step-up approach (n=48)	Surgical step-up approach (n=48)	Relative risk (95% CI)	p-value
Primary composite endpoint: Major complications or death	21 (44%)	22 (46%)	0.95 (0.61-1.49)	0.84
Secondary endpoints: major morbidity				
New-onset organ failure				
Pulmonary	4 (8%)	7 (15%)	0.57 (0.18-1.83)	0.34
Persistent pulmonary	4 (8%)	7 (15%)	0.80 (0.23-2.80)	0.73
Cardiovascular	3 (6%)	9 (19%)	0.33 (0.10-1.16)	0.06
Persistent cardiovascular	2 (4%)	8 (17%)	0.25 (0.06-1.12)	0.05
Renal	2 (4%)	6 (13%)	0.33 (0.07-1.57)	0.14
Persistent renal	2 (4%)	6 (13%)	0.33 (0.07-1.57)	0.14
Organ failure	7 (15%)	13 (27%)	0.54 (0.24-1.23)	0.13
Persistent organ failure	6 (13%)	11 (23%)	0.55 (0.22-1.36)	0.18
Multiple organ failure	2 (4%)	6 (13%)	0.33 (0.07-1.57)	0.14
Persistent multiple organ failure	2 (4%)	5 (10%)	0.40 (0.08-1.96)	0.24
Bleeding	10 (21%)	11 (23%)	0.91 (0.43-1.94)	0.81
Perforation of a visceral organ or enterocutaneous fistula	3 (6%)	9 (19%)	0.33 (0.10-1.16)	0.06
Incisional hernia	0	1 (2%)		0.32
Death	9 (19%)	6 (13%)	1.50 (0.58-3.89)	0.40
Other endpoints				
Pancreaticocutaneous fistula	0/39	15/42 (36%)		0.00
Exocrine insufficiency				
Enzyms	15/39 (39%)	14/42 (33%)	1.07 (0.58-1.97)	0.63
Fecale elastase <200 mg/g	22/39 (56%)	19/42 (45%)	1.16 (0.73-1.84)	0.32
Steatorrhoea	6/39 (15%)	7/42 (17%)	0.86 (0.31-2.36)	0.88
Endocrine insufficiency	10/39 (26%)	9/42 (21%)	1.11 (0.50-2.49)	0.66
Biliary strictures	3 (6%)	3 (6%)	1.00 (0.21-4.71)	1.00
Wound infections	2 (4%)	3 (6%)	0.67 (0.12-3.81)	0.65

Data are numbers and percentages. The two patients who were randomised in the endoscopy group but eventually treated in the surgery group (since endoscopic drainage appeared not possible after randomisation) were analysed in the surgery group and the two patients (one in de endoscopy and one in the surgery group) who did not underwent any intervention were excluded.

Healthcare utilization and costs

Economic analysis - results

Costs
Mean volumes and costs of health care utilization per patient and mean differences in costs are shown in Table A5. Mean total costs were €60,228 for the endoscopic step-up approach and €73,883 for the surgical step-up approach, leading to a cost difference of -€13,655 (BCa 95% CI -€35,782 to €10,836).

The mean length of hospital stay was 53 days in the endoscopy group and 69 days in the surgical group (BCa 95% CI -31 to 0). The mean duration of ICU admission was 13 days in both groups. The length of general ward admission differed with -16 days (BCa 95% -29 to -2) leading to a cost difference of -€10,769 (95% BCa CI -€19,784 to -€1,657). Costs for laboratory tests were higher in the surgical group, due to the longer duration of hospital admission (mean difference -€748 (BCa 95% CI -€1,491 to €1)). The costs for the endoscopically performed drainages and necrosectomies appeared to be higher than the surgically performed interventions (€934, BCa 95% CI -€82 to €2,097). Patients who were surgically treated had higher costs for emergency department visits than patients in the endoscopic transluminal approach group. Also costs for outpatient hospital care (i.e. visits to the outpatient clinic) were higher in the surgically treated group. The difference in total costs of inpatient and outpatient hospital care was -€10,294 (BCa 95% CI -€32,609 to €13,849), hence less expensive for the endoscopy group.

Total non-hospital medical costs differed considerably, mainly due to the higher costs for rehabilitation and nursing home admission in the surgery group. Respectively 9 of 51 (18%) and 15 of 47 (32%) patients were admitted to a rehabilitation centre or nursing home in the endoscopic and surgical group, of whom most of the patients to a rehabilitation centre. The mean difference in costs was -€2,659 per patient (BCa 95% CI -€4,780 to -€964). Furthermore, costs for home care were higher in the surgery group.

Travel expenses were slightly higher in the surgically treated group, but represented a very small part of the total costs.

Effect

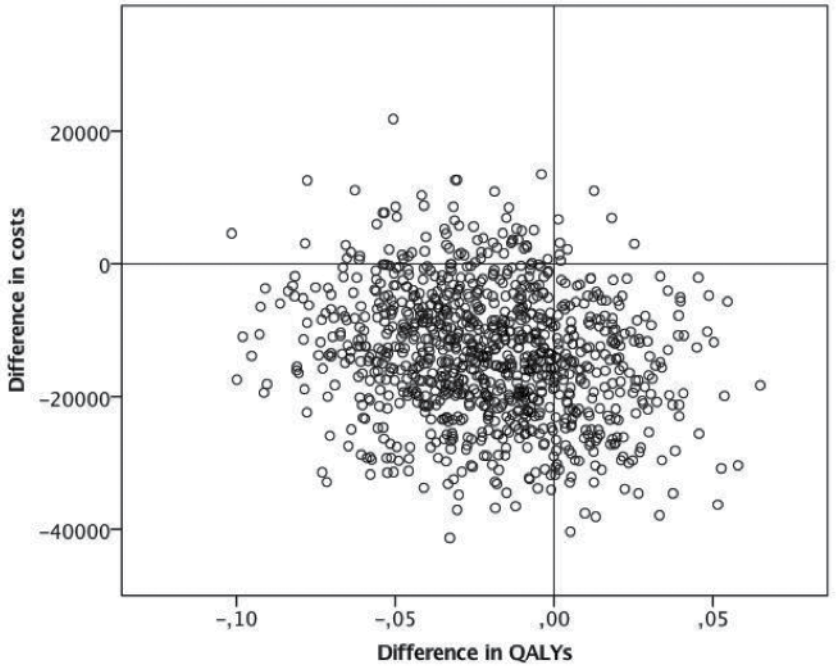
Death or major morbidity, corrected for organ failure at baseline, occurred in 22 of 51 (43.1%) patients in the endoscopy group (BCa 95% CI: 35.3% to 49%) and in 21 of 47 (44.7%) patients in the surgery group (BCa 95% CI: 34.0% to 55.3%). The endoscopic step-up approach is not better (1.5%; BCa 95% CI: -14.8% to 16.4%) than the surgical step-up approach in preventing patients having a poor outcome following infected necrotising pancreatitis.

The number of quality adjusted life-years in endoscopic step-up approach was 0.2788 (BCa 95% CI: 0.2458 to 0.3110) against 0.2988 (BCa 95% CI: 0.2524 to 0.3398) for the surgical group, based on health valuations from the Dutch general population. The difference. -0.0199 was non-significant (BCa 95% CI: -0.0732 to 0.0395). Based on health valuations from the UK general population, similar observations were made with the difference equaling -0.0161 (BCa 95% CI: -0.0743 to 0.0464; endoscopy group 0.2495 (BCa 95% CI: 0.2116 to 0.2868), surgical group: 0.2656 (BCa 95% CI: 0.2161 to 0.3105)).

Incremental cost-effectiveness ratios

The difference in total costs of -€13,655 (BCa 95% CI: -€33,273 to €6,149) divided by the difference of 1.5% in alive patients without major morbidity results in a point-estimated dominating incremental cost-effectiveness ratio of €884,383 saved per death or major morbidity prevented. The savings per loss of a single QALY were €684,455 (Dutch valuation) or €848,129 (UK valuation). The cost-effectiveness plane (Figure A1) for the differences in costs by the differences in QALYs (Dutch valuation) shows that 0.8% of the 1,000 bootstrap results lie in the upper right, 6.3% in the upper left, 70.4% in the lower left, and 22.5% in the lower right quadrant.

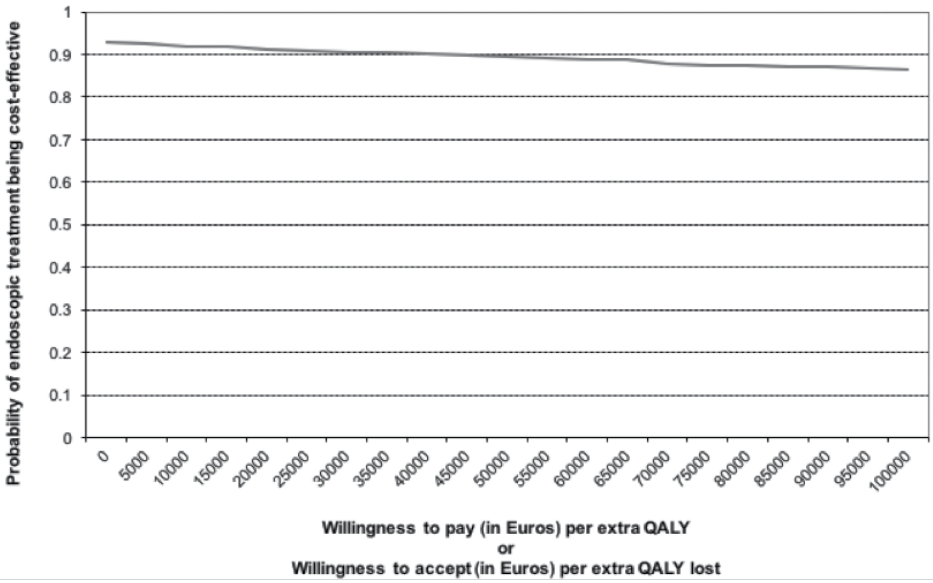
Figure A1 Cost-effectiveness plane



With hardly any results presenting in the upper right and most results presenting in the lower left quadrant the corresponding cost-effectiveness acceptability curve (Figure S2) may well be interpreted as the probability of endoscopic treatment being cost-effective (Y-axis) for different amounts that should at least be saved to society in order to make the loss of one extra QALY acceptable, the willingness-to-accept. The Figure shows that the endoscopic step-up approach seems good value for money. At a reasonable lower limit of the willingness-to-accept of €50,000 per extra QALY lost, given the functional status of the patient population at hand, the probability of endoscopic step-up being cost-effective is 0.896. Even at a minimum willingness-to-accept of €100,000 per extra QALY lost, the probability of ETN being cost-effective would still be 0.794.

Similar patterns were observed (not shown) for the extra costs per patient whose death or major morbidity would be prevented (probability of 0.883 at €50,000) and for the extra savings per additional QALY lost (UK valuation) (probability of 0.893 at €50,000).

Figure A2 Cost-effectiveness acceptability curve



Economic analysis - conclusive remarks

Endoscopic step-up treatment of infected necrotising pancreatitis is economically superior to the surgical step-up approach as the best alternative available. The TENSION trial could not demonstrate that the endoscopic approach clinically outperformed the surgical approach, but it may lower the cost burden to society.

Table A4 Unit costs of resources used per patient with infected necrotising pancreatitis

Resource	Unit	Units costs*	Source
Hospital stay			
Intensive care unit	Day	1645.00	DMC 2015
General ward - university hospital*	Day	753.37	DMC 2015†
General ward - community hospital	Day	525.08	DMC 2015†
Day care	Day	276.00	DMC 2015
Ambulance transfer during admission	Transfer	272.00	DMC 2015
Emergency department visit	Visit	259.00	DMC 2015
Laboratory			
Total costs for all laboratory tests per day	Per day	47.56	Tariff application
Microbiology‡			
Culture <2 culture media	Culture	14.27	Tariff application
Culture 2-3 media	Culture	18.59	Tariff application
Culture >3 media	Culture	26.56	Tariff application
Blood culture	Culture	31.22	Tariff application
Diagnostic radiology			
Abdominal ultrasound	Test	89.61	Tariff application
X-ray - chest	Test	43.94	Tariff application
X-ray - abdomen	Test	45.10	Tariff application
CT-scan - chest	Test	181.44	Tariff application
CT-scan - abdomen	Test	187.84	Tariff application
Endoscopy (except for study interventions)			
Gastroscopy (incl feeding tube placement)	Procedure	317.55	Tariff application
Colonoscopy	Procedure	352.48	Tariff application
Endoscopic ultrasound	Procedure	591.37	Tariff application
ERCP	Procedure	517.81	Tariff application
Study Interventions			
ETD	Procedure	973.00	Top-down cost calculation
ETN	Procedure	1075.00	Top-down cost calculation
PCD	Procedure	408.65	Tariff application#
VARD	Procedure	2152.68	Top-down cost calculation
Other interventions and surgical procedures			
Ascites or pleural fluid drainage	Procedure	220.81	Tariff application
Gallbladder or PTC drainage	Procedure	338.06	Tariff application
Nephrostomy catheter	Procedure	421.48	Tariff application

Other drainage	Procedure	220.81	Tariff application
Angiography/embolization	Procedure	907.17	Tariff application
Vascular stent	Procedure	962.93	Tariff application
Cholecystectomy	Procedure	1689.85	Tariff application
EL	Procedure	1900.23	Top-down cost calculation
EL + gastro-enterotomy/stoma/ cicatricial hernia	Procedure	2349.03	Top-down cost calculation
EL + stoma + splenectomy	Procedure	4228.38	Top-down cost calculation
EL + stoma + necrosectomy	Procedure	2216.75	Top-down cost calculation
Laparoscopy + stoma	Procedure	2447.20	Top-down cost calculation
Stoma construction	Procedure	1423.38	Top-down cost calculation
Re-exploration VARD cavity	Procedure	1647.78	Top-down cost calculation
Thoracotomy	Procedure	3835.68	Top-down cost calculation
Toe amputation	Procedure	988.60	Top-down cost calculation
Necrosectomy of decubitus wound	Procedure	1591.68	Top-down cost calculation
Outpatient clinic visits			
Outpatient clinic visit at academic hospital§	Visit	163.00	DMC 2015
Outpatient clinic visit at community hospital	Visit	80.00	DMC 2015
Non-hospital medical costs			
Rehabilitation centre	Day	460.00	DMC 2015
General practitioner visit	Visit	33.00	DMC 2015
Home care	Hour	41.50	Calculated from DMC 2015¶
Productivity loss	Hour	34.75	DMC 2015
Travel expenses	Kilometre	0.19	DMC 2015

Amounts are in Euro's. Costs base year 2014, if necessary costs were converted using Consumer Prices Indices. EL: Exploratory Laparotomy. † Additional costs for medication were calculated using the ratio of medication: costs per day derived from the DMC 2010. # Costs for PCD were calculated as costs for an (ultra-sound guided) drainage + costs for an abdominal CT-scan. ‡ Culture <2 media: line tip. Cultures 2-3 media: urine, throat, nose, perineum, rectum, MRSA/BMRO swap, liquor. Cultures >3 media: all materials of abdominal origin, pleural effusion, sputum, wound, pus, bronchial secretion, genital smear. § Costs for telephone appointment were calculated, using 5 minutes as the average duration of a telephone contact. ¶Different costs for different types of home care exist; the average price of the relevant types of home care was calculated.

Table A5 Mean volumes and costs per patient, comparing an endoscopic and surgical step-up approach in patients with infected necrotising pancreatitis

Unit	Endoscopic group (n=51)		Surgical group (n=47)		Cost Difference (BCa 95% CI)
	Mean volume	Mean costs (€)	Mean volume	Mean costs (€)	
Hospital stay	53.1	48196	68.9	58685	-10489 (-29816 to 10709)
ICU admission	13.4	22062	13.2	21700	362 (-16148 to 19712)
General ward (total)	39.2	25850	55.4	36619	-10769 (-19784 to -1657)
University hospital	23.1	17387	33.0	24877	-7491 (-17429 to 2622)
General hospital	16.1	8463	22.4	11741	-3024 (-8966 to 2906)
Day care	0.51	141	0.28	76	64 (-48 to 214)
Emergency department visits	0.43	112	0.83	214	-103 (-212 to 0)
Transfer by ambulance	0.12	32	0.28	75	-43 (-103 to 12)
Laboratory	N/A	2528	N/A	3277	-748 (-1491 to 1)
Microbiology	30.9	931	28.3	823	108 (-364 to 646)
Conventional radiology	13.7	1445	15.6	1684	-240 (-688 to 204)
Abdominal CT	4.71	884	5.85	1099	-215 (-457 to 29)
Thoracic CT	0.41	75	0.34	62	13 (-45 to 79)
Abdominal Ultrasound	0.57	51	0.74	67	-16 (-45 to 18)
Thoracic X-ray	5.49	241	6.68	294	-52 (-220 to 110)
Abdominal X-ray	1.73	78	1.09	49	29 (-14 to 74)
Other	0.78	116	0.85	114	2 (-86 to 87)
Endoscopy	2.80	973	2.15	821	153 (-212 to 507)
Gastroscopy (including feeding tube placement)	2.41	766	1.45	459	307 (-17 to 617)
Colonoscopy	0	0	0.04	15	-15 (-37 to -7)
EUS	0.06	35	0.06	38	-3 (-54 to 55)
ERCP	0.33	173	0.60	308	-136 (-322 to 52)
Study interventions	4.31	3785	4.19	2851	934 (-82 to 2097)
PCD	1.10	449	3.51	1436	-987 (-1381 to -565)
VARD	0.04	84	0.64	1374	-1290 (-1744 to -868)
ETD	1.41	1355	0.04	41	1313 (1082 to 1599)
ETN	1.76	1897	0	0	1897 (1180 to 2820)
Other interventions	0.90	387	1.36	519	-132 (-421 to 134)
Ascites drainage	0.29	65	0.47	103	-38 (-127 to 33)
Pleural effusion drainage	0.18	39	0.32	66	-27 (-72 to 20)

PTC-drain	0.14	40	0.17	58	-18 (-95 to 66)
Gall bladder drain	0.02	7	0.06	22	-15 (-44 to 8)
Vascular intervention	0.25	232	0.28	252	-20 (-257 to 185)
Other intervention	0.02	4	0.06	18	-14 (-46 to 9)
Surgical procedures	0.33	722	0.28	493	229 (-262 to 712)
Outpatient clinic contact	2.73	267	3.79	376	-109 (-218 to -1)
Non-hospital medical costs	N/A	945	N/A	4295	-3350 (-5559 to -1643)
Rehabilitation centre/ nursing home (days)	0.75	320	7.49	2979	-2659 (-4780 to -964)
Home care (total hours) (n=75)	13.5	560	29.8	1238	-678 (-1539 to 52)
General Practitioner (n=75)	1.97	65	2.37	78	-13 (-62 to 40)
Travel expenses	N/A	49	N/A	59	-10 (-28 to 8)
Total costs per patient		60228		73883	-13655 (-35782 to 10836)

Table A6 Adverse events other than primary and secondary endpoints

Adverse events	Endoscopic step-up approach (n=51)	Surgical step-up approach (n=47)
Gastrointestinal		
Ascites	7	8
Abdominal compartment syndrome	2	0
Cholecystitis or cholangitis	4	3
Gastroparesis	1	1
Reflux oesophagitis	0	1
Rectovaginal fistula	0	1
Jaundice	1	0
Spleen abscess	1	0
Bile duct injury	1	1
Bleeding in the liver	1	0
Ischaemic colitis	1	0
Cardiovascular		
Atrial fibrillation	3	2
Cardiac arrest	0	3
Deep venous thrombosis	4	2
Congestive heart failure	1	1
Myocardial infarction	0	1
Pulmonary		
Pneumonia	16	9
Exacerbation of chronic obstructive pulmonary disease	3	0
Pleural effusion requiring drainage	3	7
Pleura empyema	1	0
Hydro-pneumothorax	1	2
Pulmonary embolus	1	0
Neurologic		
Delirium	0	2
Hypercapnic coma	0	1
Epidural abscess	0	1
Hemiparesis	0	1
Trauma capitis	0	1

Urinary tract		
Urinary tract infection	6	4
Pyelonephritis	1	0
Urolithiasis	0	1
Other		
Bacteraemia	11	6
Toxicoderma	1	1

Adverse events as noted in case record forms by attending physicians and reported to the Data and Safety Monitoring Board. These adverse events were not predefined in the study protocol.

