ACUTE PANCREATITIS

New frontiers
in diagnosis
and treatment

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Acute Pancreatitis: New frontiers in diagnosis and treatment

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ACUTE PANCREATITIS

New frontiers in diagnosis and treatment

Nieuwe ontwikkelingen
in diagnose
en behandeling

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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HJALMAR CHRISTIAAN VAN SANTVOORT
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te Tegelen

PROMOTOREN:

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Dr. K.J. van Erpecum

Aan mijn ouders

CONTENTS

CHAPTER 1

General introduction
and outline of this thesis

Acute pancreatitis was first described by the Dutchman Nicolaes Tulp in 1652.[1] Three and a half centuries later, this disease continues to challenge clinicians and researchers alike. Many feel uncomfortable treating this complex and heterogeneous illness, which is potentially deadly and demands great endurance of both patient and doctor. While over the last 25 years 'evidence based medicine' has evolved to a robust framework for clinical decision making,[2-6] some important advances have been made in the clinical field of acute pancreatitis.[7-14] However, only a few prospective (multicentre) studies have been performed and many clinical questions are yet unanswered. The outlook for patients with acute pancreatitis remains grim and new frontiers have to be explored.

This thesis presents 6 years of clinical research undertaken by the Dutch Pancreatitis Study Group to improve the diagnosis and treatment of acute pancreatitis.

De anatomische les van dr. Nicolaes Tulp

door Rembrandt van Rijn (1632)

BACKGROUND OF ACUTE PANCREATITIS

Acute pancreatitis is one of the most common gastroenterological diseases. The incidence in Europe and the United States ranges from 20 to over 70 per 100.000 population,[15-17] and has increased over the last decade.[18] In an average Dutch hospital, over 30 patients with acute pancreatitis are admitted each year.[19]

Most cases of acute pancreatitis are caused by gallstones, gallsludge or alcohol

abuse.[20] More uncommon causes include a variety of drugs, endoscopic retrograde cholangiopancreatography (ERCP), hypertriglyceridemia, and many other known and unknown factors.[21] Although much is uncertain about the pathophysiology of acute pancreatitis, we know that the various etiological stimuli trigger premature activation of trypsin in pancreatic acinar cells.[22,23] Trypsin then activates pancreatic digestive enzymes causing autodigestion of the gland and the surrounding tissue.[21,23] Local pancreatic inflammation can quickly progress into a systemic inflammation by the release of pro-inflammatory mediators.[24-26]

Patients with acute pancreatitis present with characteristic severe pain *in epigastrio*, which is often accompanied by nausea and vomiting.[27] Most patients have a mild and uncomplicated further clinical course. The abdominal pain usually disappears within several days and oral intake can quickly be resumed. In 10-20% of patients, the disease has a severe clinical course with prolonged hospital stay and a considerable risk of complications and death.[10,27,28] In the first days of admission, scoring systems such as the Imrie score[29] and the Acute Physiology and Chronic Health Evaluation (APACHE II) score,[30] and biochemical parameters such as C-reactive protein (CRP),[31] are used for prediction of the clinical course and to stratify patients as 'predicted mild acute pancreatitis' or 'predicted severe acute pancreatitis' in clinical studies.

The clinical course of severe acute pancreatitis can be divided into an 'early phase' and a 'late phase'. In the early phase (i.e., the first 1-2 weeks), necrosis of the pancreatic parenchyma and peripancreatic tissue can develop within a few days.[7,32] At the same time, a systemic inflammatory response syndrome (SIRS) occurs, which often precedes multiple organ failure.[24-26] It is thought that multiple organ failure in the early phase is responsible for around half of the deaths in acute pancreatitis.[33]

In the 'late phase' (i.e., after 1-2 weeks), systemic inflammation often recedes. Prognosis in this phase is dictated more by local complications than by systemic complications.[10,32] The most dreadful local complication is secondary infection of pancreatic necrosis or peripancreatic necrosis.[7] Infected necrosis occurs in around a third of patients with necrotising pancreatitis.[28] Without intervention to remove the infected necrosis, almost every patient will eventually develop sepsis with multiple organ failure, and will eventually die. Even when intervention is performed, mortality of infected necrosis remains around 30%.[28]

TABLE 1.1. The 19 main study questions that are addressed in this thesis

CHAPTER	STUDY QUESTIONS
2	What is the interobserver agreement among radiologists for the Atlanta Classification to describe computed tomography findings in acute pancreatitis?
3	Are the definitions of the Atlanta Classification consistently used and interpreted in the literature?
4	What is the interobserver agreement among radiologists and clinicians from different parts of the world for a newly designed set of morphological criteria to describe computed tomography findings in acute pancreatitis?
5	What is the time of onset and clinical impact of infections in acute pancreatitis?
6	Does enteral nutrition, as compared to parenteral nutrition, reduce the risk of infections and death in predicted severe acute pancreatitis?
7	What are the proposed mechanisms of action of probiotics and current evidence from randomised studies, with focus on prevention of infections in surgical and critically ill patients?
8	What is the role of probiotic prophylaxis in patients with predicted severe acute pancreatitis?
9	What is the association between the clincial course of acute pancreatitis and increased intestinal permeability, enterocyte damage, and bacterial translocation, and how are these processes influenced by probiotics?
10	What is the value of commonly used radiological and biochemical predictors for choledocholithiasis early in the course of acute biliary pancreatitis?
11, 12	Does early ERCP, as compared to conservative treatment, improve clinical outcome in acute biliary pancreatitis?
13	What is the role of percutaneous drainage in necrotising pancreatitis?
14	How do you perform VARD in necrotising pancreatitis?
15	What is the feasibility of minimally invasive techniques in necrotising pancreatitis?
16	Is VARD, as compared to open necrosectomy, associated with a better clinical outcome in necrotising pancreatitis?
17	Does a minimally invasive step-up approach, as compared to primary open necrosectomy, reduce major complications and death, as well as long term complications, health care utilisation, and total costs in patients with necrotising pancreatitis?
18	What is the recent outcome of patients from the entire clinical spectrum of necrotising pancreatitis who undergo either conservative treatment or intervention?
19	How is the application procedure for medical ethical approval for a nationwide multicentre study in the Netherlands functioning, in terms of adherence to the national guideline, duration of the review process, and time and materials invested?

ERCP stands for endoscopic cholangiopancreaticography
VARD stands for video-assisted retroperitoneal debridement

In this thesis, four main topics regarding diagnosis and treatment of acute pancreatitis have been addressed:

1 Defining acute pancreatitis and its local complications
2 Preventing infections in acute pancreatitis
3 Early endoscopic intervention for biliary pancreatitis
4 Intervention for necrotising pancreatitis

The main study questions are summarized in TABLE 1.1. The background of the four topics is discussed in the following sections.

PART I: DEFINING ACUTE PANCREATITIS AND ITS COMPLICATIONS

In 1992, an international consensus conference was held in Atlanta, Georgia, which resulted in a clinically based classification to define acute pancreatitis and its complications (TABLE 1.2).[10] Although the 'Atlanta Classification' has been universally accepted, it is now apparent that the classification suffers from considerable shortcomings.[28,34,35] One of the main problems is that the definitions for local complications such as 'acute pseudocyst' and 'pancreatic abscess' are confusing. Although exact radiological criteria for these local complications were not provided, the Atlanta definitions are widely used to describe peripancreatic collections on computed tomography (CT) in daily practice. An evaluation of the use of the Atlanta Classification in clinical practice had never been performed. In CHAPTER 2 we summarise a study among Dutch radiologists to asses the interobserver agreement of categorising peripancreatic collections on CT using the Atlanta Classification.

Aside from the clear need for correct terminology and standardised definitions in daily practice, the same language should also be spoken in clinical research in order to adequately compare inter-institutional data. The use of the Atlanta Classification in the literature had never been evaluated. CHAPTER 3 presents a literature review to assess whether the Atlanta Classification is accepted in the literature, and to evaluate the extent of variation in interpretation of the definitions.

It has been suggested that objective, descriptive terms to categorize CT-findings should be incorporated in a new classification, as an alternative to the subjective definitions of the Atlanta classification.[36] CHAPTER 4 describes an interobserver

TABLE 1.2. Summary of the 1992 Atlanta Classification on acute pancreatitis[10]

	DEFINITION
Acute pancreatitis	An acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. Associated with raised pancreatic enzyme levels in blood or urine.
Severity	
Mild acute pancreatitis	Associated with minimal organ dysfunction and an uneventful recovery; lacks the features of severe acute pancreatitis. Usually normal enhancement of pancreatic parenchyma on contrast-enhanced computed tomography.
Severe acute pancreatitis	Associated with organ failure and/or local complications such as necrosis, abscess or pseudocyst
Predicted severe acute pancreatitis	Ranson score ≥3 or APACHE II score ≥8
Organ failure and systemic complications	
Shock	Systolic blood pressure <90 mmHg
Pulmonary insufficiency	*Pa* O_2 ≤60 mmHg
Renal failure	Creatinine ≥177 µmol/l or ≤2 mg/dl after rehydration
Gastrointestinal bleeding	500 ml in 24 h
Disseminated intravascular coagulation	Platelets ≤100.000/mm^3, fibrinogen <1.0 g/l and fibrin-split products > 80 µg/l
Severe metabolic disturbances	Calcium ≥1.87 mmol/l or ≥7.5 mg/dl
Local complications	
Acute fluid collections	Occur early in the course of acute pancreatitis, are located in or near the pancreas and always lack a wall of granulation of fibrous tissue. In about half of patients, spontaneous regression occurs. In the other half, an acute fluid collection develops into a pancreatic abscess or pseudocyst
Pancreatic necrosis	Diffuse or focal area(s) of non-viable pancreatic parenchyma, typically associated with peripancreatic fat necrosis. Non-enhanced pancreatic parenchyma >3 cm or involving more than 30% of the area of the pancreas.
Pancreatic abscess	Circumscribed, intra-abdominal collection of pus, usually in proximity to the pancreas, containing little or no pancreatic necrosis, which arises as a consequence of acute pancreatitis or pancreatic trauma. Often 4 weeks or more after onset. Pancreatic abscess and infected pancreatic necrosis differ in clinical expression and extent of associated necrosis.

agreement study in which an international group of surgeons and radiologists formulated a new set of descriptive, morphological terms that were tested between surgeons, gastroenterologists, and radiologists from different parts of the world.

PART II: PREVENTING INFECTIONS IN ACUTE PANCREATITIS

It is estimated that around 80% of patients that die from acute pancreatitis have concomitant infectious complications.[37] Prophylactic antibiotics have not been proven effective in reducing infections in acute pancreatitis.[13,38] Alternative preventive strategies are therefore highly needed.

The most important infectious complication is infection of pancreatic necrosis or peripancreatic necrosis.[7] Although the incidence of infected necrosis has been widely studied, the time of onset and clinical impact of other infections, such as pneumonia and bacteraemia, are uncertain. CHAPTER **5** is a summary of an observational, multicentre, cohort study that investigated the timing of infections and their association with death in acute pancreatitis.

One of the first steps in the pathophysiological process held responsible for infections in acute pancreatitis is bacterial translocation: the phenomenon that bacteria cross the gastrointestinal mucosal barrier and invade the systemic compartment.[39,40] Bacterial translocation is caused by a complex interaction of events including small-bowel bacterial overgrowth,[41] mucosal barrier failure,[42-44] and pro-inflammatory immune responses.[25,26] Strategies to prevent infections should ideally have their effect on all these events. A strategy that meets these criteria may be the administration of enteral nutrition.[45,46] In CHAPTER **6** we summarize a systematic review and meta-analysis of randomised trials comparing enteral nutrition with parenteral nutrition in terms of the risk of infections and death in patients with acute pancreatitis.

Another strategy that has been proposed to prevent infections in acute pancreatitis is prophylactic administration of probiotics.[47,48] Probiotics are non-pathogenic bacteria that, on delivery to the host's intestinal tract, may exert health-promoting effects.[49] CHAPTER **7** presents an overview of the proposed mechanisms of action of probiotics in preventing infections and the results from 14 randomised trials in surgical and critically ill patients. In CHAPTER **8** we describe the PRObiotics in

PAncreatitis TRIAl (PROPATRIA): a randomised, placebo-controlled, multicentre trial on probiotic prophylaxis in 296 patients with predicted severe acute pancreatitis. CHAPTER **9** is a summary of a study in which we assessed intestinal barrier function in 141 out of 296 patients who were randomised in PROPATRIA. We evaluated the relationship between infectious complications and **1**. enterocyte damage, **2**. increased intestinal permeability, and **3**. bacterial translocation. We also investigated the effect of probiotics on these processes.

PART III: EARLY ENDOSCOPIC INTERVENTION FOR ACUTE BILIARY PANCREATITIS

Gallstones and gallsludge are responsible for around 25 to 70% of cases of acute pancreatitis in the Western world.[17,18,20] It is thought that intermittent or persistent obstruction of stones and sludge in the common bile duct (CBD) and ampulla of Vater cause pancreatic outflow obstruction, which leads to pancreatic damage and inflammation.[50] Early intervention to relieve biliary obstruction in acute biliary pancreatitis therefore seems plausible. This may mitigate pancreatic inflammation and thereby improve clinical outcome. Early ERCP to remove CBD stones with subsequent sphincterotomy has been proposed as such an intervention.[8] It is known, however, that the majority of CBD stones and sludge pass spontaneously into the duodenum in patients with acute biliary pancreatitis.[50,51] Moreover, ERCP is an invasive procedure with a risk of complications.[52] Therefore, one would ideally perform ERCP only in patients with a high chance of CBD stones. We therefore need parameters that accurately predict CBD stones in acute biliary pancreatitis. In CHAPTER **10** we present the first study evaluating commonly used biochemical and radiological predictors for CBD stones, early in the course of acute biliary pancreatitis.
CHAPTER **11** describes a systematic review and meta-analysis of 3 randomised trials comparing ERCP with conservative treatment in terms of complications and death in patients with acute biliary pancreatitis. After this meta-analysis, the role of early ERCP still remained controversial. This was mainly caused by the fact that the pooled data comprised only few patients with predicted severe acute biliary pancreatitis: i.e. the patients most at risk for complications. Moreover, it remained unclear whether the effect of early ERCP differed between patients with and without cholestasis. Therefore, we performed the study presented in CHAPTER **12**:

a prospective, observational, multicentre cohort study comparing early ERCP with conservative treatment in terms of mortality and death in patients with predicted severe acute biliary pancreatitis. Patients with and without cholestasis were assessed separately.

PART IV: INTERVENTION FOR NECROTISING PANCREATITIS

The historical treatment of infected necrosis is primary open necrosectomy by laparotomy.[9] This procedure is aimed at completely removing the infected focus. Open necrosectomy is an invasive procedure with a high risk of complications (34 to 95%) and death (11 to 39%).[12,53-57] As an alternative, minimally invasive radiological, endoscopic, and surgical techniques are gaining popularity.[11,14,58,59] These minimally invasive techniques can be applied in a so called 'step-up approach'. In contrast to primary open necrosectomy, the step-up approach is aimed at control of the infected focus rather than complete removal of the infected necrosis. We hypothesized that infected necrosis can be successfully treated as an 'abscess'. This means that the necrosis can be left in situ and only drainage of pus under tension is sufficient. Surgical intervention to remove infected necrosis may not always be necessary. Additionally, the minimally invasive step-up approach may reduce the risk of complications and death by inducing less surgical stress (i.e., a pro-inflammatory response) in these already critically ill patients.[56]

As the first step of the step-up approach, percutaneous catheter drainage (PCD) of the peripancreatic collection with infected necrosis is performed.[11] CHAPTER **13** is summary of a systematic review on PCD in necrotising pancreatitis.

If PCD does not lead to clinical improvement, the next step of the step-up approach is drain-guided minimally invasive retroperitoneal necrosectomy. CHAPTER **14** describes the rationale and technical details of 'video-assisted retroperitoneal debridement' (VARD).

For PCD, VARD, and other minimally invasive techniques to be possible, a catheter drain has to be placed in the peripancreatic collection. It was unknown in which proportion of patients this is technically feasible. CHAPTER **15** summarizes an interobserver agreement study among Dutch radiologists to evaluate the feasibility of minimally invasive techniques in necrotising pancreatitis.

A head-to-head comparison of minimally invasive retroperitoneal necrosectomy and open necrosectomy for complications and death had never been performed. In CHAPTER **16** we summarize a retrospective, case-matched, cohort study comparing VARD with open necrosectomy in 30 patients with suspected infected necrotising pancreatitis.

Using the data from the preparative studies mentioned above, we designed a prospective study to compare treatment strategies. CHAPTER **17** presents the PAncreatitis, maximal Necrosectomy versus minimally invasive sTEp up appRoach (PANTER)-trial: a randomised, controlled multicentre trial to determine the optimal surgical strategy in infected necrotising pancreatitis in terms of clinical outcomes, health care resource utilisation, and costs.

The literature on outcome of necrotising pancreatitis comprises mainly of relatively small, retrospective studies from single expert centres, covering long time periods and presenting only the subgroup of patients undergoing necrosectomy. CHAPTER **18** presents a prospective, observational, multicentre cohort study describing outcome of conservative treatment and intervention in 639 patients with necrotising pancreatitis who were screened for eligibility in the PROPATRIA and PANTER studies. The main objective was to present a solid and up to date reference for future studies on mortality in the various subgroups of necrotising pancreatitis.

PART V: OBTAINING MEDICAL ETHICAL APPROVAL FOR A DUTCH MULTICENTRE STUDY

In the final part of this thesis, a topic other than acute pancreatitis is discussed. Before a multicentre study can be initiated, approval has to be obtained from the medical ethics committee of all participating hospitals. Dutch researchers often experience this as an inefficient and tedious process. We hypothesized that the guidelines of the Central Committee on Research Involving Human Subjects (CCMO)[60] on approval for multicentre studies are not always followed by the Dutch medical ethics committees. CHAPTER **19** describes a prospective study in which we systematically evaluated the application procedure for medical ethical approval for the PANTER trial in the 19 participating centres.

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PART I

Defining acute pancreatitis and its complications

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PART I

CHAPTER 2

Describing computed tomography findings in acute necrotising pancreatitis with the Atlanta Classification: an interobserver agreement study

– a summary –

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INTRODUCTION

Treatment of acute necrotising pancreatitis (ANP) is a challenge, and consultation with or referral to specialised institutions is advised on several occasions.[1-3] Therefore, adequate communication regarding both the severity and complications of ANP is of utmost importance. In 1992, an international symposium on acute pancreatitis was held in Atlanta to resolve lingering disputes regarding the definitions of various complications in acute pancreatitis. This resulted in the Atlanta Classification, which is a clinically based classification system that defines the severity and complications of acute pancreatitis.[4] The Atlanta Classification is frequently used to describe (peri-)pancreatic collections on computed tomography (CT).
The aim of this study was to assess the interobserver agreement of categorizing peripancreatic collections on computed tomography (CT) using the Atlanta Classification.

METHODS

Preoperative contrast-enhanced CTs from 70 consecutive patients (49 men; median age, 59 years; range, 29-79 years) operated for ANP (2000-2003) in 11 hospitals of the Dutch Pancreatitis Study Group were reviewed. Five abdominal radiologists from 5 different hospitals independently categorized the peripancreatic collections according to the Atlanta Classification: 'acute fluid collection', 'pseudocyst', 'pancreatic abscess', or 'pancreatic necrosis' (TABLE 2.1.). The option 'mixture' and 'no collection' was also an option to choose. Radiologists were only aware of the timing of the CT and the clinical condition of the patient. The interobserver agreement was calculated using κ-statistics. A κ level of less than 0.00 represents no agreement; 0.00-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; 0.81-1.00, almost perfect agreement.[5] Mean κ with SD was calculated for all 10 radiologist pairs within the 5 radiologists.

RESULTS

Among the 5 abdominal radiologists, there was slight interobserver agreement for categorizing collections according to the Atlanta Classification (κ 0.144; SD, 0.095; see TABLE 2.1.). In 3 (4%) of 70 cases, the radiologists chose the same definition (mixture, n=2; pancreatic necrosis, n=1). In 3 (4%) of 70 cases, the same Atlanta definition was chosen. In 13 (19%) of 70 cases, 4 radiologists agreed, and in 42 (60%) of

TABLE 2.1. Atlanta Classification used for defining (peri-)pancreatic collections in 70 necrotising pancreatitis patients.

HPB radiologist	Ac. fluid collection n (%)	Pancreatic abscess n (%)	Pseudocyst n (%)	Pancreatic necrosis n (%)	Mixture n (%)	No collection n (%)	Total n (%)
1	10 (14)	22 (31)	0 (0)	4 (6)	32 (46)	2 (3)	70 (100)
2	1 (1)	1 (1)	0 (0)	14 (20)	53 (76)	1 (1)	70 (100)
3	8 (11)	4 (6)	0 (0)	7 (10)	51 (73)	0 (0)	70 (100)
4	14 (20)	16 (23)	2 (3)	24 (34)	14 (20)	0 (0)	70 (100)
5	15 (21)	21 (30)	20 (29)	6 (9)	3 (4)	5 (7)	70 (100)
Mean	10 (14)	13 (18)	4 (6)	11 (16)	31 (44)	2 (2)	70 (100)

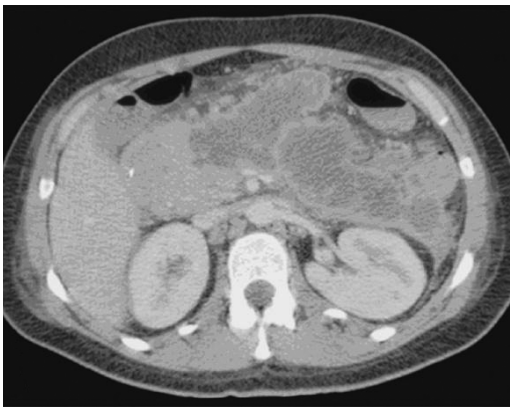

FIGURE 2.1. The use of the Atlanta Classification on CT in necrotising pancreatitis. Computed tomography scan 12 days after onset of disease. The definitions chosen for this collection were 'pseudocyst' (n=1), 'pancreatic abscess' (n=1), 'pancreatic necrosis' (n=1), and 'mixture' (n=2).

70 cases, 3 radiologists agreed on the definition. In 21 cases (30%), 1 or more of the radiologists classified a collection as 'pancreatic abscess', whereas 1 or more radiologist used another Atlanta definition. See FIGURE 2.1 for an example.

DISCUSSION

Surgeons and gastroenterologists tend to rely heavily on the radiologist's CT report of a patient with ANP to decide upon further treatment. The impact of a report descri-

bing a 'pseudocyst' is completely different from that of 'infected pancreatic necrosis' or a 'pancreatic abscess.'[1-3] Different complications require different treatment strategies, ranging from conservative management to invasive percutaneous or surgical intervention. Interobserver variability in characterization of peripancreatic collections will potentially mislead the clinician in his choice for the appropriate therapy.

Interobserver agreement studies have never been reported for the Atlanta Classification, so the present study cannot be compared with previous studies.

In conclusion, the interobserver agreement of the Atlanta Classification for categorizing peripancreatic collections in acute pancreatitis on CT is poor. The Atlanta Classification should not be used to describe complications of acute pancreatitis on CT. Radiological reports should be descriptive and mention the presence or absence of pancreatic necrosis, fluid collections, encapsulation, and/or air. A new descriptive radiological classification system for acute pancreatitis should be designed.

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PART I

CHAPTER 3

The Atlanta Classification of acute pancreatitis revisited: a review of the literature

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ABSTRACT

BACKGROUND

In a complex disease such as acute pancreatitis, correct terminology and clear definitions are important. The clinically based Atlanta Classification was formulated in 1992, but in recent years it has been increasingly criticized. No formal evaluation of the use of the Atlanta definitions in the literature has ever been performed.

METHODS

A Medline literature search sought studies published after 1993. Guidelines, review articles and their cross-references were reviewed to assess whether the Atlanta or alternative definitions were used.

RESULTS

A total of 447 articles was assessed, including 12 guidelines and 82 reviews. Alternative definitions of predicted severity of acute pancreatitis, actual severity and organ failure were used in more than half of the studies. There was a large variation in the interpretation of the Atlanta definitions of local complications, especially relating to the content of peripancreatic collections.

CONCLUSION

The Atlanta definitions for acute pancreatitis are often used inappropriately, and alternative definitions are frequently applied. Such lack of consensus illustrates the need for a revision of the Atlanta Classification.

INTRODUCTION

Over the past five decades, several classification systems on pancreatitis have emerged from interdisciplinary symposia.[1-4] The most recent international meeting on this topic, the 1992 Atlanta symposium, produced a clinically based classification system.[4,5] Definitions of acute pancreatitis, its severity, organ failure and the local complications 'acute fluid collection', 'pancreatic necrosis', 'pseudocyst' and 'pancreatic abscess' were proposed. The Atlanta Classification attempted to introduce uniformity in the assessment of clinical severity and the various complications of the disease. This is the only widely accepted classification system used by clinicians and radiologists.

With increasing knowledge of the pathophysiology of pancreatitis and the development of new means of intervention, several authors have pointed out shortcomings in the Atlanta Classification.[6-13] A recent review demonstrated that terminology abandoned by the Atlanta symposium, for instance 'phlegmon' and 'infected pseudocyst', is still used frequently in the literature, and that various new terms, such as 'organized pancreatic necrosis' and 'necroma', have been introduced since 1993.[14] A critical evaluation of the use of the Atlanta Classification in the literature has never been performed. The present review assesses whether the definitions of the Atlanta Classification are accepted in the literature and evaluates the extent of variation in interpretation of these definitions.

METHODS

A Medline search of literature published between 1993 and 2006 was performed using the following terms: 'acute pancreatitis and review' and 'acute pancreatitis and guidelines'. From the identified guidelines and reviews, cross-references were retrieved. The search included all types of publication (reviews, guidelines, original studies, case reports and editorials), but excluded those not in English and animal experimental studies. One author (T.L.B.) performed the selection and reviewed all full-text papers to assess whether the original Atlanta definitions (TABLE 1.2, page 16) or other definitions were used for the following five components of the Atlanta Classification: diagnosis (cut-off levels of pancreatic enzymes lipase and amylase); predicted severity (predictive scoring systems, cut-off levels of scoring systems); actual severity (distinction between mild and severe pancreatitis, distinction

TABLE 3.1. Characteristics of retrieved articles (1993-2006) specified per impact factor

	Total no. of studies n=447	High (>5.0) n=89	Intermediate (1.5-4.9) n=273	Low (<1.5) n=85
Meta-analyses	3	2	1	0
Randomised controlled trials	34	13	18	3
Prospective series	144	28	99	17
Retrospective series	147	23	95	29
Reviews	82	10	44	28
Guidelines	12	5	5	2
Editorials	5	2	3	0
Others	20	6	8	6

between predicted and actual severity); organ failure (determinants of individual failing organ systems, cut-off levels of determinants, distinction between single organ failure and multiple organ failure); local complications (pancreatic necrosis and peripancreatic necrosis, infection of necrosis, morphological aspects and distinction of different types of collection). If different definitions for the components were identified, this was double checked by one of two other authors (H.C.v.S., M.G.B.). All disagreements were resolved by discussion among the authors. In addition, study results leading to new insights that might have influenced the interpretation of the Atlanta Classification were recorded and are discussed. As a large number of references were retrieved, for each component of the Atlanta Classification that was assessed only the three most recent articles are cited here; the remaining references are published in APPENDIX 1 (available as supplementary material online at www.bjs.co.uk).

RESULTS

A total of 447 articles was reviewed, including 12 guidelines and 82 reviews. These articles reported on studies that were not specifically designed to evaluate the Atlanta Classification; they merely mentioned Atlanta definitions (for example a randomised trial comparing two treatment strategies with the outcome 'pseudo-

cyst'). Therefore, an assessment of methodological quality was deemed inappropriate. TABLE 3.1 gives an overview of the papers according to type of article and impact factor of the journals in which they were published. The most important discrepancies for the five components of the Atlanta Classification and discrepancies in the 12 guidelines are discussed in order.

DIAGNOSIS

The Atlanta Classification provides no cut-off value for pancreatic enzyme levels. In 116 Studies, the diagnosis of acute pancreatitis was defined as a characteristic clinical history of abdominal pain and an increased level of pancreatic enzymes to three or more times the upper limit of normal. However, 31 studies used different thresholds, ranging from two or more[15-17] to more than four[18-20] and more than five[21-23] times the upper limit of normal.

PREDICTED SEVERITY

A total of 283 articles provided criteria for predicting severity in acute pancreatitis. Some 86 reports used the severity scoring systems proposed by the Atlanta symposium.[16,17,23] However, 197 studies used a different cut-off level for defining severity, or used different or additional scoring systems, such as computed tomography (CT) severity index, Imrie (Glasgow) score, Simplified Acute Physiology score, Sequential Organ Failure Assessment or severity predictors (such as C-reactive protein).[15,24,25] Cut-off values for severity stratification differed considerably between reports. For the CT severity index, the most established radiological scoring system developed by Balthazar and colleagues[26] in 1990, the cut-off value to differentiate between mild and severe disease ranged from three or more to eight or more points.[27-29] In 32 studies, threshold values for Acute Physiology And Chronic Health Evaluation (APACHE) II score (other than eight or more) varied from five or more to 11 or more, whereas the time for calculating the score varied from day of admission to 24 and 48 h after admission.[30-32] Eleven studies used different threshold values for the Ranson criteria (other than three or more), ranging from more than three to more than five.[32-34]

Since the Atlanta symposium in 1992, many studies have identified new predictors of severity and these have been incorporated in several guidelines. Such predictors

include age (over 55[6], over 70[35] or over 80[36] years), obesity (body mass index over 30 kg/m2),[11,24,37] pleural effusion (left or bilateral) on chest radiograph,[38-40] raised haematocrit level[6,41,42] and C-reactive protein level greater than 150 mg/dl after 48 h.[43-45]

ACTUAL SEVERITY

Of 297 articles providing definitions for severe acute pancreatitis, 195 defined severe disease according to the Atlanta Classification, although 61 merely stated that the Atlanta criteria were used without specification.[46-48] The remaining 102 articles used definitions of severe disease other than those of the Atlanta Classification. These definitions were based on admission to an intensive care unit, length of intensive care unit or hospital stay, complications requiring medical or operative intervention, mortality or various other, additional or non-specified criteria1.[7,49,50] The authors of 45 articles used the absence and presence of pancreatic necrosis broadly synonymously with mild and severe acute pancreatitis respectively.[47,51,52] Some reports, however, pointed out that patients with the morphological diagnosis of interstitial pancreatitis may develop clinically severe disease.[44,53,54]

The relationship between the development of organ failure and pancreatic necrosis (the most important determinants of severe acute pancreatitis) is contentious. Several reports noted that only 51-55% of patients with pancreatic necrosis manifested organ failure.[55-57] In the study by Lankisch and colleagues,[53] 15% of patients with acute oedematous pancreatitis developed organ failure. In a recent study, organ failure was the main risk factor for mortality, regardless of the presence or absence of pancreatic necrosis[23]. Conversely, other studies showed a good correlation between organ failure and the extent of pancreatic necrosis.[16,58,59]

Finally, in 38 articles, the differentiation between 'predicted severe' acute pancreatitis (Ranson, Imrie or APACHE II score) and 'actual severe' disease (systemic or local complications) was not apparent from the published data.[17,28,60] The difference is important, because in recent studies less than 50% of patients with predicted severe disease eventually turned out to have actual severe disease according to the Atlanta criteria.[25,46] This lack of distinction may account for the variation in incidence of severe acute pancreatitis among institutions.

ORGAN FAILURE

Criteria for organ failure were found in 149 articles. In 35 reports the exact Atlanta definitions for organ failure were specifically stated and used.[23,61,62] Seven articles restricted organ failure to two of the four Atlanta determinants for organ failure: respiratory and renal insufficiency.[63-65] However, 107 articles used additional criteria for organ failure and systemic complications, such as leucocytosis, temperature, coagulopathy, nervous system failure, hepatic failure, systemic inflammatory response syndrome or sepsis, or used altered thresholds or adjustments for the Atlanta definitions of organ failure.[52,66,67] The remaining articles gave no definition of organ failure, or simply noted that the Atlanta criteria were used, without specification.

In recent years, multiple organ failure has been acknowledged as a major determinant of mortality. However, no uniform definition for multiple organ failure exists: 20 reports defined it as failure of two or more organ systems,[31,46,49] and eight as failure of three or more organ systems,[23,68,69] although most studies did not define multiple organ failure. The dynamic process of organ dysfunction is increasingly recognized, and several authors differentiated. between transient and persistent organ failure.[70-72] In addition, several studies showed that early and progressive organ failure was associated with high mortality, but most patients with transient organ failure had an uncomplicated course.[72-74] The recent UK guidelines on acute pancreatitis state that organ failure in the first week resolving within 48 h should not be considered an indicator of severe disease.[43]

Since 1993, several new organ failure grading systems have been developed (Goris score, Marshall or multiple organ dysfunction score, Bernard score, Sequential Organ Failure Assessment and logistic organ dysfunction syndrome score) that take into account the number of organ systems involved and the degree of dysfunction of each individual organ. Some systems also include the need for inotropic or vasopressor agents, mechanical ventilation and dialysis that the Atlanta symposium did not account for. Several studies have shown that dynamic scoring systems (such as the delta APACHE II score) or scoring systems that account for the physiological response to treatment (such as the delta organ failure score or cumulative Marshall score) are better predictors of outcome than static scoring systems.[31,32,71]

LOCAL COMPLICATIONS

In a recent interobserver agreement study on the Atlanta definitions regarding the various local complications, interobserver agreement was poor: five radiologists agreed on the respective Atlanta definition in only three of 70 collections depicted by contrast-enhanced CT (CECT).[8]

Acute fluid collection

In 64 articles, a definition was given for an 'acute fluid collection'. The following terms were used to describe acute fluid collections: '(peri)pancreatic fluid collections',[75-77] 'peripancreatic effusions',[78] 'extrapancreatic fluid collections',[61,79,80] 'immature pseudocyst'[81,82] and 'exudates'.[54] (Peri)pancreatic fluid collection was also used as an overall descriptive term for all types of collection related to acute pancreatitis.[83-85]

In most reports, the differentiation between acute fluid collection and pseudocyst was made after 4 weeks from onset of disease (as proposed by the Atlanta Classification). In eight reports, however, a different time period was used as a criterion for this distinction, varying from 3 weeks[75,86,87] to 6[88,89] and even 8[90] weeks. Moreover, they did not adequately describe whether acute fluid collections consisted of fluid alone or whether they may have contained necrotic debris.[85,91,92]

Authors of 17 articles regarded the occurrence of an acute fluid collection to be a local complication and so a sign of 'severe disease'.[46,62,93] However, most others did not include acute fluid collection either in the definition of local complication or in that of severe disease.

Pancreatic necrosis

Of 152 articles that gave a specific definition for 'pancreatic necrosis' or 'necrotising pancreatitis' (FIGURE 3.1), 47 used the Atlanta criterion of more than 30% parenchymal necrosis to define necrotising pancreatitis.[28,61,94] However, 85 defined necrotising pancreatitis as any evidence of pancreatic parenchymal necrosis (including less than 30% parenchymal necrosis).[47,95,96] A third definition of necrotising pancreatitis, reported in 20 papers, was the appearance of pancreatic necrosis or extrapancreatic necrosis, or both, on CECT (and a serum C-reactive protein value of more than 150 mg/dl).[52,86,97]

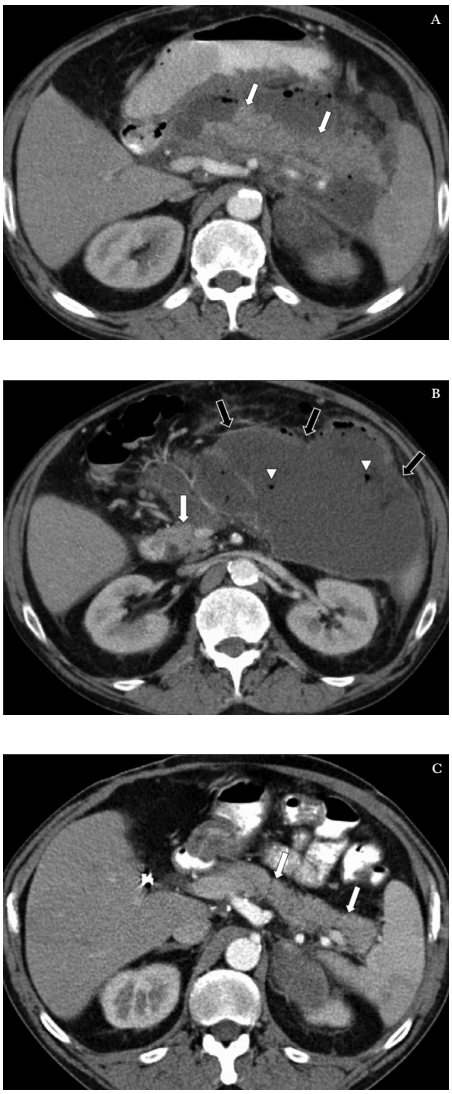

FIGURE 3.1. (A, B) Contrast-enhanced CT of a patient with acute pancreatitis 22 days after onset of symptoms. There is normal enhancement of the body and tail of the pancreas, surrounded by a large heterogeneous and encapsulated fluid collection with gas bubbles suggestive for secondary infection. Some would call this 'necrotising pancreatitis', but because there is no evidence for pancreatic parenchymal necrosis (but only 'peripancreatic necrosis'), others would call this 'interstitial pancreatitis'. A large amount of fat necrosis was debrided during operation. (C) Six months after operation, a follow-up CT reveals a normal enhancing pancreatic parenchyma.

In the Atlanta Classification, the definition of pancreatic necrosis requires pancreatic parenchymal nonenhancement on CECT.[4] However, some clinicians questioned whether non-enhancement on CECT meant irreversible damage and necrosis.[86,98,99] For instance, Traverso and Kozarek[86] defined pancreatic necrosis as devitalised tissue found at operation. This was supported by Takeda and colleagues,[100-102] who noted that pancreatic parenchymal perfusion was maintained during intraarterial angiography, while CECT showed pancreatic nonenhancement. In contrast, several studies demonstrated a good correlation between parenchymal non-enhancement on CECT and the presence of pancreatic necrosis (confirmed at operation).[103-105]

Data on the accuracy of CECT in diagnosing extrapancreatic or peripancreatic fat necrosis are conflicting. Although eight groups claimed that fat necrosis could not be determined reliably by CECT,[92,106,107] several studies demonstrated a good correlation between extrapancreatic findings on CECT and the presence of fat necrosis at operation or autopsy.[104,108,109]

The Atlanta Classification includes both infected and sterile necrosis within the definition of 'pancreatic necrosis'.[4] Several groups claimed that pancreatic parenchymal necrosis without infection is not amajor morbidity risk.[110-112] This was supported by studies showing an uncomplicated course in the presence of necrosis without infection.[23,55,56] Beger and colleagues[81,113] were the first to emphasize that necrosis is a potential nidus for secondary infection occurring in 40-70% of patients. Recent studies confirmed this, demonstrating infected necrosis as the primary cause of late mortality.[58,114,115] However, definitions of 'infected necrosis' were also conflicting. Some authors regarded the presence of parenchymal necrosis as a prerequisite for the diagnosis of infected necrosis,[116–118] but others defined infected necrosis as infection that could occur in parenchymal necrosis or peripancreatic fat necrosis (in other words, in the absence of parenchymal necrosis), or both.[67,76,119]

Pseudocyst

A specific definition for the term 'pseudocyst' was provided in 87 articles, and all were similar to that of the Atlanta Classification. Some controversies, however, remain. Thirty-eight articles included collections containing both fluid and necrotic debris under the heading of pseudocyst (FIGURE 2).[120-122] Yet Baron[123] and others[85,124] have stated that pseudocysts should be devoid of solid necrotic debris. Evidence has

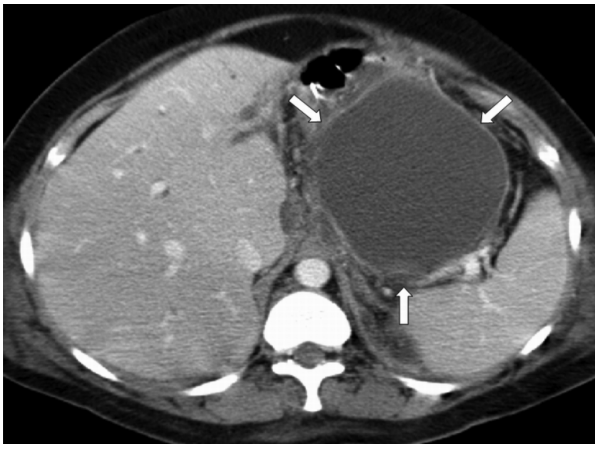

FIGURE 3.2. Contrast-enhanced CT of a patient with acute pancreatitis 30 days after onset of symptoms. The fluid collection seems to be homogenous and encapsulated and could be interpreted as a 'pseudocyst' according to the Atlanta classification. During operation, however, the collection turned out to contain large amounts of necrotic debris which was not recognized on CT.

shown that therapeutic strategy and outcome differed between collections containing fluid alone and those containing necrosis and fluid.[84,125,126] Bradley[127] considered that mischaracterization of (peri)pancreatic fluid collections as pseudocyst by CECT was an extremely common error in contemporary diagnostic radiology. This mischaracterization has two potentially dangerous consequences: first, by instrumentation of a sterile collection containing both fluid and necrosis, infection may be introduced6,[120,128]; second, a delay in appropriate intervention may occur.[33,120,129]

The incidence, natural history and options for management differed between acute and chronic pseudocysts. Several authors emphasized that the results of treatment of pancreatic fluid collections in the literature were difficult to interpret, because often no distinction was made between pseudocysts and acute fluid collections, or between pseudocysts that complicated acute and chronic pancreatitis.[122,128,130] Thirty-one original articles on the treatment of pseudocysts were reviewed but only five dealt exclusively with pseudocysts after an episode of acute pancreatitis.[89,120,131] The remaining 26 articles reported results of the treatment of pseudocysts complicating acute and chronic pancreatitis.[121,132,133]

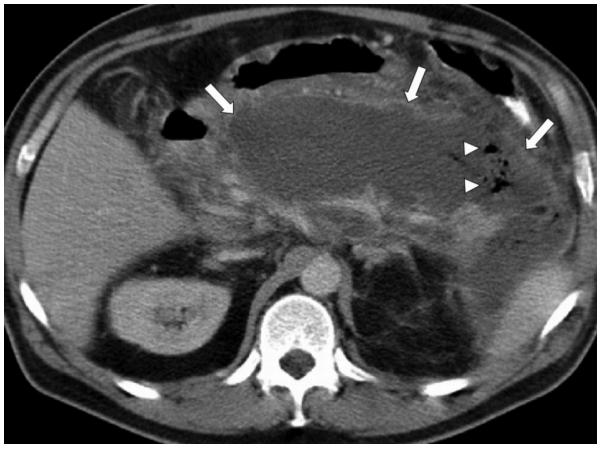

FIGURE 3.3. Contrast-enhanced CT of a patient with AP 36 days after onset of symptoms. The body and tail of the pancreas are largely non-enhancing. Adjacent to the pancreatic bed is a large collection with predominately fluid like attenuation. Because of the gas bubbles some would call this a 'pancreatic abscess' whereas others would name this 'infected pancreatic necrosis'.