Table A7 Results of the sensitivity analysis

	n	p	Exp (B)	95% CI
Primary composite endpoint: Major complications or death	98	0.58	0.78	0.31-1.92
Secondary endpoints: major morbidity				
New-onset organ failure				
Pulmonary	98	0.34	0.53	0.14-1.99
Cardiovascular	98	0.07	0.27	0.06-1.09
Renal	98	0.16	0.30	0.06-1.59
Single	98	0.14	0.45	0.16-1.30
Multiple	98	0.12	0.26	0.05-1.43
Bleeding	98	0.47	0.67	0.23-1.97
Perforation of a visceral organ or enterocutaneous fistula	98	0.14	0.33	0.07-1.43
Incisional hernia	98	1.00	0.00	-
Death	98	0.64	0.72	0.17-2.94
Other endpoints				
Pancreaticocutaneous fistula	83	0.01	0.06	0.01-0.46
Exocrine insufficiency				
Enzyms	83	0.62	1.27	0.49-3.28
Fecale elastase <200 mg/g	83	0.41	1.46	0.59-3.59
Steatorrhoea	83	0.24	0.46	0.12-1.69
Endocrine insufficiency	83	0.64	1.31	0.43-3.97
Biliary strictures	98	0.78	0.78	0.14-4.43
Wound infections	98	0.85	0.84	0.13-5.41

Baseline characteristics were equally distributed between groups although trends were found for chronic renal insufficiency (4 endoscopic vs. 0 surgical patients; p=0.05), systemic inflammatory response syndrome (SIRS) (33 endoscopic vs. 38 surgical patients; p=0.07), and modified multiple organ dysfunction syndrome (MODS) (median 0, range 0-8 vs. median 0, range 0-6; p=0.06). This table shows the endpoints corrected for baseline covariates.

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PART III

TIMING OF PRIMARY CATHETER DRAINAGE

7

CHAPTER 7

Timing of catheter drainage in infected necrotizing pancreatitis

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Abstract

Acute pancreatitis is the most common gastrointestinal indication for hospital admission, and infected pancreatic and/or extrapancreatic necrosis is a potentially lethal complication. Current standard treatment of infected necrosis is a step-up approach, consisting of catheter drainage followed, if necessary, by minimally invasive necrosectomy. International guidelines recommend postponing catheter drainage until the stage of 'walled-off necrosis' has been reached, a process which typically takes 4 weeks after onset of acute pancreatitis. This recommendation stems from the era of primary surgical necrosectomy. However, postponement of catheter drainage might not be necessary, and earlier detection and subsequent earlier drainage of infected necrosis could improve outcome. Strong data and consensus among international expert pancreatologists are lacking. Future clinical, preferably randomized, studies should focus on timing of catheter drainage in patients with infected necrotizing pancreatitis. In this Perspectives, we discuss challenges in the invasive treatment of patients with infected necrotizing pancreatitis, focusing on timing of catheter drainage.

Introduction

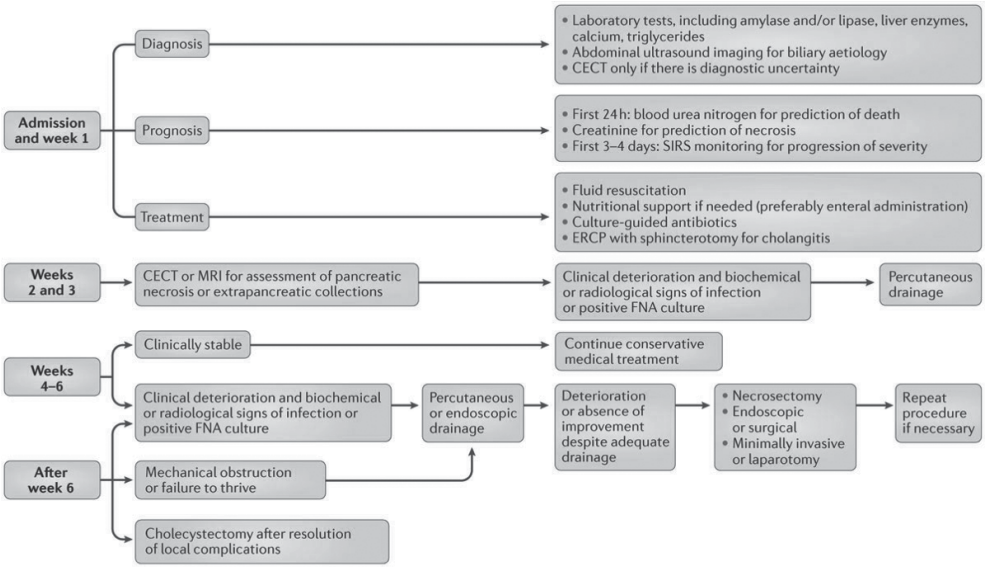
Acute pancreatitis is the most common gastrointestinal indication requiring acute hospitalization [1]. The main causes are gallstone disease, alcohol, medication or idiopathic. Acute pancreatitis is usually a self-limiting disease and most patients recover without serious complications [2]. The management of acute pancreatitis has been outlined in updated evidence-based and consensus-based guidelines [3-5]. The cornerstones of early treatment are fluid resuscitation, pain management and enteral nutrition. Despite adequate early treatment, ~20% of patients will develop necrosis of the pancreatic parenchyma, the peripancreatic tissue or both (that is, necrotizing pancreatitis) [6, 7]. Depending on the presence of persistent organ failure, necrotizing pancreatitis is considered moderately severe or severe, with mortality rates exceeding 30% [2, 8]. In two-thirds of patients the necrosis remains sterile and no invasive intervention is needed [3]. However, one-third of patients develop an infection of the necrosis [6]. Infected necrosis is thought to be caused by bacterial translocation from the gut. Translocation is provoked by disturbed intestinal motility which leads to small bowel bacterial overgrowth, and increased mucosal permeability by intestinal hypoperfusion [9-12]. The standard invasive treatment for patients with (suspected) infected necrotizing pancreatitis is the so-called 'step-up' approach [3-5]. This approach can be performed surgically (which involves percutaneous drainage) or endoscopically (which involves endoscopic, usually transgastric, drainage) [13, 14]. Current guidelines state that an invasive intervention should be postponed until the collection with infected (extra)pancreatic necrosis has become 'walled-off ' [3-5], a process which usually takes 3–4 weeks from onset of disease [2]. Debridement of non-walled-off necrosis is technically difficult, with a risk of bleeding and perforation of adjacent hollow organs. During this period of 3–4 weeks, patients are often severely ill and admitted to the intensive care unit; however, catheter drainage would technically be feasible in most of these patients. Whether catheter drainage should be performed before the stage of walled-off necrosis is reached is a pertinent question, particularly as at least 30% of patients seem to recover after catheter drainage without the need for additional necrosectomy [15]. In the era of catheter drainage as the first step in a step-up approach, postponement of catheter drainage until encapsulation might not be necessary, and this delay could in fact slow down recovery. Earlier detection of infected necrosis and subsequent earlier catheter drainage of infected necrosis could have the potential to improve outcome, but strong data are lacking. In this *Perspectives*, we discuss challenges in diagnosing infected necrosis and timing of catheter drainage in patients with infected necrotizing pancreatitis.

Diagnosing infected necrosis

As infected necrotizing pancreatitis has a very high mortality and morbidity [16], it nearly always requires intervention. Prompt and accurate diagnosis of infected necrosis is, therefore, very important. Moreover, catheter drainage of sterile necrosis carries a serious risk of introducing infection, which usually necessitates additional interventions and could theoretically increase the risk of mortality [17]. Indications for intervention in sterile necrotizing pancreatitis (4-8 weeks after onset of pancreatitis) are persistent gastric outlet, intestinal or biliary obstruction, other persistent symptoms such as pain, or disconnected pancreatic duct syndrome [3]. In clinical practice infected necrosis is diagnosed by gas in the necrotic collection on imaging, positive culture of a fine-needle aspiration (FNA), or unequivocal clinical signs of infection. The presence of gas in a necrotic collection on imaging (for example, contrast-enhanced CT of the abdomen) is considered pathognomonic for infected necrosis. This diagnosis can be made regardless of the cause of the gas, which could be related to gas-forming bacteria or to loss of integrity of the gastrointestinal tract. Collections containing gas are reported in up to 42% of patients with infected necrotizing pancreatitis [18] and can occur in every phase of the disease [19]. A positive culture or gram stain of fluid obtained via FNA can also confirm infected necrosis. Although FNA in these patients has a very low false-positive rate, false-negative rates up to 20% have been reported [20-22]. Currently, most experts only use FNA in selected cases [23]. In current practice where nearly all invasive interventions are postponed until the stage of walled-off necrosis there is usually no clinical need to detect infection early on and hence FNA is rarely performed. In a study published in 2014, infected necrosis was confirmed by FNA in 86% of 28 patients. However, the diagnostic performance of gas on imaging (94% of 88 patients) or clinical symptoms only (80% of 92 patients, $P = 0.07$) was similar [18]. Patients with necrotizing pancreatitis and clinical signs of infection (such as raised temperature, elevated levels of inflammatory serum markers or new-onset organ failure) with no other infectious focus, are suspected of having infected necrosis. Diagnosing infected necrosis on clinical symptoms alone does has certain limitations, especially in the first 2 weeks of pancreatitis when many patients often have systemic inflammatory response syndrome (SIRS). The symptoms of SIRS can mimic signs of infection. Differentiating between SIRS and sepsis in the first 2 weeks of pancreatitis, if desired, might be facilitated by FNA [19]. FIG. 1 describes an algorithm to diagnose and treat infected necrosis [24].

Figure 1

Current treatment algorithm for necrotizing pancreatitis according to the time after onset of symptoms. CECT, contrastenhanced CT; ERCP, endoscopic etrograde cholangiopancreatography; FNA, fine-needle aspiration; SIRS, systemic inflammatory response syndrome. *Permission obtained from John Wiley and Sons © da Costa, D. W. et al. Br. J. Surg. 101, e65–e79 (2014).*



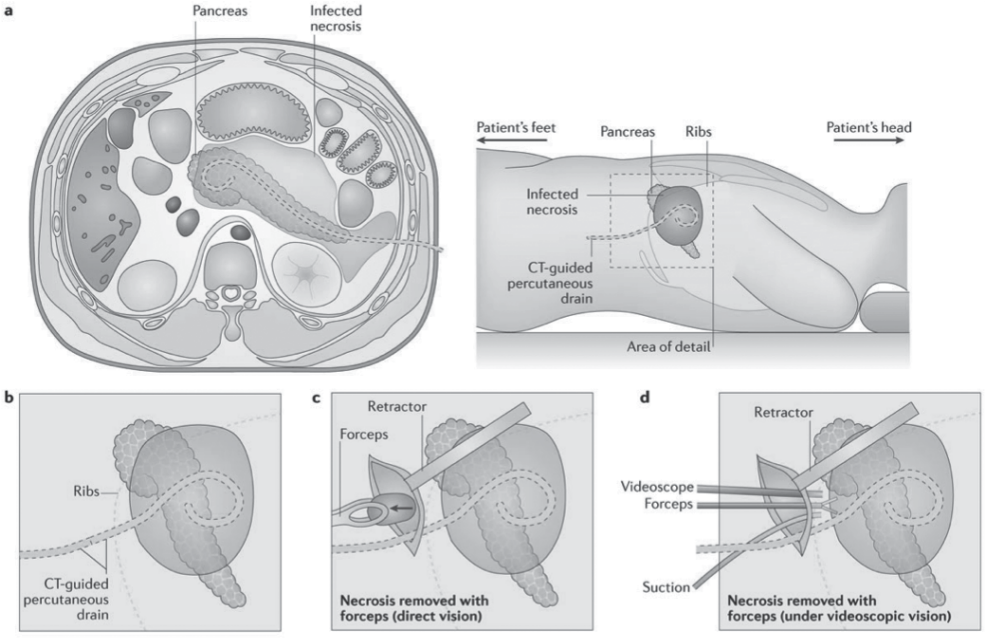
Minimally invasive interventions

As for many other gastrointestinal disorders, the use of minimally invasive interventions for infected necrotizing pancreatitis has increased [25-27]. Open surgical necrosectomy has been the standard treatment of infected necrotizing pancreatitis for decades, with the goal to remove all the necrosis [28, 29]. Open necrosectomy is associated with high mortality (~40%) and morbidity rates (up to 95%), including bleeding, gastrointestinal fistulas and pancreatic insufficiency [30-34]. In the past decade, there has been a trend towards minimally invasive retroperitoneal surgical techniques, for instance sinus tract endoscopy [35, 36]. In this and other derivative procedures, a percutaneous catheter drainage (PCD) is initially performed (FIG. 2). In cases of insufficient clinical improvement, the PCD tract is dilated under general anaesthesia and the necrosis is removed with grasping forceps, followed by continuous postoperative lavage. A videoscopic-assisted retroperitoneal debridement (VARD) is another minimally invasive necrosectomy procedure that can be performed in patients with ongoing sepsis after primary PCD. This technique is a hybrid of the classic lumbotomy and sinus tract endoscopy [37, 38]. By making a subcostal incision of 5 cm in length, larger pieces of solid debris

can be removed [39]. VARD also seems to be easier to perform than sinus tract endoscopy as owing to the small incision there is more working space, particularly as necrotizing pancreatitis is a relatively rare condition and these procedures are not performed routinely. In the randomized PANTER trial, the minimally invasive step-up approach (including VARD) was superior in terms of outcome compared with primary open necrosectomy [13]. The current hypothesis is that minimally invasive surgical necrosectomy induces a smaller proinflammatory response than open

Figure 2

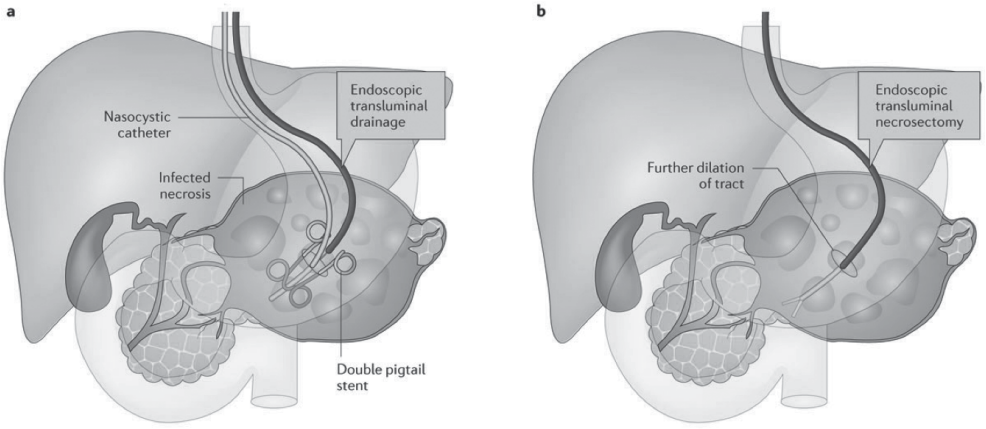
Surgical step-up approach. a | Cross-sectional image and torso depicting a peripancreatic collection with fluid and necrosis. The first step of the surgical step-up approach is percutaneous catheter drainage. The preferred access route is through the left retroperitoneal space between the left kidney, dorsal spleen and descending colon. If necessary, percutaneous catheter drainage is followed by a minimally invasive surgical necrosectomy, for example videoscopic-assisted retroperitoneal debridement. b | Enlargement of the area of detail shown in part a of the figure. c | A 5 cm subcostal incision is made, and the previously placed percutaneous drain is used as a guide into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision with a long grasping forceps. d | Further debridement is performed under videoscopic assistance. *Reprinted from van Brunschot, S. et al. Treatment of necrotizing pancreatitis. Clin. Gastroenterol. Hepatol. 10, 1190–1201 (2012), with permission from Elsevier ©, and adapted from John Wiley and Sons © da Costa, D. W. et al. Br. J. Surg. 101, e65–e79 (2014).*



surgical necrosectomy and is therefore associated with a lower rate of new-onset organ failure in these already critically ill patients. In addition to minimally invasive surgical approaches, a transluminal endoscopic approach is gaining popularity [26, 40]. Data from the pilot PENGUIN trial showed a reduction in pro inflammatory response (serum IL-6 levels) in patients treated with transluminal endoscopic necrosectomy versus a (preferably) minimally invasive surgical necrosectomy. Also, a trend towards less new-onset multi-organ failure (0% versus 50%) and reduced rate of pancreatic fistulas (10% versus 70%) was seen [41]. The endoscopic approach can also be performed as a step-up approach [39] (FIG. 3). Under endoscopic ultrasonography guidance, the necrotic collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Thereafter, plastic or metal stents are placed through the opening including a nasocystic catheter for irrigation of the necrotic collection. If necessary, endoscopic drainage is followed by an endoscopic necrosectomy. The necrotic tissue can be evacuated under endoscopic vision with a basket, net or snare [14]. No solid evidence exists yet on the superiority of either the percutaneous and surgical techniques versus the endoscopic approach. Results of

Figure 3

Endoscopic step-up approach. a | The first step of the endoscopic step-up approach is endoscopic transluminal drainage. The preferred access route for endoscopic transluminal treatment is through the posterior wall of the stomach. The necrotic collection often bulges into the stomach, facilitating endoscopic transluminal treatment. The collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation. b | If necessary, the cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed. *Reprinted from van Brunschot, S. et al. Treatment of necrotizing pancreatitis. Clin. Gastroenterol. Hepatol. 10, 1190–1201 (2012), with permission from Elsevier ©, and permission obtained from John Wiley and Sons © da Costa, D. W. et al. Br. J. Surg. 101, e65–e79 (2014).*



the TENSION trial, comparing these two step-up approaches, are expected in 2016 [14]. The theoretical pros and cons of both approaches are summarized in TABLE 1. Given the fact that at least 30% of patients can be successfully treated with catheter drainage only, without the need to undergo additional necrosectomy, drainage of infected necrosis should be the initial step [13, 15]. A survey published in 2015 showed excellent implementation of the step-up approach, with 87% acceptance among expert pancreatologists [23]. Catheter drainage is technically feasible in >95% of patients, often via the preferred left-sided retroperitoneal route [13, 27]. The rationale of catheter drainage is to treat infected necrosis as an abscess and drain infected fluid under pressure. This approach initially aims to control the source of infection without removal of the infected necrosis. Drainage of the infected fluid may temporize sepsis, improve the patient's clinical condition and allow further encapsulation.