Pancreatic abscess

Some 68 articles provided a definition of 'pancreatic abscess', which was generally in line with the original Atlanta definition. Nine original articles after 1993 were identified that reported on the treatment of 'pancreatic abscesses', and the Atlanta definition (collection of pus and virtually no necrotic debris, more than 4 weeks after onset) was strictly applied in three of these.[134-136] The others included collections that contained, in addition to pus, solid necrotic debris[137-139] or that were treated within 4 weeks of onset of disease[140] or after surgery.[141,142]

The diagnosis of pancreatic abscess on CECT is also controversial. In ten articles, the 'air bubble' phenomenon was considered 'diagnostic of a pancreatic abscess'.[93,143,144] In 31, however, gas bubbles in a heterogeneous collection on CT were regarded as highly indicative of infected pancreatic necrosis (FIGURE 3.3).[61,67,145] Varying hypotheses exist on the aetiology of pancreatic abscess. Some authors considered 'postacute pseudocysts' and pancreatic abscesses as late consequences of necrotising pancreatitis.[146-148] In contrast, others maintained that pancreatic abscesses occurred exclusively in interstitial pancreatitis with a normal enhancing pancreas on CECT.[117,149,150]

Apart from 'infection of a pseudocyst', several authors hypothesized that pancreatic abscesses evolved from progressive liquefaction of necrotic pancreatic and peripancreatic tissues, in time resulting in complete liquefaction.[76,123,151] According to the Atlanta Classification, most pancreatic abscesses arise at least 4 weeks after onset of symptoms[4], although others diagnose 'pancreatic abscesses' after 1,[50,152] 2[153,154] or 3[86,146,147] weeks. Interestingly, when performing operative necrosectomy several months after the onset of severe acute pancreatitis, Morgan and colleagues10, Howard and Wagner[155] and others[156] observed different degrees of liquefaction of necrotic tissue. Several authors acknowledged this evolving process, and they postulated that a collection may represent a transitional entity from (infected) pancreatic necrosis to an (infected) pseudocyst or pancreatic abscess, as they encountered both pus and necrotic debris in these (infected) collections.[7,12,139]

GUIDELINES

The greatest discrepancies in the 12 guidelines[6,35,36,43,148,157-165] on acute pancreatitis related to the definitions of organ failure and those of predicted severe disease. These are summarized in TABLE 3.2.

DISCUSSION

The present review has demonstrated that the Atlanta definitions of severity and local complications of acute pancreatitis are being used inconsistently, and that several components of the classification have received considerable criticism. By providing definitions, the result of consensus by over 40 experts based on the data available in 1992, the Atlanta symposium improved themanagement of acute pancreatitis and clinical research relating to the condition.

However, the past 20 years have seen not only new insights in pathophysiology and therapeutic strategies but also improved imaging techniques. Clearly, the time has come to revise the classification of acute pancreatitis. The various predictive scoring systems have not improved substantially since the Atlanta symposium. They are only moderately accurate in predicting severe disease in an individual patient. As McKay and Imrie[166] have noted, predictive systems were developed initially to allocate patients within clinical trials and not to assess severity in an individual. Defining severity based on the presence or absence of organ failure also has its limitations. It

TABLE 3.2. Overview of definitions for organ failure and predicted severe acute pancreatitis in guidelines for acute pancreatitis published after 1993

Guideline	Definitions for organ failure	Definitions for predicted severe acute pancreatitis
ACG 1997[157]	Refers to Atlanta Classification 1992	Ranson score ≥3 after 48 h APACHE II score >8 after 48 h
UK 1998[158]	Refers to Atlanta Classification 1992	Ranson/Glasgow ≥3 CRP > 210 mg/l (first 4 days) or >120 mg/l at 1 week APACHE II score ≥9 (severe acute pancreatitis) or ≥6 (includes all severe cases, but PPV of 50%)
SSAT 1998[159]	Not addressed	Not stated
Santorini 1999[160]	Not addressed	BMI >30 kg/m^2 Pleural effusion APACHE II score ≥6 (at 24 h) APACHE (obesity) score ≥6 CRP >150 mg/l
French 2000[36]	Renal failure: creatinine >170 µmol/l Shock: systolic BP<90 mmHg despite fluid replacement Pulmonary insufficiency: Pa O260 mmHgon room air Glasgow Coma Score <13 Platelets <80 g/l	At admission Age >80 years BMI >30 kg/m2 Chronic renal failure Pre-existing severe illnesses At 24-48 h Presence of organ failure by using simple measures or use of scoring system (e.g., SOFA) Ranson/Imrie score >3 CECT: CT severity index ≥4 (48-72 h) CRP >150 mg/l *Note: The non-specific scores (APACHE II, SAP II, etc) arenot recommended by the Jury*
WCG 2002[35]	SIRS ≥1 vital organ dysfunction ARDS Renal failure: increased serum creatinine >0.5 mg/dl (44 µmol/l) or 50% above baseline or reduction in calculated creatinine clearance >50% or need for dialysis Hypotension: mean arterial pressure <60 mmHg DIC Acute adrenal insufficiency Acute hepatitis Metabolic encephalopathy Ileus	At admission Age >70 years Clinical assessment BMI >30 kg/m^2 Pleural effusion/infiltrates CECT: >30% non-enhancement of the pancreas APACHE II score ≥8 Presence of organ failure At 24-48 h Clinical assessment Glasgow score (no cut-off value provided) CRP >150 mg/l Presence of organ failure
IAP 2002[161]	Not addressed	Not stated: surgical guideline
JSAEM 2002[162]	Not addressed	Clinical signs CRP (48 h: no cut-off value provided) BMI (no value provided) CECT: necrosis Scoring system, like JMHW, APACHE II at 24 h or Ranson/Glasgow at 24-48 h: no cut-off values provided Japanese score ≥2

Nathens 2004[148]	Refers to the guidelines for intensive care unit admission, published in 1999[163]	Elderly (age not specified) BMI >30 kg/m^2 Patients requiring ongoing volume resuscitation CECT: >30% non-enhancement of the pancreas Clinical assessment *Note: Disease-specific scoring systems or severity scores are useful adjuncts to identify patients at high risk of a complication, but should not replace serial clinical assessments. In addition, there is a recommendation against the use of markers such as CRP or procalcitonin to guide clinical decision making or predict clinical course of acute pancreatitis or to triage patients*
UK 2005[43]	Refers to Atlanta Classification 1992	At admission Clinical assessment BMI >30 kg/m^2 Pleural effusion APACHE score >8 At 24-48 h Clinical assessment Glasgow score ≥3 APACHE II score >8 Persistent organ failure for 48 h (especially if multiple and progressive) CRP >150 mg/l *Note: Organ failure present within 1 week, which resolves within 48 h, should not be considered an indicator of a severe attack of acute pancreatitis*
ACG 2006[6]	Refers to Atlanta Classification 1992 *Note: Criteria of organ failure will change in the future: gastrointestinal bleeding will undoubtedly be deleted*	At admission Age >55 years BMI >30 kg/m^2 Presence of organ failure Pleural effusion/infiltrates 24-48 h APACHE II score ≥8 Serum haematocrit ≥44% *Note: Ranson signs are no longer advocated, due to a comprehensive evaluation of 110 studies that concluded that Ranson signs provided very poor predictive power of severity of acute pancreatitis*
JSAEM 2006[164,165]	Pulmonary insufficiency: dyspnoea Shock Central nervous system disorders Bleeding tendency Negative base excess failure: rise of blood urea nitrogen level and creatinine level	Japanese score ≥2

ACG, Practice Parameters Committee of the American College of Gastroenterology; **APACHE**, Acute Physiology And Chronic Health Evaluation; **UK**, Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, and Association of Upper GI Surgeons of Great Britain and Ireland; **CRP**, C-reactive protein; **PPV**, positive predictive value; **SSAT**, Society for Surgery of the Alimentary Tract; **Santorini**, Santorini Consensus Conference; **BMI**, body mass index; **French**, French Consensus Conference on Acute Pancreatitis; **BP**, blood pressure; **PaO2**, arterial partial pressure of oxygen; **SOFA**, Sequential Organ Failure Assessment; **CECT**, contrast-enhanced computed tomography; **SAP**, Simplified Acute Physiology; **WCG**, World Congress of Gastroenterology; **SIRS**, systemic inflammatory response syndrome; **ARDS**, adult respiratory distress syndrome; **DIC**, disseminated intravascular coagulation; **IAP**, International Association of Pancreatology; **JSAEM**, Japanese Society of Emergency Abdominal Medicine; **JMHW**, Japanese Ministry of Health andWelfare; **Nathens**, Consensus Statement regarding the management of the critically ill patient with severe acute pancreatitis.

is increasingly recognized that persistent organ failure (for more than 48 h) is the most important determinant of morbidity and mortality, which are predominantly related to the number of organ systems failing, the degree of dysfunction of the organs involved and the duration of organ failure.

The definition of necrotising pancreatitis is controversial because it incorporates both sterile and infected necrosis, and covers both pancreatic parenchymal necrosis and peripancreatic fat necrosis. Interpretations of pseudocyst and pancreatic abscess vary widely because necrotic debris within these collections is often not accounted for. This might be explained by the incapacity of CECT to detect necrotic debris in collections predominantly containing fluid, and its incapacity to discriminate between sterile and infected collections.[7,10,12,92,167] Although magnetic resonance imaging (MRI) and (endoscopic) ultrasonography may be of additional value in classifying these collections,[10,168,169] their applicability in severely ill patients has been questioned.[92,170]

Although the Atlanta Classification incorporates a pathological and morphological description of different local complications, it does not provide exact radiological criteria for each. The recently demonstrated poor interobserver agreement on the Atlanta Classification of local complications[8] highlights the need for new descriptive morphological terms to describe CECT findings. The existing radiological grading system, the CT severity index, is a numerical scoring system that combines quantification of extrapancreatic changes with the extent of pancreatic necrosis.[26] Although the CT severity index has clear prognostic value with regard to morbidity and mortality,[26,171-174] it does not characterise the local complications of acute pancreatitis.

Much of the persisting controversy over the natural course of (peri)pancreatic collections is due to a lack of prospective data from large patient series. The authors of this review, therefore, advocate a collaborative international study to clarify pathophysiology, natural course and optimal management of (peri)pancreatic collections.

The present review has aimed to give an overview of the controversies regarding the Atlanta Classification in the literature. There are virtually no studies addressing the validation of the definitions proposed by the Atlanta Classification. Consequently, hardly any original data on this topic are available to analyse. This review, therefore, has merely categorized applications and interpretations of the Atlanta definiti-

ons. Correct terminology and standardized definitions are important for adequate communication in clinical practice and for comparing interinstitutional data for clinical research. The continuing failure to use standardized definitions for predicted and actual severe acute pancreatitis, organ failure and the local complications, and the heterogeneity of inclusion criteria of patients in clinical trials, have hampered the progress of evidence-based recommendations. This review has identified many studies that have improved insight into the natural course of the disease. These new insights should be used to design a new classification.

The authors propose the following recommendations for revision of the classification of acute pancreatitis. First, the diagnosis should incorporate two of the following three items: upper abdominal pain, amylase and/or lipase levels at least three times the upper limit of normal (as this cutoff is used most frequently in the literature), and CT or MRI findings compatible with acute pancreatitis. Second, persistent organ failure (for at least 48 h) should have an important role in defining severity of acute pancreatitis. Third, it should be decided which predictive scoring system(s), including cut-off value, should be used to define predicted severe acute pancreatitis, based on a systematic review of the available data. Fourth, future studies should always make a clear distinction between predicted severe and actual severe disease, with *a posteriori* validation of the disease severity. Fifth, a systematic review should demonstrate which organ failure scoring system should be used, and definitions for organ failure should take into account the number of organ systems failing, the duration (less or more than 48 h) of organ failure, and the need for specific therapy (such as inotropic or vasopressor agents, mechanical ventilation and dialysis). Sixth, peripancreatic fat necrosis without pancreatic parenchymal necrosis should be regarded either as a separate entity or as necrotising pancreatitis. Seventh, infected necrosis should be regarded as a separate entity. Eighth, a term should be appointed for encapsulated collections containing both fluid and necrotic debris. Ninth, in order to diagnose a collection that contains fluid only (such as pseudocyst), MRI or (endoscopic) ultrasonography should be performed first to exclude necrotic debris in the collection. Tenth, a new set of descriptive morphological terms should be designed to describe local complications on CT. Such a new classification system should be evaluated in high-quality interobserver and prospective clinical studies. Adjustments should be made every few years, based on new data. Most important-

ly, clinicians and radiologists worldwide should comply with the new classification in clinical practice and research. Progress in the field of acute pancreatitis is hampered greatly when various author groups use their own idiosyncratic definitions. When journal referees are requested to peer-review manuscripts, they should pay special attention to the correct use of definitions as defined by a new classification.

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PART I

CHAPTER 4

Describing peripancreatic collections in severe acute pancreatitis using morphological terms: an international interobserver agreement study

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ABSTRACT

BACKGROUND

The current terminology for describing peripancreatic collections in acute pancreatitis (AP) derived from the Atlanta Symposium (e.g., pseudocyst, pancreatic abscess) has shown a very poor interobserver agreement, creating the potential for patient mismanagement. A study was undertaken to determine the interobserver agreement for a new set of morphological terms to describe peripancreatic collections in AP.

METHODS An international, interobserver agreement study was performed: 7 gastrointestinal surgeons, 2 gastroenterologists, and 8 radiologists in 3 US and 5 European tertiary referral hospitals independently evaluated 55 computed tomography (CT) scans of patients with predicted severe AP. Percentage agreement (median, interquartile range [IQR]) for 9 clinically relevant morphological terms was calculated among all reviewers, and separately among radiologists and clinicians. Percentage agreement was defined as poor (<0.50), moderate (0.51-0.70), good (0.71-0.90), and excellent (0.91-1.00).

RESULTS

Overall agreement was good to excellent for the terms 'collection' (percentage agreement=1; IQR 0.68-1), 'relation with pancreas' (1; 0.68-1), 'content' (0.88; 0.87-1), 'shape' (1; 0.78-1), 'mass effect' (0.78; 0.62-1) 'loculated gas bubbles' (1; 1-1), and 'air-fluid levels' (1; 1-1). Overall agreement was moderate for 'extent of pancreatic nonenhancement' (0.60; 0.46-0.88) and 'encapsulation' (0.56; 0.48-0.69). Percentage agreement was greater among radiologists than clinicians for 'extent of pancreatic nonenhancement' (0.75 vs. 0.57, P=0.008), 'encapsulation' (0.67 vs. 0.46, P= 0.001), and 'content' (1 vs. 0.78, P=0.008).

CONCLUSION

Interobserver agreement for the new set of morphological terms to describe peripancreatic collections in AP is good to excellent. Therefore, we recommend that current clinically based definitions for CT findings in AP (e.g., pancreatic abscess) should no longer be used.

INTRODUCTION

Severe acute pancreatitis is associated with a wide spectrum of pathological changes in the pancreatic and peripancreatic region. Changes can include pancreatic gland necrosis and/or various types of intra-abdominal collections containing fluid and peripancreatic fat necrosis.[1] Secondary infection of necrosis and these collections is often an indication for operative intervention and increases mortality to almost 30%.[2] Contrast-enhanced computed tomography (CT) is the imaging study used most widely to describe these pathological changes.[2-5] Clear communication and agreement on CT findings is crucial, because the choice of treatment (conservative management, percutaneous catheter drainage and necrosectomy by laparotomy or minimally invasive approach) hinges heavily on how surgeons, gastroenterologists and radiologists interpret CT findings. The decision for operative or radiological intervention is determined by the characteristics of the collections, such as the contents (fluid or solid) and microbial status (sterile or infected).[2,3,5,6] Miscommunication can put the patient at risk by initiating an inappropriate treatment algorithm.[7] The need for precise descriptions of the many different types of peripancreatic collections in acute pancreatitis was recognized in the early 1990s, resulting in the widely used Atlanta Classification.[8] While this work represented a very important contribution, over the ensuing 15 years, it has become apparent that the clinically based definitions suggested by this symposium, such as 'pseudocyst' and 'pancreatic abscess', lead to confusion in both daily practice and clinical research. This confusion frequently results in errors in diagnosis and management and misinterpretation of communications.[2,9-14] Critics state that the Atlanta definitions do not accurately represent collections containing both liquid and solid material (i.e., pancreatic parenchymal necrosis and peripancreatic fat necrosis)[2,11-15], yet these types of collections comprise the vast majority of collections in severe acute pancreatitis. This concern was substantiated in a recent interobserver study on the use of the Atlanta definitions for describing peripancreatic collections on CT, which demonstrated very poor agreement between 5 expert radiologists.[13] Currently, an international working group is consulting the members of several international pancreatic associations to reach consensus on a revised classification of acute pancreatitis. It has been formally recognized that this classification should incorporate objective, morphological criteria for describing peripancreatic collections on CT.[10,14]

Extent of **PA**ncreatic **N**on enhancement

☐ none ☐ <30%

☐ 30-50% ☐ >50%

Is there a **CO**llection? (= any fluid more than 'fat stranding')

☐ yes ☐ no

If 'yes', please choose one **DE**scription per question:

Relation with pancreas:
☐ intrapancreatic only
☐ intrapancreatic and adjacent to pancreas
☐ only adjacent to pancreas (no parenchymal perfusion defect)

Encapsulation:
☐ complete
☐ partial
☐ none

Content:
☐ homogeneous
☐ heterogeneous (includ. fat, hemorrhage, loculation and septae)

Mass effect (= displacement of adjacent structures: vessels, organs etc.)

☐ yes ☐ no

Shape: ☐ round or oval ☐ irregular

Loculated gas bubbles: ☐ yes ☐ no

Air-fluid level: ☐ yes ☐ no

FIGURE 4.1. Scoring sheet using the descriptive morphological terms for this study. (The descriptor headings form the acronym PANCODE: **Pa**ncreatic **N**onenhancement, **Co**llection **De**scripition).

Therefore, for the present study, a new set of descriptive, morphological terms were Formulated by an international group of surgeons and radiologists. The objective of this study was to test the interobserver agreement between clinicians (surgeons and gastroenterologists) and radiologists in different parts of the world in reading the same CTs of patients with severe acute pancreatitis using these new morphological descriptors. This study provides data for the ongoing international effort to revise the Atlanta Classification.[14]

METHODS

An international panel of pancreatic surgeons and radiologists designed a scoring sheet with a set of descriptive, morphological terms to classify peripancreatic collections on CT in severe acute pancreatitis (FIGURE 4.1). Definitions for the descriptive terms were not provided, because the aim was to test the interobserver agreement using only the objective, descriptive terminology.

STUDY POPULATION

In order to test the proposed descriptive, morphological terms, contrast-enhanced CTs from patients with predicted severe acute pancreatitis were collected. One experienced radiologist (T.L.B.) reviewed all CTs of 248 patients with predicted severe acute pancreatitis that were included in a Dutch randomised controlled multicentre trial.[16] This study was approved by the independent ethics committees of all 15 participating hospitals and informed consent for participation was obtained from all patients. For each patient, a single radiologist determined the CT severity index (CTSI). The CTSI is an accepted prognostic score quantifying pancreatic and peripancreatic abnormalities.[2,5,17] The greater the score (range 0-10 points), the greater the risk of complications and death.[17] All CTs were high quality, contrast-enhanced and obtained during the portal venous phase. From these 248 patients, 55 CTs were included to cover the entire clinical spectrum of acute pancreatitis, with emphasis on severe disease (i.e., with pancreatic and/or peripancreatic collections). In order to rule out selection bias, CT selection occurred according to the following predefined and reproducible criteria: the last CT before percutaneous drainage or discharge in the first 30 consecutive patients that did not have operative therapy (5 patients with a CTSI of 1-2, 5 patients with a CTSI of 3-4, 5 patients with a CTSI of

5-6, and 15 patients with a CTSI of 7-10), and the last preoperative CT of the first 25 consecutive patients that had operative therapy for infected necrosis (irrespective of CTSI). Median time [interquartile range (IQR)] between admission and CT was 18 (9-32) days. A total of 33/55 patients had infected necrosis as proven by bacterial culture (requiring operative therapy n=25, or only percutaneous drainage n=8). Mortality was 16% (9/55).

PARTICIPATING CENTRES

The following 3 US and 5 European tertiary referral hospitals participated:

- Brigham and Women's Hospital, Harvard Medical School, Boston, Mass., USA
- Mayo Clinic, Rochester, Minn., USA
- University of Washington Medical Center, Seattle, Wash.,USA
- University Medical Center Utrecht, The Netherlands
- Academical Medical Center, Amsterdam, The Netherlands
- Erasmus MC University Medical Center Rotterdam, The Netherlands
- University of Heidelberg, Heidelberg, Germany
- Royal Liverpool University Hospital, Liverpool, UK

Seven gastrointestinal surgeons, 2 gastroenterologists and 8 hepato-pancreato-biliary radiologists acted as blinded reviewers, 1 clinician and 1 radiologist in each centre. In 1 centre (Mayo Clinic), 2 clinicians participated. All reviewers are considered experts in acute pancreatitis. Four of the 17 reviewers (2 radiologists and 2 surgeons) participated in the generation of the scoring sheet. Conversely, 13 reviewers were naïve to the scoring sheet and did not receive any form of training prior to reviewing the CTs for this study.

DATA COLLECTION

Two investigators visited each centre and had separate meetings with the clinicians and radiologists. In a single session, each reviewer evaluated individually the 55 digital CTs using DICOM viewer software (version 3.116, Acculite, San Francisco, Calif., USA) and completed the scoring sheet for each CT (FIGURE 4.1). The investigators briefly explained the scoring sheet and software to the reviewers but did not coach the reviewers during the review process in any way. The reviewers were blinded to

the clinical background and timing of the CT. In the case of multiple collections, the reviewer was asked to describe the most prominent collection. Data from the scoring sheets were entered into a database by 1 investigator and 1 independent data manager, separately. Discrepancies were solved by a third investigator using the original scoring sheets.

DATA ANALYSIS

For each item on the scoring sheet, the distribution (i.e., 20 and 80%) of options (i.e., 'yes' and 'no') within the 55 CTs was assessed for each of the reviewers individually. The median distribution of options (IQR) is shown for radiologists and clinicians separately as well as for all reviewers. Subsequently, the percentage agreement for each scored item was determined. The percentage agreement was defined as the number of reviewer combinations (e.g., reviewer 1 vs. reviewer 2, reviewer 1 vs. reviewer 3) in agreement (i.e., choosing the same option, e.g. collection: 'yes') divided by the total number of possible reviewer combinations (n=153).[18] The percentage agreement was calculated for each of the 55 CTs individually; the median of the percentage agreement (IQR) is shown for clinicians and radiologists separately and for all reviewers. A percentage agreement of 0.91-1.00 was defined as excellent agreement, 0.71-0.90 as good agreement, 0.51-0.70 as moderate agreement and <0.50 as poor agreement. When the percentage agreement was <0.71, an exploratory analysis was performed to assess whether combinations of options resulted in greater agreement. The percentage agreement was compared between clinicians and radiologists using the Wilcoxon signed-rank test. P>0.05 was considered statistically significant.

RESULTS

The distribution of the scored options within the 55 CTs is shown in TABLE 4.1. According to the reviewers, the vast majority of CTs showed pancreatic nonenhancement (84%) with collections (median 96%) that were intrapancreatic and adjacent (78%) to the pancreas. In most of the CTs, the reviewers concluded that the collections were encapsulated (either partially or completely; 88%), heterogeneous (95%), with mass effect (80%) and were irregularly shaped (89%). Loculated gas bubbles were scored in 24% of CTs, while an air-fluid level was deemed present only in 5%

TABLE 4.1. Distribution of the options of the scored descriptive terms within 55 CT scans of patients with predicted severe acute pancreatitis (not interobserver agreement)

Term	Radiologists	Clinicians	All
Extent of pancreatic nonenhancement			
0%	25 (16-29)	12 (7-20)	16 (13-27)
<30	15 (14-19)	23 (15-25)	18 (14-24)
30-50	14 (12-15)	16 (9-20)	15 (11-20)
>50	46 (42-51)	49 (49-53)	49 (44-53)
Presence of collection			
yes	96 (95-99)	95 (91-96)	96 (95-98)
no	4 (1-5)	5 (4-9)	4 (2-5)
If presence of collection 'yes'			
Relation with pancreas			
intrapancreatic only	2 (2-2)	2 (2-2)	2 (2-2)
intrapancreatic and adjacent	75 (70-80)	82 (76-89)	78 (73-84)
only adjacent to pancreas	18 (10-24)	13 (4-15)	15 (13-20)
separate	0 (0-0)	0 (0-2)	0 (0-0)
Encapsulation			
complete	11 (9-20)	15 (5-31)	11 (7-24)
partial	47 (40-52)	38 (33-51)	44 (35-51)
none	35 (26-40)	35 (27-42)	35 (27-42)
Content			
homogeneous	2 (1-4)	2 (0-7)	2 (0-5)
heterogeneous	95 (92-95)	93 (84-96)	95 (89-96)
Mass effect (on adjacent organs/ structures)			
yes	83 (76-91)	75 (58-84)	80 (69-87)
no	13 (4-17)	18 (13-29)	16 (9-29)
Shape			
round/ oval	9 (5-10)	4 (2-11)	9 (2-11)
irregular	89 (85-91)	89 (84-96)	89 (84-93)
Loculated gas bubbles			
yes	24 (23-24)	22 (22-25)	24 (22-24)
no	72 (71-76)	73 (71-75)	73 (71-75)
Air-fluid level			
yes	8 (5-12)	4 (2-5)	5 (4-7)
no	87 (83-93)	91 (91-93)	91 (84-93)

Values are median (IQR) percentages within the 55 CT studies. Percentages may not sum up to 100, because values are medians, and data are missing when the option 'no collection' was chosen.

TABLE 4.2. Percentage agreement among 17 reviewers for scored descriptive terms within 55 CT scans of patients with predicted severe acute pancreatitis (interobserver agreement)

Term	Radiologists	Clinicians	All	P value*
Extent of pancreatic nonenhancement	0.75 (0.46-1)	0.57 (0.44-0.78)	0.60 (0.46-0.88)	0.008
Presence of a collection	1 (1-1)	1 (1-1)	1 (1-1)	0.15
Relation with pancreas	1 (0.75-1)	1 (0.62-1)	1 (0.68-1)	0.55
Encapsulation	0.67 (046-0.75)	0.46 (0.36-0.61)	0.56 (0.48-0.69)	0.001
Content	1 (1-1)	0.78 (0.78-1)	0.88 (0.87-1)	<0.0001
Mass effect	1 (0.71-1)	0.78 (0.50-1)	0.78 (0.62-1)	0.01
Shape	1 (0.75-1)	1 (0.78-1)	1 (0.78-1)	0.39
Loculated gas bubbles	1 (1-1)	1 (1-1)	1 (1-1)	0.24
Air-fluid level	1 (1-1)	1 (1-1)	1 (1-1)	0.06

Values are median (IQR).

*Wilcoxon signed rank test: radiologists vs. clinicians.

A percentage agreement of 0.91-1.00 is excellent agreement; 0.71-0.90 good agreement; 0.51-0.70, moderate agreement; and <0.50 poor agreement.

Similar outcomes (e.g., 1 [1-1]) may not lead to similar P value since the range represents IQR.

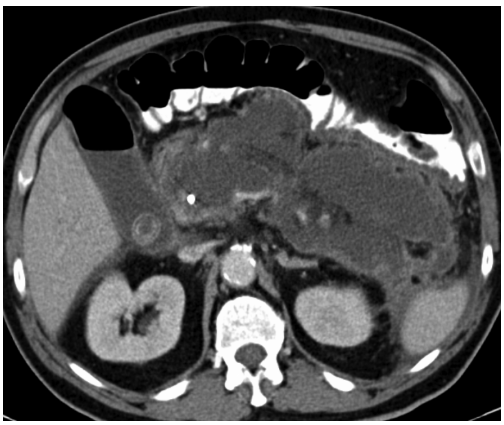

FIGURE 4.2. One of the 55 CT scans reviewed in this interobserver agreement study. The vast majority of reviewers described this CT as >50 pancreatic nonenhancement, with an intrapancreatic and adjacent collection which is encapsulated (either partially or completely), heterogeneous, with mass effect, an irregular shape, and without loculated gas bubbles or an air fluid level.

of CTs. One of the CTs that were reviewed is shown in FIGURE 4.2.

The percentage agreement for the descriptive terms is shown in TABLE 4.2. Agreement among clinicians was excellent for collection, relation, shape, loculated gas bubbles, and air-fluid level; it was good for content and mass effect, moderate for encapsulation and poor for pancreatic nonenhancement. Among radiologists, agreement was excellent for collection, relation, content, mass effect, shape, loculated gas bubbles, and air-fluid level; it was good for extent of pancreatic nonenhancement and moderate for encapsulation. Agreement among all reviewers taken together was good to excellent for all items, except for extent of pancreatic nonenhancement and encapsulation, which were only moderate. However, when in the exploratory analysis the extent of pancreatic nonenhancement option 1 (0%) and option 2 (<30%) were combined, the agreement (median percentage agreement; IQR) was good among all reviewers (0.88; 0.52-1), good among clinicians (0.78; 0.44-1) and excellent among radiologists (1; 0.75-1). When encapsulation option 1 (complete) and option 2 (partial) were combined, the percentage agreement was good among all reviewers (0.78; 0.65-0.88) and clinicians (0.71; 0.56-1), and excellent among radiologists (1.0; 0.69-1). For the extent of pancreatic nonenhancement, encapsulation, content, and mass effect, the percentage agreement was greater among radiologists than among clinicians ($P<0.05$; TABLE 4.2).

DISCUSSION

This multidisciplinary, international interobserver study showed good to excellent interobserver agreement when peripancreatic collections in severe acute pancreatitis were described using a new set of descriptive, morphological terms. This study was a follow-up to a similar interobserver study that showed very poor interobserver agreement for the widely used Atlanta Symposium terminology (e.g., 'pseudocyst', 'pancreatic necrosis', 'pancreatic abscess').[13] In the prior study, 5 experienced radiologists agreed on the Atlanta definition in only 3 of 70 contrast-enhanced CTs.[13] These inconsistent and incongruent interpretations in large part led to the current study, as well as the interest in developing a more accurate classification of acute pancreatitis.[14] The results of the present study demonstrate that, with the new set of terms, it was much easier to obtain objective agreement among all physicians, in contrast to the Atlanta definitions.

Exploratory analysis led to an even greater interobserver agreement. In this analysis, the combination of the first 2 options of encapsulation (complete and partial) and extent of pancreatic nonenhancement (0 and <30%) is acceptable, because the most important clinical differentiations are between (1) no encapsulation and some encapsulation, and (2) no or little nonenhancement (<30%) and substantial nonenhancement (>30%). Notably, in the Atlanta Symposium, pancreatic nonenhancement >30% was not even considered pancreatic necrosis.[8]

Interobserver agreement on several relevant terms was significantly greater among radiologists than surgeons and gastroenterologists. This finding was not unexpected given the noted expertise of radiologists in their field of practice. In contrast, the managing clinicians are best at correlating the radiological findings with the clinical condition in order to determine the appropriate treatment. The current data, therefore, highlight the need for a true, multidisciplinary team approach to severe acute pancreatitis, both in terms of clinical care and research publications.

Why is this study relevant? Accurate multidisciplinary communication regarding CT findings in severe acute pancreatitis is of considerable importance because decisions on treatment depend on adequate radiological interpretation of peripancreatic collections.[1-7,19] The descriptive terms used in this study each have clinical relevance regarding the type and timing of (operative) intervention. For example, the finding of pancreatic necrosis (extent of pancreatic nonenhancement) and collections with peripancreatic fat necrosis (presence of a collection, heterogeneous content, relation with pancreas) would both be treated initially without percutaneous drainage or operative intervention.[1-3,5] When and if secondary infection occurs (loculated gas bubbles), some form of intervention is generally indicated.[1-3.4.19] The content of the peripancreatic collection (homogeneous, air-fluid level) can indicate a collection with a fluid-predominant content, such that percutaneous drainage would be performed initially and, if percutaneous drainage is unsuccessful, followed by operative debridement.[2,3,5,19] The majority of peripancreatic collections, however, tend to resolve without any intervention at all. These include collections referred to by the Atlanta symposium as 'acute fluid collections', i.e. homogenous peripancreatic collections occurring early on in the disease that have not formed any capsule whatsoever and that do not contain gas bubbles or an air-fluid level.[8] Whenever intervention for collections with necrosis does seem necessary, delaying operative

intervention until demarcation (encapsulation) is documented allows easier and safer debridement,[1,2,5,20] possibly by endoscopic or minimally invasive operative techniques.[21-24] Sterile collections causing gastric or biliary obstruction (mass effect) are treated usually by percutaneous or endoscopic therapy.[2,3,5,12,21]

One might wonder whether the radiological diagnoses (i.e., the descriptive terms chosen by the reviewers) in this study really reflect the true morphological features of the peripancreatic collections, because the results of the radiological decisions were not correlated with clinical findings (e.g., operative findings). We explicitly chose not to do this because the aim of this study was merely to determine the interobserver agreement of the descriptive terms, instead of their clinical relevance. The tested terminology is commonly used in daily practice, and it is obvious that all those caring for patients with acute pancreatitis should 'speak the same language'. Although the clinical relevance of the described terms seems obvious, the exact magnitude of that relevance and, therefore, the impact on treatment decisions will need to be the subject of future large prospective studies. It should be noted, however, that the current terminology from the Atlanta Classification is also mostly based on expert opinion, rather than evidence from clinical studies, and is neither used reliably or accurately.[10,13]

A limitation of this study is that Cohen's kappa statistic could not be used because of the substantial imbalance in distributions for the majority of terms (e.g., presence of collection, yes vs. no: 96% vs. 4%; TABLE 4.1). In case of a substantial imbalance in the distribution, kappa values will be very low or even negative, while agreement may still, in fact, be good.[25] In such an event, the kappa statistic becomes meaningless.[25] To present only kappa values for the terms without imbalance was considered not possible because there is no generally accepted cut-off value for defining imbalance. Even though the percentage agreement is not a chance-adjusted measure, the interobserver agreement in the present study was good, given the high values of percentage agreement demonstrated.

Because the reviewers in the present study were from centres renowned for their experience in pancreatic disease, one might question how generalisable are the results to the general community of surgeons and radiologists. It should be noted, however, that the previous interobserver study using the Atlanta definitions between a similar group of expert radiologists showed very poor interobserver agreement,[13]

in contrast to the good to excellent agreement reported in the present study with the new descriptors. Four of the 17 reviewers in the present study were involved in designing the scoring sheet, and one might argue that this introduced bias. However, when these 4 reviewers were excluded from the current analysis the interobserver agreement did not change (data not shown). Our findings are most likely explained by the fact that the majority of the proposed morphological, descriptive terms are used already in daily clinical practice by both clinicians and radiologists and are considered intuitive and relatively easy to use. Nevertheless, despite the strength of the current study it is our intent to direct our next prospective study to further validation of the proposed descriptive, morphological terms and establishing how generalisable they are. In summary, the overall interobserver agreement using the proposed morphological terms when describing peripancreatic collections in severe acute pancreatitis, is good to excellent. This study provides another piece of important data in support of using more objective, descriptive, morphological terms to describe CT findings in acute pancreatitis rather than the subjective Atlanta Symposium terms (e.g., 'pseudocyst', 'pancreatic abscess').

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PART II

Interventions to prevent secondary infectious complications

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PART II

CHAPTER 5

Timing and impact of infections in acute pancreatitis

– a summary –

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INTRODUCTION

Although several studies have addressed the timing of the onset of infected necrosis in acute pancreatitis,[1,2] data on bacteraemia and pneumonia are lacking. The aim of this study was to determine the time of onset of infectious complications in acute pancreatitis; to establish the association between infections (particularly bacteraemia and pneumonia) and death; and to determine the infection rate in patients who died.

METHODS

This was a post hoc analysis of a prospective database of 731 patients with a primary episode of acute pancreatitis included in 15 hospitals of the Dutch Pancreatitis Study Group in 2004-2007. Clinical data were available from a prospective database. All contrast enhanced computed tomography (CT) images were re-read by one experienced radiologist to assess the presence of (peri)pancreatic necrosis and determine the CT severity index.[3]

The presence and time of onset of bacteraemia, infected pancreatic necrosis, pneumonia (including ventilator acquired and that in non-ventilated patients) and persistent organ failure and death were recorded. Mortality rates in patients with mild and severe acute pancreatitis were calculated. The impact of infections was expressed in terms of the percentage of deceased patients with an infectious complication.

Multivariable analysis was used to determine the impact of the different types of infection on mortality. The associations between bacteraemia, risk of necrosis becoming infected and death were also examined.

RESULTS

The clinical outcome of the 731 included patients is summarized in TABLE 5.1. The initial infection in 173 patients was diagnosed a median of 8 (interquartile range 3-20) days after admission (infected necrosis, median day 26; bacteraemia/pneumonia, median day 7). FIGURE 5.1. shows the time of diagnosis of the different types of infection.

Eighty % of 61 patients who died had an infection. The mortality rate was higher in patients with pneumonia (36% vs. 4.8%; P<0.001), bacteraemia (34.6% vs. 3.8%; P<0.001), infected necrosis (30% vs. 5.1%; P<0.001) and pancreatic necrosis (23.4%

TABLE 5.1. Outcome of 731 patients with a first episode of acute pancreatitis

Outcome	No. of patients[a]
Infectious complications (one or more)	173 (23.7)
Infected necrosis	98 (13.4)
Bacteraemia	107 (14.6)
Pneumonia	84 (11.5)[c]
Organ failure	129 (17.6)
Persistent organ failure	115 (15.7)
Multiple organ failure	94 (12.9)
Persistent multiple organ failure	78 (10.7)
Intensive care admission	168 (23.0)
Intensive care stay (days)[b]	11 (3-31)
Hospital stay (days)[b]	12 (7-25)
Severe acute pancreatitis[d]	203 (27.8)
Death	61 (8.3)

a = with percentages in parentheses unless indicated otherwise
b = values are median (interquartile range)
c = including 49 instances of ventilator-acquired pneumonia
d = defined as organ failure and/or pancreatic necrosis

vs. 5.4%; P<0.001) when patients with each specific infection were compared with all other patients in the study.

In 154 patients with pancreatic necrosis, bacteraemia was associated with increased risk of infected necrosis (65% vs. 37.9%; P=0.002). In 98 patients with infected necrosis, bacteraemia was associated with higher mortality (40% vs. 16%; P=0.014), as was pneumonia 40% vs. 21%; P=0.047). In multivariable analysis, persistent organ failure (odds ratio [OR] 18.0), bacteraemia (OR 3.4) and age (OR 1.1) were associated with death.

DISCUSSION

Half of all infections in patients with acute pancreatitis occurred within the first week of admission and bacteraemia was identified as an independent predictor of

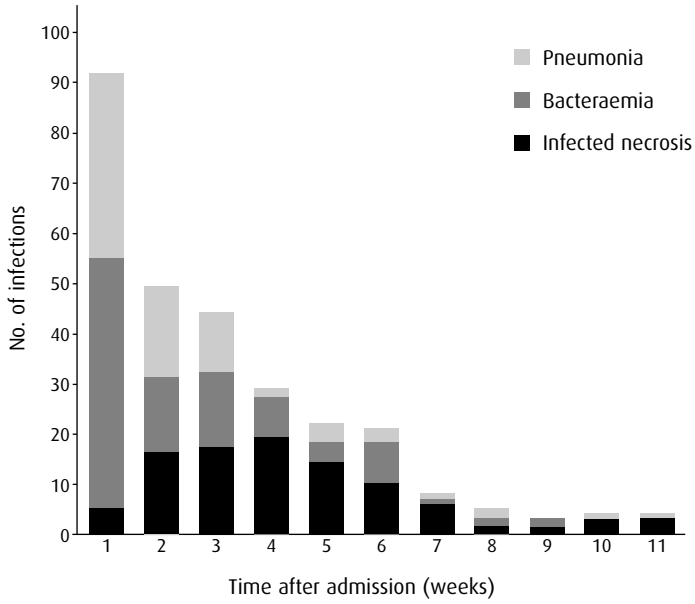

FIGURE 5.1. Time of diagnosis of pneumonia, bacteraemia and infected necrosis in 173 patients during a first episode of acute pancreatitis. A patient with more than one separate infection may be depicted several times (for example bacteraemia in week 1 and infected necrosis in week 4), but only the initial infection is listed if there were multiple infections of the same type (such as bacteraemia in week 1 and in week 3).

death. Bacteraemia was also associated with an increased risk of pancreatic necrosis becoming infected.

The cultured pathogens point to the gut as the source of both bacteraemia and infection of necrosis. The statistical relationship between bacteraemia and infection of necrosis does not automatically imply that the route of infection of necrosis is haematogenous. Theoretically the gut bacteria could also have followed a transperitoneal or lymphatic route, and become cultured from blood and necrotic pancreatic tissue as a manifestation of systemic spread of the gut-derived bacteria.

As it is now clear that infections occur the first few days of acute pancreatitis, and that this has a significant impact on mortality, prophylactic strategies should focus on early intervention.

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PART II

CHAPTER 6

Enteral nutrition and the risk of mortality and infectious complications in patients with severe acute pancreatitis: a meta-analysis of randomised trials

– a summary –

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INTRODUCTION

Animal and human studies suggest that a loss of the gut barrier function is instrumental in the the development of infectious complications during severe acute pancreatitis.[1-3] A protective role of enteral nutrition (EN), compared with parenteral nutritional (PN), in maintaining gut barrier function and reduction of bacterial translocation has been demonstrated in a rat model of acute pancreatitis.[4] These experimental findings, however, have not been convincingly supported by randomised controlled trials. The latest guidelines of the American College of Gastroenterology state that *'it is reasonable to conclude that enteral feeding is safer and less expensive than PN, but there is not yet convincing findings that there are major improvements in morbidity and mortality of acute pancreatitis.'*[5]

We performed a systematic review and meta-analysis to compare the effect of enteral versus parenteral nutrition in patients with severe acute pancreatitis for clinically relevant outcomes.

METHODS

A literature search was performed in the MEDLINE, EMBASE, and Cochrane databases for articles published from January 1, 1966, until December 15, 2006. Full-text articles were included in this systematic review if the title and/or abstract of the article reported **1**. an RCT study design; **2**. a population of patients with predicted severe acute pancreatitis **3**. EN and PN interventions, and **4**. at least 3 of the following outcome variables: total infectious complications, pancreatic infections, need for surgery, non-pancreatic infections, organ failure, and in-hospital mortality.

Information on study design, patient characteristics, and acute pancreatitis outcomes were independently extracted by two investigators using a standardized protocol. The methodological quality of the studies was assessed using the Jadad scoring system (0-5 points).[6]

Meta-analysis for all outcome variables was performed with a random-effects model as the most conservative. The presence of heterogeneity was assessed using the I^2 measure, with an I^2 value greater than 20 indicating marked heterogeneity.

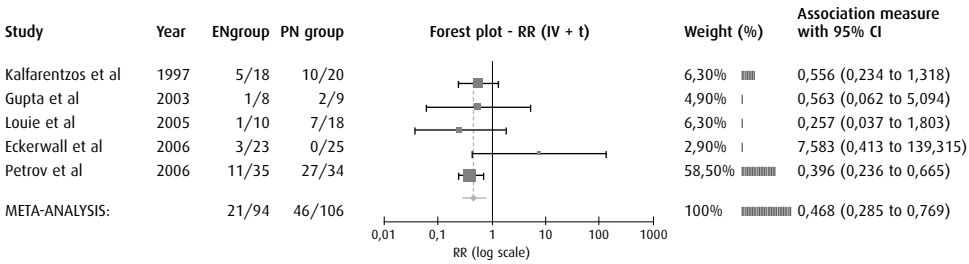

FIGURE 6.1. Forest plot for total infectious complications. CI indicates confidence interval; EN, enteral nutrition; IV, inverse variance; PN, parenteral nutrition; and RR, risk ratio.

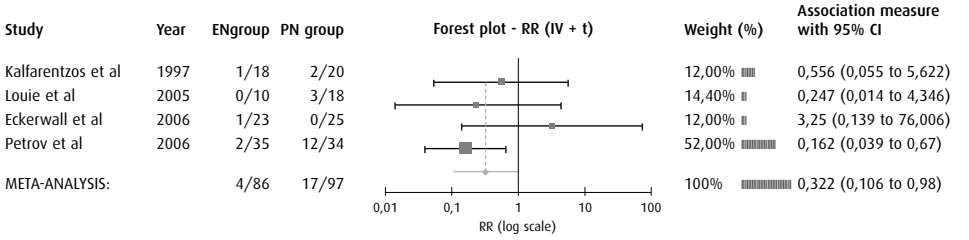

FIGURE 6.2. Forest plot for mortality. CI indicates confidence interval; EN, enteral nutrition; IV, inverse variance; PN, parenteral nutrition; and RR, risk ratio.

RESULTS

From 253 publications screened, 5 randomised controlled trials in which 95 patients were randomly allocated to the EN group and 107 to the PN group, met the inclusion criteria.[7-11] All RCTs reached a Jadad quality score of 3. Outcome of the meta-analysis was as follows: EN reduced the risk of infectious complications (risk ratio [RR], 0.47; 95% confidence interval [CI], 0.28-0.77; P=0.001; I^2=0.00), pancreatic infections (RR 0.48; 95% CI 0.26-0.91; P=0.02; I^2=0.00), need for surgical intervention (RR, 0.37; 95% CI, 0.21-0.65; P=.001; I^2=0.00) and mortality (RR 0.32; 95-% CI 0.11-0.98; P=0.03; I^2=6.43). The risk reduction for organ failure was not statistically significant (0.67; 0.30-1.52; P=0.34; 62.79). Forest plots for total infectious complications and mortality are shown in FIGURES 6.1. and 6.2.

DISCUSSION

This meta-analysis shows that EN, compared with PN, has important beneficial effects in patients with predicted severe acute pancreatitis. However, our study has several potential weaknesses. Variation occurred among the included trials in criteria for predicted severe acute pancreatitis, time of start of feeding, and EN and PN feeding formulas. Variation also occurred among the trials in terms of the location of the feeding tube (i.e., nasogastric vs. nasojeujunal). At the same time, it is unlikely that the difference between nasogastric and nasojejunal feeding would confound the results because two recent trials showed no difference in the outcomes between these approaches.[12,13] By its relatively high weight, the trial from Russia added much information to the meta-analysis of infectious complications and mortality.[9] In contrast to other trials included, the statistical power of this particular study was adequate for these outcomes, whereas no heterogeneity was found among trials in terms of the risk of infectious complications.

Future trials should focus on different aspects of feeding methods, notably, the safety of nasogastric vs nasojejunal delivery of nutrients, the composition of enteral formulations, and the optimal timing for initiation of feeding.

In conclusion, this meta-analysis has demonstrated strong evidence of the benefits of EN over PN in patients with severe acute pancreatitis in terms of clinically relevant and statistically significant reductions in the risk of infectious complications and mortality.

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PART II

CHAPTER 7

Surgical research review: probiotics in surgery

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INTRODUCTION

Postoperative infectious complications, such as sepsis, are usually caused by the patient's own intestinal microbiota.[1] Despite widespread use of perioperative antibiotic prophylaxis, these infections remain a serious problem, causing substantial morbidity associated with high costs. Antibiotic resistance is now a major issue, threatening safety in many surgical wards throughout the world. Therefore, a new array of safe and effective strategies to prevent infection in surgical patients is warranted. With increasing evidence for the role of the patient's own intestinal microbiota in surgical infection, it seems logical that attention has shifted to prophylactic strategies that act where it matters most: the gut. Prophylactic treatment with probiotics might form such a strategy. Probiotics are non-pathogenic bacteria that, on delivery to the host's intestinal tract, can exert health-promoting effects. In the last decade, numerous papers in various fields of medicine have been published on the use of probiotics. It is apparent that this topic is no longer propagated only by a small number of 'believers.' Extensive research on probiotics ranging from basic science to large, well-designed, randomised, controlled trials (RCTs) is being performed currently worldwide. This review provides a brief overview of the proposed mechanism of action of probiotics and current evidence from RCTs, with focus on prevention of infection in surgical patients.

MECHANISM OF ACTION

HOST-BACTERIAL INTERACTIONS

It is only in recent years that we have begun to understand the complex and active interaction between the intestinal microbiota and the biology of the host in whom they reside.[2,3] While the microbial ecosystem in the intestine flourishes on the available nutrients, the host benefits from several key functions fulfilled by more than 1000 different species of bacteria that comprise the intestinal flora. These interactions include a wide range of physiological processes, such as regulation of motility and mucus secretion, prevention of colonization or overgrowth by pathogenic organisms, and regulation of local and systemic immunity. The continuous interaction between bacteria and their host takes place primarily at 3 levels: **1**. the intestinal lumen, **2**. the intestinal epithelium, and **3**. the immune system.[2,3] The suggested levels of host-bacterial interaction are depicted in FIGURE 7.1.

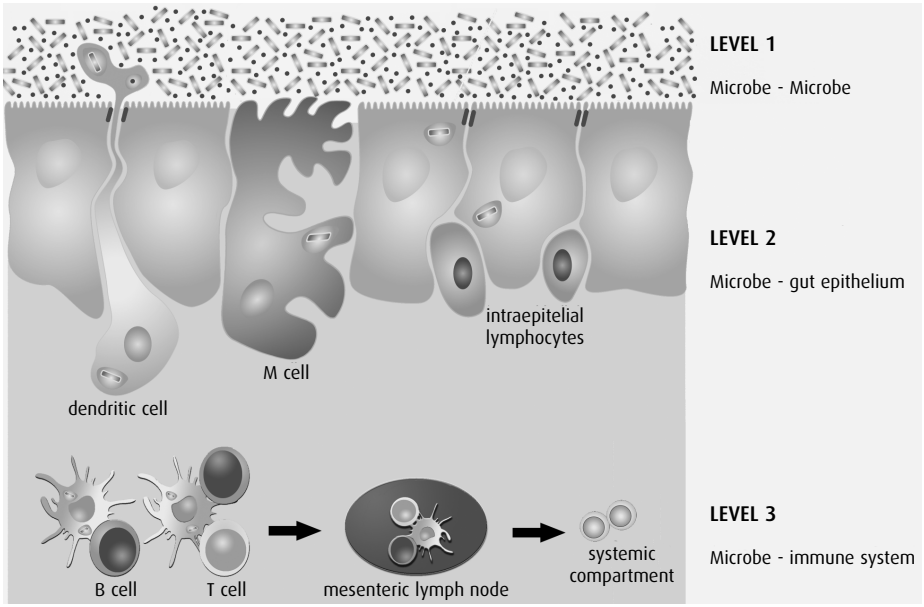

FIGURE 7.1. The interaction between the intestinal micro organisms and their host is thought to take place at 3 levels. **Level 1**: in the intestinal lumen, the microbiota serve several important functions such as digestion of food components and prevention of colonization with pathogenic bacteria. **Level 2**: the mucosal barrier formed by the epithelium lining the intestine serves to protect the sterile interior of the host from invading pathogens. Micro organisms are responsible for local gene regulation in the intestinal epithelium, thereby strengthening the mucosal barrier. The epithelium in turn provides an energy source for certain bacteria. The microbiota exert a local anti-inflammatory effect through cross-talk with local immune cells, preventing uncontrolled mucosal inflammation. **Level 3**: the immune system is also influenced by the intestinal microbiota. Dendritic cells pry open tight junctions of the epithelium to sample luminal content and take up bacteria. This continuous cross-talk between microbiotia and the immune system leads to induction of B- and T-cells with potential systemic immune responses.

BACTERIAL TRANSLOCATION

The pathophysiological mechanism held responsible for infectious complications in surgical and critically ill patients is bacterial translocation: the phenomenon that bacteria cross the gastrointestinal mucosal barrier and invade the systemic compart-

ment.[1] We have reviewed comprehensively the role of bacterial translocation and its potential regulation by probiotics previously.[4]

In short, bacterial translocation is believed to depend on a disturbance at the three levels of hostbacterial interactions. These disturbances observed in experimental and clinical studies in critically ill patients and after major abdominal surgery include: **1**. the intestinal lumen: impaired motility and bacterial overgrowth, **2**. the intestinal epithelium; failure of the structural mucosal barrier leading to increased gut permeability, and: **3**. the immune system; dysregulation of the pro- and anti-inflammatory balance of the immune system. Disturbances at these levels affect each other reciprocally, leading to a vicious circle resulting in bacterial translocation and infectious complications. In addition to disturbances of host-bacterial interactions, several other factors associated with critical illness and major abdominal surgery, such as intestinal ischaemia, immunosuppression, nutrient deprivation, and stress add further to the problem of bacterial translocation.

ROLE OF PROBIOTICS

Many investigations have suggested that probiotics prevent bacterial translocation and subsequent infectious complications through a beneficial effect at all three levels of the host-microbial interaction. In the intestinal lumen, specific probiotic strains prevent bacterial overgrowth of potential pathogens by direct antimicrobial effects (such as lactic acid production) and competitive growth.[5] In a rat model of acute pancreatitis, a multispecies probiotic mixture decreased bacterial overgrowth, with subsequent reduction in bacterial translocation, morbidity, and mortality.[6] At the level of the intestinal epithelium, specific probiotic strains preserve or reinforce the mucosal gastrointestinal barrier function through several mechanisms: prevention of bacterial adherence to the epithelial lining by competitive exclusion, inhibition of pathogenic-induced alterations of epithelial permeability, and regulation of enterocyte gene expression involved in maintenance of the mucosal barrier.[7,8] Moreover, specific probiotics strains inhibit the local pro-inflammatory reactions in enterocytes after stimuli such as pathogenic bacterial adhesion or ischaemia/ reperfusion injury.[7,8] Besides the local immunomodulatory effect in the intestinal epithelium, probiotics are also thought to exert a regulatory effect on the systemic immune system through several different pathways. In vitro, selected probiotic strains can

induce production of the anti-inflammatory cytokine interleukin (IL) 10 by monocytes and lymphocytes.[9] In clinical studies, probiotics decreased the production of pro-inflammatory cytokine IL-6 after abdominal surgery.[10] Moreover, through modulation of dendritic cells, probiotics can induce development of regulatory T cells, which play an important role in controlling inflammation.[11]

CURRENT EVIDENCE FROM RANDOMISED CONTROLLED TRIALS

Several RCTs on probiotics in surgical patients have been published in recent years. A summary and the references to these trials are provided in TABLE 7.1. Various studies have aimed at decreasing infection by application of pre- and/or postoperative regimes of different species of probiotics. Several RCT have used so-called "prebiotics" in addition to probiotic strains. Prebiotics are non-digestible fiber supplements (mostly oligosaccharides) that are meant to act as "fuel" for probiotics and other beneficial intestinal bacteria. Products that combine pre- and probiotics are called 'synbiotics'.

From the 14 RCTs listed in TABLE 7.1., 9 studies showed a significant decrease of total infectious complications in the patients treated with probiotics, but 5 studies could not demonstrate such an effect.

Rayes, et al.[12] were the first to perform an RCT of probiotic-prophylaxis in surgical patients. Ninety patients undergoing 'major abdominal surgery' were randomised to **1**. standard regimen (enteral or parenteral feeding), **2**. synbiotics, or **3**. prebiotics and heat-killed probiotics. Groups 2 and 3 also received enteral feeding. Bacterial infections were decreased significantly in the groups that had synbiotics, although it did not seem to matter whether the probiotics were viable or non-viable (heat-killed). The same German group then conducted two other placebo-controlled trials in patients undergoing liver transplantation (n=95 and n=66) in which they compared two different type of symbiotic mixtures with enteral nutrition and selective bowel decontamination (antibiotics) or enteral nutrition and prebiotics only.[13,14] In both studies, the symbiotic mixture decreased significantly the postoperative infection rate, and also when compared with selective bowel decontamination. Most recently, the same authors completed a trial in patients undergoing pylorus preserving pancreatoduodenectomy (PPPD); 89 patients were randomised to receive **1**. synbiotics

TABLE 7.1. Summary of randomised controlled trials on probiotic prophylaxis in surgical patients

1st author	Patients	Time of intake	Study arms	Route administrated	Results: total infections
Rayes N[12] (2002) Not DB, PC	Major abdominal surgery, n=90	4 days postop.	1) Probiotics + enteral feeding 2) Heat killed probiotics + enteral feeding 3) Total parenteral nutrition + enteral feeding	Nasojejunal tube	Group 1: 10% Group 2: 10% Group 3: 30% P=0.01
Rayes N[13] (2002) Not DB, PC	Liver transplantation, n=105 (n= 95 NITT)	7 days postop.	1) Synbiotics + enteral feeding 2) Heat killed probiotics + prebiotics + enteral feeding 3) Selective bowel decontamination (antibiotics) + enteral feeding	Nasojejunal tube	Group 1: 13% Group 2: 34% Group 3: 48% P=0.017
Olah[16] (2002) DB, PC	Acute pancreatitis, n=50 (n=45 NITT)	7 days post admission	1) Synbiotics + enteral feeding 2) Heat killed probiotics + prebiotics + enteral feeding	Nasojejunal tube	Group 1: 5% Group 2: 30% P=0.023
McNaught[21] (2002) Not DB, Not PC	Major abdominal surgery, n=129	Median 9 days preop., median 5 days postop.	1) Probiotics 2) Standard treatment	Oral	Group 1: 13% Group 2: 15% P=0.74
Jain[22] (2004) DB, PC	Critically ill, n=90	Median 10 days during ICU admission	1) Synbiotics 2) Powdered sucrose	Oral or nasogastric tube	Group 1: 73% Group 2: 58% P=0.120
Anderson[23] (2004) DB, PC	Major abdominal surgery, n=137	Median 12 days preop., median 5 days postop.	1) Synbiotics 2) Placebo capsules + powdered sucrose	Oral	Group 1: 31% Group 2: 32% P=0.882
Rayes N[14] (2005) DB, PC	Liver transplantation, n=66	14 days postop.	1) Synbiotics + enteral feeding 2) Prebiotics + enteral feeding	Nasojejunal tube	Group 1: 3% Group 2: 48% P<0.05
Kanazawa[18] (2005) Not DB, not PC	Liver and extrahepatic bile duct resection for biliary cancer, n=54 (n=44 NITT)	14 days postop.	1) Synbiotics + enteral feeding 2) Enteral feeding	Intraoperative jejunal feeding catheter	Group 1: 19% Group 2: 52% P<0.05

1st author	Patients	Time of intake	Study arms	Route administrated	Results: total infections
McNaught[24] (2005) DB, PC	Critically ill, n=103	Median 9 days postop.	1) Probiotics 2) Standard treatment	Oral or nasogastric tube	Group 1: 40% Group 2: 43% P>0.05
Kotzampassi[19] (2006) DB, PC	Severe multiple trauma, n=77 (n=65 NIIT)	15 days during ICU admission	1) Synbiotics + enteral feeding 2) Powedered glucose + enteral feeding	Endoscopic gastrostomy tube or nasogastric tube	Group 1: 63% Group 2: 90% P=0.01
Sugawara[10] (2006) Not DB, Not PC	Liver and extrahepatic bile duct resection, n=101 (n=81 NIIT)	*Group 1*: 14 days preop. 14 days postop. *Group 2*: 14 days postop.	1) Synbiotics + enteral feeding (only postop.) 2) Synbiotics + enteral feeding	Oral (preoperative) and intraoperatively placed jejunal feeding catheter (postop.)	Group 1: 12% Group 2: 30% P=0.049
Olah[17] (2007) DB, PC	Severe acute pancreatitis, n=83 (n=62 NITT)	Minimum of 7 days post admission	1) Synbiotics + enteral feeding 2) Prebiotics + enteral feeding	Nasojejunal tube	Group 1: 12% Group 2: 28% P>0.05
Spindler-Vesel[20] (2007) Not DB, Not PC	Severe multiple trauma n=130 (n=113 NITT)	During ICU admission; intake period not stated	1) Synbiotics + enteral feeding 2) Glutmamine enriched feeding 3) Fiber enriched feeding 4) Peptide enriched feeding	Nasogastric tube	Group 1: 15% Group 2: 50% Group 3: 59% Group 4: 50% P=0.021
Rayes[15] (2007) DB, PC	Pylorus-preserving pancreatoduo- denectomy, n=89 (n=80 NITT)	1 day preop. - 8 days postop.	1) Synbiotics + enteral feeding 2) Prebiotics + enteral feeding	Oral (preop.) Nasojejunal tube (postop.)	Group 1: 13% Group 2: 40% P=0.005

DB= double blinded
PC= placebo controlled
NITT= no intention to treat analysis

or **2**. prebiotics only.[15] After exclusion of 9 patients that did not undergo PPPD because the neoplasm was non-resectable, the incidence of postoperative infections was significantly less in the group receiving synbiotics.

Olah et al.[16] studied patients with acute pancreatitis, a disease characterised by a severe clinical course with the potential for secondary pancreatic infection due to bacterial translocation. In their first placebo-controlled RCT they randomised 45 patients with acute pancreatitis to **1**. synbiotics or **2**. prebiotics and heat-killed probiotics. A significant decrease in pancreatic infections was shown in group 1. This trial was criticized for its methodology: patients with biliary etiology of acute pancreatitis were excluded and patients not tolerating jejunal feeding were excluded from the final analysis. The authors then conducted a second study with a randomised double-blind design on patients with severe acute pancreatitis.[17] Although the methodology was substantially improved, it still lacked an intention-to-treat analysis. Infectious complications tended to be less in the synbiotics group compared to the control group, but were not statistically significant. Conversely, a significant decrease in the combination of systemic immune response syndrome and multi-organ failure, and of the number of patients recovering with complications, was observed in the treatment group.

Kanazawa, Sugawara, and colleagues[10,18] performed two RCTs in patients undergoing hepatobiliary resection for biliary cancer to study the effect of synbiotic treatment on intestinal permeability, immune response, the microbiota and surgical outcome. In the first study, 54 patients were randomised for postoperative treatment with **1**. enteral feeding with synbiotics or **2**. enteral feeding only.[18] After exclusion of the non-resectable patients (n=10) the incidence of total complications was decreased significantly in the synbiotics group. The second RCT was conducted to assess whether the addition of preoperative synbiotics, as opposed to only postoperative treatment, would further enhance the beneficial effect.[10] Of the 101 randomised patients, 20 were excluded from analysis because they had non-resectable cancer. In the remaining 81 patients, infectious complications were significantly less in the group treated with both a pre- and postoperative regime of synbiotics compared with postoperative treatment only. This trial also showed an enhanced preoperative immune response (greater natural killer cell activity) and decreased postoperative inflammatory response (less IL-6 levels, white blood cell count, and C-reactive pro-

tein) in the patients treated both preand postoperatively. In the study by Kotzampassi et al.,[19] 77 consecutive patients with severe multi-system trauma were randomised to receive **1**. a synbiotic formula or **2**. placebo (glucose only). In the 65 surviving patients, the total infection rate and incidence of sepsis was significantly less in the synbiotics group. In a second RCT in patients with severe multisystem trauma performed recently by Spindler-Vesel et al.,[20] 113 patients were randomised to either **1**. glutamine-enriched feeding, **2**. fiber-enriched feeding, **3**. peptide-enriched diet, or **4**. synbiotics with enteral feeding. Patients with synbiotics had the least infection rate. Four RCTs have been performed by the Combined Gastroenterology research unit from Scarborough General Hospital in the UK.[21-24] These RCTs in patients undergoing major abdominal surgery or with critical illness did not show a positive effect of probiotics in terms of decreasing infectious complications. This group used different probiotic strains than the other RCTs, and administration was mostly oral, rather than through an enteral feeding tube. Notably, these RCTs were very well-designed but had primary outcome measures such as bacterial translocation or gastric colonization rather than clinical endpoints.

FUTURE CHALLENGES

The trials summarized in TABLE 7.1. show conflicting results. It should be noted that methodological quality varied greatly between studies; issues such as the lack of 'intention-to-treat analysis,' post-hoc subgroup analyses, and endpoint definitions probably influenced the results to a considerable extent. Several other factors may explain the observed differences. Different probiotic species exert different effects on the three levels of the host-microbial interaction (FIGURE 7.2), and considerable variation was present in the probiotic species used among RCTs. Moreover, multi-species probiotic preparations seem to be more effective than mono-species preparations. The use of prebiotics might enhance the effect of probiotics and may even be a prerequisite for clinical efficacy of some probiotics strains. Enteral feeding, as administered in some RCTs, can also be considered a prebiotic. The route of administration may also be important, because some probiotic strains may not survive the acidic environment of the stomach. The timing of start of treatment (pre- and/or postoperative) and the duration of treatment varied between trials and may also important. Finally, patient populations were different across the various studies. It is

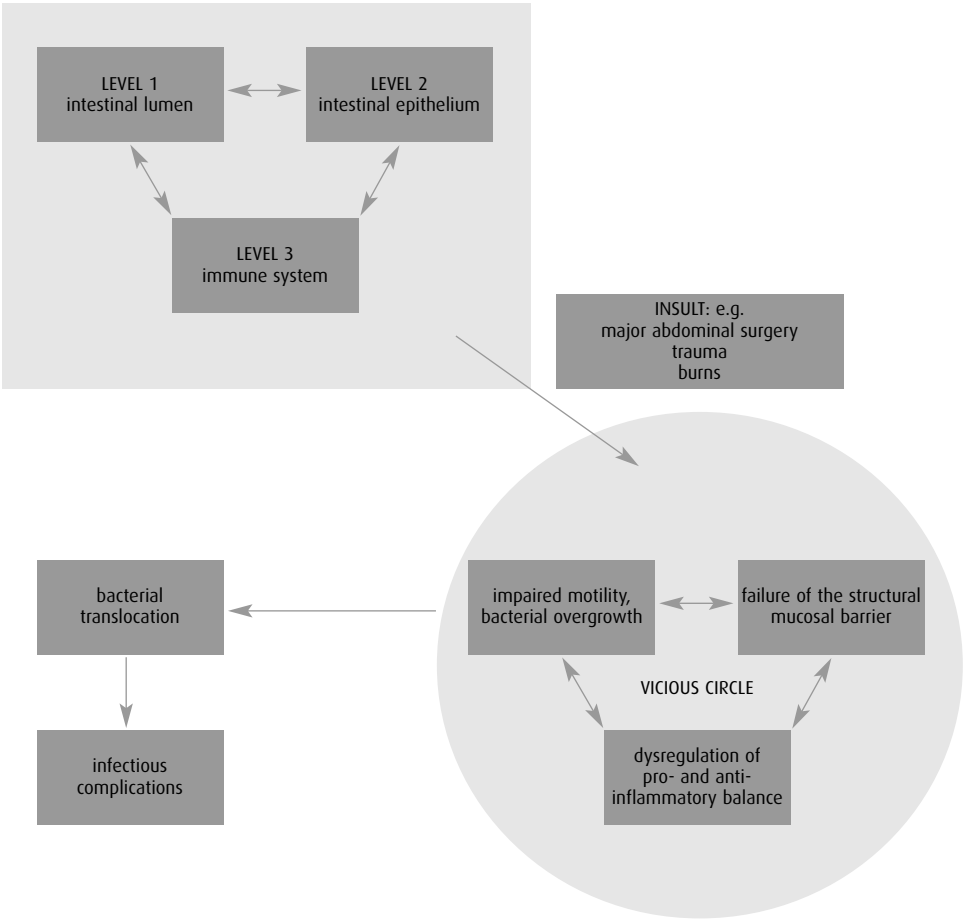

FIGURE 7.2. A hypothetic model of the disturbances at the 3 levels of the host-microbial interaction. An insult, such as major abdominal surgery, can lead eventually to bacterial translocation with subsequent infectious complications.

reasonable to assume that in a homogeneous group of patients with relatively high risk of post-operative infections, such as patients undergoing PPPD or liver transplantation, a prophylactic treatment with probiotics is more effective than in other, more heterogeneous populations of surgical patients with less risk of post-operative infections. The pathogenesis of infection may also vary between study populations. In patients undergoing elective operations, preoperative treatment with probiotics is possible, thus applying 'true' prophylaxis. Conversely, in patients with more acute

conditions, such as pancreatitis and trauma, bacterial translocation may have occurred already when the probiotic therapy is instituted; thereby, the probiotic is no longer acting as prophylactic treatment. In the near future, more basic and clinical research must be performed to study the influence of these different factors and to elucidate the mechanism(s) of action and true effect on clinically relevant outcomes of probiotics. Before probiotics can be implemented in daily practice to prevent infectious complications in general surgical patient populations, evidence for their efficacy must be obtained in these patient categories first. Very large sample sizes would be needed to have adequate power to detect effects of probiotics in decreasing the risk of clinically relevant endpoints such as mortality. In an attempt to collect such evidence, the Dutch Acute Pancreatitis Study Group is conducting a nationwide double-blind RCT currently in patients with acute pancreatitis.[25] A total of 298 patients with predicted severe acute pancreatitis (according to accepted predictive criteria) are randomised to receive enteral feeding trough a jejunal tube with **1**. a multispecies probiotic preparation or **2**. a placebo. Results will be available in 6 months.

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PART II

CHAPTER 8

Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial

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ABSTRACT

BACKGROUND

Infectious complications and associated mortality are a major concern in acute pancreatitis. Enteral administration of probiotics could prevent infectious complications, but convincing evidence is scarce. Our aim was to assess the effects of probiotic prophylaxis in patients with predicted severe acute pancreatitis.

METHODS

In this multicentre randomised, double-blind, placebo-controlled trial, 298 patients with predicted severe acute pancreatitis (Acute Physiology and Chronic Health Evaluation [APACHE II] score ≥8, Imrie score ≥3, or C-reactive protein >150 mg/L) were randomly assigned within 72 h of onset of symptoms to receive a multispecies probiotic preparation (n=153) or placebo (n=145), administered enterally twice daily for 28 days. The primary endpoint was the composite of infectious complications - i.e. infected pancreatic necrosis, bacteraemia, pneumonia, urosepsis, or infected ascites - during admission and 90-day follow-up. Analyses were by intention to treat. This study is registered, number ISRCTN38327949.

RESULTS

One person in each group was excluded from analyses because of incorrect diagnoses of pancreatitis; thus, 152 individuals in the probiotics group and 144 in the placebo group were analysed. Groups were much the same at baseline in terms of patients' characteristics and disease severity. Infectious complications occurred in 46 (30%) patients in the probiotics group and 41 (28%) of those in the placebo group (risk ratio, 1.06; 95% CI 0.75-1.51). 24 (16%) patients in the probiotics group died, compared with nine (6%) in the placebo group (risk ratio, 2.53; 95% CI 1.22-5.25). Nine patients in the probiotics group developed bowel ischaemia (eight with fatal outcome), compared with none in the placebo group (P=0.004).

CONCLUSION

In patients with predicted severe acute pancreatitis, probiotic prophylaxis with this combination of probiotic strains did not reduce the risk of infectious complications and was associated with an increased risk of mortality. Probiotic prophylaxis should therefore not be administered in this category of patients.

INTRODUCTION

The incidence of acute pancreatitis in Europe and the USA is increasing by about 5% per year, mainly owing to an increase in biliary pancreatitis.[1-3] About a fifth of patients will develop necrotising pancreatitis, which is associated with a 10-30% mortality rate, mostly attributed to infectious complications and infection of (peri)pancreatic necrotic tissue in particular.[1] These infections are thought to be the sequelae of a cascade of events starting with small-bowel bacterial overgrowth, mucosal barrier failure, and a pro-inflammatory response leading to bacterial translocation of intestinal bacteria.[4-6] Systemic antibiotic prophylaxis has long been studied as a measure to prevent secondary infection in acute pancreatitis.[1] However, two double-blind, placebocontrolled trials[7,8] and two meta-analyses[9,10] have failed to show a beneficial effect, and many clinicians have abandoned this strategy. In the two antibiotic trials, the incidence of extrapancreatic infections (e.g., bacteraemia, pneumonia) and pancreatic infection remained high.[7,8] Consequently, there is a clear need for other strategies to prevent infectious complications in patients with acute pancreatitis.

Probiotics, as an adjunct to enteral nutrition, have raised high expectations and are currently gaining worldwide popularity for their presumed health-promoting effects.[11,12] Certain strains of probiotic bacteria might prevent infectious complications by reducing small-bowel bacterial overgrowth, restoring gastrointestinal barrier function, and modulating the immune system.[11,12] A reduction of infectious complications has been reported in several clinical studies with probiotics in patients undergoing elective abdominal operations[13,14] and in patients with acute pancreatitis.[15] However, because of their small size and methodological quality, these studies do not justify global implementation of probiotics as a preventive measure in acute pancreatitis. Accordingly, we embarked on a nationwide multicentre randomised, double-blind, placebocontrolled trial - the PRObiotics in PAncreatitis TRIAl (PROPATRIA) - to assess the effects of probiotic prophylaxis in patients with predicted severe acute pancreatitis.

METHODS

PATIENTS

The design and rationale of the study have been described in detail elsewhere.[16] Adult patients admitted with a first episode of acute pancreatitis were enrolled in eight university medical centres and seven major teaching hospitals in the Netherlands. Acute pancreatitis was defined as abdominal pain in combination with serum amylase or lipase concentrations that were raised to at least three times the institutional upper limit of normal. Patients were not enrolled in the study if any of the following criteria were present: pancreatitis after endoscopic retrograde cholangiopancreaticography; suspected malignancy of the pancreas or biliary tree; non-pancreatic infection or sepsis caused by a second disease; diagnosis of pancreatitis first made at operation; or a medical history of immune deficiency. Patients with acute pancreatitis and an Acute Physiology and Chronic Health Evaluation (APACHE II) score of 8 or more,[17] Imrie/modified Glasgow score of 3 or more,[18] or C-reactive protein over 150 mg/L,[19] predicting a severe course of disease, were eligible for randomisation. All patients or their legal representatives gave written informed consent. This study was investigator-initiated and investigator-driven and done in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines. The institutional review board of each participating hospital approved the protocol.

PROCEDURES

Randomisation was done with a computer-generated permuted-block sequence and balanced by participating centre and by presumed cause (biliary vs. non-biliary) in blocks of four. Patients were randomly assigned to receive either a multispecies probiotic preparation or a placebo twice daily at the first possible occasion, but no later than 72 h after onset of symptoms of pancreatitis.

The study was double-blinded. Both the probiotic and placebo preparations were packaged in identical, numbered sachets that were stored in identical, numbered containers. The study product and placebo were both white powders, identical in weight, smell, and taste. All doctors, nurses, research staff, and patients involved remained unaware of the actual product administered during the entire study period. An independent monitoring committee was informed in cases of serious adver-

se events that were possibly associated with the study product. At the time of a prespecified interim analysis,[16] the monitoring committee advised about whether to continue the trial.

The rationale for the design of the multispecies probiotic preparation has been described in detail elsewhere.[20] In brief, the study product (*Ecologic 641*, Winclove Bio Industries, Amsterdam, Netherlands) consisted of six different strains of freeze-dried, viable bacteria: *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius, Lactococcus lactis*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis* (previously classified as *Bifidobacterium infantis*), in a total daily dose of 10^{10} bacteria, plus cornstarch and maltodextrins. The individual probiotic cultures are sold by major probiotic producers as ingredients for probiotic supplements or dairy food and carry the European Union qualified presumption of safety (QPS). Individual strains were selected on the basis of their capacity to inhibit growth of pathogens most often cultured from infected necrotising pancreatitis in vitro.[20,21] Probiotic species that were ever reported to have been associated with an infectious complication, irrespective of underlying disease, were excluded.[20] Placebo sachets contained only cornstarch and maltodextrins. Both the probiotic and placebo preparations were checked according to national regulations for any contamination with known pathogens and for the presence of endotoxins. Three different batches of probiotics and placebo were produced, tested, and used during the study.

After randomisation, each patient had a nasojejunal feeding tube inserted. The study product or placebo was administered twice daily and added to the continuously running fibre-enriched tube feeding (Nutrison Multi Fibre, Nutricia, Zoetermeer, Netherlands). The study product or placebo was dissolved in sterilised distilled water and administered for a maximum of 28 days. If placement of the nasojejunal tube was delayed for more than 12 h, the first dose of the study product or placebo was taken orally. Nasojejunal tubes were placed either by upper gastrointestinal endoscopy or under fluoroscopic guidance. When nasojejunal tubes became blocked or were pulled out, a new tube was re-inserted at the first possible opportunity, generally within 24 h. The amount of tube feeding was gradually increased over the first days with an energy target of 125 kJ/kg (up to 90 kg) on day 4 after start of enteral nutrition. When patients started oral intake, the nasojejunal tube was removed and the study product or placebo was dissolved in tap water and ingested orally for

PANEL Definitions included in the primary endpoint

Infected pancreatic necrosis	positive culture of peripancreatic fluid or pancreatic necrosis obtained by either fine-needle aspiration, during the first percutaneous drainage, or during the first surgical intervention
Bacteraemia	positive blood culture. For non-pathogens (e.g., coagulase-negative staphylococci) at least two samples had to be positive
Pneumonia	coughing, dyspnoea, chest film showing infiltrative abnormalities, lowered arterial blood gas with positive sputum culture. If in intensive care, a positive endotracheal culture is mandatory
Urosepsis[a]	dysuria with bacteraemia on the same day, without a urinary catheter in situ
Infected ascites[b]	bacteria detected in aspirate of intraperitoneal fluid or abdominal fluid sampled during surgical exploration

a= Before any analysis, the adjudication committee restricted the definition of urinary tract infection to urosepsis.
b= Before any analysis, the adjudication committee added this group of infections to the infectious complications endpoint.

the remainder of the 28 days. Administration of the study product or placebo was stopped when a patient was diagnosed with infected pancreatic necrosis. Patients discharged before 28 days were only allowed to stop treatment if CT showed the absence of pancreatic necrosis or fluid collection. During the study, patients were not allowed to use any commercially available product containing probiotics. During administration of the study product or placebo, nursing staff recorded the number of sachets administered and registered any potential side-effect (e.g., abdominal complaints).

Antibiotic prophylaxis was not given routinely in patients with necrotising pancreatitis. The use of antibiotics was recorded, irrespective of indication. When endoscopic retrograde cholangiopancreaticography was indicated in cases of biliary pancreatitis, antibiotic prophylaxis was allowed. A standard baseline (intravenous) contrast-enhanced CT scan was done 7 days after admission to detect pancreatic necrosis. One experienced radiologist (TLB), unaware of treatment allocation, re-read all CT scans to assess the CT severity index.[22] In cases of a clear clinical diagnosis of infected (peri)pancreatic necrosis (persistent fever and clinical deterioration in the third or fourth week of disease in the presence of documented necrosis or air bub-

bles in the collections with necrosis on CT, while other sources of infection were absent), fine-needle aspiration of (peri)pancreatic collections was not mandatory to confi rm the clinical suspicion. A positive culture was mandatory for the endpoint of infected necrosis. During surgical intervention or percutaneous drainage for (suspected or documented) infected necrosis, tissue or fluid samples were sent for routine microbiological assessment. Body temperature was measured at least twice daily and, in cases of fever, blood cultures were drawn. Further diagnostic and therapeutic measures were left to the treating clinicians' discretion.

The primary endpoint was the composite of any of the following infectious complications: infected pancreatic necrosis, bacteraemia, pneumonia, urosepsis, or infected ascites, during admission and 90-day follow-up (PANEL). All infections were weighted equally; multiple infections in the same patient were deemed to be one endpoint. Secondary endpoints (during admission and 90-day follow-up) were mortality, sequential organ failure assessment (SOFA) scores, (multi)organ failure during admission, onset of (multi)organ failure after randomisation, need for surgical intervention because of (documented or suspected) infected necrosis or intra-abdominal catastrophe, hospital stay, intensive-care stay, use of antibiotics, and abdominal complaints (nausea and abdominal fullness with visual analogue scales [VAS; cutoff 3.0 on a ten-point scale], and presence of diarrhoea as assessed by the patient [at days 5, 10, 14, 21, 28, and 35]). Per patient, the percentage intake of the study product or placebo was calculated and categorised as less than 80%, 80-89%, 90-95%, and over 95%. Microbiological data of the initial positive culture for each of the infectious complications of the primary endpoint were collected.

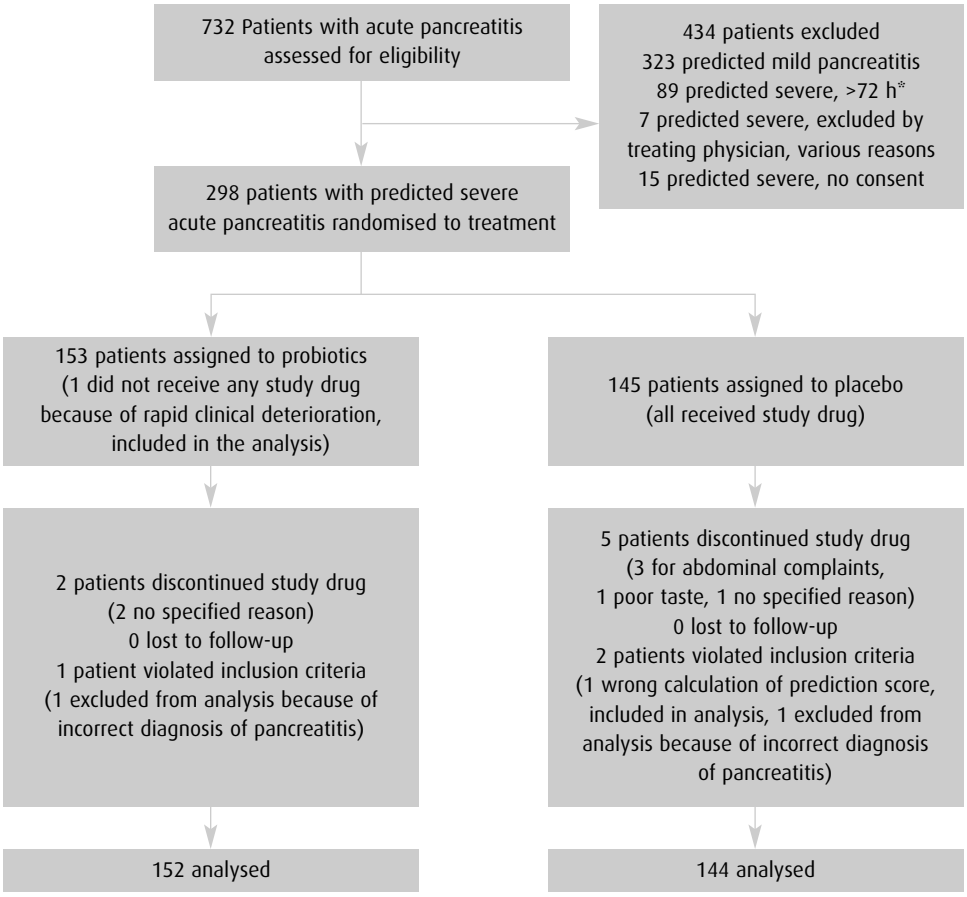
Organ failure was defined as PaO2 below 60 mm Hg despite FIO2 of 30% or the need for mechanical ventilation (pulmonary insufficiency), serum creatinine over 177 mmol/L after rehydration or need for haemofiltration or haemodialysis (renal failure), and systolic blood pressure below 90 mm Hg despite adequate fluid resuscitation or need for vasopressor (mainly noradrenalin and dopamine) support (cardiocirculatory insufficiency), adapted from the Atlanta Classification.[23] Multiple organ failure was defined as failure of at least two organ systems on the same day. Organ failure before randomisation was defined as any organ failure that started before the day of randomisation. Because the administration of the study product or placebo could start at any time during the day of randomisation, start of organ fai-

lure on that day was left out of this definition. Onset of organ failure after randomisation was defined as initial (for the first time) onset of organ failure after the day of randomisation.