Table 1 Pros and cons of the surgical and endoscopic step-up approach

Status	Surgical step-up approach	Endoscopic step-up approach
Pros	- Necrotic collection is nearly always percutaneously accessible (95% of patients) - High effectiveness of surgical necrosectomy (large pieces of necrosis can be removed)	- Reduced proinflammatory response (e.g. IL-6) - Avoids abdominal wall incision and thus related complications (e.g. external pancreatic fistula, incisional hernia and wound infection)
Cons	- Risk of chronic external pancreatic fistula - General anaesthesia is a prerequisite for surgical necrosectomy	- Some necrotic collections are not endoscopically accessible (e.g. distant from the stomach or not fully walled-off necrosis) - Several endoscopic procedures are needed for full necrosectomy (small pieces of necrosis can be removed) - Availability of expertise

Timing of catheter drainage

According to the latest evidence-based guidelines, all forms of invasive interventions in patients with infected necrosis should be ideally postponed until walled-off necrosis is present. Intravenous antibiotic treatment is the current standard treatment to bridge the period between acute necrotic collection and the formation of walled-off necrosis. Once an infection focus is determined, targeted antibiotics should be given or, in cases of no positive culture and persistent deterioration, broad spectrum antibiotics with optimal penetration must be started empirically. The latter usually consists of meropenem or imipenem, based on the local antibiotics protocol [3,4]. Antibiotic treatment itself may obviate the need for invasive interventions, with reported success rates varying from 3% (11 of 397 patients) [16] to 50% (14 of 28 patients) in selected patients [42]. The current advice to postpone invasive interventions preferably until 4 weeks after start of the disease stems from studies on timing of primary open surgical necrosectomy. The outcome of patients undergoing a late necrosectomy in walled-off necrosis seemed superior to patients undergoing early necrosectomy, including lower mortality [37,43-45]. As the initial management of infected necrotizing pancreatitis shifted from laparotomy to catheter drainage, the question arises whether catheter drainage should also be postponed. In the minimally invasive approach, encapsulation of necrosis might theoretically not be so relevant. Technically, there is often no need for postponing catheter drainage, especially PCD. In other abdominal conditions requiring PCD it is already common practice to drain before the stage of encapsulation. A systematic literature search was carried out to identify studies focusing on timing of catheter drainage in patients with infected necrotizing pancreatitis (see Supplementary information S1 (box)). No randomized studies currently exist. Several observational cohort studies reported on the timing of catheter drainage as a first intervention in patients with necrotizing pancreatitis [13, 46-58] (TABLE 2). These studies varied from seven to 117 patients, with rates of infected necrosis from 47% to 100%, confirmed either by the presence of gas in the collection on CT or a positive culture from fluid obtained by FNA or catheter drainage. PCD was the most often used intervention. Two studies also included a small subset of patients with endoscopic transluminal drainage as the primary treatment [13, 48]. Another two studies used dual-modality drainage of both primary PCD and endoscopic drainage [51, 58]. The studies reported a widespread time window of the first catheter drainage procedure, varying from a median of 9 to 75 days after onset of disease. A formal comparison or assessment of methodological quality could not be performed because the studies did not provide enough details. The proportion of patients who underwent additional necrosectomy (0% to 100%) and the number of patients with a bleeding complication (0% to 50%)

could not be related to the timing of catheter drainage. In addition, mortality rates ranged from 0% to 29%, with no evident relation with the timing of first intervention. Duration of drainage varied widely, but was shorter in the series with more patients who underwent additional necrosectomy. Nine studies provided data about length of hospital stay (37 to 96 admission days), but again no relation was seen with timing of the first catheter drainage. A few studies described other complications. For example, endocrine pancreatic insufficiency occurred in 26% of patients in the early drainage cohort of Freeny et al. [46] (median of 9 days) versus in 58% of patients in the late drainage cohort of Kumar et al. [57] (median of 36 days). However, exocrine insufficiency occurred in 32% of the early drainage cohort of Freeny et al. [46] versus in 7% of patients in the late drainage cohort of van Santvoort et al. [13] (median of 30 days).

Table 2 Studies of timing of catheter drainage in patients with (suspected) infected necrotizing pancreatitis

Study	Timing of first catheter drainage (days after onset of disease)	Patients (n)	Proven INP* (%)	Approach	Mortality (%)	Necrosectomy (%)	Bleeding (%)	Duration of drainage in days (range)	Hospital LOS in days (range)
Freeny et al. (1998)[46]	9 (1-48)	34	100	PCD	12	24	15	85 (25-152)	45 (5-95)
Navalho et al. (2006)[47]	18	30	100	PCD	17	33	NR	24 (5-94)	55
Lee et al (2007)[48]	10 PCD (1-58) 5.6 ETD (2-12)	23	100	18 PCD 5 ETD	4	17	0	NR	37.7 ± 28.5
Bruennler et al. (2008)[49]	3.5 + median 7 days transfer	80	65	PCD	23	23	0	36.5 (1-260)	51 (3-241)
Mortelé et al. (2009)[50]	12 (2-33)	13	100	PCD	8	54	8	NR	33 (11-68)
Becker et al. (2009)[51]	24 (18-30)	7	100	PCD + ETD	0	0	14	101 (8-154)	78 (45-150)
Bala et al. (2009)[52]	26 (18-88)	8	100	PCD	13	100	0	71.5 (39-90)	96 (38-131)
van Santvoort et al. (2010)[13]	30 (11-71)	43	91	41 PCD 2 ETD	19	60	16	NR	50 (1-287)
Baudin et al. (2012)[53]	19.8 ± 15.7	48	100	PCD	29	19	4	48 ± 22	83 ± 48

Tong et al. (2012)54	30.74 ± 5.67 [S] 27.80 ± 6 [A]	34	100	PCD	0 [S] 7 [A]	44	NR	61.4 ± 19.7 [S] 6.7 ± 2.9 [A]	NR
Pascual et al.| (2013)55	28 ± 17	13	100	PCD	23	54	NR	NR	NR
Wronski et al. (2013)56	33 (27-46) [S] 25 (8-116) [A]	18	100	PCD	0 [S] 17 {A]	67	11	53 (13-156) [S] 8.5 (1-53) [A]	NR
Kumar et al. (2014)57	36.4 ± 7.0	12	67	PCD	8	75	50	NR	NR
Ross et al (2014)58	75.5 (82.2)	117	47	PCD + ETD	3	0	3	63	NR

[A], patients with additional necrosectomy reported separately; ETD, endoscopic transluminal drainage; INP, infected necrotizing pancreatitis; LOS, length of stay; NR, not reported; PCD, percutaneous catheter drainage; [S], patients treated with successful PCD treatment only reported separately. *Confirmed by the presence of gas in the collection on CT or a positive culture from fluid obtained by fine-needle aspiration or catheter drainage.

Future perspectives

Whereas the incidence of infected necrosis has remained stable [6, 16], treatment of necrotizing pancreatitis has changed considerably in the past decade. Current guidelines advise postponing all forms of invasive intervention in patients with infected necrosis, preferably until 4 weeks after onset of disease [3-5]. The step-up approach has been implemented as the strategy of choice internationally for treating these patients [23]. Catheter drainage is used as a first step to control sepsis and delay or even avoid necrosectomy. For that reason, timing of catheter drainage has become a particularly relevant topic. A rationale exists for postponing catheter drainage in patients with infected necrotizing pancreatitis. First, antibiotic treatment alone might suffice as treatment. Second, diagnosing infected necrotizing pancreatitis is often easier in a later stage of the disease, when all other sources of infection or SIRS have been ruled out. Third, catheter drainage can be easier once the stage of walled-off necrosis has been reached and a collection has become more liquefied. Fourth, endoscopic transluminal drainage requires a walled-off collection. In an international survey, 55% of expert pancreatologists postponed catheter drainage in infected necrotizing pancreatitis using antibiotics, whereas the other 45% drained immediately after diagnosing infected necrosis [23]. Although the step-up approach was routinely used by 87% of pancreatologists, the timing of intervention varied hugely, especially catheter drainage. Disagreement was most notable when infected necrosis was diagnosed 2 or 3 weeks after onset of disease, which is the period between the SIRS phase and encapsulation (walled-off necrosis). The findings of this survey are comparable to

the results of the studies discussed in this article. Timing of catheter drainage varied greatly, both between and within studies. The available studies are retrospective and included a mixed group of patients, infected necrosis had not always been proven, and often insufficient information about severity of illness was provided. This lack of data hampers comparisons to determine the best time to perform catheter drainage. On the other hand, no clear evidence from clinical studies was seen to suggest superiority for the current standard practice of postponed catheter drainage. From a theoretical standpoint it is not always mandatory to wait several weeks until full encapsulation of the peripancreatic collections and (percutaneous) catheter drainage can be performed safely and successfully in the first weeks after onset of disease. For several other conditions, such as drainage of peripancreatic collections after pancreatic resection, (percutaneous) catheter drainage is also safely performed early in 'non-walled-off ' collections [59]. If there is no technical reason for postponing catheter drainage, patients with infected necrotizing pancreatitis may benefit from earlier catheter drainage by reducing complications and length of hospital stay. Future clinical studies should evaluate whether it is better to postpone catheter drainage until there is walled-off necrosis or if it should be performed immediately after infected necrosis has been diagnosed. The Dutch Pancreatitis Study Group has designed such a randomized controlled trial. The POINTER trial (ISRCTN33682933) will compare immediate and delayed catheter drainage in an attempt to further improve the outcome of these severely ill patients [60]. Besides diagnosing infected necrosis and timing of catheter drainage, other factors might also be of interest when attempting to improve the quality of interventions and thereby the outcomes of patients with infected necrotizing pancreatitis. For example, for PCD little is known about the ideal lavage strategy, optimal initial catheter size or the benefit of upsizing primary percutaneous drains. Equally, in addition to the surgical (or percutaneous) approach, the endoscopic transluminal approach is gaining popularity. In the PENGUIN randomized controlled trial, which compared endoscopic transluminal necrosectomy with minimally invasive surgical necrosectomy, endoscopic transluminal necrosectomy significantly reduced the pro-inflammatory response measured by IL-6 levels, as well as the composite clinical end point consisting of complications and mortality [41]. The TENSION trial will answer the question of whether the endoscopic step-up approach, starting with endoscopic transluminal drainage, is superior compared with the surgical step-up approach, starting with PCD, in terms of mortality and major morbidity. The results of this trial are expected at the beginning of 2016 [14].

Conclusions

As the step-up approach has been accepted as the treatment strategy of choice in patients with infected necrotizing pancreatitis, the question when to start catheter drainage (being the first step of the step-up approach) has become more relevant. The timing and technical details of catheter drainage in these patients should be further optimized. With this new approach in a 'drainage-first' era of necrotizing pancreatitis treatment, a shift from a more reactive strategy towards a more proactive strategy for diagnosing infected necrosis might be necessary.

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Supplements

Review criteria
A systematic literature search was performed in MEDLINE, EMBASE and the Cochrane Library. Details of the literature search criteria are provided in Supplementary Box 1 online.

Supplementary information is linked to the online version of the paper at www.nature.com/nrgastro

Supplementary Box 1. Literature search
On 23rd January 2015 a systematic literature search was performed in MEDLINE, EMBASE and the Cochrane Library. Terms on timing [Instant/Immediate/Early or Postponed/Delayed] or on infected necrosis [Infected or Infection] were not used in order to achieve broad search results.

MEDLINE
(("Pancreatitis, Acute Necrotizing"[Mesh] OR acute necrotizing pancreatit*[tiab] OR severe pancreatit*[tiab] OR severe acute pancreat*[tiab] OR complicated pancreat*[tiab] OR complicated acute pancreat*[tiab] OR (("Pancreatitis"[Mesh:NoExp] OR "Pancreas"[Mesh] OR pancreatitis[tiab] OR pancreas[tiab]) AND ("Necrosis"[Mesh] OR necrot*[tiab] OR necros*[tiab])))) AND ("Drainage"[Mesh:NoExp] OR "Catheterization"[Mesh:noexp] OR drain*[tiab] OR drainage[tiab] OR step up*[tiab] OR catheter*[tiab] OR endoscopic intervention*[tiab] OR percutaneous intervention*[tiab] OR radiological intervention*[tiab] OR radiologic intervention*[tiab] OR minimally invasive[tiab])

EMBASE
'pancreas necrosis'/exp OR 'acute hemorrhagic pancreatitis'/exp OR ('acute pancreatitis'/exp OR 'pancreatitis'/exp OR 'pancreas'/exp OR pancreat*:ab,ti OR pancreas:ab,ti AND ('necrosis'/exp OR necrot*:ab,ti OR necros*:ab,ti)) OR ((severe OR complicated) NEAR/2 pancreat*):ab,ti AND ('surgical drainage'/exp OR drain*:ab,ti OR drainage:ab,ti OR 'catheter'/exp OR 'catheterization'/exp OR catheter*:ab,ti OR "step up":ab,ti OR ((endoscopic OR percutaneous OR radiologic*) NEXT/1 intervention*):ab,ti OR 'minimally invasive':ab,ti)

Cochrane Library
(((pancreat*:ab,ti or pancreas:ab,ti) and (necrot*:ab,ti or necros*:ab,ti)) or ((severe or complicated) near/2 pancreat*):ab,ti) AND (drain*:ab,ti or drainage:ab,ti or catheter*:ab,ti or 'step up':ab,ti or ((endoscopic or percutaneous or radiologic*) next/1 intervention*):ab,ti or 'minimally invasive':ab,ti)

Methodological filters
Languages: restricted to English, Dutch, German, French and Spanish
Date: >1 January 1992, because no universally accepted definitions for acute pancreatitis and pancreatic collections were available before 1992, confounding the comparison of studies
For EMBASE: NOT [conference abstract]/lim

Inclusion criteria
Cohort of patients with acute necrotizing pancreatitis
Indication for intervention: (suspected or documented) infected necrosis
Catheter drainage as primary invasive intervention

Exclusion criteria
No timing of first catheter drainage reported
Included patients with chronic pancreatitis, pseudocysts, pancreatic abscesses and/or exclusively sterile pancreatic necrosis, and outcomes for necrotizing pancreatitis not reported separately
Primary catheter drainage combined with another minimally invasive strategy, and outcomes for solely primary catheter drainage not reported separately
Fewer than five patients
No full text available

8

CHAPTER 8

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

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HPB (Oxford) 2016 Jan;18(1):49-56

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.

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 counties 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 (see Appendix). 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 chisquared 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.

Figure 1 Baseline characteristics of respondents

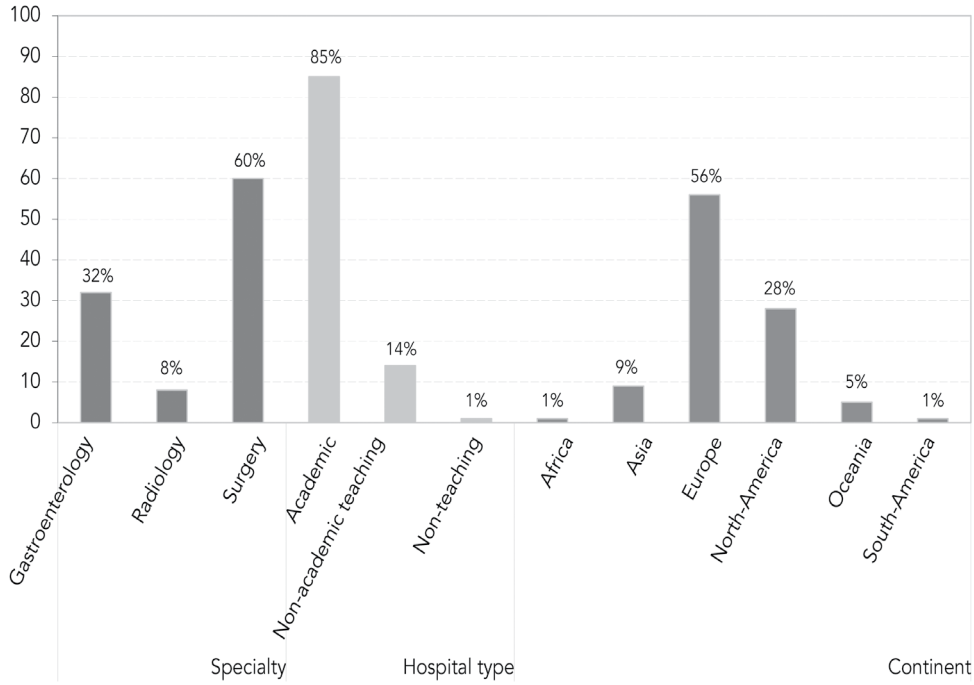


Table 1 Results survey: questions and answers of respondents

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

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

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) 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 stepup users in 75% (N = 44) and 50% (N = 14), respectively (p = .023).

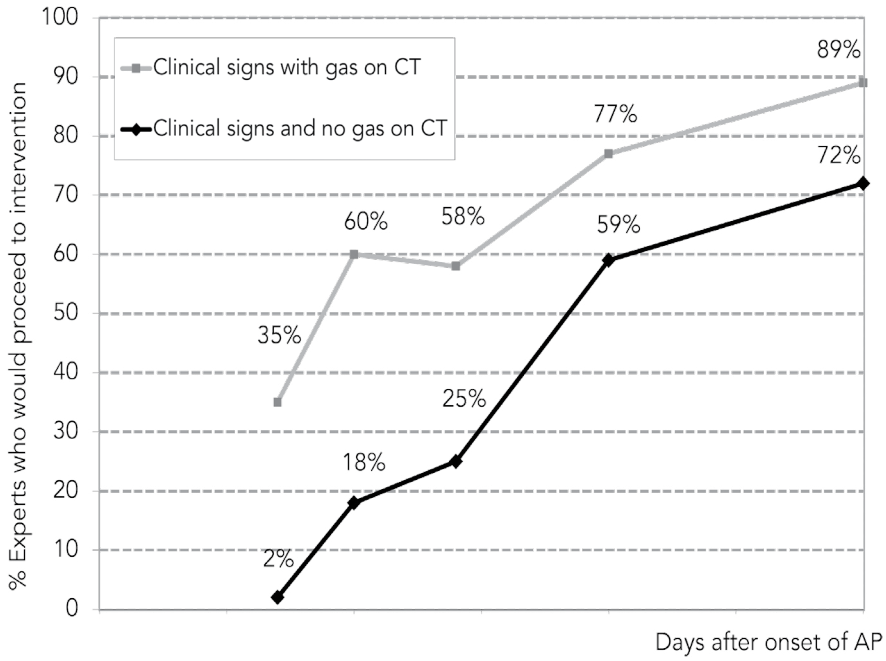
Table 2 Results subgroup analysis: survey answers based on type of step-up approach routinely used

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

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 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.

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



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, twothirds 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 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 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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8

CHAPTER 8

Appendix

Survey questions

Collections are defined according to the Revised Atlanta Classification 2012 as either acute necrotic collection (ANC) or walled-off necrosis (WON) [25].

Q1. What is your specialty?
- A) Gastroenterology
- B) Radiology
- C) Surgery

Q2. How many years of experience do you have in treating patients with necrotizing pancreatitis?
… years

Q3. What is your routine interventional approach in patients with infected necrotizing pancreatitis?
- A) Surgical step-up approach (first percutaneous catheter drainage and if indicated minimally invasive or open necrosectomy)
- B) Direct surgical necrosectomy without drainage as first step (minimally invasive, including percutaneous or videoscopic or open necrosectomy)
- C) Endoscopic transluminal step-up approach (first transluminal drainage and if indicated transluminal necrosectomy)
- D) Direct endoscopic transluminal necrosectomy without drainage as first step

Q4. In what type of hospital do you work?
- A) Academic
- B) Non-academic teaching
- C) Non-teaching

Q5. In which continent do you work?
- A) Africa
- B) Asia
- C) Europe
- D) North-America
- E) Oceania
- F) South-America

Q6. What techniques are technically feasible and available in your hospital, regardless of whether you prefer/use these techniques? Multiple answers are possible.
A) Image-guided percutaneous catheter drainage
B) Minimally invasive percutaneous necrosectomy via flank (either percutaneous or video-assisted)
C) Endoscopic transluminal drainage
D) Endoscopic transluminal necrosectomy
E) Open surgical necrosectomy
F) Diagnostic fine needle aspiration

Q7. In which scenario do you use fine needle aspiration (FNA) for diagnosing infected necrotizing pancreatitis?
A) Routinely (e.g. on a weekly basis) in all patients with necrotizing pancreatitis on CT, regardless clinical signs
B) In clinical suspicion of infected necrotizing pancreatitis, without gas in the necrotic collection on CT
C) In clinical suspicion of infected necrotizing pancreatitis, regardless the presence of gas in the necrotic collection CT
D) I very rarely use FNA for diagnosing infected necrotizing pancreatitis
E) I never use FNA for diagnosing infected necrotizing pancreatitis

Q8. In case of clinical suspicion of infected necrotizing pancreatitis (other sources of infection ruled out and CT showed no gas in the collection) and a negative FNA culture, what would you do?
A) Repeat FNA maximum once
B) Repeat FNA as often as needed to confirm infection
C) Proceed to intervention
D) Careful watch over the clinical course initially, not repeating FNA and withhold intervention at the moment
E) I never use FNA for diagnosing infected necrotizing pancreatitis

Q9. After having diagnosed infected necrotizing pancreatitis; do you treat patients with (intravenous) antibiotics and await the effect before proceeding to invasive interventions (such as catheter drainage/necrosectomy)?
A) No
B) Yes

Q10. Catheter drainage of infected necrotizing pancreatitis has failed; at what point in time should surgical necrosectomy ideally be performed?
A) As early as possible, regardless the degree of encapsulation
B) Once the collection has become walled-off necrosis

Q11. How strong do you rate the evidence supporting percutaneous catheter drainage as the first step in treatment of infected necrotizing pancreatitis?
A) No evidence
B) Weak
C) Moderate
D) Strong

Q12. How strong do you rate the evidence regarding postponing percutaneous catheter drainage of infected necrotizing pancreatitis until the collection has become (nearly) walled off?
A) No evidence
B) Weak
C) Moderate
D) Strong

Q13. Is there a time window after onset of disease during which you would absolutely not percutaneously drain an infected acute necrotic collection?
A) No
B) Yes

Q14. If Yes, before how many days after onset of disease would you absolutely not place a percutaneous drain in an infected acute necrotic collection?
… days

Q15. Do you perform percutaneous catheter drainage in patients with infected necrotizing pancreatitis before the peripancreatic collection has become (nearly) walled off?
A) No, I always try to wait with catheter drainage until the collection has reached the stage of (nearly) walled off necrosis
B) Sometimes, if maximal conservative treatment with antibiotics fails
C) Yes, I base the decision to drain on the diagnosis of infected necrotizing pancreatitis and the presence of drainable fluid, regardless of the presence of walled off necrosis

Q16. In general, do you feel upsizing a percutaneous drain (for instance from 14 to 22 Fr) is a potentially useful measure in patients who do not improve after initial percutaneous catheter drainage of infected necrotizing pancreatitis?
A) No
B) Yes

Q17. Is (nearly) walled-off necrosis in your opinion a prerequisite for safe endoscopic transluminal drainage?
A) No
B) Yes
C) I do not know

Q18. Is (nearly) walled-off necrosis in your opinion a prerequisite for safe endoscopic transluminal necrosectomy?

A) No
B) Yes
C) I do not know

Case vignettes

Now 10 short clinical cases are presented, including a CT image to illustrate the degree of encapsulation of the necrotic collection. Please make a choice what would be your first step based on the indication (suspicion of infection or/and encapsulation). All patients are 65 year old previously healthy men with necrotizing pancreatitis due to gallstones. If clinical signs or symptoms of an infection are present, other source of infection are ruled out (e.g. pneumonia, urinary tract infection).

Question in all case vignettes:

What is your first step?

A) Maximal conservative treatment (with/without antibiotics)

B) Percutaneous catheter drainage

C) Endoscopic transluminal drainage

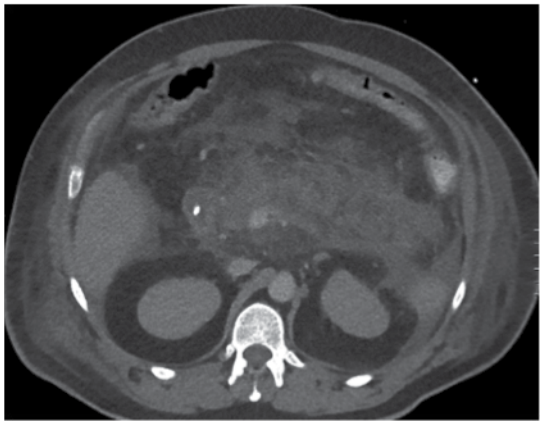
D) Surgical necrosectomy (minimal invasive/open)

E) Endoscopic transluminal necrosectomy

F) Fine needle aspiration

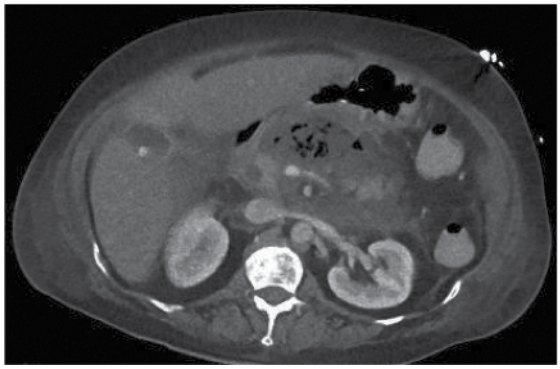
Patient A

- 7 days after onset of symptoms of acute pancreatitis
- Currently admitted to the intensive care because of respiratory failure
- There is no fever or other clinical signs or symptoms of infection
- CT shows acute necrotic collection (no full encapsulation) without gas
- FNA has not been performed



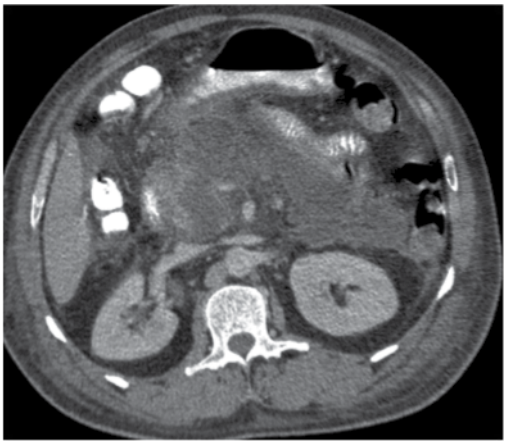
Patient B

- 7 days after onset of symptoms of acute pancreatitis
- Currently admitted to the intensive care department because of respiratory failure
- There is no fever and no other clinical signs or symptoms of infection
- CT shows acute necrotic collection (no full encapsulation) with gas
- FNA has not been performed



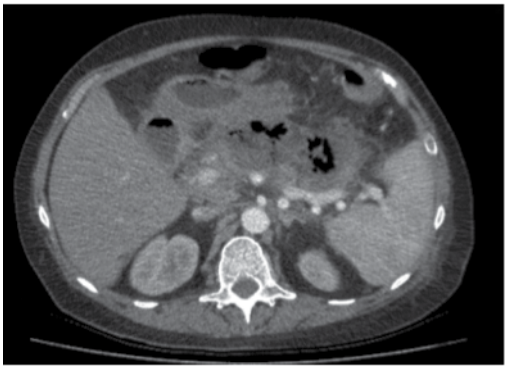
Patient C

- 10 days after onset of symptoms of acute pancreatitis
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows an acute necrotic collection (no full encapsulation) without gas
- FNA has not been performed



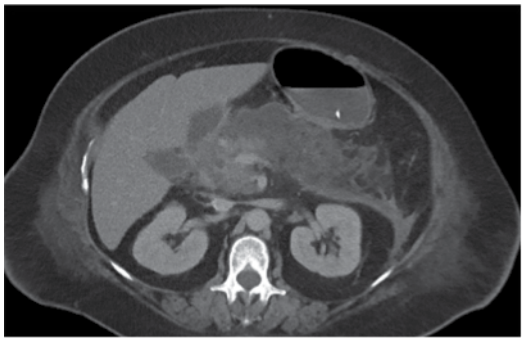
Patient D

- 10 days after onset of symptoms of acute pancreatitis
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows an acute necrotic collection (no full encapsulation) with gas
- FNA has not been performed



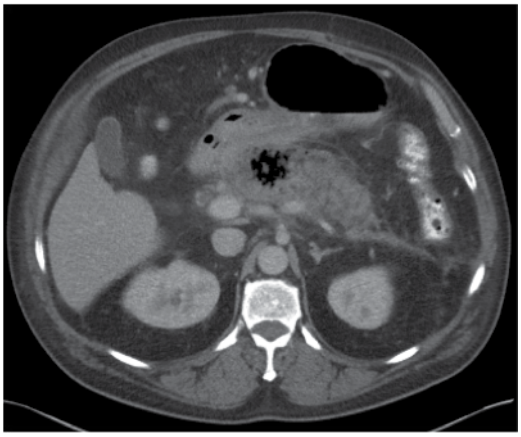
Patient E

- 14 days after onset of symptoms
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows an acute necrotic collection (no full encapsulation) without gas
- FNA has not been performed



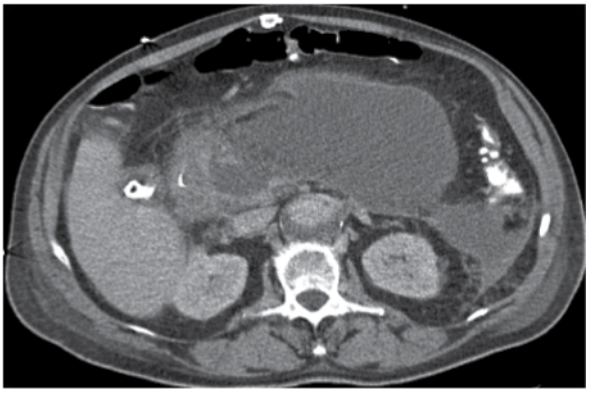
Patient F

- 14 days after onset of symptoms of acute pancreatitis
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows an acute necrotic collection (no full encapsulation) with gas
- FNA has not been performed



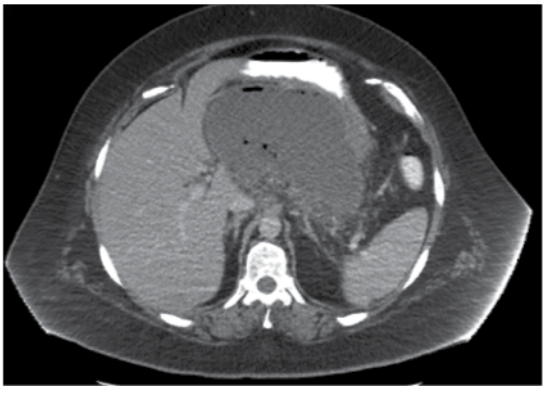
Patient G

- 20 days after onset of symptoms of acute pancreatitis
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows an acute necrotic collection (no full encapsulation) without gas
- FNA has not been performed



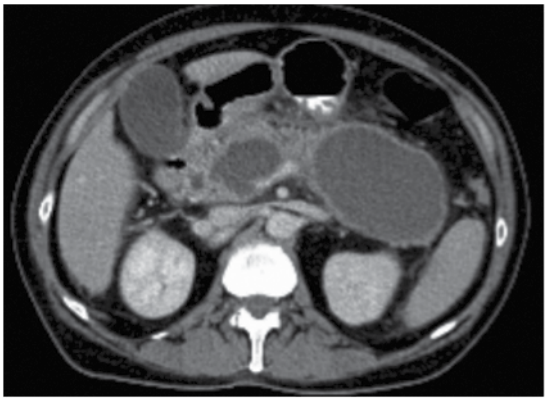
Patient H

- 20 days after onset of symptoms of acute pancreatitis
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows an acute necrotic collection (no full encapsulation) with gas
- FNA has not been performed



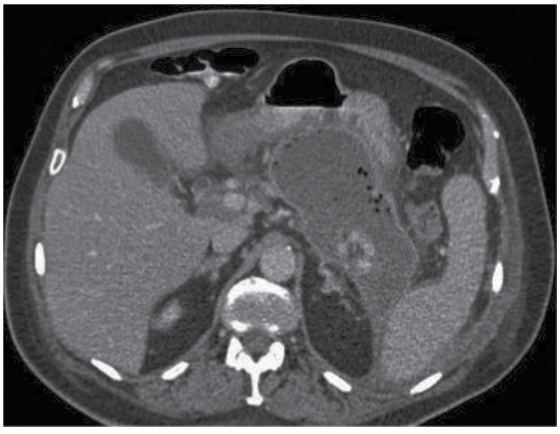
Patient I

- 30 days after onset of symptoms of acute pancreatitis
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows walled-off necrosis without gas
- FNA has not been performed



Patient J

- 30 days after onset of symptoms of acute pancreatitis
- Patient on the nursing ward with clinical deterioration with 39 degrees fever, rising CRP to 300, and leukocytosis, no signs of organ failure
- CT shows walled-off necrosis with gas
- FNA has not been performed



9

CHAPTER 9

Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): study protocol for a randomized controlled trial

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Submitted

Abstract

Background
Infected necrosis complicates 10% of all acute pancreatitis episodes and is associated with 15-20% mortality. The current standard treatment for infected necrotizing pancreatitis is the step-up approach (catheter drainage, if necessary followed by minimally invasive necrosectomy). Catheter drainage is preferably postponed until the stage of walled-off necrosis, which usually takes 4 weeks. This delay stems from the time when open necrosectomy was the standard. It is unclear whether such delay is needed for catheter drainage or whether earlier intervention could actually be beneficial in the current step-up approach. The POINTER trial investigates if immediate catheter drainage in patients with infected necrotizing pancreatitis is superior to the current practice of postponed intervention.

Methods
POINTER is a randomized controlled multicenter superiority trial. All patients with necrotizing pancreatitis are screened for eligibility. In total, 104 adult patients with (suspected) infected necrotizing pancreatitis are randomized between immediate (within 24 hours) catheter drainage and current standard care involving postponed catheter drainage. Necrosectomy, if necessary, is preferably postponed until the stage of walled-off necrosis in both treatment arms. Primary outcome is the Comprehensive Complication Index (CCI), which includes all complications between randomization and 6 months follow-up. Secondary outcomes include mortality, complications, number of (re-)interventions, hospital and Intensive Care Unit (ICU) lengths of stay, quality adjusted life years (QALYs) and (in)direct costs. Standard follow-up is at 3 and 6 months after randomization.

Discussion
The POINTER trial investigates if immediate catheter drainage in infected necrotizing pancreatitis reduces the composite endpoint of complications, as compared with the current standard treatement strategy involving a delay of intervention until the stage of walled-off necrosis.

Trial registration
Current controlled trials ISRCTN33682933 (date registration: 6 August 2015).

Background

Acute pancreatitis is one of the most common gastrointestinal conditions requiring acute hospital admission [1]. Around 20-30% of these patients develop necrotizing pancreatitis [2]. Infected necrotizing pancreatitis occurs in a third of these patients and is associated with a mortality of 15-20% [3, 4], despite radiological, endoscopic or surgical interventions [3-6]. The current, 2013 international treatment guidelines [7, 8] recommend a step-up approach, based on results of the Dutch PANTER trial [3]. The first step of this step-up approach is catheter drainage, preferably once the (extra)pancreatic collection has organized and has become fully encapsulated (walled-off necrosis). This process usually is complete after 4 weeks after onset of disease. During this time, intravenous antibiotic treatment is used which may obviate the need for any intervention in a small subset of patients [4]. If catheter drainage does not resolve the clinical signs of infection and sepsis, surgical [3] or endoscopic [9] necrosectomy is performed as the next step.

Postponing all interventions for infected necrosis until the stage of walled-off necrosis has been standard practice for many years. The rationale for this delay lies in the prevention of the 'extra hit' (i.e. a pro-inflammatory reaction) of open surgery in these already critically ill patients, as well as the relation between early open necrosectomy and mortality [10]. In line with this practice, catheter drainage in the current step-up approach has also been postponed until the stage of walled-off necrosis. Meanwhile, intravenous antibiotics are administered to reduce systemic illness from the infected necrosis, which may lead to increased incidence of Candida infections and antibiotic-resistance [10]. Notably, several observational studies have suggested that encapsulation is not mandatory for safe and successful catheter drainage [3, 11-15]. In other conditions, such as pancreatic fistula after pancreatic resection, early (percutaneous) catheter drainage has also proven safe and successful [16]. Furthermore, an international survey among expert pancreatologists demonstrated 'equipoise' between immediate and postponed catheter drainage of infected necrotizing pancreatitis [17]. The aim of immediate catheter drainage is to prevent further clinical deterioration.

Methods

Study aim

The POINTER trial aims to determine whether immediate catheter drainage in patients with (suspected) infected necrotizing pancreatitis is superior to the current standard of postponed catheter drainage with regard to clinical outcome and cost-effectiveness. The hypothesis is that pro-active diagnosis of infected necrosis and immediate catheter drainage prevents further clinical deterioration of these patients, reducing complications and possibly death, and reduces length of hospital stay and costs, as compared to postponed catheter drainage using antibiotics, preferably until the stage of walled-off necrosis.

Study design and setting

POINTER is a randomized controlled multicenter superiority trial, including hospitalized adult patients with proven or suspected infected necrotizing pancreatitis. In total, 25 centers are participating in the trial, including all 8 Dutch university medical centers. Endpoints are assessed by an adjudication committee, blinded for assigned treatment arm, based on clinical case descriptions and endpoint definitions. A Data and Safety Monitoring Committee (DSMC) monitors patient safety.