Data collection was done by local physicians, who completed case record forms. During the study an independent data monitor checked at least 10% of the individual patients' data against the primary source data, on site in the participating centres. After completion of the follow-up of the last patient but before any analysis or unblinding, two authors (MGHB and HCvS) checked all primary and secondary endpoints on site with primary source data. Before any analysis and without knowledge of treatment allocation, the blinded adjudication committee judged all exclusions, endpoints that were not fully specified in the protocol in individual patients, and serious adverse events. Only after agreement was reached on all endpoints were analyses done with blinding of the products administered preserved. After the results of the blinded analyses were presented to the monitoring committee, the randomisation code was broken on Oct 26, 2007.

STATISTICAL ANALYSIS

We calculated that 200 patients with predicted severe acute pancreatitis would be required to detect a 20% reduction in the absolute risk of the occurrence of infectious complications (from 50% to 30% of patients during admission and 90-day follow-up) for the study to attain an 80% statistical power, at a two-sided α of 0.05. This sample size calculation took into account the fact that up to 40% of patients with predicted severe pancreatitis are ultimately diagnosed with mild pancreatitis (i.e., no local or systemic complications) and thus do not progress to severe or necrotising pancreatitis. After the first 100 patients were randomised and had completed follow-up, the number of infectious complications was calculated in the total group of randomised patients without unblinding the data. The rate of infectious complications was lower than expected (28%), so the monitoring committee advised increasing the total sample size from 200 to 296 patients to maintain statistical power. After 184 patients had been randomised and had completed follow-up, a blinded interim analysis was done for the primary endpoint and mortality. Although a non-significant difference in mortality was observed (P=0.10), the monitoring committee concluded that this had been caused by skewed randomisation because more



*Not randomised because of clinical symptoms of pancreatitis for more than 72 h at time of diagnosis of predicted severe acute pancreatitis. Patients were either initially missed for randomisation, were transferred from other hospitals more than 72 h after onset of symptoms, or already had complaints for more than 72 h on admission.

Figure 8.1. Trial profile

patients in the group with higher mortality required admission to intensive care within 72 h after admission (P=0.15), whereas the overall mortality was well within the expected range (11%). According to the predefined stopping rule[16] the monitoring committee recommended that the study should be completed.

All data analyses were done in accordance with a pre-established analysis plan. The incidence of the primary endpoint was compared between the groups and the results are presented as risk ratio with exact 95% CI. The Kolmogorov-Smirnov test

was used to assess whether continuous data were normally distributed (P>0.05). For continuous variables, differences between groups were tested with Student's *t* test for normally distributed data or Mann-Whitney *U* test for non-normally distributed data. Fisher's exact test was used for proportions in all cases. In cases of significant difference in the incidence of either the primary endpoint or mortality between groups, Kaplan-Meier curves with log-rank tests were generated.

All analyses were done on the basis of the intention-to-treat principle. Prespecified subgroup analyses were done for cause of pancreatitis and for presence of pancreatic parenchymal necrosis. We used logistic regression models to do a formal test for interaction to assess whether treatment effects differed significantly between these subgroups. A two-sided P value of less than 0.05 was deemed to be statistically significant. All statistical analyses were done with SPSS (version 12.0.1).

ROLE OF THE FUNDING SOURCE

The sponsor of the study had no role in the study design, data collection, data analysis, interpretation of the study results, or writing of the manuscript. The corresponding author had full access to all the data and coordinated the decision to submit for publication.

RESULTS

732 consecutive patients with a first episode of acute pancreatitis were registered prospectively between March, 2004, and March, 2007 (Figure 8.1). 298 patients were predicted to have a severe disease course (135 patients with APACHE II score ≥8, 204 with Imrie score ≥3, 252 with C-reactive protein >150 mg/L), and were randomly assigned treatment with probiotics or with placebo (FIGURE 8.1). Two patients - one in each group - were excluded from the final analysis because of an incorrect diagnosis of acute pancreatitis; one was ultimately diagnosed with acute cholecystitis and the other with post-pancreatic surgery anastomotic leakage. One patient who did not receive any study product and one who, in retrospect, had predicted mild pancreatitis were included in the final analysis (FIGURE 8.1). Study groups were comparable for all baseline characteristics (TABLE 8.1).

All but five patients started treatment within 72 h of onset of symptoms. Median intake of probiotics or placebo per patient was 100% (25% lower limit 91%). No dif-

TABLE 8.1. Baseline characteristics

	Probiotics (n=152)	Placebo (n=144)
Age (years)	60.4 (±16.5)	59.0 (±15.5)
Sex (male)	91 (60%)	83 (58%)
Body-mass index (kg/m^2)	27.1 (±6.1)	27.8 (±5.9)
Aetiology of pancreatitis		
Biliary	92 (61%)	75 (52%)
Alcohol	27 (18%)	28 (19%)
Unknown	21 (14%)	28 (19%)
Medication	4 (3%)	6 (4%)
Hypertriglyceridaemia	4 (3%)	3 (2%)
Other	4 (3%)	4 (3%)
American Society of Anaesthesiologists class		
I (healthy status)	62 (41%)	62 (43%)
II (mild systemic disease)	76 (50%)	64 (44%)
III (severe systemic disease)	14 (9%)	18 (13%)
Severity of pancreatitis		
APACHE II score[a]	8.6 (±4.4)	8.4 (±4.5)
Imrie score (first 48h)	3.3 (±1.7)	3.4 (±1.6)
C-reactive protein level (mg/L) highest first 48h)	268 (±127)	270 (±122)
SOFA (on admission)	2.1 (±2.0)	1.9 (±1.6)
MODS (on admission)	1.6 (±1.6)	1.5 (±1.5)
Organ failure before randomisation[a]	9 (6%)	5 (4%)
Multiple organ failure before randomisation	5 (3%)	1 (1%)
Endoscopic sphincterotomy	48 (32%)	35 (24%)
Time from first symptoms to admission (days)	0 (0-3)	0 (0-3)
Time from to first dose (days)	2 (0-4)	2 (0-3)
Time from to enteral nutrition (days)	2 (0-7)	2 (0-7)
Contrast-enhanced CT		
Necrotising pancreatitis[b]	46 (30%)	34 (24%)
≤30% pancreatic parenchymal necrosis	16 (11%)	14 (10%)
>30% pancreatic parenchymal necrosis	30 (20%)	20 (14%)
No contrast-enhanced CT performed	6 (4%)	12 (8%)
CT severity index[c]	4 (0-10)	4 (0-10)

Data are n (%), mean (SD), or median (range). APACHE II=Acute Physiology and Chronic Health Evaluation score, determined on admission. MODS=multiple organ dysfunction score (range 0-24, higher scores indicating more severe disease). SOFA=sequential organ failure assessment (range 0-24, higher scores indicating more severe disease). a= Patients with multiple organ failure are included in the group patients with organ failure. b= Done on day 7-10 after admission. c= CT severity index ranges from 0 to 10, higher scores indicating more extensive pancreatic parenchymal necrosis and peripancreatic fluid collections.

TABLE 8.2. Endpoints

	Probiotics (n=152)	Placebo (n=144)	P value
Primary endpoint			
Any infectious complication[a]	46 (30%)	41 (29%)	0.80
Infected necrosis	21 (14%)	14 (10%)	0.29
Bacteraemia	33 (22%)	22 (15%)	0.18
Pneumonia	24 (16%)	16 (11%)	0.31
Urosepsis	1 (1%)	2 (1%)	0.61
Infected ascites	4 (3%)	0 (0%)	0.12
Secondary endpoint			
Use of antibiotics, any indication	75 (49%)	76 (53%)	0.56
Percutaneous drainage	14 (9%)	8 (6%)	0.23
Surgical intervention, any indication	28 (18%)	14 (10%)	0.05
Necrosectomy	24 (16%)	14 (10%)	0.16
Intensive care admission	47 (31%)	34 (24%)	0.19
Intensive care stay (days)	6.6 (±17.1)	3.0 (±9.3)	0.08
Hospital stay (days)	28.9 (±41.5)	23.5 (±25.9)	0.98
Organ failure during admission, any onset[b, c]	41 (27%)	23 (16%)	0.02
Multiple organ failure during admission, any onset[c]	33 (22%)	15 (10%)	0.01
Organ failure, onset after randomisation[b, d]	21 (14%)	16 (11%)	0.60
Multiple organ failure, onset after randomisation[d]	18 (12%)	11 (8%)	0.25
Nausea	20 (13%)	23 (16%)	0.51
Abdominal fullness	36 (24%)	43 (30%)	0.24
Diarrhoea	25 (16%)	28 (19%)	0.55
Bowel ischaemia	9 (6%)	0 (0%)	0.004
Mortality	24 (16%)	9 (6%)	0.01

Data are mean (SD) or n (%). a= Patients with one or more infectious complication. b= Patients with multiple organ failure are included in the organ failure group. c= Patients with organ failure present at any time during admission, irrespective of the date of onset of organ failure, are included. d= Patients in whom organ failure developed (for the first time) after the day of randomisation are included. Patients in whom organ failure (in any organ) started before the day of randomisation or on the day of randomisation are not included.

TABLE 8.3. Pathogens isolated from 87 patients with an infectious complication[a]

	Probiotics (n=152)	Placebo (n=144)
Gram-positive bacteria		
Staphylococcus spp.	20	20
Staphylococcus aureus	10	11
Coagulase-negative staphylococci	9	5
Enterococcus spp	10	3
Streptococcus spp	3	3
Other gram-positive microorganisms[b]	3	3
Gram-negative bacteria		
Enterobacteriaceae	28	20
Escherichia coli	17	7
Klebsiella spp.	8	8
Other gram-negative microorganisms[c]	4	8
Fungi		
Candida spp	5	1
Chrysosporium sp	1	0
Unknown	0	1

a= Only the first positive culture result of each infection consistent with the primary endpoint was used. If, in one patient, different organisms were cultured from different sites (e.g., from the initial positive blood culture and from pancreatic necrosis) these are all listed. If, in one patient, the same organism was cultured from different sites, this organism was listed only once. b= *Bacillus* spp (2), *Clostridium* sp (1), *Corynebacterium striatum* (1), *Propionibacterium* sp (1), and unknown (1). c= *Aeromonas* spp (1), *Bacteroides* spp (2), *Moraxella catarrhalis* (1), *Neisseria meningitidis* (2), *Pasteurella multocida* (1), *Pseudomonas auruginosa* (1), *Stenotrophomonas maltophilia* (3), and *Veillonella* sp (1).

ference in the categorised percentage intake between the groups was found (data not shown; P=0.78). No infections were confirmed to be caused by any of the probiotic strains administered. During the study, two serious adverse events were reported; both patients died. The monitoring committee convened on both occasions: in one patient, a ruptured caecum with ischaemia was found during emergency laparotomy and the second patient had small-bowel ischaemia diagnosed at emergency laparotomy. In both cases, the randomisation code was broken (both patients had received probiotics). This information was revealed only to members of the monito-

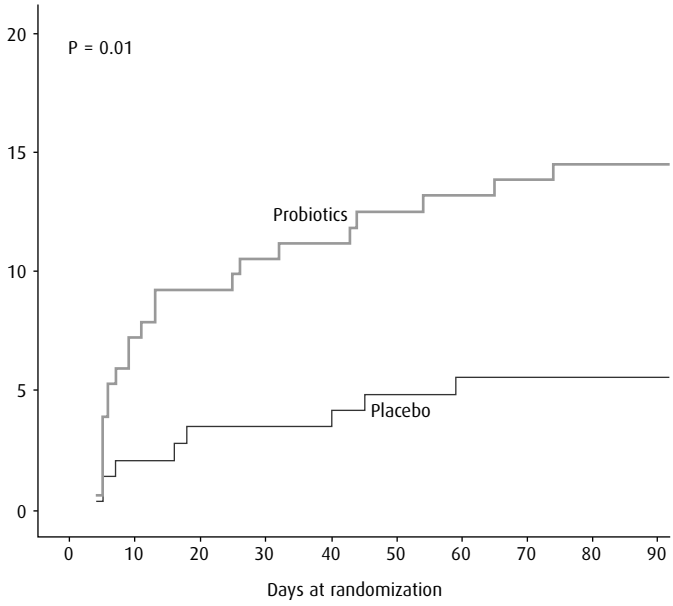


FIGURE 8.2. Kaplan-Meier time-to-event analysis for mortality in the first 90 days after randomisation A follow-up of longer than 90 days was obtained in 266 (90%) patients. Three deaths occurred after 90 days: two in the probiotics group (day 112 and 125) and one in the placebo group (day 140).

ring and steering committees. A review of published work did not reveal any evidence of a relation between bowel ischaemia and the use of probiotics. The monitoring committee subsequently advised that the study continue. The institutional review board was informed on both occasions.

There was no significant difference in the occurrence of the composite primary endpoint between the two groups, nor were there any significant differences between the groups in its individual components (TABLE 8.2). The risk ratio for the primary endpoint was 1.06 (95% CI 0.75-1.51) TABLE 8.3 shows the pathogens cultured from the 87 patients with an infectious complication; no significant differences between the groups were observed.

There were significantly more deaths in the probiotics group than there were in the placebo group P=0.01; TABLE 8.2 and FIGURE 8.2); the risk ratio for mortality was

2.53 (95% CI 1.22-5.25). Most of the deaths were caused by multiple organ failure: 20 (83%) of those in the probiotics group and seven (78%) of those in the placebo group. Other causes of death were respiratory failure after aspiration (one) and cerebral infarction/bleeding (three) in the probiotics group, and ruptured aneurysm (one) and cerebral infarction (one) in the placebo group.

Bowel ischaemia was detected during operation or autopsy in nine patients in the probiotics group; eight of these patients died as a result. No cases of bowel ischaemia were seen in the placebo group (P=0.004 for difference between groups; TABLE 8.4). The nine cases of bowel ischaemia were all diagnosed within the first 14 days of admission in seven different hospitals; four university and three teaching hospitals. In all nine patients, contrast-enhanced CT (either the baseline CT or an earlier CT) showed unequivocal evidence of acute pancreatitis. All these patients had early onset of organ failure (median 2 days after admission, range 1-6 days). At the time of diagnosis of bowel ischaemia, six patients had vasopressor support (14 patients in the placebo group and 23 in the probiotics group had vasopressor support in the first 14 days). Patients had received a median of six doses of probiotics (range 4-22 doses) before diagnosis of bowel ischaemia. The small bowel was involved in eight of the nine patients (including the survivor). During autopsy (six patients), five patients with small-bowel ischaemia had no sign of occlusive disease in the mesenteric vessels.

Apart from the patients with bowel ischaemia, 11 patients died in the 2 weeks after admission: eight in the probiotics group and three in the placebo group. These patients died of multiple organ failure without signs of bowel ischaemia.

No significant differences were noted between the groups for the serial SOFA scores (data not shown). Although more patients in the probiotics group than in the placebo group developed organ failure during the study there was no difference between the groups with regard to organ failure that started after the day of randomisation (P=0.6). During the study, 102 (34%) patients developed the most severe form of acute pancreatitis (organ failure or pancreatic parenchymal necrosis); 56 (37%) in the probiotics group and 46 (32%) in the placebo group. 18 patients did not undergo a CT: the treating physician deemed CT unnecessary in 17 patients, or the patient refused because of good clinical condition; one patient in the placebo group died on day 4 before CT could be done. The latest point at which a baseline CT was

TABLE 8.4. Clinical characteristics of nine patients with bowel ischaemia in the probiotics group

SSN	Sex	Age (years)	Day of diagnosis	Days of treatment before diagnosis	Vasopressor support at day of diagnosis	Day of onset of organ failure	Day of death	Findings
10	F	40	5	3	0	1	5	Emergency laparotomy day 5: perforated caecum with adjacent ischaemia. At autopsy: mucosal ischaemia 80 cm of small bowel
93	M	61	12	11	0	1	13	Emergency laparotomy day 12: resection of 50 cm ischaemic proximal jejunum. At autopsy: necrosis and inflammatory changes of the small bowel wall of the bowel wall
121	M	62	4	2	1	2	4	At autopsy: only the proximal jejunum vital, rest of the small bowel ischaemic
124	F	88	6	4	1	6	6	At autopsy: inflammatory changes of the duodenum wall and necrotising oesophagitis
160	F	62	4	2	1	1	4	Emergency laparotomy day 4: ischaemia of most of the small bowel
202	M	60	12	10	1	2	26	Emergency laparotomy day 12: necrosis of 40 cm jejunum. At autopsy: necrotising jejunitis
235	M	57	9	9	1	2	125	Emergency laparotomy day 9: resection of 90 cm of ischaemic ileum. Patient died 4 months later from cerebral infarction
243	M	22	4	3	0	2	Survived	Emergency laparotomy day 4: ischaemic proxmial jejunum
297	M	57	3	3	1	2	6	Emergency laparotomy day 3: ischaemia and inflammation of the entire small and large bowel

SSN=sequential study number, patient number 1 was the first patient in the trial.

done was 10 days after admission. Predefined subgroup analyses were done for the presence of pancreatic parenchymal necrosis (any extent) and cause (biliary vs. non-biliary) for both the primary endpoint and mortality. The tests for interaction were not significant - i.e. we could not confirm an interaction between probiotic administration and pancreatic necrosis or underlying cause for either the primary endpoint or for mortality. In the subgroup of patients with pancreatic parenchymal necrosis, one or more infectious complication consistent with the primary endpoint occurred in 32 (70%) of 46 patients in the probiotics group vs. 18 (53%) of 34 patients in the placebo group (P=0.16). In patients with pancreatic parenchymal necrosis, 19 (41%) of 46 patients in the probiotics group died, compared with five (15%) of 34 in the placebo group (P=0.01).

DISCUSSION

This randomised, double-blind, placebo-controlled trial in patients with predicted severe acute pancreatitis showed no beneficial effect of probiotic prophylaxis on the occurrence of infectious complications. However, mortality in the probiotics group was about twice as high as in the placebo group. Thus, this combination of probiotics should not be administered routinely in patients with predicted severe acute pancreatitis, and such preparations can no longer be considered to be harmless adjuncts to enteral nutrition.

The rate of infectious complications in our study is in line with a large German multicentre study (31%) on antibiotic prophylaxis in predicted severe acute pancreatitis.[8] Although antibiotic prophylaxis was strongly discouraged in our study, antibiotics were used in about half the patients, although only a third of all patients had a documented infection. Antibiotics were sometimes started pre-emptively, on the basis of clinical suspicion of infection before bacterial culture results becoming available. Obviously, this clinical indication for antibiotic treatment leads to false-positive diagnoses of infectious complications. The overall rate of antibiotic use in our study was no different from that in the placebo groups of trials of antibiotic prophylaxis in acute pancreatitis.[7,8]

The adverse effects of probiotics noted here were unexpected. Several studies have associated probiotics with a reduction in infectious complications.[13,14] Most of these studies have been done in patients undergoing elective abdominal operations.

However, one randomised study in 90 critically ill patients showed a non-significant increase in septic complications in the probiotics group;[24] another randomised study in 61 children admitted to a paediatric intensive-care unit was discontinued prematurely because of a non-significant increase in infections in the probiotics group.[25,26] To date, the main criticism of most randomised controlled trials of probiotic prophylaxis is methodological shortcomings - e.g., analyses not done by intention to treat and sample sizes too small to provide convincing evidence on relevant clinical endpoints.

Two small placebo-controlled randomised controlled trials of probiotic prophylaxis have been done in patients with acute pancreatitis. The first study randomised 45 patients with both predicted mild and predicted severe pancreatitis of solely non-biliary causes.[15] The infection rate was lower in the probiotics group than in the placebo group; no effect on mortality was noted. However, this study was criticised because patients with biliary pancreatitis were excluded, the sample size was small, and analyses were not by intention to treat.[27,28] In the second trial, done by the same research group in 62 patients with predicted severe pancreatitis, the difference in the rate of infectious complications seen in the first trial could not be reproduced.[29] This second study used a probiotic preparation previously found to be effective in preventing infectious complications in patients undergoing abdominal operations.[13,14]

Because the findings of our trial are in marked contrast with the previous reports, we scrutinised our results and methodology for explanations other than a deleterious effect of probiotics. Randomisation was successful, since there were no significant differences in baseline characteristics between groups. In the probiotics group there was a (non-significantly) higher proportion of patients with organ failure before randomisation as well as a greater proportion of patients with more than 30% pancreatic parenchymal necrosis than in the placebo group. When we assessed this imbalance by use of logistic regression, the (adjusted) mortality remained significantly higher in the probiotics group than in the placebo group (data not shown). There was no indication that treatment effects differed in the subgroup analyses. We also considered whether the composition of the product or the doses used explained the effects noted. The daily dose was similar to doses used in previous studies and, although the combination of probiotic strains administered was different from the

preparations used so far, the individual strains have an unblemished reputation as probiotics, both in (smaller) clinical studies and in daily practice in the food industry. The six probiotic strains used in this study were selected from 69 different probiotic bacteria on the basis of their capacity to inhibit growth of gut-derived pathogens and to modulate immune responses.[20] The combination of strains was shown to result in a better antimicrobial spectrum, induction of interleukin 10, and silencing of pro-inflammatory cytokines than the individual components.[20] The combination of strains was found capable of inhibiting the in-vitro growth of a wide variety of pathogens cultured from pancreatic necrosis.[21] Again, the combination of strains had better growth-inhibiting capacities than did the individual strains.[21] Additionally, when the preparation was administered before induction of severe acute pancreatitis in rats, a significant reduction of both infectious complications and late mortality was noted.[30] The same preparation was also used in three small clinical studies under elective circumstances in healthy volunteers, patients with ileostomy, patients about to undergo pancreaticoduodenectomy, and patients with primary sclerosing cholangitis, and no adverse events were noted (unpublished data, trial registry ISRCTN45167712, ISRCTN71637623, and NCT00161148). However, these patients were less ill than the patients in the present study.

Previous randomised trials with probiotics have been of much smaller sample size and with fewer critically ill patients than in the present study. Consequently, the power of these studies was too small to detect differences in mortality or uncommon adverse events such as bowel ischaemia. In our study, probiotics caused a significant increase in mortality, most likely a result of deleterious effects on the (small) bowel wall. After administration of probiotics, no significant increase in new-onset organ failure was seen. Possibly, probiotics especially exert their adverse effects in patients in whom organ failure has already occurred. Because the exact mechanism causing the bowel ischaemia seen here is, at present, unknown, we cannot exclude or confirm that another product - e.g., a combination of strains or one strain alone - would have resulted in similar results. However, in view of the fatal nature of these complications, the administration of any type of probiotic in this category of patients must strongly be advised against until the mechanism of the complications has been unravelled.

The occurrence of non-occlusive mesenteric ischaemia is well known in critically ill

patients,[31] and several cases of non-occlusive mesenteric ischaemia have been reported in acute pancreatitis.[32] Such complications could explain why only two of the nine cases of mesenteric ischaemia seen in this study were reported as a serious adverse event. Evidence exists to suggest that intestinal bloodflow at the mucosal level is generally reduced in acute pancreatitis. An experimental study in rats found a reduction in bloodflow to the intestinal mucosa of up to 85%.[33] A clinical study in patients with severe pancreatitis showed a significant increase in a biological marker for enterocyte death and small-bowel ischaemia.[34] In a severely ill patient going through a phase of severe systemic inflammation or organ failure, an already critically reduced bloodflow and oxygen supply in the small-bowel mucosa might be further compromised by the administration of enteral feeding, known for its increased demand for local oxygen.[35,36] This effect is probably local, since ischaemia usually occurs at the site of administration of enteral feeding.[35,36] However, until now, this occurrence has not been recognised as an argument to refrain from enteral nutrition in critically ill patients because the beneficial effects outweigh the small risk of developing ischaemia.

We can only speculate as to the mechanism of bowel ischaemia in the probiotics group. The administration of 10 billion probiotic bacteria per day on top of enteral nutrition might have even further increased local oxygen demand, with a combined deleterious effect on an already critically reduced bloodflow. A second possible explanation could be that the presence of probiotics caused local inflammation at the mucosal level. Experimental studies have shown that gut epithelial cells under metabolic stress react to commensal bacteria with an inflammatory response.[37] One could postulate that increasing the bacterial load in the small bowel could lead to aggravation of local inflammation, again with a further reduction of capillary bloodflow and ultimately ischaemia. Notably, three of the six autopsy reports of patients with bowel ischaemia mentioned inflammatory changes of the small-bowel wall.

A speculative parallel with immunonutrition can be drawn from a recent meta-analysis showing that although immunonutrition in elective surgical patients reduced the infection rate, it increased mortality in critically ill patients.[38] This effect was seen only in studies of high methodological quality and the reasons for the increased mortality could not be identified. Experimental studies in rats showed that pretreatment with glutamine protects against the effects of bowel ischaemia,[39] whereas

mortality increased when glutamine was administered after the induction of a low flow state.[40] Apparently, there is reason for concern about administration of potent immuno nutritional supplements in the presence of a low flow state, or more generally, in the critically ill.

Our findings show that probiotics should not be administered routinely in patients with predicted severe acute pancreatitis, and that the particular composition used here should be banned for the present indication. Whether other (combinations of) strains might have resulted in different results is debatable, but, until the underlying mechanism is actually revealed, administration of probiotics in patients with predicted severe acute pancreatitis must be regarded as unsafe. Most importantly, probiotics can no longer be considered to be harmless adjuncts to enteral nutrition, especially in critically ill patients or patients at risk for non-occlusive mesenteric ischaemia.

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PART II

CHAPTER 9

Intestinal barrier dysfunction in a randomised trial of a specific probiotic composition in acute pancreatitis

– a summary –

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INTRODUCTION

Infections are responsible for most of deaths in acute pancreatitis.[1] Intestinal barrier dysfunction (i.e., enterocyte damage and increased intestinal permeability) and subsequent bacterial translocation from the intestinal tract to the blood stream and/or distant organs are believed to precede these infectious.[2] Yet, no clinical study has confirmed an association between intestinal barrier dysfunction, bacterial translocation, and actual infections in acute pancreatitis.

Intestinal barrier dysfunction can be tested in several ways. Enterocyte damage can be assessed by measuring the urinary concentration of intestinal fatty acid binding protein (IFABP).[3,4] Intestinal permeability can be assessed by recovery of enterally administered polyethylene glycols (PEGs) with varying molecular weights.[5-7] Urinary nitrate excretion (NOx) is a noninvasive marker of intestinal bacterial translocation.[8]

In the present study, we assessed intestinal barrier function in a subset of patients included in a randomised, placebo-controlled multicentre trial on probiotic prophylaxis in predicted severe acute pancreatitis (PROPATRIA; probiotics in pancreatitis trial).[9] We investigated whether: **a**. enterocyte damage, increased intestinal permeability, and bacterial translocation are associated with severity of disease and clinical infections in acute pancreatitis, and whether **b**. the administered probiotics play a role in mitigating or deteriorating these associations?

METHODS

Within 24 to 48 hours after randomization in PROPATRIA, a solution of 100 mL water containing 5 g PEG 400 kDa, 1.5 g PEG 1500 kDa, 5 g PEG 4000 kDa, and 10 g PEG 10,000 kDa was administered enterally, after which 24-hour urine output was collected. This procedure was repeated after 7 days. Recovery of the PEG molecules in the urine was analysed by reverse-phase high performance liquid chromatography.

IFABP concentrations were determined in 100 μL urine samples, taken from the 24-hour urine collected for the PEG permeability test, using a human IFABP enzyme-linked immunosorbent assay kit.

The amount of NOx in the 24-hour urine sample, which was also used for the PEG analysis, was determined by automated flow injection analysis as previously described.[8]

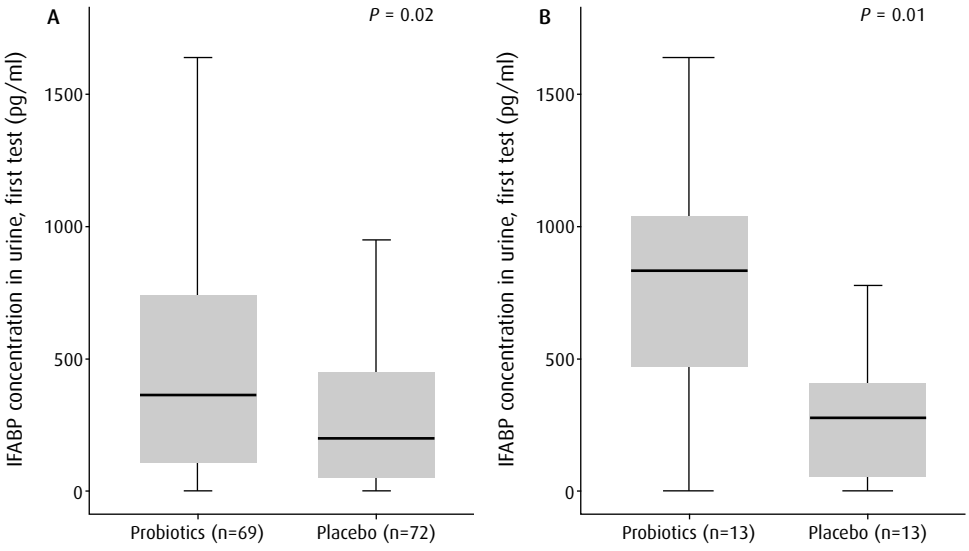

FIGURE 9.1. A IFABP (initial 72 hours), reflecting enterocyte damage, in patients receiving probiotics or placebo. B, IFABP (initial 72 hours) in the subgroup of patients with organ failure.

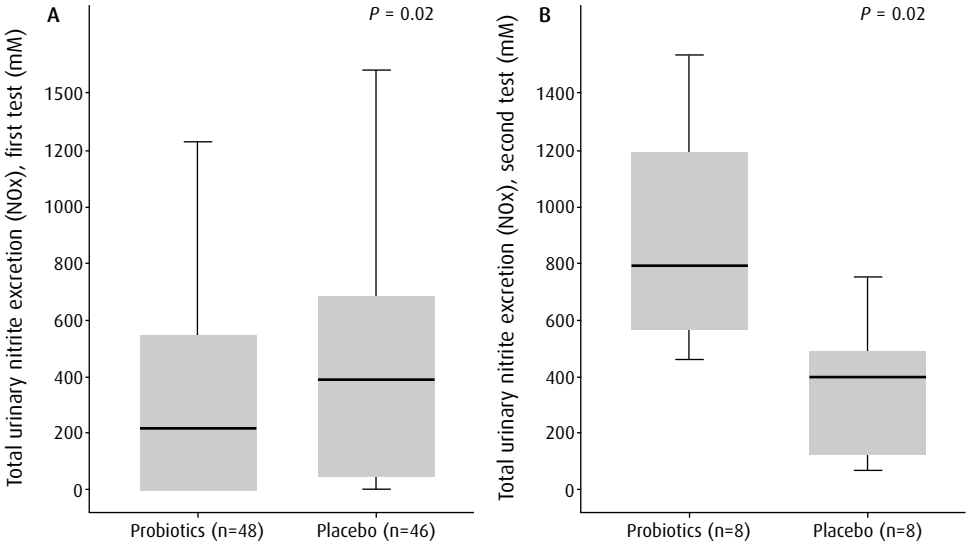

FIGURE 9.2. A, NOx (initial 72 hours), reflecting bacterial translocation, in patients receiving probiotics or placebo. B, NOx (7 days later; second test), in the subgroup of patients with organ failure.

We investigated whether IFABP, PEG, and NOx were associated with bacteraemia, infected necrosis, organ failure, severe pancreatitis, and mortality. In addition, the effect of probiotic prophylaxis on IFABP, PEG, and NOx was studied. Effects of probiotics were studied in the subgroups of patients with and without organ failure separately.

RESULTS

Between January 2005 and March 2007, 141 patients (probiotics, n=69 vs. placebo, n=72) were included. PEG recovery was higher in patients who developed bacteraemia (PEG 4000, P=0.001), organ failure (PEG 4000, $P<0.0001$), or died (PEG 4000, $P=0.009$). IFABP concentrations in the first 72 hours were higher in patients who developed bacteraemia (P=0.03), infected necrosis (P=0.01), and organ failure (P=0.008). NOx levels were higher in patients who developed bacteraemia (P=0.03), infected necrosis (P=0.02), organ failure (P<0.0001), or severe acute pancreatitis (P=0.003), but only at the second test.

Median IFABP levels 24 to 48 hours after start of treatment were higher in the probiotics group (P=0.02, FIGURE 9.1.A). This difference was greatest in the subgroup of patients with organ failure (P=0.01, FIGURE 9.1.B).

Probiotic prophylaxis did not affect intestinal permeability as assessed by PEG recovery.

Median NOx levels, 24 to 48 hours after start of treatment, were lower in patients receiving probiotics (P=0.02, FIGURE 9.2.A). In patients without organ failure, probiotics prophylaxis decreased NOx levels significantly (P=0.02). However, after 7 days, in patients suffering from organ failure, probiotics administration was associated with increased NOx levels (P=0.002, FIGURE 9.2.B).

DISCUSSION

This is the first clinical study ever demonstrating a relationship between intestinal barrier dysfunction and clinically relevant infections in acute pancreatitis. Our main findings are that: **1**. intestinal barrier dysfunction occurs early in the course of acute pancreatitis and is related to infectious complications (e.g., bacteraemia and infection of necrosis), organ failure, severe acute pancreatitis, and mortality; **2**. the probiotic preparation used in this study (Ecologic 641) did not alter intestinal permeabi-

lity as indicated by PEG permeability; **3**. in patients with acute pancreatitis and concomitant organ failure, probiotic prophylaxis was associated with an increase in enterocyte damage as measured with IFABP and an increase in bacterial translocation as measured with NOx; and **4**. in patients without organ failure, prophylaxis with this specific combination of strains did not influence enterocyte damage but reduced bacterial translocation.

Many of our findings supports the more than 20 years old 'gut as motor of sepsis' hypothesis.[2] Future studies aiming at preventing infectious complications in acute pancreatitis should focus on improving intestinal barrier function early in the course of the disease. We can only speculate at this point as to which mechanism can be held responsible for the harmful effect of probiotics in patients with organ failure due to acute pancreatitis.[9]

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PART III

Early endoscopic intervention for biliary pancreatitis

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PART III

CHAPTER 10

Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis

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ABSTRACT

BACKGROUND

Accurate prediction of common bile duct (CBD) stones in acute biliary pancreatitis (ABP) is warranted to select patients for early therapeutic endoscopic retrograde cholangio(pancreatico)graphy (ERCP). We evaluated commonly used biochemical and radiological predictors for CBD stones in a large prospective cohort of patients with ABP undergoing early ERCP.

METHODS

167 patients with ABP undergoing early ERCP (<72 hours after symptom onset) were prospectively included in 15 Dutch hospitals (2004-2007). Abdominal ultrasound (US) and/or computed tomography (CT) was performed on admission and complete liver biochemistry determined daily. We used univariate logistic regression to assess associations between CBD stones during ERCP (gold standard) and the following parameters: **1**. clinical: age, sex, predicted severity, **2**. radiological; dilated CBD, impacted stone in CBD, and **3**. biochemical; bilirubin, gammaglutamyltransferase (GGT), alkaline phosphatase (AP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

RESULTS

73/167 patients (44%) had predicted severe ABP, 51 (31%) exhibited a dilated CBD and 15 (9%) had CBD stones on US/CT. ERCP was performed at a median of 0 days (interquartile range 0-1) after admission. CBD stones were found during ERCP in 89/167 patients (53%). In univariate analysis, the only parameters significantly associated with CBD stones were GGT (per 10 units increase: odds ratio 1.02, 95%-CI 1.01-1.03, P=0.001) and AP (per 10 units increase: odds ratio 1.03, 95%-CI 1.00-1.05, P=0.028). These and all other tested parameters, however, showed poor positive predictive value (ranging from 0.53 to 0.69) and poor negative predictive value (ranging from 0.46 to 0.67).

CONCLUSIONS

The results of this study suggest that commonly used biochemical and radiological predictors for the presence of CBD stones during ERCP in the earliest stages of ABP are unreliable.

INTRODUCTION

Acute biliary pancreatitis is thought to be caused by temporary obstruction of the major duodenal papilla by gallstones and /or sludge.[1,2] These patients often early undergo therapeutic endoscopic retrograde (pancreatico)graphy (ERCP).[1,3-5] International guidelines agree that early ERCP should be performed in all patients with acute biliary pancreatitis (i.e., both predicted mild and predicted severe) and suspicion of cholangitis and/or biochemical or radiological signs of common bile duct stones.[1,3,4] In patients with predicted severe ABP without biochemical or radiological signs of CBD stones, the role of ERCP remains controversial. The rationale for therapeutic ERCP is to relieve the biliary obstruction by removal of common bile duct (CBD) stones or sludge to ultimately reduce disease severity and risk of complications. Nevertheless, in a large proportion of patients, spontaneous passage of gallstones and sludge will occur.[2] In clinical practice, the decision to perform early ERCP is often based on biochemical and radiological criteria such as the presence of cholestatic liver biochemistry and a dilated CBD. These commonly used markers have been shown to accurately predict CBD stones in patients with gallstone disease in the absence of pancreatitis.[6]

Only few studies have evaluated the accuracy of biochemical and radiological predictors for CBD stones in patients with acute biliary pancreatitis specifically.[7-9] In these studies, CBD stones were assessed relatively late in the disease (i.e. after 4-7 days after admission, usually by intraoperative cholangiography during elective laparoscopic cholecystectomy. Consequently, the predictive value of biochemical and radiological markers for CBD stones in the earliest stage of acute biliary pancreatitis (i.e. upon admission) is unknown. This is relevant because, if ERCP has to be performed, the procedure should be done as soon as possible to have the highest chance of mitigating the pancreatic inflammatory process. Indeed international guidelines advise ERCP to be performed within 24-72 hours after admission in those patients with an indication for the procedure.[1,4]

The aim of this study was to evaluate the predictive value of common biochemical and radiological parameters for the presence of CBD stones during early ERCP in a large prospective cohort of patients with acute biliary pancreatitis.

PATIENTS AND METHODS

STUDY DESIGN AND PATIENT SELECTION

We performed a retrospective analysis of a prospective database of 731 patients with acute pancreatitis admitted to the 15 centers of the Dutch Pancreatitis Study Group between March 2004 and March 2007. Acute pancreatitis was defined as abdominal pain in combination with serum amylase or lipase concentrations that were raised to at least three times the institutional upper limit of normal. The ethical review board of each participating hospital approved the protocol and all patients or their legal representatives gave written informed consent for inclusion in the prospective database. A subset of patients with predicted severe acute pancreatitis from this cohort were reported in a previously published randomized study on probiotics in pancreatitis[10] and a prospective study on the clinical outcome after ERCP in acute biliary pancreatitis.[5]

All patients had complete laboratory investigations on the first 3 days of admission and all patients underwent abdominal ultrasound (US) and/ or contrast enhanced computed tomography (CT) on admission. Predicted severity of acute pancreatitis and biliary aetiology were assessed in all patients within 72 hours after onset of symptoms. Criteria for predicted severe pancreatitis were: a) an Acute Physiology and Chronic Health Evaluation (APACHE)-II score ≥8[11], or b) Modified Glasgow score ≥3[12], or c) C-reactive protein (CRP) >150 mg/L.[13] Patients were stratified to predicted mild or predicted severe acute biliary pancreatitis based on the highest scores measured before ERCP, in order to prevent severity prediction from being influenced by ERCP. Biliary etiology was defined as the presence of at least one of the following criteria: **a**. gallstones and/or sludge on US or CT **b**. dilated CBD on ultrasound or CT (diameter >8 mm for age ≤75 years and diameter >10 mm for age >75 years) **c**. two of the following three laboratory abnormalities: **1**. serum bilirubin level concentration >2.3 mg/dL; **2**. alanine aminotransferase (ALT) activity >100 U/L with an ALT activity greater than the aspartate aminotransferase (AST) activity; **3**. alkaline phosphatase (AP) activity >195 U/L with a gammaglutamyltransferase (GGT) activity >45 U/L. Other causes of acute pancreatitis (e.g. alcohol abuse) and signs of chronic pancreatitis (clinical history and CT) had to be absent.

All patients with ABP who underwent ERCP within 72 hours after admission (i.e. early ERCP) were included in the current study. ERCP was performed at discretion

of the treating physician.

From the entire cohort of 731 patients admitted with acute pancreatitis during the study period, 418 patients (57%) met the criteria for acute biliary pancreatitis: 34/418 patients (8%) underwent previous cholecystectomy and 315/418 patients (75%) had gallbladder stones on US and/ or CT on admission.

A total of 174/418 patients (42%) underwent early ERCP. In seven patients, ERCP was unsuccessful and the CBD could not be depicted. These patients were excluded from further analysis because the presence of CBD stones could not be assessed. The 167 patients undergoing successful ERCP with depiction of the CBD formed the final study population.