Inclusion criteria (see Tables 1 and 2)

- Proven infected necrotizing pancreatitis or, if >14 days after onset of disease, clinical suspicion of infected necrosis
- Catheter drainage of the necrotic collection is technically feasible
- Age ≥18 years

Exclusion criteria

- Onset of acute pancreatitis >35 days ago
- Indication for emergency laparotomy because of an abdominal catastrophe
- Previous retroperitoneal intervention for necrotizing pancreatitis
- Documented chronic pancreatitis

Table 1 In- and exclusion criteria

Inclusion	Exclusion
Infected necrotizing pancreatitis[1] Day 0-14: gas on imaging or positive culture Day 15-35: clinical signs alone allowed	Onset of acute pancreatitis >35 days ago
Catheter drainage of the necrotic collection is technically feasible[2]	Indication for emergency laparotomy because of abdominal catastrophe[3]
Age ≥ 18 years	Previous retroperitoneal intervention for necrotizing pancreatitis[4, 5]
	Documented chronic pancreatitis[6]

[1] See criteria in Table 2
[2] As deemed by the expert panel and/or treating physician (i.e. enough encapsulation and liquefaction)
[3] For example bleeding, bowel perforation or abdominal compartment syndrome
[4] Ascites drainage is permitted
[5] Emergency laparotomy without opening the bursa is permitted
[6] According to the M-ANNHEIM criteria [34]

Table 2 Criteria for infected necrotizing pancreatitis

Day 0-14 after onset of disease: proven infected necrosis	Day 15-35 after onset of disease: proven or suspected infected necrosis
Gas in the necrotic collection on imaging	Gas in the necrotic collection on imaging
Positive gram stain/culture of fine-needle aspiration from the necrotic collection	Positive gram stain/culture of fine-needle aspiration from the necrotic collection
	Clinical signs of infection without obvious another focus than infected necrosis for 3 consecutive days[7]

[7] Either persistent (multiple) organ failure in patients admitted to the Intensive Care Unit. Or 2 of the 3 inflammatory parameters not decreased (temperature (T>38.5 °C), C-Reactive Protein or leukocyte count) during 3 consecutive days in patients on regular wards (with no other infection focus). These clinical criteria alone are considered sufficiently reliable only after the initial 14 days of acute pancreatitis.

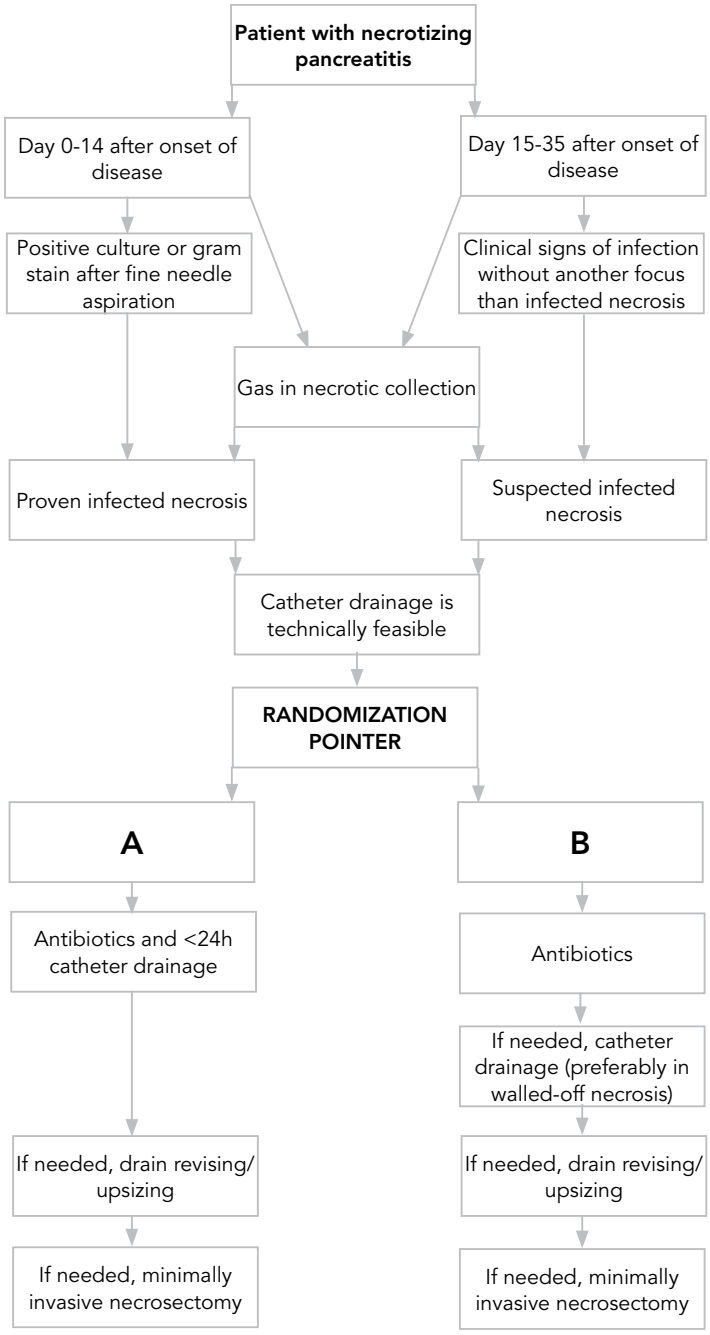
Treatment groups
All patients with signs of infected necrotizing pancreatitis are pro-actively assessed for the presence of infected necrosis, either by imaging (gas configurations), fine-needle aspiration (FNA), or clinical signs of infection which may include persistent organ failure. See Figure 1 for the inclusion flowchart. FNA is only used on indication and not as a screening tool. Patients who fulfill the eligibility criteria are randomly assigned to group A or B. Since diagnosing infected necrosis and decision-making for invasive intervention in these patients are both challenging, the Dutch pancreatitis expert panel [18] is 24/7 available to assess indication for intervention and eligibility for randomization as was done in the PANTER [3] and TENSION [9] trials.

Intervention group (A)
Group A: immediate catheter drainage, within 24 hours after randomization, while starting (or continuing) antibiotic treatment. In case of no clinical improvement within 72 hours thereafter, the possibility of additional drainage is evaluated, including drain revision or drain upsizing. In case of no clinical improvement thereafter and no possibilities for additional catheter drainage, a necrosectomy is performed, once the (extra)pancreatic collection has developed into walled-off necrosis. No clinical improvement is defined as new organ failure or 2/3 parameters that failure to decrease (temperature, CRP and leukocyte count), see Figure 1.

Control group (B)
Group B: postponed catheter drainage, using antibiotics, preferably until the (extra) pancreatic necrotic collection has reached the stage of walled-off necrosis. In case of no clinical improvement within 72 hours after drainage, the possibility of additional drainage is evaluated, including drain revision or drain upsizing. In case of no clinical improvement thereafter and no possibilities for additional catheter drainage, a minimally-invasive necrosectomy is performed. No clinical improvement is defined as new organ failure or 2/3 parameters that failure to decrease (temperature, CRP and leukocyte count), see Figure 1.

Diagnosing infected necrosis
All patients with signs of infected necrotizing pancreatitis are screened for eligibility (Figure 1). We distinguish diagnosing infected necrosis in patients in the first 14 days after onset of disease versus thereafter. In the first 14 days a proven infection is mandatory, as in this early course of the disease it is impossible to distinguish systemic inflammatory response syndrome (SIRS) from sepsis. This proof requires either a positive gram stain or culture from FNA or gas configurations in the (peri) pancreatic collection with necrosis on imaging (Contrast Enhanced Computed

Figure 1 Inclusion and randomization flowchart



Tomography (CECT) or Magnetic Resonance Imaging (MRI)). In case of unclear signs of infection, percutaneous FNA is performed in patients with necrotizing pancreatitis within 14 days after onset of disease with 2 consecutive days of clinical signs of infection (i.e. new (multiple) organ failure or 2/3 parameters raised: temperature, CRP or leukocyte count). After the first 14 days, clinical signs of infection suffice for diagnosing infected necrosis (having no other focus for infection, e.g. pneumonia), based on our experiences in previous trials [3, 9]. Obviously, in case of clinical doubt, FNA is still allowed after the first 14 days. The presence of gas in the (extra) pancreatic necrosis on CECT is considered proven infected necrosis in all patients, regardless of the disease stage (i.e. before or after 14 days).

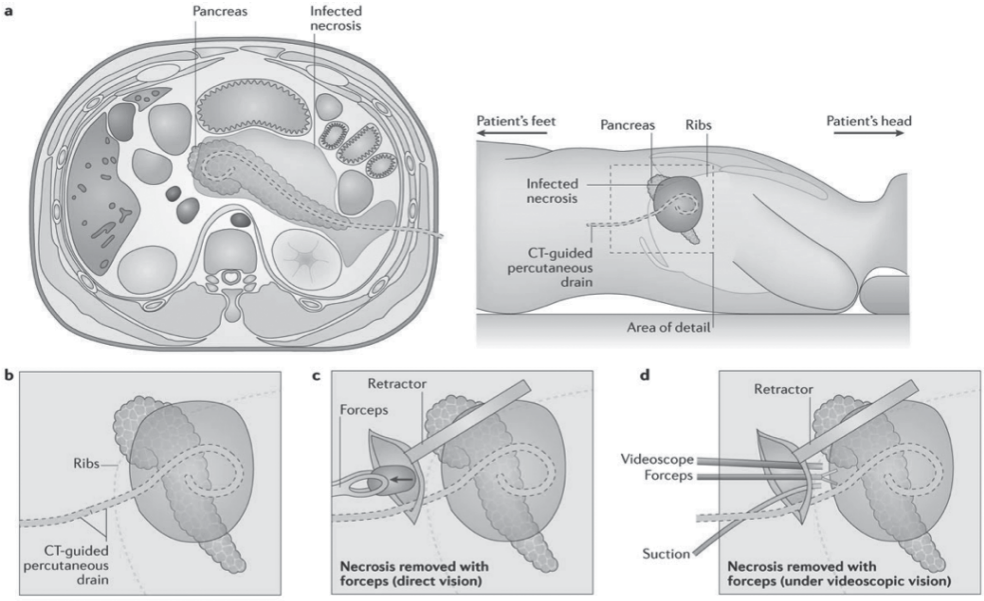
Supportive treatment

Current standard management of acute (necrotizing) pancreatitis is extensively described in the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines in 2013 [7]. These international guidelines have been adopted by the Dutch Pancreatitis Study Group (DPSG) and the national professional organizations involved. In accordance with these guidelines, patients receive fluid resuscitation, pain management and enteral feeding (oral, if not tolerated enteral). Antibiotic prophylaxis is not given. Patients who deteriorate with clinical signs of infection will undergo infectious focus detection, with cultures of blood, urine, sputum, ascites and diagnostic imaging (e.g. chest X-ray and abdominal CECT). Once an infectious focus is diagnosed, targeted antibiotics are given or, in case of high suspicion of infected necrosis and persistent deterioration, broad spectrum antibiotics with optimal tissue penetration are started empirically. The latter usually consists of meropenem or imipenem, based on the local antibiotics protocol.

Step-up approach

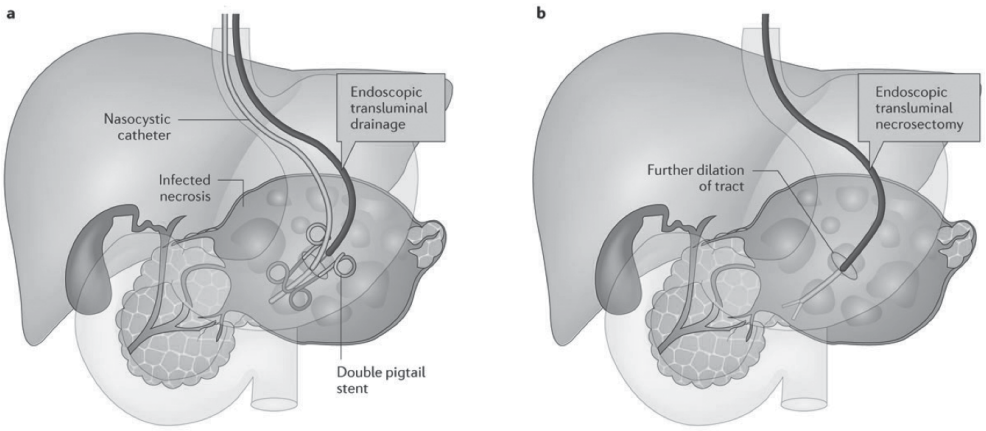
Both a percutaneous-surgical and an endoscopic step-up approach are permitted in the POINTER trial, depending on the location of the necrotic collection(s), the extent of encapsulation and the preference of the treating physician. Catheter drainage can be performed transluminal (transgastric or transduodenal) endoscopically or percutaneous via the retroperitoneal route. In case of no clinical improvement within the first 72 hours after initial catheter drainage, an additional or upsizing drainage procedure is performed (Figure 1). In absence of clinical improvement after this second drainage procedure and no further possibilities for optimized or additional drainage, necrosectomy is performed. After percutaneous catheter drainage, additional necrosectomy should be performed surgically (e.g. videoscopic assisted retroperitoneal debridement (VARD)) and after endoscopic transluminal drainage, endoscopic transluminal necrosectomy is performed.

Figure 2 Surgical step-up approach [31]



A| Cross-sectional image and torso depicting a peripancreatic collection with fluid and necrosis. The first step of the surgical step-up approach is percutaneous catheter drainage. The preferred access route is through the left retroperitoneal space between the left kidney, dorsal spleen and descending colon. If necessary, percutaneous catheter drainage is followed by a minimally invasive surgical necrosectomy, for example videoscopic-assisted retroperitoneal debridement. B| Enlargement of the area of detail shown in part a of the figure. C| A 5 cm subcostal incision is made, and the previously placed percutaneous drain is used as a guide into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision with a long grasping forceps. D| Further debridement is performed under videoscopic assistance. *Reprinted from van Brunschot, S. et al. Clin. Gastroenterol. Hepatol. 10, 1190-1201 (2012) [35], with permission from Elsevier ©, and adapted from John Wiley and Sons © da Costa, D. W. et al. Br. J. Surg. 101, e65-e79 (2014) [36].*

Figure 3 Endoscopic step-up approach [31]



A| The first step of the endoscopic step-up approach is endoscopic transluminal drainage. The preferred access route for endoscopic transluminal treatment is through the posterior wall of the stomach. The necrotic collection often bulges into the stomach, facilitating endoscopic transluminal treatment. The collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation. B| If necessary, the cystostomy tract is further dilated, the collection is entered by a forward viewing endoscope, and necrosectomy is performed. *Reprinted from van Brunschot, S. et al. Clin. Gastroenterol. Hepatol. 10, 1190-1201 (2012) [35], with permission from Elsevier ©, and permission obtained from John Wiley and Sons © da Costa, D. W. et al. Br. J. Surg. 101, e65-e79 (2014 [36]).*

Only in case (additional) necrotic collections are not technically approachable via the standard second step, additional catheter drainage or necrosectomy may be performed via the 'other' approach. Both step-up approaches are performed conform the PANTER and TENSION trial protocols [3, 9], see also Figures 2 and 3. The participating centers have documented expertise, defined as having performed at least 10 independent VARD procedures, 10 independent endoscopic transluminal drainage procedures and 10 independent endoscopic transluminal necrosectomies. In case of insufficient local experience available (e.g. during weekends), the patient is transferred to a tertiary referral center with sufficient experience.

Primary endpoint

Primary endpoint is the Comprehensive Complications Index (CCI) [19, 20], including all complications, graded according to the Clavien-Dindo classification, after randomization until 6 months after, other than pre-existent complications, e.g. treatment for infected (extra)pancreatic necrosis. These complications are assessed by an adjudication committee, blinded for assigned treatment arm, based on clinical case descriptions using definitions.

Secondary endpoints

Secondary endpoints are: mortality, new-onset (multiple) organ failure, bleeding requiring intervention, perforation of a visceral organ requiring intervention, enterocutaneous and pancreatic fistula, incisional hernia (including burst abdomen), wound infections, endocrine and exocrine pancreas insufficiency, number of patients with severe complications (Clavien-Dindo III or higher), number of patients per Clavien-Dindo classification, number of surgical, endoscopic and radiological (re-)interventions, length of hospital stay, length of ICU admission, quality adjusted life years (QALYs), and total direct and indirect costs (see Appendix for relevant definitions). Also, for mutual comparison the primary endpoint of the previous PANTER trial will be a secondary endpoint of the POINTER trial (i.e. a composite of major complications; new-onset multiple organ failure, enterocutaneous fistula or perforation of a visceral organ requiring intervention, intra-abdominal bleeding requiring intervention or death during admission or during the 3 months after discharge) [3].

Sample size

The sample size is calculated based on the primary endpoint Comprehensive Complication Index. A mean CCI score of 40 (with a standard deviation of 27) for the postponed catheter drainage is based on the number of complications in the step-up arm of the PANTER trial [3] and preliminary data of the TENSION trial [9]. A Student's T-test will have 80% power to detect a clinically relevant reduction of 15 to a CCI score of 25 [20] at a significance level of 0.05, if the sample size equals 2 x 51, is 102 evaluable patients. Assuming a dropout rate of about 2%, 104 patients are included.

Randomization, blinding and treatment allocation

Patients are randomized using a centrally operated computer (ALEA system) with variable block randomization for allocation concealment between group A (immediate catheter drainage) and group B (postponed catheter drainage). Stratification at randomization is applied for the factors: presence of organ failure (yes vs. no), disease duration (day 0-20 vs. day 21-35) and center (expected high number of included patients vs. other centers). For randomization of a patient, physicians can contact the study coordinator via telephone (www.pancreatitis.nl) 24 hours per day, 7 days per week in order to check the eligibility criteria and to verify whether informed consent has been obtained. Blinding of patients and physicians for treatment strategy is not feasible, since both treatments are highly different timing-wise. Patients are coded by a numeric randomization code (anonymized).

Follow-up

The follow-up duration is 6 months from randomization. Outpatient follow-up visits take place at the discretion of the responsible physician, but in any case 3 and 6 months after randomization that can be considered as standard care. All patients undergo imaging (preferably CECT) at 3 and 6 months post-randomization. Furthermore at these points in time exocrine and endocrine pancreatic function is measured, with respectively blood glucose measurements and fecal elastase tests. No blood or fecal samples are stored at the DPSG datacenter. The treating physician is responsible for the application, interpretation and treatment when needed. Also every patient receives a combined questionnaire at home (SF-36 [21], EQ-5D [22], iMedical Consumption Questionnaire (iMCQ) [23] and iProductivity Cost Questionnaire (iPCQ) [24]) at 3 and 6 months. Data from patient records is collected until 6 months post-randomization.

Baseline values
Baseline criteria (all <24 hours prior to randomization) are: age, sex, center, body mass index, etiology of pancreatitis, American Society of Anesthesiologist's (ASA) classification, co-morbidity, disease severity (SIRS, ICU admission, single or multiple organ failure), Acute Physiology and Chronic Health Evaluation (APACHE) II score, Multiple Organ Dysfunction Score (MODS) [25], Sequential Organ Failure Assessment (SOFA) scores [26], C-reactive protein (CRP), CT severity index (CTSI), suspected or proven infected necrosis, time from admission to randomization (days), time from admission to tertiary referral (days).

Statistical analysis
All randomized patients are evaluated for primary and secondary endpoints at 6 months after randomization. Using primary source data, a blinded adjudication committee will assess the occurrence of the primary endpoint and/or secondary outcomes after the last patient has completed the predefined follow-up of 6 months after randomization.

The primary analysis is based on intention to treat principles. For exploratory reasons also a per-protocol analysis is performed. A tabular listing of all patients excluded from the intention-to-treat populations is provided together with the reasons for exclusion. For the intention-to-treat population the protocol deviations for each randomization arm is listed. Predefined subgroup analyses are performed for patients with and without (multiple) organ failure, disease duration (cut-off 20 days) at time of randomization and per center (high expected number of included patients and other centers). All analyses are performed in SPSS for Windows or SAS System for Windows. All data handling and analyses are saved in a syntax/program file. Results are presented with all centers combined. A two-tailed p-value <0.05 is considered statistically significant. No corrections for multiple tests are applied.

The primary outcome is a sum of all complications that are weighted for their severity (multiplication of the median reference values from patients and physicians), the Comprehensive Complication Index [19, 20]. Comparison of the primary endpoint is expressed in terms of an absolute difference in mean CCI score and standard deviation (SD). Subsequent analyses are directed at secondary endpoints. Data are presented as mean ± SD and in case of skewed distributions as median and range. Values are compared by the Student's t test, Wilcoxon rank sum test, X2 test or Fischer exact test as appropriate. In the event of imbalance between groups at baseline, regression analysis is used to correct for the effect of the covariates.

The economic evaluation addresses the question whether or not immediate catheter drainage in patients with infected necrosis is cost-effective compared to the current management of postponed catheter drainage. A cost-effectiveness analysis as well as a cost-utility analysis are performed, both from a societal perspective. The primary outcome parameters in the cost-effectiveness and cost-utility analyses respectively are the costs per unit of the CCI score and the costs per quality adjusted life year (QALY).

Monitoring and quality assurance
Clinical trial monitoring is performed by an independent monitor. The trial monitor checks and verifies documents and reports in every site in the electronic or paper record of the trial patient. The frequency may be changed based on the total enrolment period and enrolment rate. The monitor checks the site files according the Medical Research Involving Human Subjects Act (WMO)/Good Clinical Practice (GCP) standards if and how essential documents are collected/administered and verifies all reported severe adverse events (SAE's). Also, the monitor verifies the protocol compliance. A monitoring report is made after each monitoring visit in a specific site.

Safety
All physicians who are involved in the trial are asked to report all adverse events to the coordinating investigator. An independent Data Safety Monitoring Committee (DSMC) is assigned to evaluate safety parameters at regular intervals. The DSMC consists of 5 members: 2 surgeons, a gastroenterologist, a radiologist and an epidemiologist. Evaluations are planned after patient number 25, 50 and 75 have completed their 6 months follow-up. Per 25 patients, all deceased patients and every possible trial related serious adverse event are listed and discussed within the DSMC unblinded. During the inclusion period of the study the DSMC performs interim-analyses only on safety. Only in case of safety reasons the POINTER trial will be prematurely terminated, as assessed by the DSMC. There is no interim-analysis for treatment effect. Adverse events are reported using the online module (https://www.toetsingonline.nl) of the Dutch Central Committee on Research involving human subjects.

Discussion

Infected necrosis is a potentially lethal complication of acute pancreatitis, typically requiring invasive intervention. The treatment of infected necrotizing pancreatitis is associated with lengthy hospital stay and high costs. The POINTER trial is the first randomized controlled trial designed to determine the optimal timing catheter drainage in infected necrotizing pancreatitis: i.e. immediate or postponed, once walled-off necrosis has occurred.

According to current evidence-based international guidelines [7, 8], suspected or proven infected necrosis in patients with clinical signs of infection is an indication for invasive intervention. There should be a strong reluctance towards intervening in sterile collections [7, 27]. Currently, an intervention is advised when the infected necrosis has become walled-off, which occurs typically 4 weeks after onset of disease [28]. This practice of postponing interventions until the stage of walled-off necrosis is based on literature from the time where open necrosectomy was the standard intervention [10, 29-30]. It has been recognized that early necrosectomy has major impact on the already critically ill patient, whereas postponed necrosectomy allows the immune system to recover from the pro-inflammatory response due to pancreatitis.

Since the step-up approach is now considered standard of care, the issue regarding the optimal timing of catheter drainage has become highly relevant. Current literature reports that 35-64% of patients with infected necrotizing pancreatitis can be treated with catheter drainage alone, without the need for invasive necrosectomy [3, 5]. Therefore, several expert pancreatologists have stated that they already practice immediate catheter drainage in patients with infected necrosis. In a recent international survey performed in preparation for this study, 55% of expert pancreatologists stated that they typically postpone catheter drainage using antibiotics, whereas the other 45% proclaimed to drain immediately after diagnosing infected necrosis [17]. Thus, in practice immediate catheter drainage is already performed in individual patients, regardless of the effect of antibiotics alone or the degree of encapsulation. Several retrospective cohorts [31] described (percutaneous) catheter drainage for infected necrosis at a median of 2 weeks (9-15 days) after onset of disease instead of 4 weeks (28 days).

In the step-up approach arm of the PANTER trial, patient outcomes were significantly better compared to the control group (primary open necrosectomy), but mortality (19%) did not differ between both groups [3]. To further reduce mortality and morbidity, the POINTER trial assesses whether early detection of infected necrosis and immediate catheter drainage improve outcomes. Earlier intervention may prevent patients from further deterioration while often waiting several weeks before undergoing an invasive intervention, and thereby reduce complications and length of hospital stay and improve patient quality of life. In the control group, the effect of antibiotics is awaited while letting the (extra)pancreatic necrotic collections become walled-off. In a small minority patients [4], antibiotic treatment alone may suffice, which is another possible benefit for the control group.

Infected necrosis can be diagnosed by the presence of gas in the (extra)pancreatic necrotic collection on imaging (e.g. CECT), irrespective of the source of the gas (i.e. through gas-forming bacteria or loss of integrity of the gastrointestinal tract). Collections with gas are seen in up to 42% of patients with infected necrosis [32] and can occur in every phase of the disease [33]. Infected necrosis can also be confirmed by a positive gram stain or culture gathered with FNA. In a recent study, infected necrosis was confirmed by FNA in 86% (of 28 patients) which was similar to the diagnostic performance of clinical symptoms (80% of 92 patients) or gas on imaging (94% of 88 patients) [32]. Until recently, FNA was not routinely used for diagnosing infected necrosis in the Netherlands [17] since its outcome did not change treatment because invasive intervention was postponed until the stage of walled-off necrosis, also in case of a positive culture. In the POINTER trial, however, it is pivotal to detect infected necrosis as early as possible to be able to perform an immediate drainage (group A). Differentiating SIRS from sepsis is, however, very difficult in the first 14 days of the disease. Therefore, in the absence of gas on imaging but with clinical signs of infection in the first 14 days, a positive gram stain or culture after FNA is obligatory prior to randomization. Since the false-negative rate of FNA is relatively high [32], a second FNA is advised in patients with persistent deterioration and a primary negative FNA. After the first 14 days clinical signs alone are sufficient to diagnose (suspected) infected necrotizing pancreatitis [3].

After the first 14 days, clinical signs of infected necrosis are much more reliable. In the PANTER trial [3] it was possible to reach a 91% accuracy rate of infected necrosis based on clinical criteria. In the POINTER trial, after the first 14 days, randomization can take place based on the clinical diagnosis of infected necrosis as was done in the PANTER trial [3].

Patients are randomized to undergo either immediate (<24 hours) or postponed (in walled-off necrosis) catheter drainage of infected collections. Depending on the location of the necrotic collection(s), the extent of encapsulation and the preference of the treating physician, both the surgical and the endoscopic step-up approach are allowed. It is known that both approaches are effective and safe and that not all (peri)pancreatic collections are approachable via one technique [6, 9].

The Comprehensive Complication Index [19, 20] is the primary endpoint of the trial. Patients with infected necrotizing pancreatitis often have a long disease course with multiple complications, and therefore the CCI score is considered a representative tool to take all these complications into account. The individual complications (e.g. organ failure and mortality), number of (re-) interventions, hospital and ICU lengths of stay, QALYs and (in)direct costs are also analyzed as secondary end points.

Patients are stratified based on organ failure at baseline, since it is known that patients with organ failure have poorer outcomes, as compared to patients with no organ failure. , Stratification is also performed for disease duration (cut-off 20 days) since this is obviously related to the onset of walled-off necrosis. Finally, stratification takes place for expected high vs. low volumes of patient inclusions.

In conclusion, the POINTER trial is a multicenter randomized controlled trial that investigates whether immediate catheter drainage reduces the Comprehensive Complication Index in patients with infected necrotizing pancreatitis, as compared to postponed catheter drainage.

Trial status

The trial was registered on the 6th of August 2015 as ISRCTN33682933. The first patient was randomized on the 4th of August 2015. To date, 70 of the 104 patients have been randomized and inclusion is on schedule.

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9

CHAPTER 9

Appendix

List of abbreviations

APA	American Pancreatic Association
APACHE	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiologist's classification
CCI	Comprehensive Complication Index
CECT	Contrast Enhanced Computed Tomography
CRP	C-reactive Protein
CTSI	Computer Tomography Severity Index
DPSG	Dutch Pancreatitis Study Group
DSMC	Data Safety Monitoring Committee
FNA	Fine Needle Aspiration
GCP	Good Clinical Practice
IAP	International Association of Pancreatology
ICU	Intensive Care Unit
iMCQ	iMedical Consumption Questionnaire
iPCQ	iProductivity Cost Questionnaire
MODS	Multiple Organ Dysfunction Score
MRI	Magnetic Resonance Imaging
QALY	Quality Adjusted Life Year
SAE	Serious Adverse Event
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SSI	Surgical Site Infection
VARD	Videoscopic Assisted Retroperitoneal Debridement
WMO	Medical research involving human subjects act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met mensen)

Relevant definitions

Acute pancreatitis

Upper abdominal pain and serum amylase and/ or lipase >3x upper limit of normal, potentially with cross-sectional imaging if first two criteria unclear.

Endocrine pancreatic insufficiency

The need for insulin or oral anti-diabetic drugs; this requirement was not present before onset of pancreatitis.

Enterocutaneous fistula

Secretion of fecal material from a percutaneous drain or drainage canal after drain removal or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery.

Exocrine pancreatic insufficiency

Fecal elastase <0.2 gram and the need for pancreatic enzyme supplementation; this requirement was not present before onset of pancreatitis.

Incisional hernia

Incisional hernia is defined as full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction.

Intra-abdominal bleeding

Bleeding requiring surgical, radiologic, or endoscopic intervention.

M-ANNHEIM criteria

One or more of the following criteria [34]:
1) Pancreatic calcifications
2) Moderate or marked ductal lesions
3) Marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation
4) Typical histology of an adequate histological specimen

Multiple Organ Dysfunction Score (MODS)

Scale that ranges from 0 to 24, with higher scores indicating more severe organ dysfunction [24].

Multiple organ failure

Failure of 2 or more organ systems (respiratory, cardiovascular or renal) occurring in the same 24 hours.

Necrotizing pancreatitis

Either pancreatic necrosis or extrapancreatic necrosis. Pancreatic necrosis is defined as diffuse or focal area(s) of non-enhancing pancreatic parenchyma as detected on CECT. Extrapancreatic necrosis is defined as persistent peripancreatic fluid collections on CECT in the absence of pancreatic parenchymal non-enhancement.

New onset (multiple) organ failure

Failure of one (or more) organ systems that was not present prior to randomization or at any time in the 24 hours before intervention.

Organ failure

Failure of one or more of the following organ systems (adapted from the Atlanta classification) and as previously used in the PANTER and TENSION trial [4, 18]:

1) Respiratory: PaO2 <60 mm Hg despite FiO2 30% or the need for mechanical ventilation (pulmonary insufficiency)

2) Cardiovascular: systolic blood pressure <90 mm Hg despite adequate fluid resuscitation or the need for vasopressor support (cardiocirculatory insufficiency)

3) Renal: serum creatinine level >177 umol/L after rehydration or the need for hemofiltration or hemodialysis (renal failure) (in case patients already suffered from renal insufficiency before this episode of AP [creatinine >177 umol/L] this does not count as renal failure)

Pancreaticocutaneous fistula

Output through a percutaneous drain or drainage canal after removal of drains from a surgical wound, or any measurable volume of fluid with an amylase content >3 times the serum amylase level.

Persistent organ failure

Failure of one or more organ systems for at least 48 hours.

Proven infected necrosis

A positive culture or gram stain obtained by fine-needle aspiration from the necrotic collection or gas configurations in the necrotic collection on imaging.

Perforation of visceral organ

Perforation requiring surgical, radiologic, or endoscopic intervention.

Sequential Organ Failure Assessment (SOFA) score

Scale that ranges from 0 to 24, with higher scores indicating more severe organ dysfunction [25].

Suspected infected necrosis

Either persistent (multiple) organ failure in patients admitted to the Intensive Care Unit. Or 2 of the 3 inflammatory parameters not decreased (temperature (>38.5 °C), C-Reactive Protein or leukocyte count) during 3 consecutive days in patients on regular wards (with no other infection focus). These clinical criteria alone are considered sufficiently reliable only after the initial 14 days of acute pancreatitis.

Wound infection

Defined as a superficial incisional surgical site infection (SSI) and must meet the following criterion: infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least 1 of the following:

1) Purulent drainage from the superficial/deep incision but not from the organ/space component of the surgical site

2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision

3) At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.

4) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination

5) Diagnosis of superficial/deep incisional SSI by the surgeon or attending physician

Declarations

Ethics approval and consent to participate
The study is conducted according to the principles of the Declaration of Helsinki (59th version, October 2008) and in accordance with Dutch Law regarding research with humans (Medical Research Involving Human Subjects Act (WMO)). The study was approved by the medical research ethics committee of the Academic Medical Center Amsterdam on 19th of June 2015. Patients are preferably recruited by the principal investigators. If this is not possible for practical reasons, he/she is replaced by a designated substitute (the study coordinator, local treating physicians or a study nurse) who is fully informed and aware of study procedures and requirements. Written informed consent is obtained from each participant. In case of incapacitated patients, informed consent is obtained from the patients' legal representatives. This applies only to patients who are temporarily incapacitated because of the severity of pancreatitis.

Consent for publication
Not applicable, the study results will not contain any data from any individual person.

Availability of data and material
Patients are coded by a numeric randomization code (anonymized) and the principal investigators are the only ones to have access to this code. The source data is kept by the project leader for 15 years at the datacenter of the DPSG. All data generated or analyzed during this study will be included in the published results.

Competing interests
The authors declare that they have no competing interests.

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PART IV

CONCLUDING REMARKS

10

CHAPTER 10

General discussion and future perspectives

This chapter is partly based on Chapter 15 of the textbook 'Prediction and management of severe acute pancreatitis', editors C.E. Forsmark and T.B. Gardner, written by Janneke van Grinsven, Marc G. Besselink, Olaf J. Bakker, Sandra van Brunschot, Marja A. Boermeester, Hjalmar C. van Santvoort

I Decision-making on invasive interventions

The treatment of necrotizing pancreatitis has changed considerably over the last decades. Management of patients with (extra)pancreatic necrosis has become more individualized, requiring consideration of all available data (clinical, radiological, laboratory) and available expertise [1, 2]. Intervention is now performed almost exclusively in case of infected necrotizing pancreatitis. Invasive intervention for sterile necrosis is only performed in patients with persistent gastric outlet obstruction or with intractable pain for at least 4-6 weeks [1, 2].

The incidence of infected necrotizing pancreatitis is relatively low and the disease is known for its heterogeneous character. For this reason, decision-making on invasive interventions in these patients can be very challenging. First, diagnosing infected necrosis is not always easy. Second, even if infected necrosis is proven, timing of invasive interventions and the preferred route is often a point of discussion (i.e. percutaneous, surgical or endoscopic). Therefore, a multidisciplinary approach may lead to improved clinical outcomes. In this thesis, we evaluated the unique 24/7 online nationwide multidisciplinary expert panel for necrotizing pancreatitis of the Dutch Pancreatitis Study Group [3]. This expert panel was found to be an accessible and valuable tool in treating necrotizing pancreatitis patients and was also helpful for research purposes (e.g. inclusion of patients). In the future, a similar expert panel might be of similar value to other relatively rare and complex diseases. Currently, the Dutch Pancreatitis Study Group is trying to improve their expert panel service, e.g. implementing software to easily share complete CTs between hospitals.

There are several clinical and imaging parameters used for the decision-making regarding invasive intervention in patients with necrotizing pancreatitis. First, for diagnosing infected necrosis the presence of gas configurations in necrotic collections imaging is important. In this thesis, we found that gas configurations can be present at any time after onset of disease, not just in a later phase [4]. Second, the degree of encapsulation of necrotic collections on imaging plays a significant role in the decision to proceed to invasive intervention in these patients. According to the Revised Atlanta Criteria and as described in this thesis, fully walled-off necrosis is seen 4 weeks after disease onset [4, 5]. Although, in contrast to traditional views, we found that clinically relevant walled-off necrosis (largely or fully encapsulated necrotic collections) was seen in 162/379 (43%) patients within the first 3 weeks. Thus, in a considerable number of patients invasive intervention (i.e. catheter drainage) is theoretically possible relatively earlier in the disease course.

Little is known about clinical and imaging parameters that identify necrotizing pancreatitis patients at high risk for a complicated disease course. Identification parameters could also attribute to the decision-making in treating these patients. In this thesis, we found no association of CT-assessed body composition analysis (i.e. skeletal muscle mass, skeletal muscle density and visceral adipose tissue) and mortality of patients with necrotizing pancreatitis [6]. Nevertheless, a significant decrease in muscle mass and muscle density was seen over the first month after hospital admission, for both males and females. Finally a decrease in skeletal muscle density of ≥10% in 1 month was independently associated with in-hospital mortality: OR 5.87 (95%CI 2.09-16.50, P=0.001). In future research, these and other clinical and imaging identification parameters should be further investigated.

II Drainage and debridement techniques

The current rationale of treating infected necrotizing pancreatitis, is to consider the necrotic collection as an abscess and drain infected fluid which is under pressure, without removing the necrosis. Drainage of the infected fluid may reduce sepsis, improve the patient's clinical condition, and allow for further encapsulation. The preferred route for intervention in current guidelines is through the left retroperitoneum so that the drain can be used as a guide wire for VARD procedure (if necessary) and the peritoneal cavity is not contaminated. Previous studies have showed that, in 35-64% of cases, patients can be successfully treated with PCD alone and do not need to undergo an additional necrosectomy [7, 8].

In this thesis, we performed the first retrospective multicenter study to compare the traditional surgical step-up approach with a more 'proactive' drainage strategy in patients with infected necrotizing pancreatitis [9]. The proactive drain strategy was associated with a reduced need for additional necrosectomy (29% versus 52%), but had similar outcomes regarding complications and length of hospital stay. Unfortunately, from our data no treatment algorithm of when to proceed to re-intervention (i.e. drain revising or upsizing or minimally invasive necrosectomy) could be made. Future prospective studies should focus on for example adequate start drain size, optimal number of drain procedures before proceeding to necrosectomy and drain flushing management.