PREDICTORS AND OUTCOME

The following predictors were investigated: **1**. clinical predictors: age, sex, predicted severity of pancreatitis; **2**. radiological predictors: the presence of a CBD stone or dilated CBD (diameter >8 mm for age ≤75 years and diameter >10 mm for age >75 years) on US or CT and **3**. biochemical predictors: maximum values of bilirubin, AST, ALT, GGT and AP as measured before ERCP. The outcome was the presence of a CBD stone during early ERCP.

STATISTICAL ANALYSIS

All analyses were performed using SPSS version 15.0.0 (SPSS, Chicago, IL, USA). Continuous variables are shown as median (interquartile range). Associations between the individual predictors and the presence of a CBD stone during ERCP were assessed by univariate logistic regression. Predictors significantly associated with CBD stones (P>0.05) were entered in a multivariate logistic regression model. Results are shown as odds ratio's (OR) and 95%-confidence intervals (CI). For all biochemical parameters except bilirubin, odds ratio's corresponding to a change of 10 units are reported. The fit of the logistic models for continuous variables was assessed using the Hosmer-Lemeshow test. The biochemical predictors were plotted in a receiver operator characteristics (ROC) curve. Sensitivity, specificity, positive predictive values and negative predictive values were calculated for all predictors. For the biochemical predictors, cut-off points were based on the 25th, 50th and 75th percentiles. A P-value <0.05 was considered statistically significant.

TABLE 10.1 Prevalence and median values of predictors for common bile duct stones in 167 patients with acute biliary pancreatitis undergoing early ERCP

Predictor	All patients (n=167)	Patients with CBD stone during ERCP (n=89)	Patients without CBD stone during ERCP (n=78)
Clinical			
Male sex – no. (%)	74 (44)	47 (53)	46 (59)
Age	61 (28-74)	63 (48-75)	59 (49-71)
Predicted severe biliary pancreatitis – no. (%)	94 (56)	46 (52)	48 (62)
Radiological			
Dilated CBD – no. (%)	51 (31)	30 (34)	21 (27)
Impacted CBD stone – no. (%)	15 (9)	8 (9)	7 (9)
Biochemical			
Bilirubin	2.8 (1.6-4.2) mg/dL	2.9 (1.9-4.3)	2.6 (1.3-4.0)
AST	257 (160-410) U/L	285 (174-417)	221 (137-409)
ALT	318 (150-539) U/L	340 (158-560)	295 (129-456)
GGT	433 (249-700) U/L	487 (317-776)	355 (209-523)
AP	170 (115-294) U/L	209 (220-308)	154 (111-241)

* Continuous data are medians (interquartile range)
Upper limits of normal values for biochemical predictors are: bilirubin: 1.2 mg/dL; AST: 45 U/L; ALT: 55 U/L; GGT: 45 U/L; and AP: 125 U/L.

RESULTS

From the 167 patients undergoing successful ERCP with depiction of the CBD, 15 patients (9%) underwent previous cholecystectomy and 122 patients (73%) had gallbladder stones on US and/ or CT on admission. ERCP was performed at a median of 0 days after admission (interquartile range 0-1). Time from onset of symptoms to ERCP was less than 24 hours in 43 patients (26%), between 24 and 48 hours in 99 patients (59%) and between 48 and 72 hours in 25 patients (15%). CBD stones were found during ERCP in 89/167 patients (53%). CBD stones and/or sludge was detected during ERCP in 109/167 patients (66%). Endoscopic sphincterotomy with or without stone removal was performed in 150/167 patients (90%).

The prevalence of clinical and radiological predictors and median values of bioche-

TABLE 10.2 Univariate logistic regression analysis of clinical, radiological and biochemical predictors for CBD stones in patients with acute biliary pancreatitis undergoing early ERCP

Predictor	Odds Ratio	95%-CI	P Value
Clinical			
Sex	0.78	0.42-1.44	0.42
Age	1.01	0.99-1.03	0.43
Predicted severe ABP	0.67	0.36-1.24	0.20
Radiological			
Dilated CBD	1.38	0.71-2.68	0.34
Impacted CBD stone	1.00	0.35-2.90	0.99
Biochemical			
Bilirubin	1.00	0.99-1.01	0.79
AST*	1.01	0.99-1.00	0.38
ALT*	1.02	0.99-1.00	0.41
GGT*	1.02	1.01-1.03	0.001
AP*	1.03	1.00-1.05	0.028

* presented odds ratio is for these biochemical predictors is for every increase of 10 units

mical predictors in the study population is given in TABLE 10.1.

There were no significant differences in prevalence of CBD stones for patients without radiological or biochemical signs of cholestasis (n=51), patients with radiological or biochemical signs of cholestasis (n=87), and patients with radiological and biochemical signs of cholestasis (n=29): 43%, 58% and 59% respectively (P=0.22). There was also no significant association between timing of ERCP (i.e. time from onset of symptoms to ERCP) and the prevalence of CBD stones. The percentage of CBD stones for patients undergoing ERCP on day 0 (n=43), day 1 (n=99) or day 2 (n=25) after onset of symptoms was: 56%, 54% and 48% respectively (P=0.82).

The results of logistic regression are summarized in TABLE 10.2. The Hosmer-Lemeshow goodness of fit test indicated satisfactory fit (P>0.05) for all continuous variables. None of the clinical or radiological parameters were significantly associated with the presence of CBD stones. When both GGT and AP were entered as

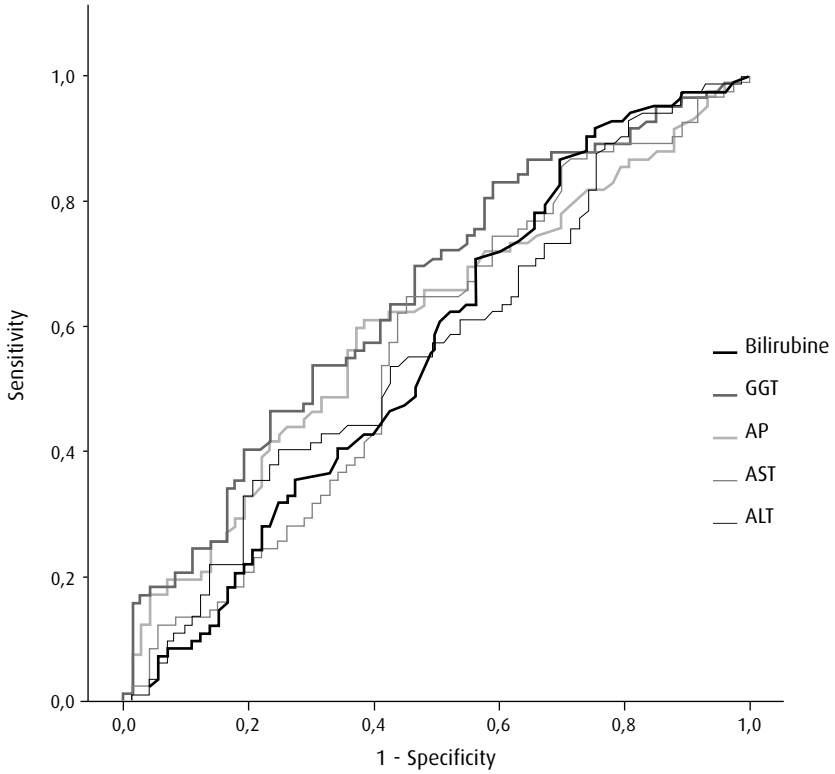

FIGURE 10.1. Receiver operator characteristics curve for biochemical predictors of CBD stones in 167 patients undergoing early ERCP

covariates in a multivariate logistic regression model, only GGT remained a significant predictor for CBD stones: OR 1.01 (per 10 units increase); 95% CI 1.00-1.03 P=0.02). There was no significant difference in the predictive values of all biochemical and radiological parameters between patients with predicted mild and predicted severe ABP (data not shown).

We also analyzed the clinical, biochemical and radiological predictors for the presence of ampullary stones: 31/167 patients (19%) had ampullary stones during ERCP. The only predictor significantly associated with ampullary stones during ERCP was age: OR 1.03; 95% CI 1.00-1.05; P=0.036. There was no significant difference in biochemistry values and the percentage of patients with dilated CBD or impacted CBD stones on first imaging between patients with impacted ampullary

TABLE 10.3 Discrimination and predictive values of radiological and biochemical predictors for CBD stones early in the course of acute biliary pancreatitis

Predictor	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Radiological				
Dilated CBD	0.34	0.73	0.59	0.49
Impacted CBD stone	0.11	0.89	0.53	0.46
Biochemical*				
Bilirubin				
cut-off > 1.6 mg/dL	0.83	0.29	0.58	0.60
cut-off > 2.6 mg/dL	0.55	0.49	0.56	0.49
cut-off > 4.2 mg/dL	0.28	0.77	0.59	0.48
AST				
cut-off > 160 U/L	0.82	0.29	0.57	0.60
cut-off > 259 U/L	0.55	0.57	0.59	0.53
cut-off > 411 U/L	0.25	0.76	0.54	0.48
ALT				
cut-off > 153 U/L	0.77	0.27	0.54	0.51
cut-off > 313 U/L	0.54	0.53	0.56	0.51
cut-off > 538 U/L	0.30	0.81	0.64	0.51
GGT				
cut-off > 252 U/L	0.85	0.36	0.60	0.67
cut-off > 433 U/L	0.60	0.59	0.63	0.56
cut-off > 704 U/L	0.32	0.84	0.69	0.52
AP				
cut-off > 114 U/L	0.81	0.27	0.56	0.56
cut-off > 168 U/L	0.61	0.59	0.62	0.57
cut-off > 291 U/L	0.31	0.81	0.64	0.51

* Cut-off values are based on the 25th, 50th and 75th percentiles

stones and patients with free floating CBD stones during ERCP (data not shown). From the biochemical values, only GGT and AP were significantly associated with CBD stones. The ROC curves for the individual biochemical predictors for CBD stones are shown in FIGURE 10.1. The areas under the curve were as follows: bilirubin, 0.56, GGT, 0.65; AP, 0.60; AST, 0.56; ALT, 0.56. Discrimination and predictive values for all predictors, including different cut-off values for the biochemical predictors, are given in TABLE 10.3. Diagnostic value was poor for all individual predictors, including GGT and AP, despite their significant association with CBD stones in univariate logistic regression. The results were similar when combining sludge and stones in CBD as outcome measure, and when combining the individual biochemical and radiological parameters in a predictive model (data not shown).

DISCUSSION

This study evaluated the predictive value of commonly used radiological and biochemical markers for CBD stones in patients undergoing ERCP in the earliest stages of acute biliary pancreatitis. We found that none of the investigated criteria, which included cholestatic liver biochemistry and dilated CBD on US or CT, accurately predicted the presence of CBD stones. In roughly half the patients with signs of biochemical or radiological signs of cholestasis, a CBD stone was not detected during ERCP, and vice versa.

Our findings can be explained in several ways. First, although the interval between ERCP and admission (thus the time of laboratory measurements and imaging) was generally very short, CBD stones may have spontaneously passed before ERCP could have been performed in some patients. Second, cholestatic liver biochemistry may have been caused by other factors than CBD stones in these patients with acute biliary pancreatitis, for instance local oedema from the pancreatic head due to pancreatic inflammation. Third, radiographic signs of cholestasis (i.e. a dilated CBD) and impacted CBD stones may have been inaccurately interpreted, as it has been demonstrated that abdominal US is less accurate in patients with acute pancreatitis, as compared to general patient population with gallstone disease.[14,15]

In contrast to our results, several other studies reported high predictive values for biochemical and radiological markers for CBD stones in patients with acute biliary pancreatitis.[7-9] However, there are some important differences between these studies

and the current analysis. First of all, previous studies were retrospective. Moreover, our study is the first to evaluate the prediction for CBD stones very early in the course of acute biliary pancreatitis in all patients. It is generally agreed upon that, if the decision to perform ERCP is taken, the procedure should be performed as soon as possible.[1,4] We assessed CBD stones with ERCP which was performed on admission in most patients. Conversely, other studies usually evaluated CBD stones with intra-operative cholangiography which was performed at a later stage (i.e., after 4-7 days after admission), by which time CBD stones may have spontaneously passed into the duodenum.[7-9] These studies reported high predictive value for biochemical and radiological markers. However, because the patients in these studies were assessed at a relatively late stage of the disease, the predictive values reported are probably only relevant for persistent CBD stones. As suggested by our findings, the commonly used radiological and biochemical markers do not reliably predict CBD stones early in the course of disease (i.e. the potential window for therapeutic ERCP). There was also no significant association between predicted severity of acute biliary pancreatitis and the presence of CBD stones. It should be noted, that even if commonly used scoring systems to predict disease severity[11-13] would also be accurate in predicting CBD stones, they would still be of limited value since assessment of these scores often needs longer time (i.e., 48 hours) than one wants to wait to perform early ERCP. Moreover, if predictive sores would be assessed after therapeutic ERCP, predicted severity might even be influenced by the procedure.

A theoretical shortcoming of this study is the fact that the decision to perform ERCP was left to the treating physician. This decision was without any doubt influenced by the presence of biochemical and radiological signs of cholestasis. As a result, selection bias may have occurred and therefore the *a priori* risk for CBD stones in our study population is probably greater than the risk in the general population of patients with acute biliary pancreatitis. However, the indication for ERCP varied greatly among the 15 participating centers: some centers performed ERCP in almost every patient, whereas other centers performed ERCP only in patients with concurrent cholangitis. Consequently, a considerable number of patients in our study did not have biochemical or radiological signs of cholestasis, and CBD stones were only found in half of the patients. It is therefore unlikely that patient selection explains the negative findings of this study. Notably, selection of patients with a high

a priori risk for CBD stones would theoretically only increase the chance the finding associations, whereas we did not find any.

A limitation of the current study was, that predicted severity was assessed based on the highest laboratory values and the worst physical examination parameters measured before ERCP. The rationale was that the procedure itself could have influenced the severity scores. Also, severity scores have generally been validated without ERCP being performed in the first 48 hours. As in our study ERCP was generally performed on the day of admission and several predictive severity scores have been validated based on the highest score in the first 48 hours of admission,[1-13] some patients in this study may have been incorrectly classified as predicted mild acute pancreatitis, while in fact, they would have met the criteria for predicted severe disease after 48 hours in-hospital observation. In contrast, we can be sure that patients with predicted severe pancreatitis before ERCP were correctly classified.

Our findings suggest that, if the decision to perform early therapeutic ERCP in patients with acute biliary pancreatitis is to be based on the likelihood of CBD stones, other diagnostic modalities than the commonly used biochemical and radiological criteria should be considered. Alternatives could be endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreaticography (MRCP). These techniques have shown good discrimination for CBD stones in patients with acute biliary pancreatitis.[16-20] However, it is known that with MRCP small CBD stones (i.e. < 5 mm) are easily missed.[21,22] Moreover, as EUS and MRCP require an experienced operator and are time consuming, these techniqees may introduce delay in therapeutic ERCP, and may lead also to false positive results because CBD stones may pass spontanteously before ERCP is performed.[2] Although there is some evidence that EUS has a higher diagnostic accuracy for CBD stones in acute biliary pancreatitis than ERCP,[20,23] EUS is currently not a standard procedure early in the course of acute biliary pancreatitis worldwide. In the Netherlands, EUS is currently also not performed to assess the presence of CBD stones early in the course of ABP. These modalities could therefore not be evaluated in the current study.

In conclusion, the results of the current study suggest that commonly used biochemical and radiological predictors for CBD stones are unreliable in the earliest stages of acute biliary pancreatitis.

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PART III

CHAPTER 11

Early endoscopic retrograde cholangiopancreatography versus conservative managment in acute biliary pancreatitis without cholangitis: a meta-analysis of randomised trials

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ABSTRACT

BACKGROUND

Early endoscopic retrograde cholangiopancreatography (ERCP) should be performed in all patients with acute biliary pancreatitis (ABP) and co-existing acute cholangitis. In patients without cholangitis and predicted mild ABP it is generally accepted that early ERCP should not be performed. Nevertheless, there is a controversy regarding the role of early ERCP in the treatment of patients with predicted severe ABP without cholangitis. We reviewed randomised trials on early ERCP versus conservative management in patients with ABP without acute cholangitis.

METHODS

Relevant publications in 3 electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials) were systematically reviewed and meta-analysed.

RESULTS

Seven randomised trials on ERCP in acute pancreatitis were found, of which 3 including a total of 450 patients (230 in the ERCP arm and 220 in the control arm) qualified for a meta-analysis according to predefined criteria. In all patients with ABP (predicted mild and severe), early ERCP was associated with a non-significant reduction in overall complications (risk ratio [RR], 0.76; 95% confidence interval (CI), 0.41-1.40; P=0.38) and a non-significant increase in mortality (RR 1.13, 95% CI 0.23-5.63, P=0.88). Subgroup analysis based on predicted severity did not affect these outcomes (overall complications: predicted mild: RR 0.86; 95% CI 0.62-1.19; P=0.36; predicted severe: RR 0.82; 95% CI 0.32-2.10; P=0.68; mortality: predicted mild: RR 1.90; 95% CI 0.25-14.55, P=0.53; predicted severe: RR 1.28; 95% CI 0.20-8.06; P=0.80).

CONCLUSION

In this meta-analysis, early ERCP in patients with predicted mild and predicted severe ABP without acute cholangitis did not lead to a significant reduction in the risk of overall complications and mortality.

INTRODUCTION

Acute biliary pancreatitis (ABP) is the most frequent form of acute pancreatitis in Western countries.[1,2] There are 2 mechanisms generally accepted regarding the pathogenesis of ABP: reflux of bile into the pancreatic duct and transient ampullary obstruction caused by sludge or an impacted stone in the ampulla.[3,4] Patients with small gallstones and sludge are particularly at risk for acute pancreatitis.[5] By early endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) bile-duct stones and sludge can be removed, and obstruction released with potentially improved outcome. Nevertheless, despite technical improvements shown in recent years and an increased experience of endoscopists, there is a documented risk of procedure-related complications.[6-8] In addition, it is well recognized that most small gallstones pass spontaneously without causing further harm.[4,9] Indisputable benefits of endoscopic biliary drainage in patients with acute cholangitis have been stressed in the recent Tokyo Guidelines.[10] It is generally accepted that patients with predicted mild ABP without signs of acute cholangitis do not benefit from early ERCP.[1] Controversy persists, however, whether patients with predicted severe ABP in absence of acute cholangitis should undergo early ERCP.[11-13] The 2005 UK guidelines on acute pancreatitis state that all patients with predicted severe ABP (irrespective of the presence of acute cholangitis) should undergo early ERCP,[14] whereas the recent guidelines of the American College of Gastroenterology recommend that early ERCP is performed only in patients with acute cholangitis and severe acute pancreatitis (organ failure).[1] The 2007 guidelines of the American Gastroenterology Association state that early ERCP in patients with predicted severe ABP without signs of acute cholangitis is controversial and the available data are not uniform in support of this practice.[15] Indeed, several randomised controlled trials (RCTs) that compared early ERCP, with or without ES, to conservative treatment with selective ERCP, with or without ES, have shown conflicting results.[16-19] The first meta-analysis on this subject did not provide a definite answer.[20] The second meta-analysis aimed to control for a possible modifying effect of acute cholangitis and showed that early ERCP decreased complications in all patients with predicted severe ABP, regardless of the presence of cholangitis.[21] However, this meta-analysis included a RCT in which 35% of patients suffered from acute pancreatitis of a nonbiliary cause.[17] Finally, 1 new RCT has been published since that

time.[19] Therefore, the present meta-analysis aims to compare early ERCP, with or without ES, with conservative management in patients with ABP without signs of cholangitis. A predefined subgroup analysis on patients with predicted severe and predicted mild ABP will be performed.

METHODS

SEARCH STRATEGY AND SELECTION CRITERIA

A systematic literature search with predefined search terms was carried out in the MEDLINE, EMBASE, and Cochrane databases for articles published until March 1, 2007 (FIGURE 11.1). All identified articles and review articles were screened for cross-references of articles that included information on ERCP in acute pancreatitis. Language restrictions were not applied. The title and abstract of all identified articles were screened for the following inclusion criteria:

1. Study population: patients with ABP without signs of acute cholangitis. Acute cholangitis should be either an exclusion criterion or separate data on patients without acute cholangitis should be presented.
2. Intervention: early ERCP (i.e., within 72 hours after admission) with or without ES.
3. Comparison: conservative treatment with selective ERCP with or without ES.
4. Study outcomes: mortality and overall complications.
5. Study design: participants were assigned to either ERCP or comparator by random allocation.

DATA EXTRACTION AND QUALITY ASSESSMENT

Titles and abstracts of all retrieved records and subsequently full-text articles were examined independently by 2 authors (MSP, HCvS) to identify trials that satisfied the inclusion criteria. Discrepancies in selection were resolved by discussion between the authors of this meta- analysis. The Jadad scale was used to grade the methodological quality of the trials included.[22] This scale consists of 3 items regarding: 1. random allocation, 2. masking of patients, 3. dropouts and withdrawals. The quality scale ranges from 0 to 5 points, with 2 or less indicating low quality and 3 or higher indicating high quality. In addition, 3 other criteria were applied regarding: 4. allocation concealment (yes or no), 5. blinding of end point assessment (yes or no,

Database	Search strategy
MEDLINE	('acute pancreatitis' [Title/Abstract] OR 'pancreatitis' [Title/Abstract]) AND ('gallstone' [Title/Abstract] OR 'gallstones' [Title/Abstract] OR 'biliary' [Title/Abstract]) AND ('ERCP' [Title/Abstract] OR 'endoscopic retrogade cholangiopancreatography' [Title/Abstract] OR 'sphincterotomy' [Title/Abstract] OR 'papillotomy' [Title/Abstract]) AND ('conservative' [Title/Abstract])
EMBASE	'pancreatitis' AND ('ERCP' OR 'endoscopic retrogade cholangiopancreatography' OR 'Vater papillotomy' OR 'sphincterotomy') AND [humans]/lim
Cochrane library	'pancreatitis' AND ('endoscopic retrogade cholangiopancreatography' OR 'papillotomy' OR 'sphincterotomy'

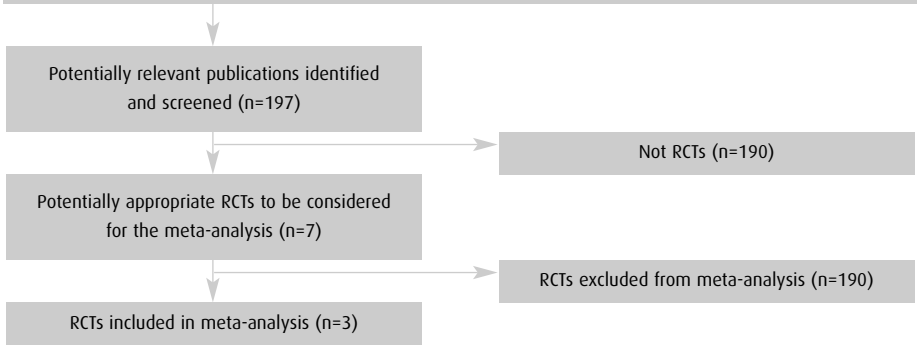

FIGURE 11.1. Flow chart illustrating the details of the search and study selection process

irrespective of blinding of treatment for patient and physician), and **6**. missing data (at least 90% of the data reported). Data with regard to the reported group size, baseline characteristics, and numbers of events for each end point were extracted and documented independently by 2 authors (MSP, HCvS).

STATISTICAL ANALYSIS

The data analysis was performed with the meta-analysis software Comprehensive Meta-Analysis (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Metaanalysis Version 2, Biostat, Englewood, NJ, 2005). From the pooled data, the risk ratio (RR) and risk difference (RD) with the 95% confidence interval (CI) were calculated for the following end points: mortality and overall complications. The Mantel-Haenszel method was used for the pooled analysis of included trials. When no events were observed in both treatment groups of a particular trial, we added an

TABLE II.1. Summary of study characteristics for the included trials

	Number of patients				Predicted Severe AP			
Study	Intervention group	Control group	Time to ERCP	Definition of cholangitis	Criteria Predicted Severe ABP	Intervention group (%)	Control group (%)	Criteria of ABP
Neoptolemos et al.[24]	53	57	<72 h of admission	Not stated	Glasgow ≥3	20 (38)	25 (44)	Gallstones on US or cholestatic laboratory abnormalities
Fölsch et al.[23]	26	112	<72 h of onset >5 mg/dl (90 μ mol/L)[a]	Bilirubin	Glasgow ≥3	26 (23)[b]	20 (18)[b]	Gallstones on US or CT or cholestatic laboratory abnormalities
Oria et al.[19]	51	51	<48 h of onset	Charcot's triad	APACHE-II ≥6	17 (33)	21 (41)	Gallstones on US or CT
Total	**230**	**220**	-	-	-	**63 (27)**	**66 (30)**	-

a= Twelve patients had serum bilirubin concentrations higher 5 mg/dL (90 μ mol/L) but were analysed on an intention-to-treat basis.
b= Patients were assigned severity score post hoc.
ERCP indicates endoscopic retrograde cholangiopancreatography; ABP, acute biliary pancreatitis; US, ultrasound; CT, computed tomography.

TABLE II.2. Quality assessment of trials included in the meta-analysis

Study	Primary endpoint	Double blinding	Randomization	Withdrawals[a]	Jadad score	Allocation concealment	Blinded endpoint assessment	Missing data[a]
Neoptolemos et al.[24]	Mortality	No	Not stated	6/4	2	Unclear	No	0/0
Fölsch et al.[23]	Mortality	No	Not stated	0/0	2	Unclear	Yes	16/16[b]
Oria et al.[19]	Organ failure	No	Sealed envelope	0/1	3	Potentially manipulable	No	0/0

a= Early ERCP group/conservative treatment group.
b= Patients with undefined severity.

TABLE II.3. Baseline characteristics of patients

			Female		Age in years	
Study	**Setting**	**Centres**	**Intervention group (%)**	**Control group (%)**	**Intervention group**	**Control group**
Neoptolemos et al.[24]	UK	1	34 (58)[a]	35 (56)[a]	55 (20-86)/ 74	67.5 (30-87)/ 76.5
					(38-85)[a,b,c]	(37-96)[a,b,c]
Fölsch et al.[23]	Germany	22	66 (52)	76 (68)	63 (24-90)[c]	63 (15-93)[c]
Oria et al.[19]	Argentina	1	35 (69)	38 (75)	49.9 ± 17.4[d]	44 ± 17.7[d]

a= Including patients with acute cholangitis.
b= Predicted mild/predicted severe groups.
c= Values are median (range).
d= Values are mean ± SD.

TABLE II.4. Meta-analysis (random effects model) for complications and mortality comparing early ERCP with conventional treatment

	Relative risk (95% confidence intervals)	**P value**	**Risk difference (95% Confidence intervals)**	**P value**
Overall complications				
Predicted mild and severe ABP	0.76 (0.41-1.40)	0.38	-0.08 (-0.22-0.07)	0.29
Predicted mild ABP	0.86 (0.62-1.19)	0.36	-0.05 (-0.13-0.04)	0.32
Predicted severe ABP	0.82 (0.32-2.10)	0.68	-0.09 (-0.49-0.30)	0.64
Mortality				
Predicted mild and severe ABP	1.13 (0.23-5.63)	0.88	0.001 (-0.08-0.09)	0.97
Predicted mild ABP	1.90 (0.25-14.55)	0.53	0.01 (-0.02-0.04)	0.40
Predicted severe ABP	1.28 (0.20-8.06)	0.80	0.01 (-0.22-0.24)	0.91

ABP indicates acute biliary pancreatitis.

event fraction (0.001) to the ERCP group to allow inclusion of such trials in the pooled data analysis. Funnel plots were created to explore possible biases (i.e., reporting, publication and reviewer bias).

RESULTS

The literature search yielded 197 publications. The details of the literature search and selection of studies are shown in FIGURE 11.1. Seven potentially eligible RCTs on ERCP in acute pancreatitis were identified and 4 studies were excluded. The first excluded trial[17] studied all patients with acute pancreatitis, irrespective of the cause, instead of only ABP. Moreover, neither patients with acute cholangitis were excluded nor was data for this subgroup presented separately. Patients in the second excluded RCT[23] were randomised to early ERCP, with or without ES, only in the case of persisting ampullary obstruction (based on clinical, biochemical, and imaging criteria) during more than 24 hours. Consequently, ERCP was performed only in 47% of patients in the intervention arm. The third excluded RCT[24] aimed to study exclusively patients with severe nonbiliary pancreatitis. The fourth trial[25] was excluded because patients undergoing duodenoscopy for suspected ABP were subsequently randomised to ES or no ES (i.e., a RCT with different intervention and comparison than the current meta-analysis). Moreover, the last 2 studies[24,25] were only published in abstract form. In the 3 RCTs satisfying the inclusion criteria, patients with acute cholangitis were either excluded specifically,[18,19] or outcome of patients without acute cholangitis was presented separately.[16] With funnel plots publication bias for the different outcomes could not be detected (data not shown). The study characteristics for the 3 trials, including their definition of acute cholangitis, are shown in TABLE 11.1. A total of 450 patients were included: 230 were allocated to early ERCP with or without ES; 220 were allocated to conservative treatment with elective ERCP with or without ES. In the early ERCP groups of the 3 trials altogether, ERCP was successful in 214 of 230 patients (93%). In these 214 patients, ES was performed in 114 patients (53%) and a common bile duct stones were removed in 111 patients (52%). ERCP procedure- related complications occurred in 5 patients (2%). In the conservative treatment groups of the 3 trials altogether, 33 of the 220 patients (15%) underwent ERCP, of which 30 (91%) were successful. In addition, 14 patients underwent ES (47%), common bile duct stones were

removed in 33 patients (43%), and ERCP procedure-related complications did not occur. Two of 3 RCTs had a Jadad quality score[22] grade 2 (TABLE 11.2). The demographic data of patients are summarized in TABLE 11.3. Complications and mortality were reported in all 3 trials. The results of the meta-analysis of the included trials for complications and mortality are presented in TABLE 11.4. Early ERCP reduced the risk for overall complications (pooled RR for all ABP patients: 0.76; 95% CI 0.41-1.40) (FIGURE 11.2) while it increased the risk of mortality (pooled RR for all ABP patients: 1.13; 95% CI 0.23-5.63) (FIGURE 11.3). These results did, however, not reach statistical significance. Because of the low absolute risks for mortality and complications, these RRs translate in a very small reduction in the absolute risk for complications (pooled RD for all ABP patients: -0.08; 95% CI -0.22 to 0.07) and a very small increase in the absolute risk for mortality (pooled RD for all ABP patients 0.001; 95% CI -0.08 to 0.09) (TABLE 11.4). These results did, however, not reach statistical significance. Based on the reported data the meta-analysis was stratified for predicted severe and predicted mild ABP. For this analysis additional unpublished data were provided by Oria et al.[19] It should be noted that Fölsch et al.[18] failed to report the disease severity for 32 patients due to post hoc classification of their data. Consequently, the data on these 32 patients could not be analysed. The stratification for severity did not result in significant differences for the risk of complications (FIGURES 11.4, 11.5) and mortality (FIGURES 11.6, 11.7) between the ERCP group and the conservative treatment group in both patients with predicted mild and predicted severe ABP.

DISCUSSION

In this meta-analysis of RCTs comparing early ERCP, with or without ES, with conservative treatment in patients with ABP without signs of acute cholangitis, no beneficial effect of early ERCP on mortality and overall complications was observed both in patients with predicted mild and patients with predicted severe ABP. These results suggest that early ERCP in patients with ABP without coexisting cholangitis is an unnecessary invasive procedure. Notably, in the included RCTs, only about half the patients that underwent a successful ERCP were found to have common bile duct stones. This finding is in accordance with the recent study by Acosta et al.,[23] in which 62% of patients with ABP and ampullary obstruction (defi-

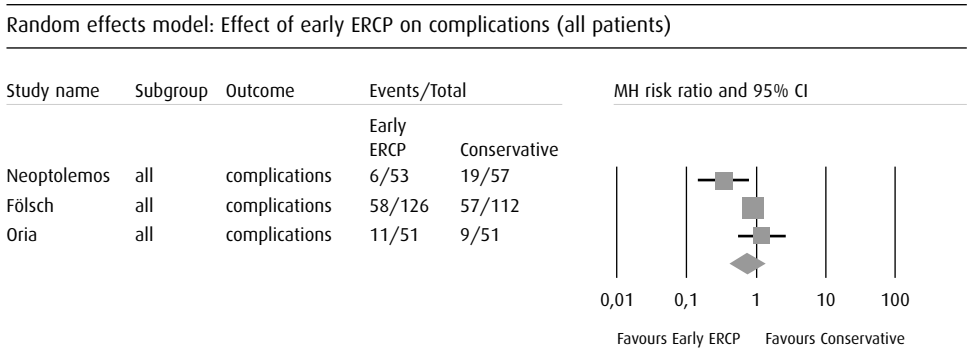

FIGURE 11.2. Forest plot for overall complications associated with early ERCP with or without ES compared with conservative management in all patients with acute biliary pancreatitis.

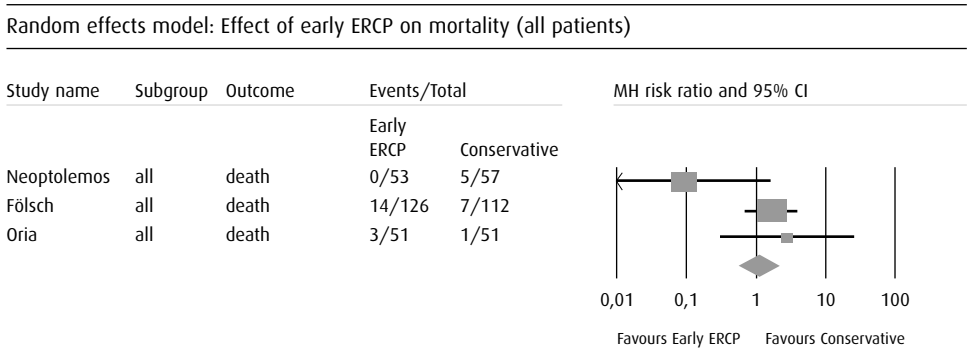

FIGURE 11.3. Forest plot for mortality associated with early ERCP with or without ES compared with conservative management in all patients with acute biliary pancreatitis.

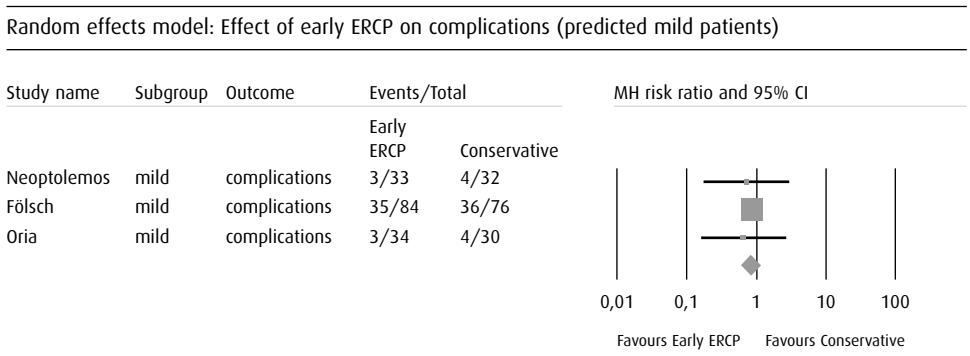

FIGURE 11.4. Forest plot for overall complications associated with early ERCP with or without ES compared with conservative management in patients with predicted mild acute biliary pancreatitis.

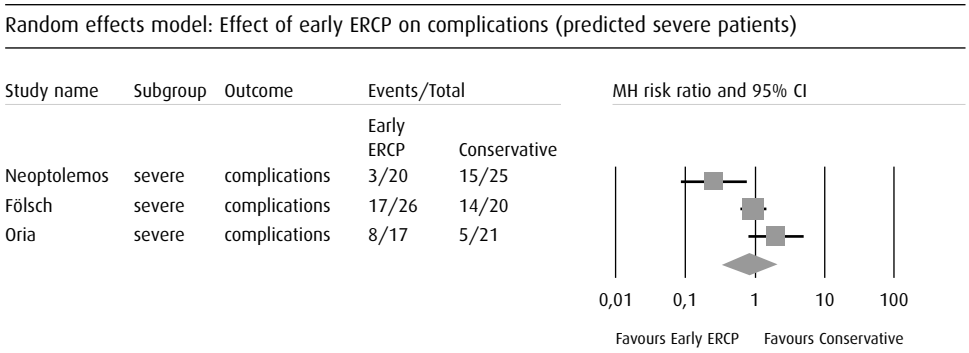

FIGURE 11.5. Forest plot for overall complications associated with early ERCP with or without ES compared with conservative management in patients with predicted severe acute biliary pancreatitis.

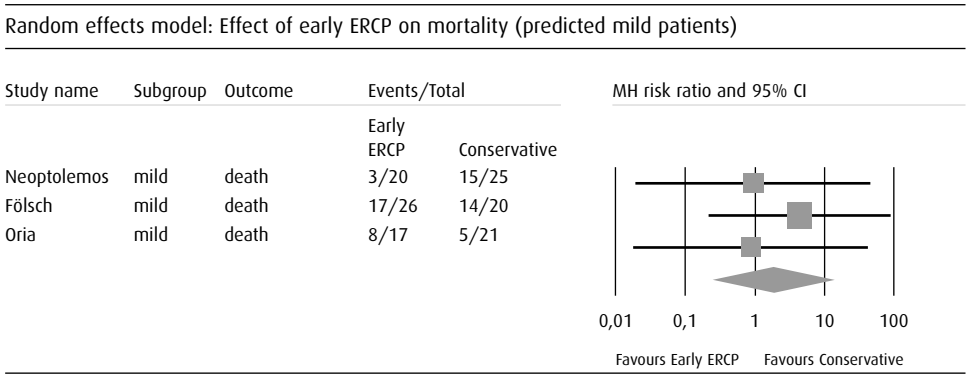

FIGURE 11.6. Forest plot for mortality associated with early ERCP with or without ES compared with conservative management in patients with predicted mild acute biliary pancreatitis.

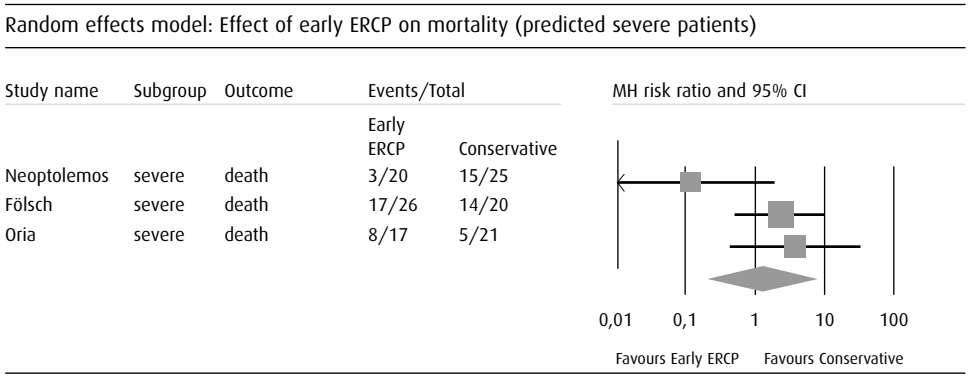

FIGURE 11.7. Forest plot for mortality associated with early ERCP with or without ES compared with conservative management in patients with predicted severe acute biliary pancreatitis.

ned in this study as severe and continuous epigastric pain, bilefree gastric aspirate, and elevated serum bilirubin level) showed spontaneous relief of obstruction within 48 hours from the onset of symptoms. In the RCTs included in this meta-analysis, ES was performed only when common bile duct stones were visualised during ERCP. In daily clinical practice, however, ES is often also performed in the absence of common bile duct stones because of a potential falsenegative ERCP in case of sludge, microlithiasis or missed common bile duct stones. The design of an optimal strategy in biliary pancreatitis is frustrated by a low sensitivity of pre-ERCP diagnostic tools to confirm the presence of common bile duct stones. To increase on this sensitivity several studies with new imaging modalities have been performed. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) have been proposed as minimal invasive diagnostic techniques to identify common bile duct stones, to further reduce the number of unnecessary ERCPs.[26-30] A recent RCT comparing EUS (with selective ERCP and ES in case of common bile duct stones) with ERCP and selective ES in 140 patients with ABP showed a higher success rate for examination rate of the biliary tree with a comparable morbidity and mortality risk in patients undergoing EUS with selective ERCP.[31] On the other hand, MRCP is known to miss small gallstones (<6 mm),[32] while these are associated with the risk for acute pancreatitis.[5] Moreover, both MRCP and EUS are not yet widely available and because experience is scant, EUS may be technically difficult to perform in the early stage of ABP. In the interpretation of the present meta-analysis the following aspects deserve attention. Firstly, the methodological quality of the included trials was relatively low (i.e., Jadad score[22] below 3 for 2 of the 3 included trials). However, these data are still the best available. Secondly, the included trials used different definitions with respect to acute cholangitis, and included different subgroups of patients with ABP (TABLE II.I). Neoptolemos et al.[16] included all patients with ABP and presented separate data on patients without acute cholangitis. Oria et al.[19] included only patients with ABP and clinical evidence of biliopancreatic obstruction without acute cholangitis. Fölsch et al.[18] excluded all patients with a bilirubin >5 mg per deciliter (90 μmol per liter), thereby expelling a proportion of patients with acute cholangitis, but also likely excluding some patients with biliopancreatic obstruction without acute cholangitis. Furthermore, the incidence of cholestasis varied among the 3 included RCTs as a

consequence of the different eligibility criteria of these trials. Although focus has historically been on acute cholangitis rather than cholestasis (without cholangitis), the presence of cholestasis alone might also be of influence on the clinical impact of early ERCP. Thirdly, the 3 studies used different definitions for 'early' ERCP. Neoptolemos et al.[16] considered early ERCP as within 72 hours after admission, regardless of duration of symptoms at time of admission. The 2 other trials[18,19] defined early as within 48 to 72 hours after onset of symptoms. Fourthly, there was considerable variation among the 3 trials in the definition of 'overall complications' as outcome (e.g., gallbladder empyema, recurrent pancreatitis, respiratory insufficiency, ascites, lumbar osteitis, infected pancreatic necrosis). As a likely result of this variation, the incidence of complications in the patients treated conservatively varied from 19%[19] to 51%.[18] The above mentioned differences in patient populations and definitions on intervention and outcome might explain the different outcomes of various trials.

Fifthly, based on the individual findings of the performed RCTs[16-19] and previous meta-analyses,[20,21] the role of early ERCP is most controversial in the subgroup of patients suffering from a predicted severe attack of ABP without signs of acute cholangitis. Although in the current meta-analysis patients with predicted severe ABP did not benefit from early ERCP, it should be noted that the number of patients with predicted severe APB included was relatively small (n=129). Moreover, the accuracy of current clinical scores for predicting severity is known to be quite poor. Oria et al.[19] used quite a low cutoff level (APACHE II >6) for "predicted severe" ABP. As a result, few patients identified as predicted severe eventually did suffer from clinically severe pancreatitis, as shown by low rates of organ failure and limited pancreatic necrosis (a low computed tomography severity index).[19] Fölsch et al.[18] defined severity post hoc which resulted in a failure to define severity in 13% of randomised patients. Finally, the results of this meta-analysis conflict with those of a previous Cochrane meta-analysis,[21] which, unlike this study, included the trial by Fan et al.[17] We excluded the trial of Fan et al. because this study included patients with a nonbiliary cause of acute pancreatitis and included patients with acute cholangitis, without presenting separate data for patients without acute cholangitis. However, when we provisionally included trial by Fan et al. in the calculations, the pooled estimates of this meta-analysis did not change (data not shown). In conclusion, the pre-

sent meta-analysis does not demonstrate a beneficial effect of early ERCP, with or without ES, in both patients with predicted mild and severe ABP without cholangitis. There is, however, a lack of data on the subgroup of patients with predicted severe ABP. Therefore, a new adequately powered RCT in this setting may be justified. In the future study, patients with acute cholangitis should be excluded, timing after onset of the disease should be clearly defined, and stratification for the presence or absence of cholestasis (biochemical and radiological) seems appropriate.

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PART III

CHAPTER 12

Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicentre study

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ABSTRACT

BACKGROUND

The role of early endoscopic retrograde cholangiopancreatography (ERCP) in acute biliary pancreatitis (ABP) remains controversial. Previous studies have included only relatively small number of patients with predicted severe ABP. We investigated the clinical effects of early ERCP in these patients.

METHODS

We performed a prospective, observational multicentre study in 8 university medical centres and 7 major teaching hospitals. 153 patients with predicted severe ABP without cholangitis enrolled in a randomised multicentre trial on probiotic prophylaxis in acute pancreatitis were prospectively followed. Conservative treatment or ERCP within 72 hours after symptom onset (at discretion of the treating physician) were compared for complications and mortality. Patients without and with cholestasis (bilirubin >2.3 mg/dL and/or dilated common bile duct) were analysed separately.

RESULTS

81/153 patients (53%) underwent ERCP and 72/153 patients (47%) conservative treatment. Groups were highly comparable at baseline. 78 patients (51%) had cholestasis. In patients with cholestasis, ERCP (52/78 patients: 67%), as compared with conservative treatment, was associated with fewer complications (25% vs. 54%, P=0.020, multivariate adjusted odds ratio [OR], 0.35; 95% confidence interval [CI], 0.13-0.99; P=0.049). This included fewer patients with >30% pancreatic necrosis (8% vs. 31%, P=0.010). Mortality was nonsignificantly lower after ERCP (6% vs. 15%, P=0.213, multivariate adjusted OR 0.44; 95% CI 0.08-2.28; P=0.330). In patients without cholestasis, ERCP (29/75 patients: 39%) was not associated with reduced complications (45% vs. 41%, P=0.814, multivariate adjusted OR, 1.36; 95% CI 0.49-3.76; P=0.554) or mortality (14% vs. 17%, P=0.754, multivariate adjusted OR 0.78; 95% CI 0.19-3.12; P=0.734).

CONCLUSIONS

Early ERCP is associated with fewer complications in predicted severe ABP if cholestasis is present.

INTRODUCTION

Acute biliary pancreatitis (ABP) is the most common form of acute pancreatitis in the western world.[1,2] It is believed that stones and sludge in the bile duct cause (ampullary) obstruction with subsequent inflammation of the pancreas.[3] In approximately 80% of patients, the disease runs a mild clinical course, whereas in 20% of patients a severe clinical course occurs. The latter is associated with various complications such as pancreatic necrosis, multi-organ failure, and high mortality (up to 30%).[4-6] Theoretically, early endoscopic retrograde cholangiopancreatography (ERCP) may prevent complications in ABP through decompression of the common bile duct (CBD) by removal of gallstones and/or sludge and subsequent sphincterotomy. Therefore, in the last 20 years, several randomised controlled trials (RCTs) have investigated the clinical effect of early ERCP in ABP.[7-10] From these studies it is generally concluded that patients with ABP and concurrent cholangitis should undergo early ERCP, and that patients with predicted mild ABP without cholangitis should not.[1,5] The role of early ERCP in patients with predicted severe ABP, however, remains controversial. While the 2005 UK guidelines on acute pancreatitis recommend emergency ERCP in these patients,[11] two more recent American guidelines state that the value of early ERCP in predicted severe ABP without cholangitis is yet undetermined.[1,5] This is explained by the fact that the published RCTs included only small numbers of patients with predicted severe ABP (range 38-58 patients), and were hence statistically underpowered to detect clinical effects in the group of most severely ill patients.[7-10] In a recent updated meta-analysis, we could not show a beneficial effect of early ERCP in patients with predicted severe ABP without cholangitis.[12] However, the study population was heterogeneous and the sample size remained fairly small. Moreover, there are presently no solid data to determine whether the effect of early ERCP in predicted severe ABP differs between patients with and without radiographic/ biochemical signs of cholestasis.

In the current prospective, observational, multicentre study we examined whether early ERCP, as compared with conservative treatment, is associated with a reduced risk of complications and mortality in patients with predicted severe ABP without cholangitis. Patients with and without cholestasis were assessed separately and the association of ERCP characteristics with clinical outcome was evaluated.

METHODS

STUDY POPULATION AND DESIGN

This study evaluated a subset of patients with predicted severe ABP from a larger cohort of patients enrolled in the Dutch RCT on probiotic prophylaxis in acute pancreatitis (ISRCTN38327949): the PRObiotics in PAncreatitis TRIAl (PROPATRIA).[13] The present observational study was prospectively designed and the study questions and all definitions (e.g., inclusion criteria, treatment groups, endpoints) were established prior to inclusion of the first patient.

PROPATRIA included adult patients with a primary episode of predicted severe acute pancreatitis of all causes. Acute pancreatitis was defined as abdominal pain with serum amylase and/or lipase levels elevated to at least three times the institutional upper limit of normal. Criteria for predicted severe acute pancreatitis were: **a**. an Acute Physiology and Chronic Health Evaluation (APACHE)-II score ≥8,[14] or **b**. Imrie score ≥3,[15] or **c**. C-reactive protein (CRP) >150 mg/L[16] within 72 hours after onset of symptoms. Between March 2004 and March 2007, PROPATRIA enrolled 296 consecutive patients with predicted severe acute pancreatitis in 8 university medical centres and 7 major teaching hospitals.

The current study included all patients from PROPATRIA diagnosed with ABP within 72 hours after onset of symptoms. ABP was defined as: **a**. gallstones and/or sludge diagnosed on trans-abdominal ultrasound or computed tomography (CT) performed on admission or **b**. dilated CBD on ultrasound or CT (diameter >8 mm for age 75 years and diameter >10 mm for age >75 years) **c**. two of the following three laboratory abnormalities: **1**. serum bilirubin level >2.3 mg/dL [40 μmol/L]; **2**. alanine aminotransferase (ALAT) level >100 U/L with an ALAT level greater than the aspartate aminotransferase (ASAT) level; **3**. alkaline phosphatase (AF) level >195 U/L with a gamma-glutamyltransferase (GGT) level >45 U/L. Other causes of acute pancreatitis (e.g., alcohol abuse) and signs of chronic pancreatitis (history and CT) had to be absent. The published RCTs on this topic have used similar radiographical[7,9,10] and/ or biochemical[7,9] prediction for ABP.

Based on the situation within 72 hours after onset of symptoms and before ERCP, patients were divided into three predefined groups: **1**. potential cholangitis (serum bilirubin level >1.2 mg/dL [20 μmol/L] and/ or dilated CBD on ultrasound or CT and temperature >38.5°C); **2**. cholestasis (serum bilirubin level >2.3 mg/dL [40

μmol/L] and/or dilated CBD, and temperature <38.6°C) and 3. no cholestasis or potential cholangitis. To prevent confounding by cholangitis (an established indication for emergency ERCP[17]) patients with potential cholangitis were excluded from further analysis. We used a broad definition for cholangitis (including a lower cut off level for bilirubin than in the criteria for cholestasis) to prevent the unintentional inclusion of patients with cholangitis and over-estimating the effects of ERCP.
This study was conducted in accordance with the principles of the Declaration of Helsinki. The ethical review board of each participating hospital approved the protocol. All patients or their legal representatives gave written informed consent.

TREATMENT PROTOCOL

Patients were treated according to a fixed treatment protocol.[13] This consisted of nasojejunal enteral feeding with a probiotic preparation or placebo according to treatment allocation, administered within 72 hours after onset of symptoms for a maximum of 28 days. Antibiotic prophylaxis in necrotising pancreatitis was not allowed. Physical examination and laboratory measurements were performed daily. Contrast-enhanced CT was performed routinely on 7-10 days after admission. Patients with infected necrotising pancreatitis were treated with percutaneous drainage and/or operative intervention according to decision of the treating physician.

EARLY ERCP AND CONSERVATIVE TREATMENT GROUPS

The decision to perform ERCP with or without sphincterotomy was left to the treating physician. ERCP was readily available in all centres. Patients were assigned to the 'early ERCP' group when ERCP was performed within 72 hours after onset of symptoms. Patients not undergoing ERCP or undergoing ERCP later than 72 hours were included in the 'conservative treatment group'. ERCP was considered successful when the CBD could be cannulated and stones or sludge (if present) were evacuated after sphincterotomy. All ERCP procedures were performed by experienced endoscopists.

ENDPOINTS

The primary endpoints were mortality and overall complications (see box for definitions) during admission and 90-day follow-up after admission. All complications

were weighted equally; multiple complications in the same patient were considered as one endpoint. Organ failure was defined as PaO_2 <60 mmHg despite FiO_2 of 30%, or the need for mechanical ventilation (pulmonary insufficiency); serum creatinine >177 mmol/L after rehydration or need for haemofiltration or hemodialysis (renal failure), and systolic blood pressure <90 mmHg despite adequate fluid resuscitation or need for vasopressor support (cardiocirculatory insufficiency), adapted from the Atlanta Classification.[4] Multi-organ failure was defined as failure of two or more organ systems on the same day.

Secondary endpoints were the CT severity index (CTSI),[18] the need for percutaneous drainage or operative intervention because of (documented or suspected) infected necrosis, hospital stay, and intensive care stay.

DATA COLLECTION

Local physicians completed the case-record forms prospectively. An independent data monitor performed an on site cross-check of at least 10% of the individual patient data. One experienced radiologist (TLB) blinded for treatment (early ERCP or conservative) and clinical outcome re-evaluated all CTs for the presence and extent of pancreatic necrosis and CTSI. Before any analysis and blinded for treatment, two investigators (HCvS and MGHB) checked all data on baseline characteristics and primary or secondary endpoints with primary source data. All ERCP procedures were double-checked with primary source data by an experienced endoscopist (KJvE) unaware of clinical outcome. Analyses were performed only after agreement was reached on all endpoints.

STATISTICAL ANALYSIS

Analyses for the current study were performed according to a pre-established analysis plan using SPSS version 12.01 (SPSS, Chicago, IL, USA). The early ERCP group was compared with the conservative treatment group for primary and secondary endpoints. Patients with and without cholestasis were analysed separately. Continuous data are presented as mean (± SD) and in case of skewed distributions as median (range). Differences were tested by the Student's t test or Mann-Whitney U test, respectively. Proportions were compared by the Fisher's exact test. Being interested in the effect on the primary endpoint of early ERCP only, multivariate

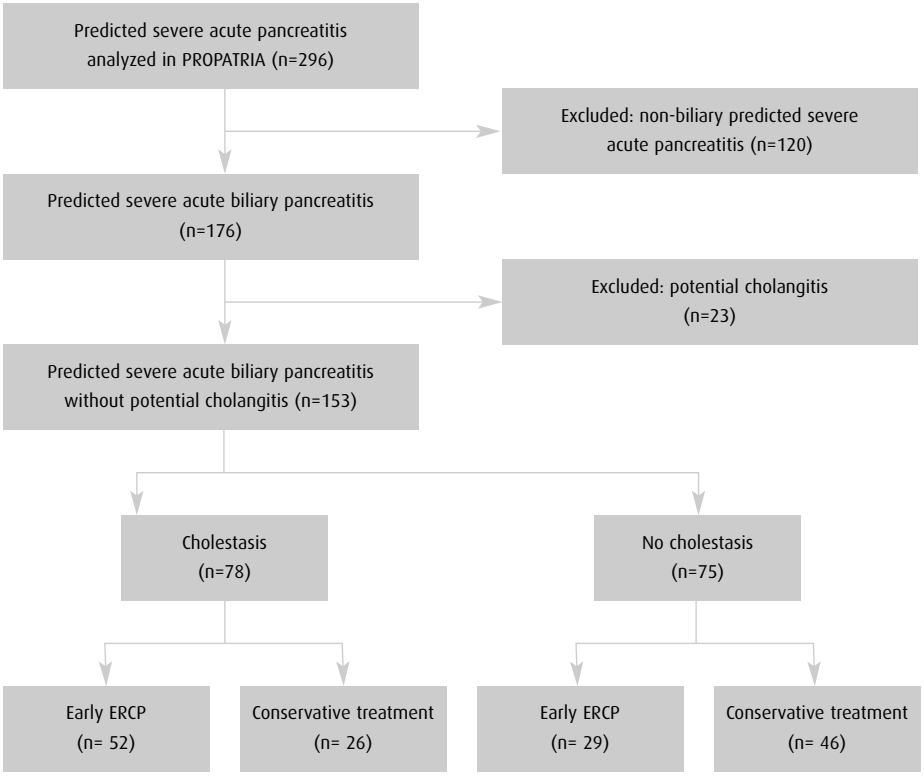

FIGURE 12.1. Patient inclusion flowchart

logistic regression was used to adjust for possible confounders. All baseline variables that differed between the early ERCP group and conservative treatment group ($P<0.200$) were entered in the model as covariates. The APACHE-II score was always included to adjust for disease severity. Backward stepwise regression was used to exclude variables with $P>0.050$. Accordingly, we used logistic regression to investigate whether, in patients undergoing ERCP, there was any association between the primary endpoints and the following ERCP characteristics: sphincterotomy, pre-cut sphincterotomy, and cannulation/contrast injection of the pancreatic duct. Results of logistic regression are presented as adjusted odds ratios (OR) with exact 95% confidence intervals (CI). A two-sided $P<0.050$ was considered statistically significant.

RESULTS

Patient inclusion is shown in FIGURE 12.1. During the study period, 176 patients with predicted severe ABP were included. On admission, gallbladder stones were detected in 125 patients, gallbladder sludge in 10 patients, dilated CBD in 37 patients and biochemical criteria were met in 140 patients.

Presence of gallstones was proven unequivocally during admission (admission US or CT or ERCP) in 147/ 176 patients (84%). A total of 23 patients (13%) met the criteria for potential cholangitis and were excluded. Of the remaining 153 patients, 78 (51%) had cholestasis and 75 (49%) did not have cholestasis. Median time from onset of symptoms to admission was 0 days (range 0-3). Median number of patients enrolled per centre was 9 (range 1-26). Median percentage of patients with predicted severe ABP who underwent early ERCP in each centre was 50% (range 0-100%). There were three centres in which more than 80% of patients underwent ERCP and three centres in which fewer than 30% of patients underwent ERCP. Frequency of ERCP was not associated with patient characteristics: patient demographics, disease severity, and incidence of cholestasis were similar among the 15 centres (data not shown).

From the total of 153 patients, 81 patients (53%) underwent early ERCP and 72 patients (47%) underwent conservative treatment. Median time from onset of symptoms to early ERCP was 1 day (range 0-2). ERCP was performed in the first 24 hours after symptom onset in 17 patients (20%), between 25 and 48 hours after symptom onset in 53 patients (66%) and between 49 and 72 hours after symptom onset in 11 patients (14%).

In the conservative treatment group, elective ERCP was performed in 7 patients at a median of 5 days (range 4-18) after onset of symptoms. None of these patients had cholangitis, but 5 had cholestasis within 72 hours after onset of symptoms. Reasons for ERCP in the conservative treatment group were: persisting cholestasis (n=4), new onset cholestasis (n=1), contraindication for cholecystectomy due to co-morbidity (n=1) and suspicion of an impacted stone in CBD on CT (n=1).

PATIENTS WITH CHOLESTASIS

In the group with cholestasis (n=78), 52 patients (67%) underwent early ERCP and 26 patients (33%) conservative treatment. The APACHE-II score on admission

TABLE 12.1. Baseline characteristics of 153 patients with predicted severe biliary pancreatitis undergoing early ERCP or conservative treatment

	PATIENTS WITH CHOLESTASIS (n=78)			PATIENTS WITHOUT CHOLESTASIS (n=75)		
Characteristics	**Early ERCP (n=52)**	**Conservative treatment (n=26)**	**P value**	**Early ERCP (n=29)**	**Conservative treatment (n=46)**	**P value**
Age in years	64.1 (±15.7)	66.3 (±13.3)	0.56	62.9 (±15.6)	65.9 (±15.5)	0.43
Male sex	23 (44%)	15 (58%)	0.34	11 (38%)	23 (50%)	0.35
Probiotics	26 (50%)	15 (58%)	0.63	18 (62%)	27 (59%)	0.81
Body Mass Index	28 (±5.6)	29 (±8.8)	0.89	28 (±6.3)	27 (±6.8)	0.75
ASA class[a]			0.42			0.02
I (healthy status)	28 (54%)	10 (38%)		18 (62%)	14 (31%)	
II (mild systemic disease)	23 (44%)	15 (58%)		10 (35%)	24 (52%)	
III (severe systemic disease)	1 (2%)	1 (4%)		1 (3%)	8 (17%)	
Time from symptoms to admission	1 (0-2)	1 (0-3)	0.69	0 (0-3)	0 (0-1)	0.39
Severity of disease						
APACHE-II (on admission)	8.0 (0.0-17.0)	9.5 (3.0-18.0)	0.06	8.0 (1.0-19.0)	9.0 (1.0-15.0)	0.37
Imrie score (first 48 hrs)	3.0 (0.0-0.7)	4.0 (0.0-6.0)	0.22	3.0 (1.0-7.0)	3.0 (1.0-6.0)	0.73
C-reactive protein (mg/L)[b]	80 (±103)	111 (±136)	0.30	65 (±86)	61 (±77)	0.87
Leucocytes (x 109/L)[b]	15.3 (6.1-33.8)	14.7 (9.2-31.6)	0.93	17.5 (8.4-22.5)	16.8 (8.4-30.7)	0.82
MODS (on admission)[c]	2.0 (0.0-6.0)	1.0 (0.0-8.0)	0.93	1.0 (0.0-3.0)	1.0 (0.0-4.0)	0.47
SOFA (on admission)[d]	2.0 (0.0-7.0)	2.5 (0.0-8.0)	0.45	1.0 (0.0-4.0)	1.0 (0.0-5.0)	0.59
Organ failure[e]	1 (2%)	2 (8%)	0.26	2 (7%)	0 (0%)	0.15
Multi-organ failure[e]	0 (0%)	0 (0%)	0.99	0 (0%)	0 (0%)	0.99
Body temperature (°C)[b]	37.4 (±0.7)	37.4 (±0.8)	0.89	37.5 (±1.0)	37.9 (±0.7)	0.05
Cholestasis						
Dilated common bile duct	20 (39%)	12 (46%)	0.63	0 (0%)	0 (0%)	0.99
Bilirubin (mg/dL)[f]	4.0 (±2.7)	4.6 (±2.8)	0.35	1.4 (±0.5)	1.3 (±0.5)	0.22

Data are presented as n (%), mean (±SD), or median (range).
a= ASA: assessed based on the patient's history just prior to admission; there were no patients with ASA class 4 or 5.; b= In the early ERCP group: highest value before ERCP, in the conservative treatment group: highest value during the <24 h after onset of symptoms or on admission; c= MODS ranges from 0 to 24, with higher scores indicating more severe disease; d= SOFA ranges from 0 to 24, with higher scores indicating more severe disease; e= In the early ERCP group: organ failure before ERCP, in the conservative treatment group: organ failure during the <24 hours after onset of symptoms or on admission; f= In the early ERCP group: highest value before ERCP, in the conservative treatment group: highest value during the <72 hours after onset of symptoms.

TABLE 12.2. Outcome of 153 patients with predicted severe acute biliary pancreatitis undergoing early ERCP or conservative treatment

	PATIENTS WITH CHOLESTASIS (n=78)			PATIENTS WITHOUT CHOLESTASIS (n=75)		
Characteristics	Early ERCP (n=52)	Conservative treatment (n=26)	P value	Early ERCP (n=29)	Conservative treatment (n=46)	P value
Primary endpoints						
Overall complications	13 (25%)	14 (54%)	0.02	13 (45%)	19 (41%)	0.81
Pancreatic necrosis	8 (17%)	9 (38%)	0.08	10 (36%)	13 (30%)	0.79
<30% pancreatic necrosis	4 (8%)	1 (4%)	0.66	4 (14%)	7 (15%)	0.99
>30% pancreatic necrosis	4 (8%)	8 (31%)	0.01	6 (21%)	6 (13%)	0.52
Infected pancreatic necrosis	4 (8%)	5 (20%)	0.15	5 (17%)	5 (11%)	0.49
Bacteraemia	6 (12%)	6 (23%)	0.20	7 (24%)	6 (13%)	0.23
Infected ascites	0 (0%)	1 (4%)	0.33	1 (3%)	1 (2%)	0.99
Pneumonia	4 (8%)	4 (16%)	0.43	3 (10%)	4 (9%)	0.99
New onset organ failure	6 (12%)	4 (16%)	0.72	6 (20%)	7 (15%)	0.55
New onset multi-organ failure	6 (12%)	3 (12%)	0.99	6 (20%)	9 (20%)	0.99
Bowel ischaemia*	1 (2%)	0 (0%)	0.99	1 (4%)	1 (2%)	0.99
Mortality	3 (6%)	4 (15%)	0.21	4 (14%)	8 (17%)	0.75
Secondary endpoints						
CTSI†	3.0 (0.0-10.0)	3.5 (0.0-10.0)	0.46	4.0 (0.0-10.0)	4.0 (0.0-10.0)	0.81
Percutaneous drainage	4 (8%)	2 (8%)	0.99	3 (10%)	2 (4%)	0.37
Operative necrosectomy	4 (8%)	4 (15%)	0.43	6 (21%)	4 (9%)	0.17
Intensive care admission	12 (23%)	7 (27%)	0.78	9 (31%)	8 (17%)	0.26
Total intensive care stay in days	0 (0-89)	0 (0-110)	0.76	0 (0-30)	0 (0-40)	0.16
Total hospital stay in days	14 (3-140)	20 (5-112)	0.22	13 (5-155)	16 (3-85)	0.93

Data are presented as n (%) or median (range).
*Bowel ischaemia was probably an adverse event of probiotic treatment, as suggested by the PROPATRIA-study13, and was added to the endpoints post-hoc in the current study.
†CTSI, ranges from 0-10, with higher score indicating more extensive pancreatic necrosis and peripancreatic fluid collections.

tended to slightly higher in the conservative treatment group than in the early ERCP group (P=0.064; TABLE 12.1). The early ERCP and conservative treatment groups were comparable for all other baseline variables (TABLE 12.1).

Primary and secondary endpoints are presented in TABLE 12.2. Significantly fewer patients after early ERCP suffered from one or more complications (P=0.020). Especially substantial (>30%) pancreatic necrosis occurred in significantly fewer patients in the early ERCP group (P=0.010). After adjustment for the APACHE-II score in multivariate analysis, early ERCP remained associated with a lower risk of overall complications (adjusted OR 0.35; 95% CI 0.13-0.99; P=0.049). Mortality was non-significantly lower in the early ERCP group (P=0.130, adjusted OR in multivariate analysis, 0.44; 95% CI 0.08-2.28; P=0.330). Additional adjustment for individual institution with multivariate analysis did not affect the results: the statistically significant beneficial effect of ERCP remained.

PATIENTS WITHOUT CHOLESTASIS

In the group without cholestasis (n=75), 29 patients (39%) underwent early ERCP and 46 patients (61%) received conservative treatment. On admission, patients in the conservative group had a significantly higher American Society of Anesthesiologists (ASA) class than patients in the early ERCP group (P=0.016; TABLE 12.1). All other baseline variables were similar for both treatment groups.

The incidence of overall complications and mortality was similar in the early ERCP group and the conservative treatment group (P=0.814 and P=0.754 respectively; TABLE 12.2). Multivariate analysis (with the APACHE-II score as the only significant covariate after backward stepwise regression) did not show a significant beneficial effect of early ERCP (overall complications: adjusted OR 1.36; 95% CI 0.49-3.76; P=0.554, mortality: adjusted OR 0.78; 95% CI 0.19-3.12; P=0.734). Adjustment for individual institution in multivariate analysis did not change these results.

DETAILS OF EARLY ERCPS

The characteristics of the 81 early ERCPs are presented in TABLE 12.3. The incidence of CBD stones during ERCP was higher in patients with cholestasis than in patients without cholestasis, although not statistically significant (P=0.254). There were no other differences between patients with and without cholestasis, including

TABLE 12.3. Characteristics of ERCP procedures performed in 81 patients with predicted severe acute biliary pancreatitis

ERCP characteristic	Patients with cholestasis (n=52)	Patients without cholestasis (n=29)	P value
Cannulation common bile duct	47 (90%)	24 (82%)	0.48
Stones in common bile duct	29 (56%)	12 (41%)	0.25
Sludge in common bile duct	17 (33%)	10 (34%)	0.99
Cannulation of pancreatic duct	25 (48%)	15 (52%)	0.82
Contrast in pancreatic duct	25 (48%)	12 (41%)	0.99
Papillotomy performed	45 (87%)	24 (83%)	0.99
Pre-cut papillotomy performed	9 (17%)	5 (17%)	0.99
ERCP Successful	46 (89%)	24 (82%)	0.51

Data are presented as n (%).

the percentage of sludge found in the CBD during ERCP. In 3 out of the 81 patients undergoing early ERCPs a stent was placed in the CBD. Reasons for biliary stents were: an impacted stone in the CBD that could not be removed during ERCP (n=1), the fact that the endoscopist was not completely sure that the CBD was free of stones at the end of the procedure (n=1) and contra-indication for sphincterotomy because of clotting disturbance (n=1). The first two of these patients also underwent sphincterotomy during the procedure. No stents were placed in the pancreatic duct. Sphincterotomy was performed in the large majority of ERCPs. In one patient in the group without cholestasis, diffuse bleeding occurred after sphincterotomy, requiring local injections of epinephrine. Although deterioration of pancreatitis as a direct result of ERCP is difficult to assess, all indicators, including daily serum levels of amylase and CRP during the first week of admission, were similar in the ERCP and conservative groups (data not shown).

When evaluating the association of ERCP characteristics with clinical outcome in multivariate analysis, the APACHE-II score remained the only significant covariate after backward stepwise regression. There was no significant relation between timing of ERCP (days between symptom onset and ERCP) and complications (adjusted OR 1.32; 95% CI 0.58-2.99; P=0.505) or mortality (adjusted OR 0.47; 95%

CI 0.11-2.01; P=0.307). Sphincterotomy was associated with a significant reduction in overall complication rate (adjusted OR 0.24; 95% CI 0.06-0.93; P=0.040) albeit without a significant effect on mortality (adjusted OR 1.38; 95% CI 0.13-14.44; P=0.786). The apparent reduction in complications included fewer patients with bacteraemia (11% vs. 45%, P=0.010) and pneumonia (6% vs. 27%, P=0.049). Of the 69 patients who underwent sphincterotomy, clinical outcome was similar for those with stones and/or sludge in the CBD and without stones and/or sludge in the CBD: complications occurred in 10/40 patients (25%) and 8/29 patients (28%) respectively (P=1.000). Pre-cut sphincterotomy was also not significantly associated with the incidence of overall complications (adjusted OR 1.64; 95% CI 0.49-5.44; P=0.423) or mortality (adjusted OR 2.75; 95% CI 0.40-18.75; P=0.303). Furthermore, cannulation/contrast injection of the pancreatic duct showed no significant association with overall complications (adjusted OR 0.79, 95% CI 0.29-2.13, P=0.643) or mortality (adjusted OR 1.15, 95% CI 0.21-6.18, P=0.871). In addition, indicators for pancreatic inflammation such as daily serum levels of amylase and CRP during the first week of admission did not differ between patients who had pancreatic duct cannulation/contrast injection and patients who did not have pancreatic duct cannulation/contrast injection (data not shown).

DISCUSSION

This study is the largest prospective study conducted so far comparing early ERCP with conservative treatment in patients with predicted severe ABP without cholangitis. Outcome was compared according to the presence of cholestasis. The major findings are: **1**. In patients with predicted severe ABP and concurrent cholestasis, early ERCP was associated with significantly fewer complications, including substantial pancreatic necrosis, and a non-significantly lower mortality; **2**. In patients with predicted severe ABP without concurrent cholestasis, early ERCP was not associated with a significant reduction of complications or mortality; **3**. In patients undergoing early ERCP, sphincterotomy was significantly associated with fewer complications, whereas precut sphincterotomy or pancreatic duct cannulation/contrast injection were not significantly associated with obvious adverse effects.

Four published RCTs have studied the effect of early ERCP in ABP.[7-10] Only the first two studies found beneficial effects of early ERCP.[7,8] When comparing the four

RCTs with the current study, several issues about these trials need to be taken into account. First, different subgroups of pancreatitis were included: **1**. all patients with ABP, including those with cholangitis,[7] **2**. acute pancreatitis of all causes,[8] **3**. only patients with ABP without 'severe' obstructive jaundice (bilirubin <5 mg/dL),[9] and **4**. only patients with ABP with 'biliopancreatic obstruction' (bilirubin >1.3 mg/dL) and CBD ≥8 mm), but without cholangitis.[10] Secondly, definitions varied considerably between studies: e.g., for 'ABP', 'cholangitis', 'early ERCP' (ranging from <48 hours after symptom onset[10] to within 72 hours after admission[7]), and 'overall complications'. Thirdly, complications evaluated were often clinically only marginally relevant and not clearly defined. Finally, the RCTs mostly included patients with predicted mild ABP, who have a low *a priori* risk of complications. The vast majority of gallstones in predicted mild ABP probably pass spontaneously before ERCP is performed. Several meta-analyses on the current topic have been performed with conflicting results.[12,19,20] Only the most recent meta-analysis included all RCTs that studied patients with predicted severe ABP without cholangitis (3 RCTs, 129 patients).[12] Early ERCP (n=63) did not significantly reduce the risk of overall complications (relative risk, 0.82; CI 0.32-2.10; P=0.68) or mortality (relative risk 1.13; 95% CI 0.23-5.60; P=0.88). While these data suggest that early ERCP is not beneficial, there is a substantial risk of a type II statistical error because patient numbers were relatively small. More importantly, only a handful of patients in the pooled data suffered from predicted severe ABP with concurrent cholestasis. Data on these patients were not separately presented in the individual trials precluding subgroup analysis.

Baseline characteristics of the current study population can not be compared with other studies on early ERCP in ABP, because this is the first study to investigate patients with predicted severe ABP only. Patient demographics and disease severity are, however, in line with recent multicentre studies on other interventions in predicted severe acute pancreatitis.[21,22] In patients without cholestasis, ASA class was somewhat lower in the early ERCP group than in the conservative treatment group. Despite this potential advantage in clinical condition for the ERCP group, ERCP was not associated with a beneficial effect, both in the crude and adjusted multivariate analysis. In the group with cholestasis, patients undergoing early ERCP tended to have a lower APACHE-II score (1.5 points) on admission. Although this

slight difference is probably clinically not meaningful, we adjusted for this in the multivariate analysis: this did not change our results.

Regarding the ERCP characteristics in the present study, ERCP success rate, the rate of ERCP-associated complications and the percentage of CBD stones found during ERCP were similar to previous reports.[7,10] In multivariate analysis, sphincterotomy was associated with a significant reduction in overall complication rate. This suggests that sphincterotomy should always be performed after early ERCP in patients with predicted severe ABP, also in absence of CBD stones. In the latter situation, sphincterotomy can be useful to remove sludge and microlithiasis (only detected during microscopical examination)[23] which are important factors in the pathogenesis of ABP.[24] If ERCP is performed for other indications than acute pancreatitis, specific characteristics of the procedure (e.g., precut sphincterotomy, pancreatic duct cannulation or contrast injection) are associated with an increased risk of complications.[25] In the current study, precut sphincterotomy and pancreatic duct cannulation or contrast injection were not associated with clinical outcome. Numbers were, however, too small to draw solid conclusions. Although the incidence of CBD stones during ERCP seemed higher in patients with cholestasis than in patients without cholestasis, the magnitude of the difference was not convincing. Probably, biliary obstruction is caused by other factors than gallstones (e.g., sludge, microlithiasis or an oedematous pancreas) in a considerable number of patients in the cholestasis group. Stones may also have passed to the duodenum shortly before ERCP.

We found definite evidence of gallstone etiology in 84% of our patients. Because the sensitivity of trans-abdominal ultrasound to detect gallbladder stones in patients with acute pancreatitis is decreased to approximately 65%, as compared to 90-95% in patients without pancreatitis,[26-28] and because some patients exhibit only microlithiasis and biliary sludge,[24] one has to rely on additional criteria to establish a likely biliary cause of acute pancreatitis on admission. Indeed, microscopic evaluation of bile detects cholesterol crystals or sludge in 35-70% of patients presumed to have acute 'idiopathic' pancreatitis.[29-31] We relied in the present study, on a combination of radiological and biochemical criteria, similar to earlier RCTs on this topic.[7,9] A recent authorative review[26] advises the criteria of either gallbladder stones on trans-abdominal US and/or serum ALAT >60 IU during the first 48 hours of admission

as diagnostic criteria for ABP. In our study, 166/176 patients (94%) met these diagnostic criteria on admission. Nevertheless, we can not rule out that we have unintentionally included some patients with idiopathic pancreatitis. If this occurred, however, it did not affect the results: when excluding patients without definite gallstone etiology as based on admission radiology and/or ERCP from our analysis, patients in the cholestasis group (n=65) who underwent ERCP still had significantly fewer complications than those treated conservatively (56% vs. 25%, P=0.03).

We aimed to exclude patients with cholangitis because inclusion of these patients would lead to potential bias toward a favourable effect of ERCP. Also, cholangitis is an established indication for early ERCP.[1,5,11] Despite our broad criteria for 'potential cholangitis', we can not rule out the possibility that we unintentionally included some patients with cholangitis, because cholangitis can also occur without elevated bilirubin and with temperatures below 38.5°C (i.e., our criteria for 'potential cholangitis'). Therefore, we want to stress that especially in case of conservative approach, the clinician has to monitor the patient carefully for signs of emerging cholangitis, which can also develop at a later stage in the course of the disease. A theoretical advantage of early sphincterotomy is that it largely prevents risk of subsequent cholangitis. It should be noted, however, that none of the patients in the conservative group (including the 7 patients who had a late ERCP) developed clinical signs of cholangitis. Of the 23 excluded patients with 'potential cholangitis' 12 patients underwent early ERCP (complications 42%, mortality 0%) and 11 conservative management including antibiotics (complications 46%, mortality 18%). Although this subgroup is obviously too small to generate statistically sound conclusions, we agree with international guidelines that ERCP is indicated in patient with cholangitis.[1,5,11] In a post-hoc analysis combining patients with 'cholestasis' and 'potential cholangitis' in the current study (n=101), ERCP was still associated with significantly fewer complications (50% vs. 29%, P=0.03).

A limitation of the current study is that it did not have randomised design. On the other hand, we included a large number of patients (153 patients, as compared with 129 patients in the pooled data of the available RCTs[12]) with a high percentage of concurrent cholestasis (51%) and we performed rigorous prospective data collection. Moreover, baseline characteristics were highly similar between the early ERCP and conservative treatment group. This is explained by the great variation in indi-

cation for ERCP among centres (0-100%) independent of disease severity and the incidence of cholestasis in each centre. Consequently, when pooling the data from all centres, early ERCP and conservative treatment could be compared with a minimal risk of selection bias (thereby increasing internal validity). Therefore, we believe the variation in indication for ERCP among the participating centres is not a shortcoming, but rather an advantage that allowed us to perform the current analysis. Furthermore, as selection bias can never be completely ruled out in a non-randomised design, we adjusted for potential differences at baseline and disease severity with logistic regression. Notably, this did not change our results.

One may argue that future studies on this topic are needed. Based on the data of the current study, a new RCT would need a sample size of 2 x 50 patients with predicted severe ABP and cholestasis to show a statistically significant effect of early ERCP in patients with concurrent cholestasis (reduction of complications from 54% to 25% by ERCP, β=0.20, two sided α=0.05). Although this represents quite a challenge requiring a collaboration of multiple high volume (international) centres, such a study would be feasible. However, to detect a significant effect of early ERCP in patients without cholestasis (the result of the current study suggest the effect of ERCP, if present at all, would be very small), a very large sample size would be needed: i.e. to show a 10% absolute difference in complications 2 x 365 patients with predicted severe ABP without cholestasis would have to be randomised. It is recognized that a new RCT on early ERCP in (predicted severe) ABP will probably not be performed in the near future.[32] In the situation were it is unfeasible to perform RCTs, well-designed, prospective, observational studies must yield the evidence needed for clinical decision making.

What is the relevance of the current study for clinical practice? Our results illustrate that consensus on this topic is lacking in daily practice, as the decision to perform early ERCP varied greatly between 15 Dutch hospitals (including all university medical centres). In patients without cholestasis, conservative treatment did not lead to poorer outcome or secondary cholangitis, suggesting that early ERCP can be withheld when cholestasis is absent. Nevertheless, these patients should still be carefully monitored for emerging cholangitis at later stage.

In the presence of cholestasis, patients treated conservatively had poorer outcomes than those undergoing early ERCP. We therefore feel ERCP should be especially

considered whenever a patient with predicted severe ABP shows signs of cholestasis.

In conclusion, the present study shows that early ERCP is associated with a significantly reduced risk of clinically relevant complications in patients with predicted severe ABP with concurrent cholestasis. In patients without concurrent cholestasis, there were no beneficial effects associated with early ERCP. These findings may be relevant for decision making in patients with predicted severe ABP.

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PART IV

Intervention for necrotising pancreatitis

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PART IV

CHAPTER 13

Percutaneous catheter drainage as primary treatment for necrotising pancreatitis: a systematic review of the literature

– a summary –

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INTRODUCTION

For long, the first choice intervention in infected necrotising pancreatitis has been primary open necrosectomy with the aim to remove all infected necrosis.[1-3] This approach is associated with considerable morbidity (34-95%) and mortality (11-39%)[1,3-8] Some patients with sterile necrosis will ultimately also undergo necrosectomy in case of clinical deterioration (i.e., multiple organ failure) despite maximal supportive therapy on the basis of suspected infection.

In 1998, Freeny et al. first described a consecutive series of patients exclusively with infected necrosis who were primarily treated with imaging-guided percutaneous catheter drainage (PCD), as an alternative to primary surgical necrosectomy.[9] The rationale for PCD was to temporize sepsis and thereby postpone the need for surgical necrosectomy. In the last decade, several cohort studies on PCD have been published. We aimed to determine the proportion of patients that can be treated with PCD without the need for additional necrosectomy from the published literature.

METHODS

A systematic literature search was performed in EMBASE, MEDLINE and the Cochrane libraries from January 1st, 1992 to May 31st, 2010. We screened studies reporting on patients undergoing PCD of peripancreatic collections associated with pancreatitis. Inclusion criteria were: **1**. a consecutive cohort of patients with acute necrotising pancreatitis (ANP) undergoing PCD as a primary treatment of peripancreatic collections; **2**. indication for PCD: (suspected) infected necrosis or symptomatic sterile pancreatic necrosis (e.g., clinical deterioration or significant mechanical obstruction); **3**. essential outcomes reported: percentage of infected peripancreatic collections, need for additional surgical necrosectomy, complications and mortality.

Exclusion criteria were: **1**. very small cohorts (<5 patients); **2**. cohorts including chronic pancreatitis (and results for acute pancreatitis not reported separately); **3**. studies on a selected subgroup of patients with acute pancreatitis, classified as 'pseudocysts' or 'pancreatic abscesses' (as defined by the Atlanta Classification) or sterile pancreatic necrosis exclusively; **4**. cohorts of patients undergoing minimally invasive surgical necrosectomy which included previous PCD and cases treated by PCD only were not separately reported. From the included articles we extracted data on

disease severity, indication and details of PCD, success of PCD (defined as survival without the need for additional surgical necrosectomy) and clinical outcome.

RESULTS

After screening of titles and abstracts of 4670 relevance eleven studies were included in the current systematic review.[9-19] Nine studies were retrospective, non-controlled case-series,[9-17] one study was a prospective, non-controlled case-series[18] and one study was a multicentre randomised controlled trial.[19] The pooled data comprised a total of 384 patients undergoing PCD as primary treatment for (suspected) infected necrosis or symptomatic sterile pancreatic necrosis (range of number of patients per study 8-80).