In addition to retroperitoneoscopic approaches, an endoscopic approach has gained popularity [10, 11]. This approach has several theoretical advantages in comparison with percutaneous techniques. Endoscopic treatment of infected necrosis can be performed under deep sedation, thereby avoiding general

anesthesia. Also, there is no need for any abdominal wall incision, thereby inducing less surgical stress and potentially reducing complications such as incisional hernia, pancreatic fistula, and wound infections. Until recently, only one small randomized controlled trial compared endoscopic necrosectomy with surgical necrosectomy in twenty patients [12]. In the endoscopic arm there was a significantly reduction of the pro-inflammatory response measured by interleukin-6 levels, as well as the composite clinical endpoint consisting of complications and mortality. The endoscopic necrosectomy seemed a safe and successful alternative treatment for surgical interventions. The endoscopic approach can also be performed step-up wise, starting with first endoscopic transluminal drainage, followed, if necessary, by endoscopic transluminal necrosectomy. We performed a multicenter randomized (TENSION) trial to compare the endoscopic step-up approach to the percutaneous-surgical step-up approach in patients with infected necrotizing pancreatitis [13]. The results did not show the hypothesized superiority of the endoscopic step-up approach in reducing major complications or death in patients with infected necrosis. However, total hospital stay and the number of pancreatic fistulas were lower in the endoscopy group.

In the surgery group, 51% patients were successfully treated with catheter drainage only. This number is comparable to a previously published systematic review [8] and to the 'standard drainage' group in the above-mentioned study [9]. But also 43% of patients in the endoscopy group were successfully treated with endoscopic drainage only. And comparable with percutaneous drainage, endoscopic drainage was feasible in almost all patients (96%). Some endoscopically treated patients (28%) needed additional percutaneous catheter drainage, mostly when necrosis was extending down via the paracolic gutters.

Despite this additional percutaneous drainage, the incidence of pancreatic fistula was significantly lower in the endoscopy group (5% vs 32%). The pancreatic fistula that occurred in the surgery group were external pancreatic fistula (i.e. pancreaticocutaneous fistula). These fistulas may account for serious morbidity (i.e. pain, loss of pancreatic juices), additional interventions, extended hospital stay and intensified follow-up. It is likely that internal pancreatic fistula occurred in the endoscopy group, but these were not diagnosed because they were internal and asymptomatic. These internal fistulas are therefore clinically irrelevant and provide an additional argument in favor of endoscopic drainage.

In our opinion, treatment of patients with infected necrosis should be performed in tertiary referral centers by multidisciplinary teams where both the endoscopic and surgical step-up approach are available, because a combined approach may be required in some patients. A tailored approach with a preference for endoscopic drainage when possible, based on patient characteristics, location of collections, and degree of encapsulation will probably become the new standard.

III Timing of primary drainage

Current evidence clearly shows that catheter drainage (endoscopic or percutaneous) should be the initial treatment step for infected necrosis. Internationally, the step-up approach has been implemented as the strategy of choice for these patients [1, 2]. Catheter drainage is used as a first step to control sepsis and delay or even avoid necrosectomy. For that reason, timing of catheter drainage has become a particularly relevant topic. A rationale exists for postponing catheter drainage in patients with infected necrotizing pancreatitis. First, antibiotic treatment alone might suffice as treatment. Second, diagnosing infected necrotizing pancreatitis is often easier in a later stage of the disease, when all other sources of infection or SIRS have been ruled out. Third, catheter drainage can be easier once the stage of walled-off necrosis has been reached and a collection has become more liquefied. Fourth, endoscopic transluminal drainage requires a walled-off collection.

On the other hand, it is not always mandatory to wait several weeks until full encapsulation of the necrotic collections and (percutaneous) catheter drainage can be performed safely and successfully in the first weeks after onset of disease [4]. For several other conditions, such as drainage of peripancreatic collections after pancreatic resection, (percutaneous) catheter drainage is also safely performed early in 'non-walled-off' collections [14]. If there is no technical reason for postponing catheter drainage, patients with infected necrotizing pancreatitis may benefit from earlier catheter drainage by reducing complications and length of hospital stay.

We performed a literature search for studies on timing of catheter drainage in patients with infected necrotizing pancreatitis [15]. Several (mainly retrospective) studies were found including patients treated with primary catheter drainage at different disease durations (range median 9 to 75 days after onset of disease). However, data from these studies could not be compared.

Our international expert survey in this thesis showed a lack of international expert consensus on timing of primary catheter drainage in patients with infected necrotizing pancreatitis [16]. Although the step-up approach was routinely used by 87% of pancreatologists, the timing of intervention varied hugely, especially catheter drainage. Of the expert pancreatologists, 55% postponed catheter drainage in infected necrotizing pancreatitis using antibiotics, whereas the other 45% drained immediately after diagnosing infected necrosis. This disagreement was most striking when infected necrosis was diagnosed 2 or 3 weeks after onset of disease, the period wherein clinical symptoms based on a systemic inflammatory response syndrome and sepsis are difficult to distinguish.

In short, there is a lack of evidence and international expert consensus on timing of primary catheter drainage in infected necrotizing pancreatitis. Theoretically patients might benefit from earlier primary catheter drainage. Future clinical studies should evaluate whether it is better to postpone catheter drainage until walled-off necrosis or if it should be performed immediately after infected necrosis has been diagnosed. For that reason, we designed the POINTER trial (ISRCTN33682933), with the aim to compare immediate and delayed catheter drainage in an attempt to further improve the outcome of these severely ill patients [17].

Over the last decade we have learned a lot about acute pancreatitis in general and about infected necrosis specifically. Due to a unique multidisciplinary and multicenter collaboration, research questions were answered and implemented in evidence-based international guidelines [1, 2]. Nevertheless important questions remain. Therefore, the Dutch Pancreatitis Study Group will continue its relevant work with the aim to optimize the outcome of all pancreatitis patients.

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CHAPTER 11

English summary

The aim of the studies described in this thesis is to optimize the step-up approach in patients with infected necrotizing pancreatitis. To that end, research results are presented on (I) decision-making on invasive interventions, (II) advancing strategies and techniques of drainage and debridement, and (III) assessing the optimal timing of primary catheter drainage in infected necrotizing pancreatitis.

Part I Decision-making on invasive interventions

In **Chapter 2** the value of a 24/7 online nationwide multidisciplinary expert panel for necrotizing pancreatitis was assessed. Both clinicians and experts were satisfied with the format of this expert panel and considered it to be a valuable and accessible tool in treating necrotizing pancreatitis patients. It was found to be a successful example of an approach to coordinate care and research in the field of acute necrotizing pancreatitis. A multidisciplinary and multicenter approach may lead to improved clinical outcomes and better quality control in clinical studies. Also, an expert panel might be of additional value to other relatively rare and complex diseases.

Decision-making on invasive interventions in patients with clinical signs of infected necrotizing pancreatitis is often related to the presence of gas configurations in and degree of encapsulation of necrotic collections on imaging. **Chapter 3** outlies the natural history of gas configurations and encapsulation in 639 necrotizing pancreatitis patients on computed tomography (CT). Gas configurations may occur in every week after onset of disease: 2-3-13-11-10-19-12-21-12% for week 1-8 and thereafter, respectively. Overall, gas configurations were found in 113 of 639 patients (18%) and in 113 of 202 patients (56%) with infected necrosis. The incidence of walled-off necrosis increased each week: 0-3-12-39-62-76-93-97-100% for week 1-8 and thereafter, respectively. Opposed to traditional views, clinically relevant walled-off necrosis (largely or fully encapsulated necrotic collections) was seen in 162 of 379 patients (43%) within the first 3 weeks.

Identification of patients with necrotizing pancreatitis at high risk for a complicated disease course could facilitate clinical decision-making. Therefore, the association of CT-assessed body composition analysis and mortality in 496 patients with necrotizing pancreatitis was investigated in **Chapter 4**. Skeletal muscle mass, skeletal muscle density, and visceral adipose tissue were measured at the third lumbar vertebra level (L3) on contrast-enhanced CT within 10 days after initial admission and 1 month thereafter. Skeletal muscle mass and density and visceral adipose tissue on first CT were not independently associated with in-hospital mortality. Although, a significant decrease in muscle mass and muscle density was

seen over the first month after hospital admission, for both males and females, with a median relative loss of muscle mass of 12.9% and 10.2% (both P<0.001), respectively. Skeletal muscle density decreased with 7.2% and 7.5% (both P<0.001) for males and females, respectively. A skeletal muscle density decrease of ≥10% in 1 month was independently associated with in-hospital mortality: OR 5.87 (95%CI 2.09-16.50, P=0.001).

Part II Drainage and debridement techniques

A proactive percutaneous catheter drainage (PCD) strategy, including frequent and early drain revising and upsizing, may reduce the need for surgical necrosectomy and could improve outcomes in patients with infected necrotizing pancreatitis. In **Chapter 5** a proactive (42 patients) and a standard (75 patients) PCD strategy were compared in 117 patients treated with primary catheter drainage for infected necrosis. Patients in the proactive group had more drain-related procedures, larger final drain sizes, and fewer patients underwent additional necrosectomy, 12 (28.6%) versus 39 (52.0%) (adjusted OR, 0.349; 95%CI 0.137-0.889; P=0.027), with similar mortality, hospital stay and complications between groups.

In **Chapter 6** an endoscopic step-up approach was compared to a surgical step-up approach in patients with infected pancreatic necrosis in the multicenter randomized controlled TENSION trial. The endoscopic approach consisted of endoscopic ultrasound guided transluminal drainage, followed, if necessary, by endoscopic necrosectomy. The surgical approach consisted of percutaneous catheter drainage followed, if necessary, by video-assisted retroperitoneal debridement. Ninety-eight patients were enrolled in 19 hospitals. The endoscopic step-up approach was not superior to the surgical step-up approach in reducing the composite end point of major complications or death: 22 of 51 patients (43%) in the endoscopy group and in 21 of 47 patients (45%) in the surgery group (risk ratio 0.97; 95%CI 0.62-1.51, P=0.88). The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group, respectively 5% versus 32% (P=0.001) and mean (±SD) 53 (±47) days versus 69 (±38) days (P=0.01). Mortality did not differ between groups, 18% vs 13% (P=0.50).

Part III Timing of primary catheter drainage

Chapter 7 discusses challenges in the management of infected necrotizing pancreatitis, particularly in relation to the timing of primary catheter drainage. International guidelines recommend postponing catheter drainage until the stage

of walled-off necrosis has been reached, a process which typically takes 4 weeks after onset of acute pancreatitis. This recommendation stems from the era of primary surgical necrosectomy. However, postponement of catheter drainage might not be necessary, and earlier detection and subsequent earlier drainage of infected necrosis could improve outcome. A systematic search revealed that high-quality data were lacking. Future clinical, preferably randomized, studies should focus on timing of catheter drainage in patients with infected necrotizing pancreatitis.

Since the optimal diagnostic strategy and timing of invasive interventions in infected necrotizing pancreatitis are subject to debate and to prepare for a randomized trial, an international expert survey and case vignette study was performed in **Chapter 8**. The response rate was 74% (87 of 118 international pancreatologists). None of the respondents used fine needle aspiration routinely for diagnosing infected necrosis. Most respondents (87%) used a step-up approach in patients with infected necrosis. Walled-off necrosis was considered a prerequisite for endoscopic drainage and for percutaneous drainage by 66% and 12%, respectively. After diagnosing infected necrosis, 55% routinely postponed invasive interventions, whereas 45% proceeded immediately to intervention. This lack of consensus about timing of intervention was most apparent on day 14 with proven infected necrosis (58% proceeding to invasive intervention vs. 42% non-invasive) as well as on day 20 with only clinically suspected infected necrosis (59% proceeding to invasive intervention vs. 41% non-invasive).

It is unclear whether the delay of primary catheter drainage in patients with infected necrotizing pancreatitis or whether earlier intervention could be beneficial. **Chapter 9** describes the design and rationale of the randomized controlled multicenter POINTER trial. POINTER investigates whether immediate catheter drainage in patients with infected necrosis is superior compared to the current practice of postponing intervention until the stage of walled-off necrosis. Patients with necrotizing pancreatitis will be screened for eligibility including a protocolized approach to patients with signs of infection. One hundred four adult patients with (suspected) infected necrotizing pancreatitis will be randomized between immediate (within 24 hours) catheter drainage and current standard care involving postponed catheter drainage. Necrosectomy, if necessary, will be preferably postponed until the stage of walled-off necrosis. Primary outcome is the Comprehensive Complication Index (CCI), which includes all complications between randomization and 6 months follow-up. Secondary outcomes include mortality, complications, number of (re-) interventions, hospital and intensive care unit length of stay, quality-adjusted life years (QALYs) and (in)direct costs.

APPENDICES

NEDERLANDSE SAMENVATTING

Het doel van het onderzoek beschreven in dit proefschrift is het optimaliseren van de stapgewijze invasieve behandeling ('step-up approach') van patiënten met een geïnfecteerde necrotiserende pancreatitis. Het proefschrift bestaat uit drie delen: (I) besluitvorming over invasieve interventies, (II) verbeteren van katheterdrainage en necrosectomie strategieën en technieken, (III) evaluatie van het ideale moment van primaire katheterdrainage.

Deel I Besluitvorming over invasieve interventies

In **Hoofdstuk 2** werd de waarde van een 24/7 'online' nationaal multidisciplinair expertpanel voor acute necrotiserende pancreatitis onderzocht. Zowel behandeld artsen als de pancreatitis experts zelf zijn tevreden over het expertpanel. Zij beschouwen het expertpanel als een waardevol en toegankelijk instrument in de behandeling van patiënten met necrotiserende pancreatitis. Het expertpanel wordt gezien als een succesvol voorbeeld van ondersteuning in zowel de zorg voor patiënten met necrotiserende pancreatitis als voor medisch onderzoek naar deze ziekte. Dit multidisciplinaire en multicentrische initiatief kan leiden tot verbetering van klinische uitkomsten en klinische studies. Ook bij andere relatief zeldzame en complexe ziektebeelden zou een vergelijkbaar expertpanel van toegevoegde waarde kunnen zijn.

In de besluitvorming over een invasieve interventie bij patiënten met een verdenking op geïnfecteerde necrotiserende pancreatitis, spelen zowel de aanwezigheid van gasconfiguraties als de mate van afkapseling van necrotische collecties een belangrijke rol. In **Hoofdstuk 3** werd het natuurlijk beloop van het ontstaan van gas en afkapseling op computertomografiescans (CT-scans) onderzocht in 639 patiënten met necrotiserende pancreatitis. Gas configuraties werden voor het eerst gezien in iedere week na start van de ziekte: 2-3-13-11-10-19-12-21-12%, respectievelijk week 1-8 en verder. Gas werd gezien in 113 van de 639 patiënten (18%) en in 113 van de 202 patiënten met geïnfecteerde necrose (56%). De incidentie van volledig afgekapselde necrose ('walled-off' necrose) nam per week toe: 0-3-12-39-62-76-93-97-100%, respectievelijk week 1-8 en verder. In tegenstelling tot wat eerder gedacht werd, ontstond klinisch relevante 'walled-off' necrose, oftewel (bijna) volledig afgekapselde necrose, in een aanzienlijk deel van de patiënten al in de eerste 3 weken na start van de ziekte (in 162 van 379 patiënten (43%)).

Identificatie van patiënten met een hoog complicatierisico is belangrijk in de besluitvorming over de behandeling. Daarom werd in **Hoofdstuk 4** de associatie tussen lichaamssamenstelling parameters op CT-scans en ziekenhuissterfte onderzocht in 496 patiënten met een necrotiserende pancreatitis. Skeletspiermassa, skeletspierdensiteit en visceraal vetweefsel werden gemeten op lumbaal niveau (L3) op CT-scans met contrast op dag 10 en 1 maand na opname. Spiermassa, spierdensiteit en visceraal vet op de eerste CT-scan waren niet onafhankelijk geassocieerd met ziekenhuissterfte. Wel was er sprake van een significante daling van spiermassa en spierdensiteit gedurende de eerste maand na opname, met een mediaan spiermassaverlies van 12.9% en 10.2% (beide P<0.001) en een spierdensiteit verlies van 7.2% en 7.5% (beide P<0.001), voor mannen en vrouwen, respectievelijk. Een spierdensiteit verlies van ≥10% in de eerste maand was onafhankelijk geassocieerd met ziekenhuissterfte: OR 5.87 (95%BI 2.09-16.50, P=0.001).

Deel II Drainage en necrosectomie technieken

Een proactieve percutane katheterdrainage strategie, bestaande uit frequente en vroege drainrevisies en plaatsen van dikkere drains, zou een necrosectomie operatie kunnen voorkomen en daarmee de uitkomst van patiënten met geïnfecteerde necrotiserende pancreatitis kunnen verbeteren. In **Hoofdstuk 5** werden een proactieve drainage strategie (42 patiënten) en een standaard drainage strategie (75 patiënten) vergeleken in 117 patiënten, behandeld met primaire drainage voor geïnfecteerde necrose. Patiënten in de proactieve groep ondergingen vaker een drainage procedure en kregen dikkere drains. Maar minder patiënten in de proactieve groep ondergingen een aanvullende necrosectomie, 12 (28.6%) versus 39 (52.0%) (aangepaste OR, 0.349; 95%BI 0.137-0.889; P=0.027), met gelijke sterfte, ziekenhuisopnameduur en complicaties in beide groepen.

In **Hoofdstuk 6** werd de endoscopische stapsgewijze benadering vergeleken met de chirurgische stapsgewijze benadering in patiënten met geïnfecteerde necrotiserende pancreatitis in de multicentrische gerandomiseerde TENSION trial. De endoscopische arm bestond uit endoscopisch echogeleide transluminale drainage, indien nodig gevold door een endoscopische necrosectomie. De chirurgische arm bestond uit primaire percutane katheterdrainage, indien nodig gevolgd door een video-geassisteerde retroperitoneale necrosectomie (VARD). In totaal werden 98 patiënten gerandomiseerd in 19 ziekenhuizen. De endoscopische stapsgewijze benadering was niet superieur aan de chirurgische stapsgewijze benadering met oog op het samengestelde eindpunt van ernstige complicaties en

sterfte: 22 van 51 patiënten (43%) in de endoscopie groep en 21 van 47 patiënten (45%) in de chirurgie groep (risk ratio 0.97; 95%BI 0.62-1.51, P=0.88). Het aantal pancreasfistels en de ziekenhuisopnameduur waren lager in de endoscopie groep, respectievelijk 5% versus 32% (P=0.001) en gemiddeld (±SD) 53 (±47) dagen versus 69 (±38) dagen (P=0.01). Sterfte was niet significant verschillend in beide groepen, 18% versus 13% (P=0.50).

Deel III Timing van primaire katheterdrainage

Hoofdstuk 7 bespreekt de uitdagingen in de behandeling van geïnfecteerde necrotiserende pancreatitis patiënten, met name de 'timing' van primaire katheterdrainage. Internationale richtlijnen adviseren om deze drainage zo lang mogelijk uit te stellen, in ieder geval tot er sprake is van 'walled-off' necrose, vanaf ongeveer 4 weken na start van de acute pancreatitis. Het bewijs voor deze aanbeveling stamt uit het tijdperk dat men nog een primaire necrosectomie verrichtte. Uitstel van (een minimaal invasieve) drainage is misschien niet nodig. Theoretisch zou de vroege diagnose van geïnfecteerde necrose, gevolgd door directe drainage, de uitkomst van deze patiënten zelfs kunnen verbeteren. Er werd een systematische literatuurzoekopdracht verricht, maar er werd onvoldoende wetenschappelijk bewijs gevonden over 'timing' van drainage in deze patiënten. Toekomstige, bij voorkeur gerandomiseerde, studies zouden zich moeten richten op 'timing' van drainage in patiënten met geïnfecteerde necrotiserende pancreatitis.