Four studies (116 patients) reported on percentage of patients suffering from organ failure prior to PCD. Out of these 116 patients, 78 (67%) had organ failure (34 single and 44 multiple organ failure) prior to PCD. Out of the total of 384 patients, 271 patients (71%) had infected peripancreatic necrosis.

The success rate of PCD, defined as the percentage of patients surviving without additional surgical necrosectomy, was 214/384 patients (56%). Eight studies reported specific data on patients with infected necrosis (n=166): 87/166 patients (52%) recovered after PCD only. Five series reported on the time between insertion and removal of drains, varying from 16 to 98 days. Additional surgical necrosectomy was performed in 133/384 patients (35%). The time interval between first PCD and surgery was reported in six series and ranged from 18 to 109 days.

The complication rate was described in all series. One or more complications occurred in 76/384 patients (20%). The majority of complications were pancreatico-cutaneous and pancreatico-enteric fistulas (n=53), being 51% of all complications and present in 14% of all patients treated with PCD. In total, nine other procedure-related complications were described.

A total of 67/384 patients died (17%). Nine studies reported the mortality for PCD in patients with infected necrosis: 15% (27/175 patients). In these studies, mortality for PCD in patients with sterile necrosis was 15% as well (10/69 patients).

DISCUSSION

The results from this systematic review on PCD in (infected) necrotising pancreati-

tis showed that approximately half of the patients recovered after PCD only, without the need for further surgical intervention. In patients who did require surgical intervention, PCD allowed for postponing additional intervention for several weeks.

In the mixed group of patients, overall mortality was 17%, but 15% in patients with infected necrosis. Although not all studies provided data on mortality of patients with infected necrosis, mortality of 15% is similar to numbers reported for open and minimally invasive necrosectomy.[20]

The indication for PCD differed between the 11 included series. Although all 384 patients suffered from necrotising pancreatitis, only 71% indeed had infected peripancreatic collections proven by bacterial culture. Other indications for intervention were symptomatic 'organized necrosis' and 'severe clinical deterioration despite maximum conservative treatment'. These last two indications are not very well-defined and one may question whether these patients could not have been successfully treated conservatively.

In the pooled data of this systematic review, the complication rate was 20%, with only nine reported procedure-related complications. Series on surgical necrosectomy report a considerable higher complication rate, ranging from 34% to 68%.[3,7,8] Furthermore, in the current study, only 14% of patients developed a pancreatic fistula, compared to 22-47% in the studies on surgical necrosectomy.[21-23] However, mostly studies only reported early complications. Late complications do occur and the reported 20% complication rate in this review is therefore probably higher.

It is conceivable, that drain placement into a sterile peripancreatic collection can introduce bacteria resulting in secondary infection. None of the studies included reported on the rate of iatrogenic infection, but underreporting is likely to have occurred. A limitation of the current systematic review is that many of the included studies were small and retrospective. Moreover, in some series essential data were not presented (e.g., total number of interventions, outcome related to infectious status of collections, percentage of patients with organ failure at time of PCD). A formal assessment of methodological quality could not be performed because the papers did not provide enough detailed information for such an assessment.

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PART IV

CHAPTER 14

Video-assisted retroperitoneal debridement in infected necrotising pancreatitis: a technical report

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INTRODUCTION

In 2000 Carter et al. reported on minimally invasive retroperitoneal necrosectomy in the treatment of infected necrotising pancreatitis (INP).[1] This technique, consisting of endoscopic necrosectomy over a dilated percutaneous drain tract, was later also described by Connor et al.[2] The first results were exciting but the authors stated that the technique might also be associated with drawbacks.[1,2] The pure endoscopic character of the technique makes it a time-consuming effort that requires multiple repeated procedures to remove sufficient necrotic material. In recent years, our groups have adopted video-assisted retroperitoneal debridement (VARD).[3] This technique can be considered a hybrid between pure endoscopic retroperitoneal necrosectomy and the open (20 cm incision) translumbar approach, described by Fagniez et al. in 1989.[4] In this article, we describe the technical aspects of VARD because we feel that this minimally invasive technique carries advantages over other surgical strategies in INP and is not yet known to a wide audience.

SURGICAL TECHNIQUE

Once infection of (peri-)pancreatic necrosis is either suspected based on contrast-enhanced CT scan and clinical status or even confirmed by fine needle aspiration, a 12-14 French percutaneous drain is placed in the (peri-)pancreatic collection through the left retroperitoneum (FIGURE 14.1). If drainage does not lead to clinical improvement (subsidence of organ failure, reduction of temperature, white blood cell count and C-reactive protein), surgical intervention is deemed necessary and the patient is operated upon. Surgery is preferably postponed until after 4 weeks from the onset of the disease. This is considered essential as it allows for (peri-)pancreatic collections to sufficiently demarcate and the wall to mature, thus optimizing conditions for debridement.

The patient is placed in supine position with the left side 30-40° elevated. A subcostal incision of 5 cm is placed in the left flank at the mid-axillary line, close to the exit point of the percutaneous drain (FIGURE 14.2). With the help of CT images and by using the in situ percutaneous drain as a guide into the (peri-)pancreatic collection, the fascia is dissected and the retroperitoneum is entered. The cavity is cleared of purulent material using a standard suction device. The first necrosis encountered is carefully removed with the use of long grasping forceps (FIGURE 14.3). Following

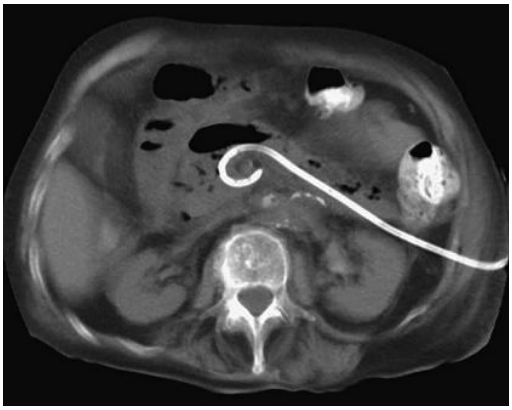

FIGURE 14.1. A percutaneous catheter drain is positioned in the collection through a left retroperitoneal approach.

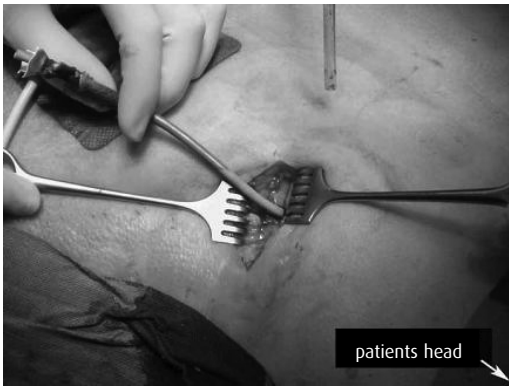

FIGURE 14.2. A 5 cm subcostal incision is placed in the patient's left flank.

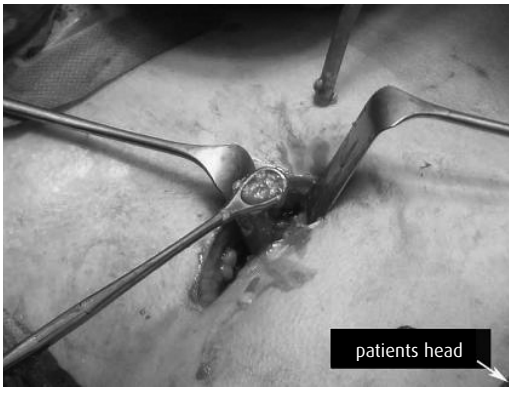

FIGURE 14.3. The first necrosis is removed with a grasping forceps.

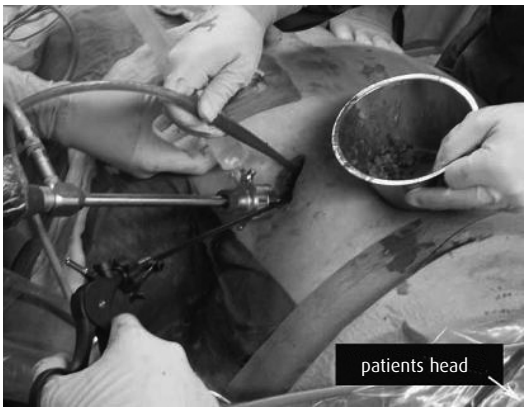

FIGURE 14.4. A videoscope is inserted and residual necrosis is removed with a laparoscopic grasping forceps. A single trocar is used.

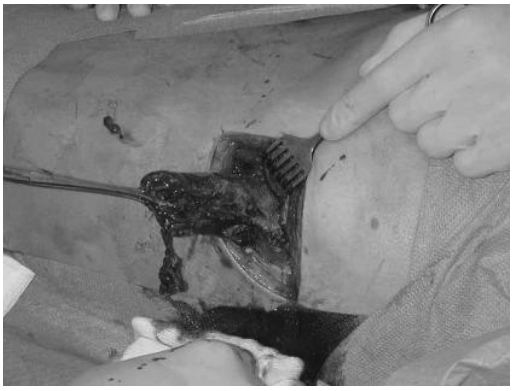

FIGURE 14.5. VARD allows for large pieces of necrosis to be removed.

the percutaneous drain deeper into the cavity, loose necrotic material is removed while periodic irrigation and consequent suction are performed to enhance vision. When debridement can no longer be performed under direct vision, a single extra-long laparoscopic port is placed into the incision and a 0° videoscope is introduced. At this stage CO2 gas (10 l/min) can be infused through the percutaneous drain, still in position, to inflate the cavity, thereby facilitating inspection. Under videoscopic assistance further debridement of retained necrotic tissue is performed with laparoscopic forceps (FIGURE 14.4). Complete necrosectomy is not the ultimate aim of this procedure. Only loosely adherent pieces of necrosis are removed, thereby keeping the risk of tearing underlying blood vessels to a minimum. In the rare case of exten-

sive bleeding, packing of the retroperitoneal cavity should be performed, either as definite treatment or as a bridge to laparotomy or angiographic coiling in the situation of persistent haemorrhage.

When the bulk of necrosis is removed, the cavity is irrigated with saline until the fluid becomes clear. The percutaneous drain is removed and two large-bore single-lumen drains are positioned in the cavity extending through the edges of the incision. The first drain is placed at the deepest point of the cavity and is positioned more shallow. The fascia and skin are closed and the drains are sutured to the skin. Continuous postoperative lavage is performed with 10 litres of normal saline or dialysis fluid per 24 h until the effluent is clear. One week after the procedure repeat CT is performed to evaluate resolution of the collection and to assess whether necrosis is still present.

DISCUSSION

A recent systematic review showed that mortality after necrosectomy by laparotomy for INP is 15-27%.[5] In several series mortality rates after the open translumbar approach were not superior to laparotomy and major morbidity such as haemorrhage and fistulae occurred in 25-68% of patients.[4,6,7] This high incidence of complications is attributed to the relative blindness of this technique.[8] The concept of necrosectomy under direct vision by video-endoscopy might offer a partial solution to this problem.

Patients with INP are often severely ill and mortality is mainly due to septic multiple organ failure. Necrosectomy by minimally invasive techniques by inducing less preoperative and postoperative physiological stress as compared with laparotomy might be beneficial in these patients.[1]

In recent years several relatively small series (range 6-46 patients) on necrosectomy by minimally invasive retroperitoneal approach have been reported.[1-3,9-12] However, the described techniques show some variation and different nomenclature is used. We find this to be quite confusing. In 1998 Gambiez et al. described the results of the first patients in which they performed necrosectomy through a small (6 cm) left flank incision under visualisation with a mediastinoscope.[11] Castellanos et al. published a prospective series of 11 consecutive patients treated with a technique that involves a 15 cm translumbar incision which they call 'retroperitoneal endoscopy'.[12]

Although comparable to VARD, it is questionable whether the 15 cm incision should be considered 'minimally invasive'.

The alternative method originally reported by Carter et al., which obviated the need for an incision, is known as 'sinus tract endoscopy' (STE).[1] In this technique a percutaneous catheter drain tract is serially dilated to a 30 French tract using fluoroscopic guidance in the operating room and necrosectomy is performed under continuous irrigation using a nephroscope and a long grasping forceps. Connor et al. applied the same technique as STE but use a different term: 'minimally invasive retroperitoneal pancreatic necrosectomy' (MIRPN).[2]

In 2001, the results of the first six patients who underwent VARD in one of our institutions were published.[3] At that time the technique was still called 'laparoscopic assisted percutaneous drainage'. Two minor complications occurred and all patients survived. Recently, an abstract was published on a second series of 13 VARD patients. Complications occurred in 54% of patients and 1 patient died (8%).[13] The various reports on different minimally invasive techniques by other authors show a mean morbidity of 44% (range 0-93%) and mortality of 23% (range 10-27%).[1,2,9-12] However, the type of complications and classification of severity of disease vary greatly, which makes comparison of these retrospective studies difficult.

VARD is essentially a combination of the open translumbar approach and STE and we feel it contains 'the best of both worlds'. Theoretically, it has the advantages of both an open approach and an endoscopic technique without many of the disadvantages. In the series of Connor et al. a median of 3-4 procedures was necessary to remove all infected material,[2,10] which was reflected by a 2 weeks longer postoperative hospital stay.[10] In VARD, the small incision enables the surgeon to remove larger pieces of necrosis (FIGURE 14.5), with a shorter operating time and less need for repetitive procedures. In our experience, the VARD technique is very simple and cost-effective. STE has the additional disadvantage of requiring a C-arm fluoroscopy in the operating room, which has the additional risks of radiation exposure to the patient and the operating team, as well as possible increased costs. Finally, as opposed to the 15 cm incision for the translumbar approach[12], the 5 cm incision in VARD can still be considered minimally invasive. The use of a videoscope may reduce the risk of complications reported with the open translumbar approach in the past.

In our experience, VARD is a relatively easy technique that is applicable in the majority of patients with INP[14] and provides an excellent alternative to necrosectomy by laparotomy. However, life-threatening complications are still possible, necessitating 24 h availability of experienced gastrointestinal surgeons, endoscopists and radiologists. In the absence of large prospective (randomised) studies, the true value of VARD in the treatment of INP obviously remains unclear. For this reason two multicentre studies have been initiated (one single arm[15] and one randomised[16]).

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PART IV

CHAPTER 15

Feasibility of minimally invasive approaches in patients with infected necrotising pancreatitis

– a summary –

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INTRODUCTION

Minimally invasive procedures to treat infected necrotising pancreatitis (INP) are gaining popularity.[1-3] These approaches include computed tomography (CT) - guided percutaneous catheter drainage[4] and drain-guided minimally invasive (retroperitoneal) surgery.[1-3,5,6] All the minimally invasive procedures (radiological, endoscopic or surgical) have a common first step, with the placement of a drain in the peripancreatic collection. The collections must therefore be accessible for drain placement if minimally invasive approaches are to be widely implemented. However, the proportion of patients suitable for minimally invasive approaches remains unknown.

The aim of this study was to evaluate the intraabdominal distribution, 'accessibility' and 'drainability' of peripancreatic collections in a large series of consecutive patients who had surgery for INP, to see what proportion of patients might be suitable for a Dutch nationwide trial comparing minimally invasive techniques with laparotomy for INP.

METHODS

Between October 2000 and October 2003, 106 consecutive patients (older than 18 years) who had surgical intervention for suspected INP were identified by a database search in 11 Dutch hospitals. Patients were included in the current study if a preoperative CT scan was available for review.

Scans were reviewed in consensus by two authors (HvS, MB) to classify peripancreatic collections by intra-abdominal location. The distance between the left lateral border of the collection and the left abdominal wall ('inner' abdominal wall, not the skin) was measured using the original metric scale on the CT scan. The collections were classified as follows: left (left lateral border of the collection 5 cm or less from the left abdominal wall), intermediate (left lateral border of the collection more than 5 cm from the left abdominal wall and 5 cm or less from the midline) or central (left lateral border of the collection less than 5 cm from the midline).

Five experienced radiologists from five Dutch tertiary referral centres independently reviewed all preoperative CT scans. They were given the dates of admission, CT scan and first surgical intervention. Each radiologist individually judged the accessibility of the peripancreatic collections for placement of a percutaneous or endosco-

TABLE 15.1. Preferred route of drain placement based on appearance by computed tomography

Radiologist	Not possible	Left retro-peritoneum	Right retro-peritoneum	Anterior transperitoneal	Transgastric endoscopic procedure	Total
1	12 (15)	50 (63)	2 (3)	11 (14)	5 (6)	80 (100)
2	9 (11)	57 (71)	0 (0)	9 (11)	5 (6)	80 (100)
3	16 (20)	43 (54)	0 (0)	16 (20)	5 (6)	80 (100)
4	11 (14)	38 (48)	3 (4)	27 (34)	1 (1)	80 (100)
5	18 (23)	35 (44)	1 (1)	19 (24)	7 (9)	80 (100)
Mean	13 (17)	45 (56)	1 (1)	16 (21)	5 (6)	80 (100)

Values in parentheses are percentages.

pic transgastric drain in the collection. They were asked the following question, with the possible answers ranked in order on the basis that a left retroperitoneal drain is preferable for performing minimally invasive drain-guided surgery: 'Which route is most feasible and safe for the placement of a 14-French drain in the collection: **a**. through the left retroperitoneal space, **b**. through the right retroperitoneal space, **c**. through the transperitoneal space, **d**. through an endoscopic transgastric entrance or **e**. no route possible?'. Each radiologist then judged whether the peripancreatic collection was 'drainable'. A collection was defined as 'drainable' if it was expected to contain at least 50 ml of aspirate immediately after first drain placement.

The interobserver agreement was calculated using κ-statistics. The mean (± SD) κ coefficient was calculated for all 10 possible radiologist pairs. A κ level less than 0.00 represented no agreement, 0.00-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial and 0.81-1.00 almost perfect agreement.[7]

RESULTS

CT scans of 80 patients (75%) were available (59 men; age range 29-80 years). The median interval between hospital admission and preoperative CT scan was 20 days. Of the peripancreatic collections, 55 of 80 (69%) were classified as left, 19 (24%) as intermediate and six (8%) as central. Drain placement was considered feasible in 67 of 80 patients (84% [range 77-89%]). The interobserver agreement for accessibility was therefore moderate (mean κ 0.4 ± 0.09). In 45 of these 67 patients (67%), it was deemed feasible to place a retroperitoneal drain from the left flank (TABLE 15.1). All radiologists agreed that it would not be possible to place a drain in only two out of

80 patients (2.5%). In 43 patients (54% [range 49-82%]), collections were judged to contain a drainable fluid component. Interobserver agreement on 'drainability' was poor, mean κ 0.29 (± 0.10).

DISCUSSION

The present pilot study for a trial comparing minimally invasive procedures with laparotomy in INP demonstrated that most (84%) peripancreatic collections in INP are accessible from a minimally invasive approach and that more than two-thirds are within 5 cm of the left abdominal wall.

Success rates of percutaneous catheter drainage in INP (defined as obviating the need for surgery) vary from 30 to 100%.[4,8-10] Several variations of minimally invasive 'drain-guided' surgery have been reported[1-3,5] and it has been suggested that minimally invasive procedures are possible only in a subgroup of patients. The present results contradict this, with drainage deemed feasible in 84% of patients.

Agreement on drainability of the peripancreatic collections among radiologists was poor. This probably reflects the fact that CT cannot always discriminate between fluid and necrotic content in INP.[11,12]

The wider implementation of minimally invasive procedures for INP should be based on prospective, controlled studies undertaken by dedicated multidisciplinary teams.[13,14] To that end, the Dutch Pancreatitis Study Group has recently started a prospective, randomised, multicentre trial to compare the minimally invasive approach with laparotomy in INP.[15]

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PART IV

CHAPTER 16

Case-matched comparison of the retroperitoneal approach with laparotomy for necrotising pancreatitis

– a summary –

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INTRODUCTION

We started using open necrosectomy followed by the open abdomen strategy with planned relaparotomy for necrotising pancreatitis at our institution in 1988.[1] Because of high morbidity and mortality, we switched to open necrosectomy with continuous postoperative lavage (CPL) in 1995.[1,2] In a comparative study, we found that the results of open necrosectomy and CPL still were not satisfactory.[3] As an alternative, in 2001 necrosectomy by the retroperitoneal approach using a small flank incision was introduced. Minimally invasive retroperitoneal necrosectomy is gaining popularity for the treatment of necrotising pancreatitis.[4-6] There is, however, no substantial evidence from comparative studies in favour of this technique over open necrosectomy. Selection bias may account for the favourable outcomes of minimally invasive retroperitoneal necrosectomy. A head-to-head comparison (e.g., a case-matched study or a randomised controlled trial) of both techniques has never been performed. We performed a case-matched comparison of the minimally invasive retroperitoneal approach with open necrosectomy and CPL. This retrospective pilot study was undertaken in preparation for a nationwide randomised controlled trial.[7]

METHODS

Between 2001 and 2005, there were 15 out of 841 consecutive patients with acute pancreatitis who underwent minimally invasive retroperitoneal necrosectomy in the University Medical Centre Utrecht and the St. Antonius Hospital Nieuwegein in the Netherlands. Each of these patients was matched with one out of 46 patients treated with open necrosectomy and CPL in the same hospitals during 1995-2005. Patients were matched for all of the following criteria: **1**. organ failure at any time prior to primary necrosectomy (yes or no); **2**. infection of pancreatic or peripancreatic necrosis as determined by fine-needle aspiration and/or intraoperative culture (yes or no); **3**. timing of surgery: number of days admitted before primary necrosectomy (± 7 days, at least 15 days after admission); **4**. age (± 10 years); and **5**. CT-severity index[8] (± 2 points). These criteria were chosen because it was anticipated that they reflect the most important prognostic factors. Matching for the date (year) of operation to exclude possible confounding due to time effects was not possible because after 2000 the minimally invasive retroperitoneal necrosectomy was increasingly

used. To minimize bias introduced by using "historical controls", open necrosectomy/CPL patients were consecutively enrolled in reversed order (i.e., if more than one open necrosectomy/CPL patient could be matched with a patient in the minimally invasive retroperitoneal necrosectomy group, the patient operated on most recently was selected).

RESULTS

In addition to all matched preoperative characteristics, there were no significant differences between the treatment groups in sex, preoperative intensive care unit (ICU) admission, preoperative ICU stay, preoperative Acute Physiology and Chronic Health Evaluation (APACH)-II scores, and preoperative multiple organ failure (MOF). There were 22 men with a median age of 52 years (34-75 years). During the 24 hours preoperatively, 12 patients (40%) had organ failure and 8 (27%) had MOF. The median APACHE-II score 24 hours preoperatively was 9 (range 5-20). The median CT-severity index score was 8 (range 4-10). The median time between admission and primary necrosectomy was 41 days (range 15-164). The indication for intervention was suspected or confirmed infected necrosis in all patients. Infected necrosis was proven by intraoperative culture in 28 patients (93%).

Postoperative complications requiring reintervention occurred in six patients in each group (P=1.000). Postoperative new-onset MOF occurred in 10 patients (67%) in the open necrosectomy/CPL group vs. 2 patients (13%) in the minimally invasive retroperitoneal necrosectomy group (P=0.008). Six patients (20%) died in the open necrosectomy/CPL group vs. 1 patient (3%) in the minimally invasive retroperitoneal necrosectomy group (P=0.080).

DISCUSSION

This study is the first case-matched study comparing minimally invasive retroperitoneal necrosectomy with open necrosectomy/CPL for necrotising pancreatitis. The main findings are that **1**. postoperative new-onset MOF occurred less often after the minimally invasive retroperitoneal necrosectomy and **2**. there was a trend toward lower mortality in the minimally invasive retroperitoneal necrosectomy.

A possible explanation for our results is that minimally invasive retroperitoneal necrosectomy induces less perioperative and postoperative stress than open necro-

sectomy because a small (5 cm) incision is used, the peritoneum is left intact, and the peritoneal cavity is not contaminated. Several other authors hypothesized that by minimizing the inflammatory 'hit' of necrosectomy the retroperitoneal approach may lessen the risk of postoperative MOF in the already critically ill patient.[4-6] In a similar retrospective study,[9] Connor et al. compared 47 patients undergoing minimally invasive retroperitoneal necrosectomy with 41 patients undergoing open necrosectomy: mortality was 19% vs. 39% (P=0.06). Although no differences in postoperative complication rates were observed, the postoperative APACHE-II score was lower and the postoperative ICU stay shorter in their minimally invasive retroperitoneal necrosectomy group.

Being left with historical controls for comparative studies is not uncommon when new surgical techniques are enthusiastically implemented in clinical practice.[10] This points out the need for randomised controlled trials performed in a timely fashion (i.e., before an experimental technique has become 'routine care' without evidence from well designed comparative studies being available). Although this study represents the highest level of evidence on the subject thus far, the sample size was too small and the risk of selection bias precludes any firm conclusions. Therefore, comparison in a randomised design is warranted, especially when considering the improvement in outcome after open necrosectomy in the recent literature. To address this issue, we have recently started a randomised controlled multicentre trial comparing open necrosectomy/CPL with a minimally invasive step-up approach.[7]

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PART IV

CHAPTER 17

A step-up approach or open necrosectomy for necrotising pancreatitis

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ABSTRACT

BACKGROUND

Necrotising pancreatitis with infected necrotic tissue is associated with a high rate of complications and death. Standard treatment is open necrosectomy. The outcome may be improved by a minimally invasive step-up approach.

METHODS

In this multicentre study, we randomly assigned 88 patients with necrotising pancreatitis and suspected or confirmed infected necrotic tissue to undergo primary open necrosectomy or a step-up approach to treatment. The step-up approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The primary end point was a composite of major complications (new-onset multiple organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding) or death.

RESULTS

The primary end point occurred in 31 of 45 patients (69%) assigned to open necrosectomy and in 17 of 43 patients (40%) assigned to the step-up approach (risk ratio with the step-up approach, 0.57, 95% confidence interval, 0.38 to 0.87, P=0.006). Of the patients assigned to the step-up approach, 35% were treated with percutaneous drainage only. New-onset multiple organ failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% vs. 40%, P=0.002). The rate of death did not differ significantly between groups (19% vs. 16%, P=0.70). Patients assigned to the step-up approach had a lower rate of incisional hernias (7% vs. 24%, P=0.03) and new-onset diabetes (16% vs. 38%, P=0.02).

CONCLUSIONS

A minimally invasive step-up approach, as compared with open necrosectomy, reduced the rate of the composite end point of major complications or death among patients with necrotising pancreatitis and infected necrotic tissue. (Current Controlled Trials number, IRCTN13975868.)

INTRODUCTION

Acute pancreatitis is the third most common gastrointestinal disorder requiring hospitalisation in the United States, with annual costs exceeding $2 billion.[1,2] Necrotising pancreatitis, which is associated with an 8 to 39% rate of death, develops in approximately 20% of patients.[3] The major cause of death, next to early organ failure, is secondary infection of pancreatic or peripancreatic necrotic tissue, leading to sepsis and multiple organ failure.[4] Secondary infection of necrotic tissue in patients with necrotising pancreatitis is virtually always an indication for intervention.[3,5-7]

The traditional approach to the treatment of necrotising pancreatitis with secondary infection of necrotic tissue is open necrosectomy to completely remove the infected necrotic tissue.[8,9] This invasive approach is associated with high rates of complications (34 to 95%) and death (11 to 39%) and with a risk of long-term pancreatic insufficiency.[10-16] As an alternative to open necrosectomy, less invasive techniques, including percutaneous drainage,[17,18] endoscopic (transgastric) drainage,[19] and minimally invasive retroperitoneal necrosectomy, are increasingly being used.[14,20-22] These techniques can be performed in a so-called step-up approach.[23] As compared with open necrosectomy, the step-up approach aims at control of the source of infection, rather than complete removal of the infected necrotic tissue. The first step is percutaneous or endoscopic drainage of the collection of infected fluid to mitigate sepsis; this step may postpone or even obviate surgical necrosectomy.[17-19] If drainage does not lead to clinical improvement, the next step is minimally invasive retroperitoneal necrosectomy.[14,20-22] The step-up approach may reduce the rates of complications and death by minimizing surgical trauma (i.e., tissue damage and a systemic proinflammatory response) in already critically ill patients.[14,21]

It remains uncertain which intervention in these patients is optimal in terms of clinical utcomes, health care resource utilisation, and costs. We performed a nationwide randomised trial called Minimally Invasive Step Up Approach versus Maximal Necrosectomy in Patients with Acute Necrotising Pancreatitis (PANTER).

METHODS

STUDY DESIGN

The design and rationale of the PANTER study have been described previously.[24]

Adults with acute pancreatitis and signs of pancreatic necrosis, peripancreatic necrosis, or both, as detected on contrast- enhanced computed tomography (CT), were enrolled in 7 university medical centres and 12 large teaching hospitals of the Dutch Pancreatitis Study Group. Patients with confirmed or suspected infected pancreatic or peripancreatic necrosis were eligible for randomization once a decision to perform a surgical intervention had been made and percutaneous or endoscopic drainage of the fluid collection was deemed possible.

Infected necrotic tissue was defined as a positive culture of pancreatic or peripancreatic necrotic tissue obtained by means of fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the fluid collection on contrast-enhanced CT. Suspected infected necrosis was defined as persistent sepsis or progressive clinical deterioration despite maximal support in the intensive care unit (ICU), without documentation of infected necrosis.

The exclusion criteria were a flare-up of chronic pancreatitis, previous exploratory laparotomy during the current episode of pancreatitis, previous drainage or surgery for confirmed or suspected infected necrosis, pancreatitis caused by abdominal surgery, and an acute intraabdominal event (e.g., perforation of a visceral organ, bleeding, or the abdominal compartment syndrome).

Patients were randomly assigned to either primary open necrosectomy or the minimally invasive step-up approach. Randomization was performed centrally by the study coordinator. Permuted-block randomization was used with a concealed block size of four. Randomization was stratified according to the treatment centre and the access route that could be used for drainage (i.e., a retroperitoneal route or only a transabdominal or endoscopic transgastric route).

STUDY OVERSIGHT

All patients or their legal representatives provided written informed consent before randomization. This investigator-initiated study was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board of each participating hospital approved the protocol.

QUALITY CONTROL

The indication for intervention and the optimal timing of intervention in necroti-

sing pancreatitis are frequently subject to discussion.[25] Therefore, an expert panel consisting of eight gastrointestinal surgeons, one gastroenterologist, and three radiologists was formed. Whenever infected necrosis was suspected or there was any other indication for intervention in a patient, the expert panel received a case description, including CT images, on a standardized form by e-mail. Within 24 hours, the members of the expert panel individually assessed the indication for intervention and the patient's eligibility for randomization.

Whenever possible, the randomization and intervention were postponed until approximately 4 weeks after the onset of disease.[5,6,26,27] All interventions were performed by gastrointestinal surgeons who were experienced in pancreatic surgery and by experienced interventional radiologists and endoscopists. Whenever necessary, the most experienced study clinicians visited the participating centres to assist with interventions.

OPEN NECROSECTOMY

The open necrosectomy, originally described by Beger et al.,[8] consisted of a laparotomy through a bilateral subcostal incision. After blunt removal of all necrotic tissue, two large-bore drains for postoperative lavage were inserted, and the abdomen was closed.

MINIMALLY INVASIVE STEP-UP APPROACH

The first step was percutaneous or endoscopic transgastric drainage. The preferred route was through the left retroperitoneum, thereby facilitating minimally invasive retroperitoneal necrosectomy at a later stage, if necessary. If there was no clinical improvement (according to prespecified criteria[24]) after 72 hours and if the position of the drain (or drains) was inadequate or other fluid collections could be drained, a second drainage procedure was performed. If this was not possible, or if there was no clinical improvement after an additional 72 hours, the second step, videoassisted retroperitoneal débridement (VARD) with postoperative lavage,[21,22] was performed. (Details on the step-up approach and postoperative management in both groups are included in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

TABLE 17.1. Definitions of morbidity in primary in primary and secondary endpoints

Major morbidity
New onset multi organ failure or systemic complications: new-onset failure (i.e., not present at any time in the 24 hr before first intervention) of 2 or more organs or occurrence of 2 or more systemic complications at the same moment in time
Organ failure[a]
- Pulmonary failure: PaO_2 <60 mm Hg despite FIO2 of 30%, or need for mechanical ventilation
- Circulatory failure: circulatory systolic blood pressure <90 mm Hg despite adequate fluid resuscitation, or need for inotropic catecholamine support
- Renal failure: creatinine level >177 μmol/L after rehydration or new need for hemofiltration or hemodialysis
Systemic complications[a]
- Disseminated intravascular coagulation: platelet count <100 x 10^9/L
- Severe metabolic disturbance: calcium level <1.87 mmol/L
- Gastrointestinal bleeding: >500 ml of blood /24 hours
Enterocutaneous fistula: 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[b]
Perforation of a visceral organ requiring intervention: perforation requiring either surgical, radiological or endoscopic intervention[b]
Intra-abdominal bleeding requiring intervention: bleeding requiring surgical, radiological or endoscopic intervention
Other morbidity
Pancreatic fistula: output through a percutaneous drain or drainage canal after removal of drains or from a surgical wound of any measurable volume of fluid with an amylase content >3 times the serum amylase level[c]
New-onset diabetes: insulin or oral antidiabetic drugs required 6 months after discharge; this requirement was not present before onset of pancreatitis
Use of pancreatic enzymes: oral pancreatic-enzyme supplementation required to treat clinical symptoms of steatorrhea 6 months after discharge; this requirement was not present before onset of pancreatitis
Incisional hernia: full-thickness discontinuity in abdominal wall and bulging of abdominal contents, with or without obstruction, 6 months after discharge[d]

a= Adapted from the 1992 Atlanta Classification for acute pancreatitis.[28]
b= Prior to any analysis, the adjudication committee decided to combine the endpoints enterocutaneous fistula and perforation of a visceral organ, because one is often caused by the other and may coexist in the same patient.
c= Adapted from the International Study Group on Pancreatic Fistula Definition (ISGPF) criteria for postoperative pancreatic fistula.[29]
d= The original study protocol[24] stated "incisional hernia requiring intervention". Before any analysis, the adjudication committee decided to report incisional hernias with or without intervention because surgical reconstruction of the abdominal wall is usually not performed within 6 months after recovery of necrotising pancreatitis.
FIO_2 denotes fraction of inspired oxygen, and PaO_2 partial pressure of arterial oxygen.

END POINTS AND DATA COLLECTION

The predefined primary end point was a composite of major complications (i.e., new-onset multiple organ failure or systemic complications, enterocutaneous fistula or perforation of a visceral organ requiring intervention, or intraabdominal bleeding requiring intervention) (TABLE 17.1) or death during admission or during the 3 months after discharge. The individual components of the primary end point were analysed as secondary end points. Secondary end points also included other complications (TABLE 17.1), health care resource utilisation, and total direct medical costs and indirect costs from admission until 6 months after discharge (details are available in the Supplementary Appendix).

Follow-up visits took place 3 and 6 months after discharge. Data collection was performed by local physicians using Internet-based case-record forms. An independent auditor who was unaware of the treatment assignments checked all completed case-record forms against on-site source data. Discrepancies detected by the auditor were resolved on the basis of a consensus by two investigators who were unaware of the study-group assignments and were not involved in patient care. All CT scans were prospectively evaluated by one experienced radiologist who was unaware of the treatment assignments and outcomes.

A blinded outcome assessment was performed by an adjudication committee consisting of eight experienced gastrointestinal surgeons who independently reviewed all data regarding complications. Disagreements were resolved during a plenary consensus meeting with concealment of the treatment assignments.

STATISTICAL ANALYSIS

We calculated that we would need to enroll 88 patients[24] in order to detect a 64% relative reduction in the rate of the composite primary end point with the step-up approach (from 45% to 16%), with a power of 80% and a two-sided alpha level of 0.05. The large risk reduction with the step-up approach was expected on the basis of results from a Dutch nationwide retrospective multicentre study[30] and other previous studies.[17,31] Moreover, a larger sample was not thought to be feasible because necrotising pancreatitis with secondary infection is uncommon.

All analyses were performed according to the intention-to-treat principle. The occurrences of the primary and secondary end points were compared between the

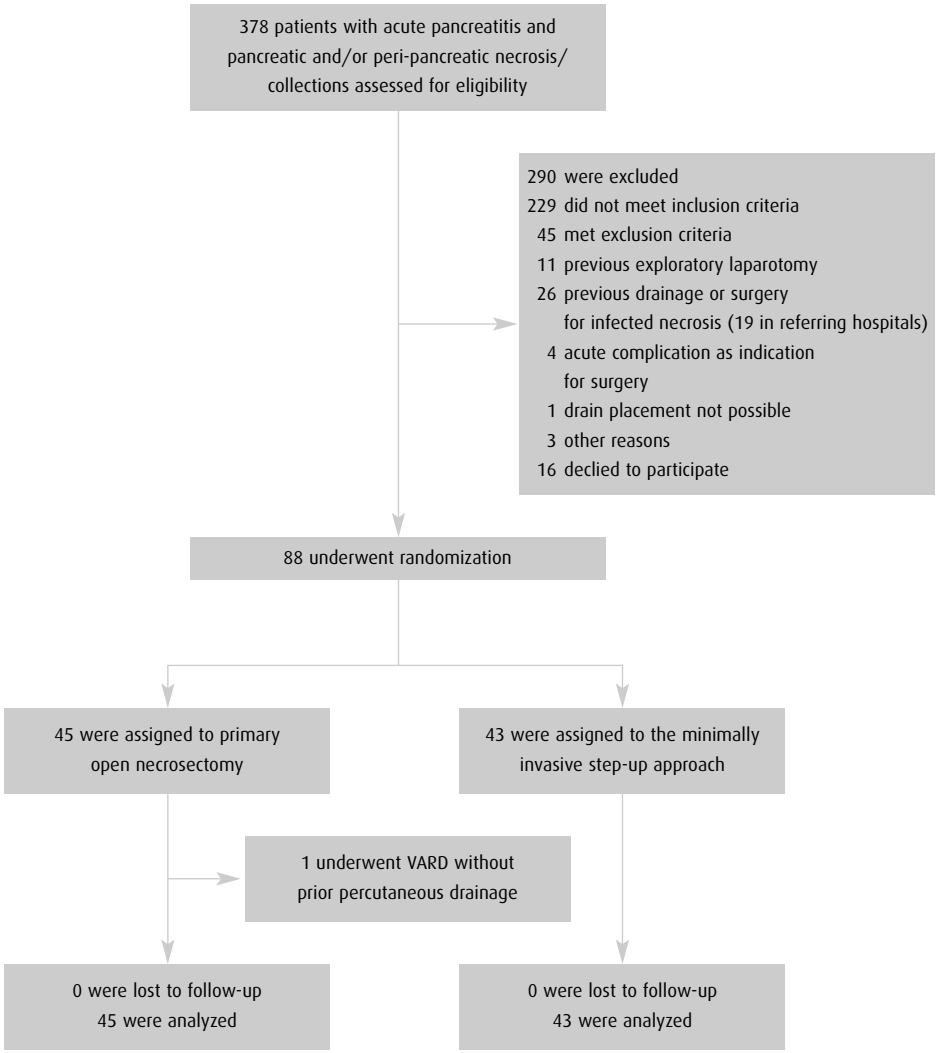

FIGURE 17.1. Enrollment, randomization, and follow-up of the study patients.

VARD denotes video-assisted retroperitoneal débridement.

treatment groups. Results are presented as risk ratios with corresponding 95% confidence intervals. Differences in other outcomes were assessed with the use of the Mann-Whitney U test.

Predefined subgroup analyses were performed for the presence or absence of organ failure at randomization and the timing of intervention (≤28 days or >28 days after

the onset of symptoms). A formal test of interaction in a logistic-regression model was used to assess whether treatment effects differed significantly between the subgroups.

No interim analysis was performed. As a precautionary measure, an independent biostatistician who was unaware of the study-group assignments performed sequential monitoring[32] of the major complications and deaths reported during the trial (details are available in the Supplementary Appendix).

All reported P values are two-sided and have not been adjusted for multiple testing.

RESULTS

STUDY PARTICIPANTS

Between November 3, 2005, and October 29, 2008, a total of 378 patients with acute pancreatitis who had signs of pancreatic necrosis, peripancreatic necrosis, or both were enrolled in the study. A total of 88 patients were randomly assigned to a treatment group (FIGURE 17.1). Baseline characteristics of the treatment groups were similar (TABLE 17.2). Of the 45 patients assigned to primary open necrosectomy, 44 underwent a primary laparotomy. In one patient, who had previously undergone esophagectomy, it was decided after randomization that laparotomy would potentially compromise the gastric conduit. Therefore, primary VARD without previous percutaneous drainage was performed.

Patients underwent a median of 1 open necrosectomy (range, 1 to 7). Nineteen patients (42%) required one or more additional laparotomies for additional necrosectomy because of ongoing sepsis (in eight patients), complications (in five patients) or both (in six patients). Fifteen patients (33%) required additional percutaneous drainage after laparotomy.

MINIMALLY INVASIVE STEP-UP APPROACH

Forty of 43 patients assigned to the step-up approach (93%) underwent retroperitoneal percutaneous drainage; 1 patient (2%) underwent transabdominal percutaneous drainage and 2 patients (5%) underwent endoscopic transgastric drainage. After the first 72 hours of observation, 19 patients (44%) underwent a second drainage procedure. Details of the drainage procedures are available in the Supplementary Appendix.