De optimale diagnostische strategie en 'timing' van interventies bij geïnfecteerde necrotiserende pancreatitis staan ter discussie. Om deze reden en als voorbereiding op een gerandomiseerde studie werd in **Hoofdstuk 8** een internationale expertenquête inclusief casuïstiek afgenomen. De enquête werd door 74% (87 van de 118 internationale experts) ingevuld. Een fijne naald aspiratie wordt door geen van de respondenten routematig gebruikt om de diagnose geïnfecteerde necrose te stellen. Wel passen de meeste respondenten (87%) de 'step-up' behandeling toe bij patiënten met geïnfecteerde necrose. 'Walled-off' necrose wordt als een vereiste beschouwd voor zowel een endoscopische als een percutane drainage, door respectievelijk 66% en 12% van de respondenten. Na het stellen van de diagnose geïnfecteerde necrose, stelt 55% altijd alle vormen van invasieve interventies zo lang mogelijk uit, terwijl 45% onmiddellijk tot een invasieve interventie overgaat. Er was met name geen consensus over het moment van eerste drainage op dag 14 en bewezen geïnfecteerde necrose (58% over tot invasieve interventie versus 42% blijft non-invasief) en op dag 20 met klinische verdenking op geïnfecteerde necrose (59% over tot invasieve interventie versus 41% blijft non-invasief).

Het is nog onduidelijk of uitgestelde primaire katheterdrainage of directe drainage bij patiënten met geïnfecteerde necrotiserende pancreatitis de beste strategie is. **Hoofdstuk 9** beschrijft de rationale en studieopzet van de gerandomiseerde multicentrische POINTER trial. POINTER onderzoekt of directe drainage in patiënten met geïnfecteerde necrose superieur is aan uitgestelde drainage tot volledig afgekapselde necrose. Honderdvier volwassen patiënten met een (verdenking op) geïnfecteerde necrotiserende pancreatitis worden gerandomiseerd tussen directe drainage (binnen 24 uur na stellen van de diagnose) en de huidige standaardbehandeling van uitgestelde drainage, bij voorkeur tot volledig afgekapselde necrose. Een aanvullende necrosectomie, indien nodig, wordt in beide armen van de studie uitgesteld tot volledig afgekapselde necrose is ontstaan. De primaire uitkomstmaat van de studie is de 'Comprehensive Complication Index' (CCI), ofwel alle complicaties per patiënt vanaf randomisatie tot 6 maanden follow-up. Secundaire uitkomstmaten zijn onder andere mortaliteit, complicaties, aantal (re-)interventies, ziekenhuis en intensive care opnameduur, 'quality-adjusted life years' (QALY's) en (in)directe kosten.

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KPvL	Krijn P. van Lienden
VBN	Vincent B. Nieuwenhuijs
JWP	Jan-Werner Poley
RT	Robin Timmer
PT	Pieter Timmerman
HCvS	Hjalmar C. van Santvoort
AFS	Alexander F. Schaapherder
NJS	Nicolien J. Schepers
RPV	Rogier P. Voermans
JLAvV	Jeroen L. A. van Vugt

Chapter 2 | The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis

Study protocol design: JvG, SvB, MGB, HCvS. Data collection: JvG, SvB, NJS, BD, OJB, SAWB, MGB, HCvS. Data analyses: JvG. Manuscript draft: JvG, SvB, MGB, HCvS. All co-authors and collaborators critically edited the manuscript and approved the final version. Members of the expert panel (2006-2014): MAB, TLB, MJB, VCC, CHCD, CHJvE, PF, HvG, HGG, JWH, HSH, JSL, MSvL, KPvL, VBN, JWP, AFS, RT. Coordinating research fellows of the expert panel (2006-2014): JvG, SvB, NJS, OJB, SAWB, MGB, HCvS.

Chapter 3 | Natural history of gas configurations and encapsulation in necrotic collections during necrotizing pancreatitis

Study protocol design and evaluation CT scans: TLB. Clinical data collection: MGB and HCvS. Data collection and analyses: JvG, SvB and MCvB. Manuscript draft and revisions: JvG. All co-authors critically edited the manuscript and approved the final version: SvB, MCvB, MGB, PF, HvG, HCvS, and TLB.

Chapter 4 | The association of computed tomography-assessed body composition analysis and mortality in patients with necrotizing pancreatitis

Study protocol design, data collection, data analyses, manuscript draft and revisions: JvG and JLAvV. Data collection and body composition measurements: AG. CT assessment: TLB. Data collection and supervision study: HCvS, MGB, CHJvE, and DB. All authors critically edited the manuscript and approved the final version.

Special thanks to W. J. Niessen and M. Koek from the Department of Radiology and Medical Informatics, Erasmus MC University Medical Centre, Rotterdam, the Netherlands, for providing the FatSeg software program and technical support, J.C. Kelder from the Department of Cardiology, St Antonius Hospital, Nieuwegein, the Netherlands, for statistical advice, and all the collaborators of the Dutch Pancreatitis Study Group for data collection.

Chapter 5 | Proactive versus standard percutaneous catheter drainage for infected necrotizing pancreatitis

Study protocol design: JvG, KPvL, MAB, MGB. Data collection: JvG and PT, under supervision of MGB (Academic Medical Center, Amsterdam), CHJvE (Erasmus Medical Center), DB (St Antonius Hospital), and JWH (University Medical Center Groningen). Data analyses: JvG and PT. CT assessment: KPvL. Manuscript draft and revisions: JvG, PT, MGB. All coauthors critically edited the manuscript and approved the final version.

Chapter 6 | Endoscopic or surgical step-up approach for infected necrotising pancreatitis (TENSION trial): a multicentre randomised trial

Study protocol design: SvB, HCvS, MGB, OJB, RPV, MGD, MAB, MJB, TLB, RT, HGG, PF. Sample size calculation: SvB, HCvS, RPV, MGD. Study coordination during inclusion: SvB and JvG. Statistical analysis and manuscript draft: SvB. Economic evaluation supervision: MGD. Co-authored manuscript: HCvS, JvG, OJB, MGB, HGG, MGD, PF. All authors critically assessed the study design or included patients in the study and edited, read and approved the final manuscript (see also the acknowledgements in chapter 6).

Chapter 7 | Timing of catheter drainage in infected necrotizing pancreatitis

Data collection and analyses: JvG and MGB. Manuscript draft and revisions: JvG. Co-authored manuscript: MGB. HCvS, MAB, CHCD, CHJvE, PF.

Chapter 8 | Diagnostic strategy and timing of intervention in infected necrotizing pancreatitis: an international expert survey and case vignette study

Study protocol and questionnaire design: JvG, SvB, TLB, HCvS, MGB. Editing survey and case vignettes: all co-authors. Data collection and analyses: JvG. Manuscript draft and revisions: JvG. The complete writing committee co-authored, read, and approved the final version.

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Chapter 9 | Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): study protocol for a randomized controlled trial

Study protocol design: JvG, HCvS, MAB, TLB, MJB, SvB, CHD, MGD, CHvE, KPvL, PF, MGB. Manuscript draft and revisions: JvG. Co-authored manuscript: SMvD, HCvS, MGB. Sample size calculation: JvG, MGB and MGD. All authors critically assessed the study design, edited the manuscript, and read and approved the final manuscript (see also the acknowledgements in chapter 9).

PhD PORTFOLIO

PhD student	Adriana Henrica Johanna (Janneke) van Grinsven
Period	May 2013 - March 2018
Location	Dept. of Surgery, Academic Medical Center Amsterdam (2013-2016) Dutch Pancreatitis Study Group, St. Antonius Hospital Nieuwegein (2014-2016) Dutch Pancreatitis Study Group, Radboudumc Nijmegen (2013-2014)
Promotores	Prof. dr. P. Fockens Dept. of Gastroenterology and Hepatology, AMC Amsterdam
	Prof. dr. M.G.H. Besselink Dept. of Surgery, AMC Amsterdam
Copromotores	Prof. dr. M.A. Boermeester Dept. of Surgery, AMC Amsterdam
	Dr. H.C. van Santvoort Dept. of Surgery, St. Antonius Hospital Nieuwegein UMC Utrecht

Year	AMC graduate school courses	ECTS
2015	Practical biostatistics course	1.1
2015	Systematic review course	1.0
2013	Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	1.0
	Other courses	
2015	Workshop cost-effectiveness analysis, Utrecht	0.5
2014	SPSS basis, St. Antonius Ziekenhuis, Nieuwegein	0.5
2014	Scientific writing in English, St. Antonius Ziekenhuis, Nieuwegein	1.0
2014	Scientific presenting in English, St. Antonius Ziekenhuis, Nieuwegein	1.0
2013	Randomised Controlled Trials (RCT), Pembroke College Oxford, UK	2.0
	Seminars and meetings	
2013-2018	Quarterly meetings of the Dutch Pancreatitis Study Group	2.0
2014-2016	Weekly surgical department seminars AMC	0.5
2016	Pancreasdag, Utrecht	0.3
2014	Mini-symposium Dutch Pancreatitis Study Group, NVGE, Veldhoven	0.3
2014	Pancreasdag, Utrecht	0.3
	Teaching	
2017	Acute and chronic pancreatitis, CASH 2.2 course, Amsterdam	0.5
2016	Acute pancreatitis, MDL keuzeonderwijs AMC-UvA, Amsterdam	0.2
2015	Acute and chronic pancreatitis, CASH 2.2 course, Eemnes	0.5
2015	Acute pancreatitis, MDL keuzeonderwijs AMC-UvA, Amsterdam	0.2
2014	Acute pancreatitis, MDL keuzeonderwijs AMC-UvA, Amsterdam	0.2
	Tutoring students	
2015	Marin Strijker, master student UMC Utrecht	1.0
2015	Arvind Gharbharan, master student EMC Rotterdam	0.5
2015	Hugo van Willigen, bachelor student AMC Amsterdam	1.0
2014	Birgit Vogels, voluntary internship	1.0
2014	Benthe Doeve, student UMC Utrecht	1.0
2014	Pieter Timmerman, master student UMCG Groningen	1.0
	Invited lectures	
2016	Invited lecture, 8th Panhellenic Congress of Pancreatology, Athens, Greece	0.5
2016	Invited lecture, Scientific Boston Symposium, Utrecht	0.5

2015	Invited lecture, MDL nascholing regio oost, Ravenstein	0.5
2015	Invited lecture, Gastroenterologie und Viszeralchirurgie congres, Leipzig	0.5
2015	Invited lecture, symposium MDL Noord-Oost, Meppel	0.5
2014	Invited lecture, Pancreatitisavond, RdGG Delft	0.5
	Oral presentations at (inter)national conferences and seminars	
2016	Oral presentation, Pancreasdag Tramedico/Allergan, Utrecht	0.5
2015	Oral presentation, Dutch Highlights E-AHPBA, Zeist	0.5
2015	Oral presentation, NVvH voorjaarsvergadering, Veldhoven	0.5
2015	Oral presentation, Digestive Disease Week, Washington DC, USA	0.5
2015	Oral presentation, NVGE voorjaarsvergadering, Veldhoven	0.5
2014	Oral presentation (2x), NVGE najaarsvergadering, Veldhoven	0.5
2014	Oral presentation, European Pancreatic Club, Southampton, UK	0.5
2014	Oral presentation, NVvH voorjaarsvergadering, Veldhoven	0.5
2014	Oral presentation, Pancreasdag Tramedico, Utrecht	0.5
	Poster presentations at (inter)national conferences and seminars	
2016	Poster presentation (2x), Digestive Disease Week, San Diego, USA	0.5
2016	Poster presentation (3x), Pancreasclub, San Diego, USA	0.5
2016	Poster presentation (3x), IHPBA congres, São Paulo, Brasil	0.5
2015	Poster presentation (1x), European Pancreatic Club, Toledo, Spain	0.5
2015	Poster presentation (1x), E-AHPBA congres, Manchester, UK	0.5
2014	Poster presentation (1x), United European Gastroenterology Week, Vienna, Austria	0.5
	Obtained grants	
2015	Fonds NutsOhra; POINTER trial	€ 189,634
2015	Innovatiefonds Zorgverzekeraars; acute pancreatitis expert panel 2.0	€ 22,506
2013	Tramedico BV; participation RCT course in Oxford, UK	€ 1,942
	Other	
2014-2016	Board member PhD students club, St. Antoniusziekenhuis Nieuwegein	
	Clinical work	
2017-2018	Surgical resident (AIOS) Tergooiziekenhuis, Hilversum	
2016-2017	Surgical resident (AIOS) OLVG Oost, Amsterdam	
2012-2013	Surgical resident (ANIOS) Tergooiziekenhuis, Hilversum	

LIST OF PUBLICATIONS

2018 Van Grinsven J, van Dijk SM, Dijkgraaf MG, Boermeester MA, Bollen TL, Bruno MJ, van Brunschot S, Dejong CH, van Eijck CH, van Lienden KP, et al. **Postponed or immediate drainage of infected necrotizing pancreatitis (POINTER trial): study protocol for a randomized controlled trial.** *Submitted*

2018 Van Dijk SM*, van Grinsven J*, van Oostveen GJC , Bruno MJ, Besselink MG. **Patient input into future clinical research in acute and chronic pancreatitis.** *Submitted*

2018 Van Eck van der Sluijs A, van Grinsven J, Abrahams AC, Brema C, Bakker OJ, Bos WJW, van Santvoort HC, Bruno MJ, van Goor H, van Brunschot S, et al. **Impact of intravenous fluid therapy in predicted severe acute pancreatitis: post-hoc analysis in a prospective multicenter cohort.** *Submitted*

2018 Van Grinsven J*, van Brunschot S*, van Baal MC, Besselink MG, Fockens P, van Goor H, van Santvoort HC, Bollen TL. **Natural history of gas configurations and encapsulation in necrotic collections during necrotizing pancreatitis.** *Accepted by J Gastrointest Surg 2018*

2017 Van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SA, Bruno MJ, et al. **Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial.** *Lancet. 2018 Jan 6;391(10115):51-58*

2017 Van Grinsven J*, van Vugt JLA*, Gharbharan A, Bollen TL, Besselink MG, van Santvoort HC, van Eijck CHJ, Boerma D. **The association of computed tomography-assessed body composition analysis and mortality in patients with necrotizing pancreatitis.** *J Gastrointest Surg. 2017 Jun;21(6):1000-1008*

2017 Van Grinsven J, Timmerman P, van Lienden KP, Haveman JW, Boerma D, van Eijck CH, Fockens P, van Santvoort HC, Boermeester MA, Besselink MG. **Proactive versus standard percutaneous catheter drainage for infected necrotizing pancreatitis.** *Pancreas. 2017 Apr;46(4):518-523*

2017 Van Grinsven J, van Brunschot S, van Santvoort HC, Dutch Pancreatitis Study Group. **The value of a 24/7 online nationwide multidisciplinary expert panel for acute necrotizing pancreatitis.** *Gastroenterology. 2017 Mar;152(4):685-688.e6*

2017 Van Dijk SM, Van Grinsven J, van Santvoort HC, Besselink MG, namens de Pancreatitis Werkgroep Nederland. **Timing van eerste interventie bij geïnfecteerde necrotiserende pancreatitis.** *Ned Tijdschr Heelkunde. 2017 Febr;26(1):31-33*

2016 Hollemans RA, van Grinsven J, Besselink MG, van Santvoort HC. **Re: Better outcomes if percutaneous drainage is used early and proactively in the course of necrotizing Pancreatitis.** *J Vasc Interv Radiol. 2016 Dec;27(12):1936*

2016 Van Grinsven J, namens de Pancreatitis Werkgroep Nederland. **Directe versus uitgestelde drainage bij geïnfecteerde necrotiserende pancreatitis, de POINTER-studie.** *Ned Tijdschr Geneeskd. 2016;160:D473*

2016 Van Grinsven J, van Santvoort HC, Boermeester MA, Dejong CH, van Eijck CH, Fockens P, Besselink MG. **Timing of catheter drainage in infected necrotizing pancreatitis.** *Nat Rev Gastroenterol Hepatol. 2016 May;13(5):306-12*

2016 Van Grinsven J, van Brunschot S, Bakker OJ, Bollen TL, Boermeester MA, Bruno MJ, Dejong CH, Dijkgraaf MG, van Eijck CH, Fockens P, et al. **Diagnostic strategy and timing of intervention in infected necrotizing pancreatitis: an international expert survey and case vignette study.** *HPB (Oxford). 2016 Jan;18(1):49-56*

2016 Schepers NJ, Bakker OJ, Besselink MG, Bollen TL, Dijkgraaf MG, van Eijck CH, Fockens P, van Geenen EJ, van Grinsven J, Hallensleben ND, et al**. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial.** *Trials. 2016 Jan 5;17:5*

2015 Van Grinsven J, Besselink MG, Fockens P, van Santvoort HC. **Expertpanel acute pancreatitis: unieke landelijke online multidisciplinaire samenwerking.** *MAGMA, NVGE; nr 3 jrg 21; 2015 Sep, p105-107*

2014 Van Grinsven J, Besselink MG, Bakker OJ, Van Brunschot S, Boermeester MA, van Santvoort HC. **Retroperitoneoscopic approaches for infected necrotizing pancreatitis.** *Textbook CE Formark and TB Gardner. Prediction and management of severe acute pancreatitis. New York: Springer Science; 2015, p189-195*

2013 Van Brunschot S, van Grinsven J, Voermans RP, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SA, Bruno MJ, et al. **Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial. [ISRCTN09186711**]. *BMC Gastroenterol. 2013 Nov 25;13:161*

2010 Van de Wall BJ, Reuling EM, Consten EC, van Grinsven J, Schwartz MP, Broeders IA, Draaisma WA. **Endoscopic evaluation of the colon after an episode of diverticulitis: a call for a more selective approach.** *Int J Colorectal Dis. 2012 Sep;27(9):1145-50*

**Contributed equally*

ABOUT THE AUTHOR

Janneke van Grinsven was born in 's-Hertogenbosch, the Netherlands, on December 13th 1986. She was raised together with her two brothers in a supportive family. In 2005 she graduated from Gymnasium Beekvliet in Sint-Michielsgestel. The same year she started medical school at the University of Utrecht. After internships in the Netherlands and Suriname, she obtained her medical degree in 2011. Hereafter she traveled through South-America. In 2012, she started as a medical doctor (ANIOS) at the department of surgery in Tergooi hospital Hilversum, the Netherlands, under supervision of dr. J.P. Eerenberg. In 2013 she started as a PhD student for the Dutch Pancreatitis Study Group to coordinate the multicenter TENSION trial. Meanwhile she designed the multicenter POINTER trial. She successfully obtained funding for this study and inclusion started in July 2015. These and other research projects are presented in this thesis. In July 2016, she started as a surgical resident (AIOS) in the OLVG hospital Amsterdam, the Netherlands, under supervision of dr. M.F. Gerhards. She is currently assigned in Tergooi hospital Hilversum as a second year surgical resident, under supervision of dr. A.A.W. van Geloven and will continue her training in the Academic Medical Center Amsterdam hereafter. Janneke lives in Amsterdam together with her boyfriend Teunis and their daughter Mans.

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Ceci n'est pas un pancréas