TABLE 17.2. Baseline characteristics of the patients

Characteristic	Minimally invasive step-up approach (n=43)	Primary open necrosectomy (n=45)	P value
Age - yr	57.6 (±2.1)	57.4 (±2.0)	0.94
Male sex - no. (%)	31 (72)	33 (73)	0.89
Cause of pancreatitis - no. (%)			0.98
Gallstones	26 (60)	29 (64)	
Alcohol abuse	3 (7)	5 (11)	
Other	14 (33)	11 (24)	
Coexisting condition - no. (%)			
Cardiovascular disease	19 (44)	21 (47)	0.82
Pulmonary disease	4 (9)	4 (9)	0.95
Chronic renal insufficiency	3 (7)	2 (4)	0.61
Diabetes	5 (12)	4 (9)	0.67
ASA class on admission - no. (%)[a]			0.99
I: healthy status	11 (26)	11 (24)	
II: mild systemic disease	19 (44)	20 (44)	
III: severe systemic disease	13 (30)	14 (31)	
Body-mass index on admission - kg/m^2 [b]	28 (20-55)	27 (22-39)	0.12
Computed tomography[c]			
CT-severity index[d]	8 (4-10)	8 (4-10)	0.95
Extent of pancreatic necrosis - no. (%)			0.52
<30%	17 (40)	19 (42)	
30% - 50%	14 (33)	10 (22)	
>50%	12 (28)	16 (36)	
Necrosis extending > 5cm down the paracolic gutter - no. (%)	24 (56)	27 (60)	0.69
Retroperitoneal access route to collection possible - no. (%)	40 (93)	40 (89)	0.50
Disease severity[e]			
SIRS - no. (%)[f]	42 (98)	45 (100)	0.49
Admitted on ICU at time of randomization - no. (%)	23 (54)	21 (47)	0.52
Admitted on ICU at anytime before randomization - no. (%)	28 (65)	29 (64)	0.95

Organ failure - no. (%)	21 (49)	22 (49)	0.99
Multiple organ failure - no. (%)	15 (35)	13 (29)	0.55
Positive blood culture within previous 7 days - no. (%)	14 (33)	15 (33)	0.94
Positive blood culture at anytime before randomization - no. (%)	22 (51)	25 (56)	0.68
APACHE II score[g]	14.6 (±6.1)	15.0 (±5.3)	0.75
APACHE II score ≥20 - no. (%)	10 (23)	9 (20)	0.71
MODS[h]	2 (0-9)	1 (0-10)	0.71
SOFA score[i]	3 (0-11)	2 (0-12)	0.39
C-reactive protein - mg/L	213.6 (±106)	215.9 (±111)	0.93
White blood cell count - x 10^9/liter	17.6 (±10.6)	15.9 (±6.3)	0.38
Time since onset of symptoms - days	30 (11-71)	29 (12-155)	0.86
Antibiotic treatment at anytime before randomization - no. (%)	37 (86)	38 (84)	0.83
Nutritional support at anytime before randomization - no. (%)			0.92
Enteral feeding only	23 (54)	23 (51)	
Parenteral feeding only	3 (7)	4 (9)	
Enteral feeding and parenteral feeding	12 (28)	11 (24)	
Oral diet	5 (12)	7 (16)	
Tertiary referrals - no. (%)	21 (49)	23 (51)	0.83
Confirmed infected necrotic tissue - no. (%)[j]	39 (91)	42 (93)	0.65

Continuous data are means (±SD), or medians (range).

a= American Society of Anesthesiologists (ASA).

b= The body-mass index is the weight in kilograms divided by the square of the height in meters.

c= Data were derived from the CT performed just before randomization.

d= Scores on the CT severity index range from 0 to 10, with higher scores indicating more extensive pancreatic necrosis and peripancreatic fluid collections.

e= Data were based on maximum values during 24 hours before randomization unless stated otherwise.

f= The systemic inflammatory response syndrome (SIRS) was defined according to the consensus-conference criteria of the American College of Chest Physicians-Society of Critical Care Medicine.

g= Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II scores range from 0 to 71, with higher scores indicating more severe disease.

h= The Multiple organ dysfunction score (MODS) ranges from 0 to 24, with higher scores indicating more severe organ dysfunction.

i= Scores on the Sequential organ failure assessment (SOFA) scale range from 0 to 24, with higher scores indicating more severe organ dysfunction.

j= Infected necrotic tissue was defined as a positive culture of pancreatic or peripancreatic necrotic tissue obtained by means of fine-needle aspiration or from the first drainage procedure or operation, or the presence of gas in the fluid collection on contrast-enhanced CT.

Fifteen patients (35%) survived after percutaneous or endoscopic drainage only, without the need for necrosectomy. The condition of two patients with progressive multiple organ failure was too unstable for surgery, and they subsequently died. The remaining 26 patients (60%) underwent necrosectomy a median of 10 days (range 1 to 52) after percutaneous drainage. A VARD procedure was performed in 24 of the patients, and the other 2 patients underwent primary laparotomy according to the protocol because there was no retroperitoneal access route. A median of 1 VARD procedure (range 0 to 3) was performed in each patient. In one patient, VARD was intraoperatively converted to laparotomy because it was not possible to reach the pancreatic necrosis through the retroperitoneum.

Fourteen patients (33%) required one or more additional operations for further necrosectomy (five patients), complications (seven patients), or both (two patients). Seven of the 26 patients who underwent necrosectomy (27%) required percutaneous drainage afterward.

CLINICAL END POINTS

The primary and secondary end points are listed in TABLE 17.3. The composite primary end point of major complications or death occurred in 31 of 45 patients after primary open necrosectomy (69%) and in 17 of 43 patients after the step-up approach (40%) (risk ratio with the step-up approach, 0.57, 95% confidence interval [CI], 0.38 to 0.87, P=0.006). All major complications tended to occur more frequently after primary open necrosectomy than after the step-up approach, although the difference was significant only for the composite end point of new-onset multiple organ failure or multiple systemic complications (P=0.001). This difference was mainly driven by the occurrence of organ failure (TABLE 17.3).

The rate of death between the two study groups did not differ significantly (P=0.70) (TABLE 17.3). A total of 15 patients in the study died (17%): 8 patients in the step-up group (19%) and 7 patients in the open-necrosectomy group (16%). The causes of death were multiple organ failure in seven patients in the step-up group and six patients in the open-necrosectomy group, postoperative bleeding in one patient in the step-up group and no patients in the open-necrosectomy group, and respiratory failure due to pneumonia in no patients in the step-up group and one patient in the open-necrosectomy group.

TABLE 17.3. Primary and secondary endpoints

Outcome	Minimally invasive step-up approach (n=43)	Primary open necrosectomy (n=45)	Risk Ratio (95%-CI)	P value
Primary endpoint: major morbidity or death - no. (%)[a]	17 (40)	31 (69)	0.57 (0.38-0.87)	0.006
Secondary endpoints				
Major complication - no. (%)				
New-onset multiple organ failure or systemic complications[b]	5 (12)	19 (42)	0.28 (0.11-0.67)	0.001
Multiple organ failure	5 (12)	18 (40)		
Multiple systemic complications	0 (0)	1 (2)		
Intraabdominal bleeding requiring intervention	7 (16)	10 (22)	0.73 (0.31-1.75)	0.48
Enterocutaneous fistula or perforation of a visceral organ				
requiring intervention	6 (14)	10 (22)	0.63 (0.25-1.58)	0.32
Death - no. (%)	8 (19)	7 (16)	1.20 (0.48-3.01)	0.70
Other outcome - no. (%)				
Pancreatic fistula	12 (28)	17 (38)	0.74 (0.40-1.36)	0.33
Incisional hernia?	3 (7)	11 (24)	0.29 (0.09-0.95)	0.03
New-onset diabetes[c]	7 (16)	17 (38)	0.43 (0.20-0.94)	0.02
Use of pancreatic enzymes[c]	3 (7)	15 (33)	0.21 (0.07-0.67)	0.002
Health care utilisation				
Necrosectomies (laparotomy or VARD) - no. (%)				<0.001
0	17 (40)	0 (0)		
1	19 (44)	31 (69)		
2	6 (14)	8 (18)		
≥3	1 (2)	6 (13)		
Total no. of operations (range per patient)[d]	53 (0-6)	91 (1-7)		0.004
Total no. of drainage procedures (range per patient)[e]	82 (1-7)	32 (0-6)		<0.001
New ICU admission at anytime after first				
intervention - no. (%)[f]	7 (16)	18 (40)	0.41 (0.19-0.88)	0.01
Days in ICU	9 (0-281)	11 (0-111)		0.26
Days in hospital	50 (1-287)	60 (1-247)		0.53

Continuous data are medians (range). ICU denotes intensive care unit, and VARD video-assisted retroperitoneal débridement. a= Multiple events in the same patient were considered as one endpoint; b= Thic category included only patients without multiple organ failure or multiple systemic complications at any time in the 24 hours before first intervention; c= Patients were assessed at 6 months after discharge from the index admission (readmission within 10 days was considered the same admission); d= This category included necrosectomies (laparotomies or VARD procedures) and additional operations to treat complications (e.g., laparotomy for abdominal bleeding) during the index admission; e=This category included primary drainage procedures as part of the minimally invasive step-up approach and additional drainages procedures after necrosectomy in both treatment groups during the index admission; f= This category included only patients who were not admitted to the ICU at any time in the 24 hours before the first intervention.

At the 6-month follow-up, patients who had undergone primary open necrosectomy, as compared with patients who had been treated with the step-up approach, had a higher rate of incisional hernias (24% vs. 7%, P=0.03), new-onset diabetes (38% vs. 16%, P=0.02), and use of pancreatic enzymes (33% vs. 7%, P=0.002).

HEALTH CARE RESOURCE UTILISATION AND COSTS

Utilisation of health care resources for operations (i.e., necrosectomies and reinterventions for complications) was lower in the group of patients who were treated with the step-up approach than in the group of patients who underwent primary open necrosectomy (P=0.004) (TABLE 17.3). After primary open necrosectomy, 40% of patients required a new ICU admission, as compared with 16% of patients who had been treated with the step-up approach (P=0.01).

The mean total of direct medical costs and indirect costs per patient during admission and at the 6-month follow-up was €78,775 ($116,016) for the step-up approach and €89,614 ($131,979) for open necrosectomy, for a mean absolute difference of €10,839 ($15,963) per patient. Thus, the step-up approach reduced costs by 12% (details of costs are available in the Supplementary Table in the Supplementary Appendix).

PREDEFINED SUBGROUP ANALYSES

Treatment effects with respect to the primary end point were similar across the subgroups on the basis of organ failure at the time of randomization and the timing of intervention (≤28 days or >28 days after the onset of symptoms). None of the tests for interaction were significant (P>0.05).

DISCUSSION

This study showed that the minimally invasive step-up approach, as compared with primary open necrosectomy, reduced the rate of the composite end point of major complications or death, as well as long-term complications, health care resource utilisation, and total costs, among patients who had necrotising pancreatitis and confirmed or suspected secondary infection. With the step-up approach, more than one third of patients were successfully treated with percutaneous drainage and did not require major abdominal surgery.

There are several possible explanations for the favourable outcome of the step-up approach. First, as we postulated when designing the study,[24] infected necrosis may be similar to an abscess because both contain infected fluid (pus) under pressure. Although a true abscess is more easily resolved with percutaneous drainage because it is composed entirely of liquid, simple drainage may also be sufficient to treat infected necrotic tissue. After the infected fluid is drained, the pancreatic necrosis can be left in situ, an approach that is similar to the treatment of necrotising pancreatitis without infection. This hypothesis apparently holds true, since 35% of our patients who were treated with the step-up approach did not require necrosectomy. Second, it has been suggested that minimally invasive techniques provoke less surgical trauma (i.e., tissue injury and a proinflammatory response) in patients who are already severely ill.[14,20,21] This hypothesis is supported by the substantial reduction in the incidence of new-onset multiple organ failure in our step-up group. Third, in the attempt to completely débride necrosis, viable pancreatic parenchyma may be unintentionally removed. This could explain why, at the 6-month follow-up, significantly more patients who underwent primary open necrosectomy had new-onset diabetes or were taking pancreatic enzymes. For pragmatic reasons, we defined pancreatic insufficiency on the basis of the use of pancreatic-enzyme supplements to treat clinical symptoms of pancreatic insufficiency instead of objective analyses of exocrine insufficiency (e.g., the fecal elastase test). It is possible that some of these patients did not have exocrine insufficiency, although the rate of pancreatic-enzyme supplementation in the opennecrosectomy group is consistent with data on exocrine insufficiency after open necrosectomy.[15]

Our findings are consistent with observations from several retrospective studies. It has been suggested previously that percutaneous drainage can be performed in almost every patient who has necrotising pancreatitis with infection and obviates the need for necrosectomy in approximately half the patients.[17,18,33] Several authors have reported promising results of minimally invasive necrosectomy,[14,20,22] including endoscopic procedures.[19,34-36] Most studies, however, included only a small number of patients and may have unintentionally selected patients who were less ill than the patients treated with open necrosectomy or were better candidates for minimally invasive techniques. In contrast, the current study was randomised and included a relatively large number of patients, with a high incidence of confirmed infected

necrotic tissue and organ failure at the time of intervention.

The benefit of the step-up approach in terms of preventing major abdominal surgery and associated complications, such as multiple organ failure requiring ICU admission, is of obvious importance. The reduction in long-term complications, including new-onset diabetes and incisional hernias, is also clinically relevant. Diabetes due to necrotising pancreatitis is known to worsen over time.[15] Moreover, secondary complications from diabetes have a considerable effect on the quality of life and potentially on life expectancy. Incisional hernias often cause disabling discomfort and pain, carry a risk of small-bowel strangulation, and frequently require surgical intervention.[37] Aside from these clinical implications, the estimated economic benefit from reduced health care resource utilisation and costs may be substantial. Approximately 233,000 patients are admitted with a new diagnosis of acute pancreatitis in the United States each year,[38] and necrotising pancreatitis with secondary infection develops in about 5% of these patients.[3,28] On the basis of these numbers, the step-up approach may reduce annual costs in the United States by $185 million.

The nationwide multicentre setting of our study and the applicability of the minimally invasive techniques provide support for the generalisability of its results. Percutaneous catheter drainage is a relatively easy and well-established radiological procedure. VARD is considered a fairly straightforward procedure that can be performed by any gastrointestinal surgeon with basic laparoscopic skills and experience in pancreatic necrosectomy.[21,22]

Our study specifically compared two treatment strategies and does not provide a direct comparison of open necrosectomy with minimally invasive retroperitoneal necrosectomy. Although there are theoretical advantages of a minimally invasive approach, we have not proved that VARD is superior to open necrosectomy in patients in whom percutaneous drainage has failed.

This study was not designed or powered to demonstrate a difference in the rate of death between the two treatment strategies. A study showing a clinically relevant difference in mortality would require thousands of patients and is not likely to be performed.

Our results indicate that the preferred treatment strategy for patients with necrotising pancreatitis and secondary infection, from both a clinical and an economic

point of view, is a minimally invasive step-up approach consisting of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy.

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SUPPLEMENTARY APPENDIX TO:

A step-up approach
or open necrosectomy
for necrotising
pancreatitis

METHODS

MINIMALLY INVASIVE STEP-UP APPROACH

Step 1: percutaneous or endoscopic drainage

A percutaneous drain was placed in the peripancreatic collection under guidance of CT or ultrasound (**step 1a**). Minimal drain size was 12-French and multiple drains were allowed. The preferred route was through the left retroperitoneum, thereby facilitating minimally invasive retroperitoneal necrosectomy at a later stage. Transabdominal drainage was performed if a retroperitoneal access route for drainage was not possible. Details on the percutaneous drainage procedures and irrigation protocol have been described elsewhere.[1] Only if neither retroperitoneal nor transabdominal drainage was possible, was endoscopic transgastric drainage performed. For the endoscopic drainage procedures, the collections were punctured with a 19 Gauge needle (Cook). A standard 0.035 inch guidewire was introduced through the needle into the collection, after which the needle was removed. Over the guidewire the outside sheet of a 7 Fr cystotome (Cook) was introduced into the collection using cutting current. Thereafter the tract was dilated with a 8-mm Maxforce dilation balloon (Boston Scientific). Thereafter, 2 double-pigtail plastic stents (7 French, 4 or 5 cm) and a nasocystic catheter were placed in the infected collection. For irrigation the drains were flushed with a bolus of 250 cc of normal saline four times a day.

The next treatment step depended on whether or not the patient's condition improved. *Clinical improvement* was defined as follows: **1**. on ICU: improved function of at least two organ systems (i.e., circulatory, pulmonary, renal) and **2**. on the ward: at least 10% improvement of two out of three of the following parameters: temperature, white blood cell count and C-reactive protein. In absence of clinical improvement after 72 hours, CT was repeated. If the position of the drain(s) was inadequate or other collections could be drained, a drainage procedure was repeated once (**step 1b**) with reassessment after the next 72 hours, if not; minimally invasive necrosectomy was the next step (**step 2**).

If at any moment after the first and second 72 hours following percutaneous drainage, a patient who initially stabilised failed to show further clinical improvement or even clinically deterioration (according to the predefined criteria), minimally invasive necrosectomy was also performed.

Step 2: minimally invasive retroperitoneal necrosectomy

Videoscopic assisted retroperitoneal debridement (VARD) was performed via a 5 cm incision according to the previously published technique.[2,3] Using the retroperitoneal drain for guidance, only loosely adherent necrosis was removed from the collection with videoscopic assistance after which two large bore drains were inserted. If VARD was technically not possible, (i.e., no retroperitoneal access route), laparotomy was performed according to the technique used in the open necrosectomy group.

POSTOPERATIVE MANAGEMENT

Continuous postoperative lavage amounting up to at least 10 L per 24 hours on the third postoperative day was performed both after open necrosectomy and VARD. All patients underwent contrast-enhanced CT one week after randomization. Other CT scans were performed on demand. Reinterventions for persisting sepsis or complications were performed on demand and, if possible, in accordance with the strategy the patient was initially assigned to. All patients received intravenous antibiotics (imipenem/ cilastatin, meropenem or piperacillin/tazobactam depending on treatment centre) after randomization, which were switched according to culture results. Nutritional support was also standardized.[1]

COSTS

Cost-minimization analysis was used to determine economic differences between the minimally invasive step-up approach and primary open necrosectomy. Costs were estimated from a societal perspective.[4] Direct medical costs and indirect costs related to absence from work were estimated during admission and 6 months follow-up. Primary data were used to assess the use of health care resources. In addition, at 3 and 6 months after discharge, patients filled out the validated Health and Labor questionnaire[5] and a diary to capture additional resource use. Costs were assessed according to the Dutch guidelines for (pharmaco-)economic research.[6] Guideline unit costs were used for ICU stay, hospital stay, medication (i.e., antibiotics during admission and antidiabetic medication and pancreatic enzymes during follow-up), visits to primary and outpatient health care clinicians, home care and admission to rehabilitation centres or nursing homes.[6,7] Unit costs for operations,

radiological procedures, endoscopic procedures and microbiology diagnostics were calculated at one of the university hospitals in 2008 and included all personnel costs, costs of materials, costs of equipment, and overhead costs. Productivity losses due to absence from paid work were calculated according to the cost friction method.[8] Costs per patient were calculated by multiplying volumes of resource with unit costs.[4] All costs were set at the year 2008 price level using the price index rate of the Dutch health care sector.

STATISTICAL ANALYSIS

The original study protocol[1] stated that, for safety reasons, continuous sequential monitoring would be performed on mortality and major morbidity included in the primary endpoint. An independent biostatistician who was blinded for treatment allocation performed continuous sequential analysis on mortality and major morbidity reported during the trial. The analysis was performed with PEST (PEST 4: user manual. MPS Research Unit (2000), the University of Reading) according to the restricted procedure as described by Whitehead.[9,10] The boundaries for the sequential analysis plot were based on the assumption that the minimally invasive step-up approach would reduce the occurrence of the primary endpoint from 45% to 16%, with 80% power and a two-sided alpha level of 0.05. A conventional sample size analysis yielded a total study population of 88 patients.

If one of the boundaries of the sequential analysis plot was crossed during the analysis of the cumulative data, meaning that the difference in treatment was of at least the predefined expected magnitude (in either direction), the biostatistician would inform the independent monitoring committee which would advise the steering committee on continuation or termination of the study. If the boundaries would not be crossed during the study, the trial would continue until the total of 88 patients was randomised. The prespecified boundaries guarantee the type I error wherever they are crossed.

The prespecified boundaries were not crossed during the period of patient enrollment and consequently the independent monitoring committee and the steering committee were not informed of results of the sequential analysis. The outcome of the sequential analysis was only known to the independent biostatistician.

Early on in the trial it became apparent that the sequential analysis suffered from

SUPPLEMENTARY TABLE. Total direct medical and indirect costs

	Minimally invasive step-up approach (n=43)		Primary open necrosectomy (n=45)		Difference*	
	Total costs	Mean cost per patient	Total costs	Mean costs per patient	Mean costs per patient (95% CI)	
During admission						
Hospital stay	965,294	22,449	988,503	21,967	-482	(-8,135-7,171)
ICU stay	1,247,952	29,022	1,326,387	29,475	453	(-20,850-21,756)
Necrosectomies (VARD or laparotomy)	84,258	1,960	173,472	3,855	1,896	(881-2910)
Other operations	46,623	1,084	113,628	2,525	1,441	(60-2823)
Drainage procedures (endoscopic and percutaneous)	33,348	776	13,592	302	-474	(-698-249)
Radiological procedures (except drainage)	72,027	1,675	95,735	2,127	452	(-368-1272)
Endoscopic procedures (except drainage)	11,990	279	28,323	629	351	(-158-859)
Microbiology	35,503	826	54,521	1,212	386	(-85-857)
Medication	96,557	2,245	138,964	3,088	843	(-441-2126)
Absence from work	283,679	6,597	297,417	6,609	12	(-4428-4451)
During 6 months follow- up						
Visits to general practitioner	6,039	140	10,255	228	88	(13-162)
Visits to outpatient clinic	21,573	502	35,251	783	282	(55-508)
Readmissions to hospital	67,528	1,570	91,710	2,038	468	(-993-1,928)
Admission to rehabilitation centre	145,325	3,380	162,808	3,618	238	(-4,495-4,972)
Admission to nursing home	53,066	1,234	133,215	2,960	1,726	(-1,275-4,727)
Operations	28,360	660	34,979	777	118	(-716-952)
Endoscopic procedures	6,915	161	10,850	241	80	(-271-432)
Diagnostic procedures	9,740	227	13,930	310	83	(-51-217)
Microbiology	1,155	27	513	11	-16	(-35-4)
Medication	4,368	102	12,602	280	179	(59-298)
Home care	7,122	166	6,301	140	-26	(-139-87)
Physiotherapy	7,939	185	11,080	246	62	(-104-228)
Aids	339	8	570	13	5	(-12-22)
Absence from work	152,302	3,542	283,038	6,290	2,748	(-1,444-6,940)
Total direct medical and indirect costs	**3,387,335**	**78,775**	**4,032,648**	**89,614**	**10,839**	**(-23,878-45,556)**

Amounts are in Euro's, for conversion to US dollars multiply by 1,47.
* This is the difference in costs between primary open necrosectomy and the minimally invasive step-up approach.

significant delay because only data on mortality and evident major morbidity reported by local investigators could be sent to the biostatistician, whereas a patient could only be analysed as not having an endpoint once the follow-up period of 3 months after discharge was completed and data collection was complete. Moreover, it was anticipated that, once the data were checked by the independent auditor, morbidity endpoints could be found in patients who were already analysed by the biostatistician as not having an endpoint. Therefore, it was decided that, instead of the sequential monitoring of the provisionally audited primary outcomes, a conventional analysis would be performed after the last patient completed 3 months follow-up and all data were checked by the auditor. Prior to this analysis, an adjudication committee consisting of eight experienced gastrointestinal surgeons assessed all primary (and secondary) endpoints. Every patient was evaluated by each committee member individually with data presented in a standardized format, including all available data collected during follow-up. Disagreements were resolved during a plenary consensus meeting. The adjudication committee was unaware of the outcome of the sequential analysis and was blinded for treatment allocation at all times.

The conventional analysis was performed only after agreement was reached on all endpoints. The occurrence of the primary endpoint was compared between the two treatment groups and results are presented as risk ratios with corresponding 95% confidence intervals (CI). In line with the protocol, we also performed sequential analysis on the adjudicated primary endpoints. Results were in agreement with those of the conventional analysis.

A P value of 0.05 or less was considered statistically significant. All statistical analyses were done with SPSS software (version 15.0).

RESULTS

DETAILS ON PERCUTANEOUS DRAINAGE PROCEDURES

In the 41 patients undergoing percutaneous drainage in the step-up approach (2 underwent endoscopic drainage), drains were upsized in 4 patients and drains were replaced in 7 patients. The median drain size was 14 French (range 12-24). The median number of drains placed during the first or second drainage procedure was 1 (range 1-3). Multiple drains were placed during the same procedure in 7 patients.

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PART IV

CHAPTER 18

Clinical course and treatment of necrotising pancreatitis: a prospective multicentre study of 639 patients

ABSTRACT

BACKGROUND

Most series on necrotising pancreatitis are retrospective, small, from single centres, cover decades and report only operated patients. We present a prospective, multicentre cohort of 639 patients with necrotising pancreatitis included in a 4.5-year period who were treated conservatively or with an intervention.

METHODS

This was an observational cohort study. During 2004-2008, patients with acute pancreatitis and signs of pancreatic necrosis or peripancreatic necrosis alone on computed tomography were prospectively included in 21 hospitals. Data on disease severity, interventions (i.e., radiological, endoscopic or surgical) and outcome were recorded.

RESULTS

Mortality in all 639 patients was 15%. Organ failure occurred in 240 patients (38%), with 35% mortality. Conservative treatment was performed in 397 patients (62%), with 7% mortality. An intervention was performed in 242 patients (38%), with 27% mortality. The longer the time between admission and intervention, the lower the risk of mortality: 0-14 days; 56%, 14-29 days; 26% and >29 days; 15%, P<0.001. An emergency laparotomy (i.e., for other reasons than infected necrosis) was performed in 32 patients (5%), at a median of 5 days (interquartile range [IQR] 2-14) after admission, with 78% mortality. An intervention for suspected or confirmed infected necrosis was performed in 208 patients (33%), with 19% mortality. The longer the time between admission and first intervention, the fewer the complications: 0-14 days: 72%, 14-29 days: 57%, and >29 days: 39%, P=0.007. Primary percutaneous drainage was performed in 130/208 patients (63%) undergoing a first intervention for suspected or confirmed infected necrosis. After a median of one drainage procedure (IQR 1-2), 35% was successfully treated without the need for further necrosectomy. In total, 169 patients underwent necrosectomy (laparotomy: n=104, video-assisted retroperitoneal debridement [VARD]: n=54, endoscopic transgastric necrosectomy [ETN]: n=11), with mortality of 24%. Post- procedural complications occurred more often following laparotomy than after VARD and ETN: 71%, 56% and 9% respectively, P<0.0001. Of all 93 patients who died, 41 (44%) had primary infected

necrosis, 11 (12%) had secondary infected necrosis and 41 (44%) died without documented infected necrosis. The vast majority of 52 patients who died without primary infected necrosis had organ failure (91%), which mostly occurred in the first week of admission (85%).

CONCLUSIONS

Mortality in necrotising pancreatitis remains high. Outcome of infected necrosis seems to improve with postponement of intervention and the use of minimally invasive techniques. Patients with sterile necrosis still suffer from considerable mortality in case of multiple organ failure and emergency laparotomy early in the course of disease.

INTRODUCTION

Acute pancreatitis is complicated by necrosis of the pancreatic parenchyma and/or the peripancreatic fat tissue in around 20% of patients.[1,2] The clinical course of necrotising pancreatitis can be divided into two phases. In the first phase (i.e., 1-2 weeks after onset of symptoms), a systemic inflammatory response syndrome (SIRS) occurs, which is often followed by multiple organ failure.[3-5] Interventions in the early phase of necrotising pancreatitis are relatively contra-indicated, although some patients require an emergency laparotomy for acute complications such as the abdominal compartment syndrome or bowel ischemia.[3] Data on this subgroup of patients are scarce. It has been suggested that around half the deaths from necrotising pancreatitis are caused by multiple organ failure in the early phase.[6,7] In the late phase of the disease (i.e., after 1-2 weeks), systemic inflammation often regresses and secondary infection of necrosis occurs in about 30% of patients with necrotising pancreatitis.[8,9] In the absence of radiological, endoscopic or surgical intervention, infected necrosis ultimately leads to death in nearly every patient.

Over the last 20 years, several major changes have occurred in the management of necrotising pancreatitis. First, the indication for intervention has shifted. Whereas historically most patients with sterile necrosis underwent necrosectomy, it is now accepted that sterile necrosis should largely be managed conservatively and that the main indication for intervention is infected necrosis.[3,10-12] Second, the timing of intervention has changed. Where necrosectomy was once performed at a very early stage[13], it is now thought that intervention should be delayed to around 3-4 weeks after onset of disease.[14-16] This timeframe allows for encapsulation of peripancreatic collections, which may improve conditions for intervention and thereby decrease the risk of complications such as bleeding and perforation. Third, new methods for intervention have been introduced. Historically, the standard intervention was primary open necrosectomy.[17] As an alternative, minimally invasive, radiological, endoscopic and surgical techniques are increasingly being used.[18-23] We recently reported the results of the randomised multicentre PANTER trial which showed that a step-up approach of percutaneous drainage, if necessary, followed by minimally invasive retroperitoneal debridement, as compared to primary open necrosectomy, is the preferred strategy from a clinical and economic point of view.[24]

The outcome of patients with necrotising pancreatitis after the implementation of

these changes over the last 20 years is unknown. A recent literature review (1993-2005) reported a median 17% mortality (range 14 to 62%) for necrotising pancreatitis (i.e., both sterile and infected) and 30% mortality (range 8 to 39%) for infected necrotising pancreatitis.[9] Most of the reviewed studies were performed in time periods where the abovementioned changes regarding intervention had not yet fully occurred. Moreover, most studies published in the last 20 years were retrospective in design and included only small numbers of patients. There are a few large studies, with sample sizes ranging from 281 to 392 patients, but these cover long time periods, ranging from 12 to 19 years.[25-27] Most studies only report on the subgroup of patients that underwent necrosectomy.[22,26,28,29] Consequently, data on the outcome of conservatively treated patients with necrotising pancreatitis in terms of (persistent) organ failure and mortality are scarce. In many of the most recent series on necrosectomy, the proportion of patients with infected necrosis is still relatively low (range 63 to 74%).[22,28,29] Moreover, the percentage of patients undergoing percutaneous drainage prior to necrosectomy is also low (range 5 to 30%) or not reported.[12,25,28-30] Finally, the vast majority of data comes from highly experienced single centres.[12,25,26,28-30] It is questionable whether these results can be extrapolated to daily practice in non-expert centres. Given all the above, we need new data from large prospective multicentre studies to serve as a standard reference for the current outcome of necrotising pancreatitis.

The aim of this study was to report on the outcome after intervention or conservative treatment of necrotising pancreatitis in a prospective, nationwide cohort of 639 patients. The main focus was on mortality in the several subgroups of necrotising pancreatitis based on pancreatic necrosis, peripancreatic necrosis alone, organ failure, sterile or infected necrosis, early emergency laparotomy, radiological, endoscopic and surgical interventions and conservative treatment.

METHODS

PATIENTS AND STUDY DESIGN

We performed a prospective, observational, multicentre cohort study between March 2004 and November 2008. All 8 Dutch university medical centres and 13 large teaching hospitals of the Dutch Pancreatitis Study Group (DPSG) participated. Four of these hospitals joined the study group in November 2005. During the study

period, all patients admitted with acute pancreatitis were screened for eligibility for the Dutch PROPATRIA and PANTER trials.[24,31] Regardless of eligibility for the randomised trials, patients were asked for informed consent for registration in the database on admission. In the current study, all patients from the entire cohort of patients with acute pancreatitis who showed signs of pancreatic necrosis and/or peripancreatic necrosis on contrast enhanced computed tomography (CECT) were prospectively included. This is the first time this complete cohort is reported.

CECT was performed per protocol in the patients randomised in the PROPATRIA study on 7-10 days after admission and on demand therefore and thereafter.[31] In all other patients, CECT was performed by discretion of the treating physician, but generally only in case there was no clinical improvement after the initial 7-10 days of admission. Local radiologists judged the CECT for pancreatic necrosis and/or peripancreatic necrosis, and based on their evaluation, the patients were prospectively included in the current study. However, after the study was completed, all digitalised CECTs were reviewed by a single experienced abdominal radiologist (TLB) who was unaware of the patient's clinical background and possible interventions and made the final decision on inclusion or exclusion based on the highest CT-severity index[32] measured on all CECTs performed during the index admission. Median time between onset of symptoms and the final CECT before discharge was 14 days (interquartile range [IQR] 7-47). *Pancreatic necrosis* was defined as a CT-severity index of greater than 4, which means that there is focal non-enhancement of the pancreatic gland. *Peripancreatic necrosis alone* (i.e., without pancreatic parenchymal necrosis) was defined as a CT-severity index of 3 or 4, which means peripancreatic morphological changes exceeding fat stranding. In the most recent draft of the revised Atlanta Classification, the definition of necrotising pancreatitis includes both pancreatic parenchymal necrosis with or without peripancreatic necrosis, and peripancreatic necrosis alone (see: http://www.pancreasclub.com/resources/AtlantaClassification.pdf).

The study was conducted in accordance with the principles of the Declaration of Helsinki, and was investigator initiated and investigator driven. The ethics review board of each participating hospital approved the study. All patients or their legal representatives gave written informed consent. We adhered to the STROBE statement guidelines for reporting on observational cohort studies.[33]

TREATMENT ON ADMISSION

Patients were treated according to a fixed treatment protocol. Following admission, patients received rigorous fluid resuscitation and full laboratory investigations were performed on the first three days of admission and in the 24 hours prior to any intervention. Nasojejunal enteral feeding was initiated if an oral diet was not tolerated. Parenteral nutrition was only initiated when enteral nutrition was persistently not tolerated or not sufficient. A subset of patients randomised in the PROPATRIA trial received probiotic prophylaxis (n=105).[31] Antibiotics were not administered prophylactically but only in the presence of suspected or documented infection. Patients with (pending) organ failure were treated in the intensive care unit (ICU).

INTERVENTION

In line with international guidelines, intervention was generally only performed in case of suspected or confirmed infection of pancreatic necrosis or peripancreatic necrosis alone.[3,10,11] Whenever possible, intervention was postponed until approximately 4 weeks after the onset of disease.[14-16] Intervention could be primary necrosectomy, primary percutaneous drainage with 12 to 14 French drains[18] or endoscopic drainage[21], with or without subsequent necrosectomy. Necrosectomy consisted of open necrosectomy by laparotomy and continuous postoperative lavage,[17] or minimally invasive necrosectomy: video-assisted retroperitoneal debridement (VARD)[20] or endoscopic transgastric necrosectomy (ETN).[21] A subgroup of patients included in the previously reported PANTER trial[24] was randomly assigned to either primary open necrosectomy (n=45), or a protocolised minimally invasive step-up approach which included primary drainage, followed, if necessary, by VARD (n=43).

In some patients an emergency laparotomy was performed. The indication for emergency laparotomy was severe clinical deterioration suspected to be caused by abdominal compartment syndrome, bowel ischemia, perforation of a visceral organ or acute bleeding, but not suspected or confirmed infection of pancreatic necrosis or peripancreatic necrosis.

Early 2006, the DPSG installed a multidisciplinary expert panel consisting of eight gastrointestinal surgeons, one gastroenterologist, and three radiologists to guide decision making on intervention. Whenever infected necrosis was suspected or whe-

TABLE 18.1. Definitions of study outcomes regarding morbidity

Outcome	Definition
Infected necrosis	A positive culture of pancreatic necrosis or peripancreatic necrosis obtained by means of fine-needle aspiration or from the first drainage procedure or necrosectomy, or the presence of gas in the peripancreatic collection on contrast-enhanced CT
Organ failure	
Pulmonary failure	PaO2 <60 mm Hg, despite FIO2 of 0.30, or need for mechanical ventilation
Circulatory failure	Circulatory systolic blood pressure <90 mm Hg, despite adequate fluid resuscitation, or need for inotropic catecholamine support
Renal failure	Creatinine level >177 μmol/liter after rehydration or new need for hemofiltration or hemodialysis
Multiple organ failure	Failure of at least two organ systems on the same day
Persistent organ failure	Presence of organ failure on at least 3 consecutive days (lasting more than 48 hours)
New-onset multiple organ failure	New-onset failure (i.e., not present at any time in the 24 hr before first intervention) of two or more organs
Enterocutaneous fistula	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
Perforation of visceral organ	Perforation requiring surgical, radiological, or endoscopic intervention
Intraabdominal bleeding	Bleeding requiring surgical, radiological, or endoscopic intervention

never there was any other indication for intervention in a patient, the expert panel was text-messaged and received a case description, including CT images, on a standardized form by e-mail. Within 24 hours, the members of the expert panel individually advised on the indication for intervention and optimal methods of interventions. The final decision was made by the treating physicians.

DATA COLLECTION

Data from patients randomised in the PROPATRIA and PANTER trial were collected as described previously.[24,31] In addition, data from registered patients were entered prospectively into the database. This included data regarding patient demographics, laboratory investigations on the first three days of admission and 24 hours prior to intervention, clinical course (e.g., organ failure, complications after intervention), microbiology cultures, health care resource utilisation (e.g., number of

operations). In cases where patients had been referred from other centres, all CECTs, clinical data, and laboratory investigations were retrieved from the referring centres.

OUTCOMES

The primary study outcome was mortality during index admission. Readmission within 10 days after discharge from index admission was considered a prolonged index admission. Secondary outcomes were organ failure, infected necrosis, the number of percutaneous and endoscopic drainage procedures, endoscopic and surgical necrosectomies, other operations, complications after intervention (i.e., new-onset multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula or perforation of a visceral organ). See TABLE 18.1 for definitions of the study outcomes regarding morbidity.

STATISTICAL ANALYSIS

Analyses were performed with SPSS version 15.0 (SPSS, Chicago, IL). Continuous data are presented as mean ± standard deviation (SD) and in case of non-normal distributions as median with interquartile range (IQR). In case of missing data, patients were not included in the analyses for the specific parameter and this is reported. Differences were tested by the Student's *t* test or Mann-Whitney *U* test, respectively. Proportions were compared by the χ^2 test or the Fisher exact test, as appropriate. A two-sided $P<0.05$ was considered statistically significant.

RESULTS

PATIENT INCLUSION

During the 4.5 years study period, 1150 patients with acute pancreatitis were prospectively registered on admission. From this cohort, 639 patients with signs of pancreatic necrosis or peripancreatic necrosis alone on CECT were included in the current study. No data were missing with regard to the primary and secondary study outcomes. Patient characteristics on admission and details from the CECTs prior to any intervention are given in TABLE 18.2, for patients treated conservatively (n=397) and with an intervention (n=242) separately. Patients who underwent intervention had higher Imrie scores and American Society of Anaesthesiologists (ASA) class on admission, and had more extensive pancreatic necrosis.

TABLE 18.2. Characteristics of 639 patients with acute pancreatitis and pancreatic necrosis or peripancreatic necrosis alone

Characteristic	All patients (n=639)	Conservative treatment (n=397)	Intervention[a] (n=242)	P value
Age - yr	58 (45-70)	57 (43-71)	59 (48-69)	0.41
Male sex	398 (62%)	237 (60%)	161 (67%)	0.08
Etiology				0.41
Gallstones	304 (48%)	192 (48%)	112 (46%)	
Alcohol abuse	150 (24%)	95 (24%)	55 (23%)	
Other	63 (10%)	42 (11%)	21 (9%)	
Unknown	122 (19%)	68 (17%)	54 (22%)	
ASA class on admission				0.04
I (healthy status)	202 (32%)	136 (34%)	66 (27%)	
II (mild systemic disease)	347 (54%)	214 (54%)	133 (55%)	
III (severe systemic disease)	90 (14%)	47 (12%)	43 (18%)	
Predicted severity of pancreatitis				
APACHE-II score at admission	8 (5-11)	7 (5-10)	8 (5-11)	0.25
Imrie/modified Glasgow score	3 (2-5)	3 (2-4)	4 (3-5)	<0.001
Highest CRP level in first 48 h	291 (±130)	287 (±133)	294 (±129)	0.51
Data missing[b]	44 (7%)			
CT-severity index	4 (4-8)	4 (4-6)	8 (6-10)	<0.001
Peripancreatic necrosis alone	315 (49%)	257 (65%)	57 (24%)	<0.001
Pancreatic necrosis	324 (51%)	139 (35%)	185 (76%)	<0.001
Extent of pancreatic necrosis				<0.001
<30%	447 (70%)	329 (83%)	118 (49%)	
30% to 50%	83 (13%)	25 (6%)	58 (24%)	
>50%	109 (17%)	43 (11%)	66 (27%)	
Transferred from other hospital	156 (24%)	39 (10%)	117 (48%)	<0.001
peripancreatic necrosis alone				

a= Any form of radiological, endoscopic or surgical intervention
Continuous variables are mean (±SD) or median (interquartile range)
b= CRP stands for C-reactive protein. It was not possible to measure CRP in 1 hospital. APACHE stands for Acute Physiology And Chronic Health Evaluation
ASA stands for American Society of Anaesthesiologists

ORGAN FAILURE

At any time during admission, organ failure occurred in 240/639 patients (38%) and persistent organ failure in 214 patients (34%). Multiple organ failure occurred in 194 patients (30%), and persistent multiple organ failure in 161 patients (25%). More than half of the cases (58%) of organ failure occurred within the first week of admis-

sion. Organ failure occurred more often in patients with pancreatic necrosis as compared to patients with peripancreatic necrosis alone: 163/324 patients (50%) vs. 77/315 patients (24%) (P<0.001).

An emergency laparotomy was performed in 32/639 patients (5%), at a median of 5 days (IQR 2-14) after admission. These laparotomies were not performed for suspected or confirmed infected necrosis, but because an abdominal catastrophe for another reason was suspected. There were signs of an abdominal compartment syndrome in 15 patients. Bowel ischemia was observed during laparotomy in 11 patients. Of the 32 patients undergoing emergency laparotomy, 25 patients (78%) died.

INFECTION OF NECROSIS

Primary infection of necrosis was diagnosed in 202/639 patients (32%), at a median of 26 days (IQR 18-38) after admission. The incidence of infected necrosis was higher in patients with pancreatic necrosis as compared to patients with peripancreatic necrosis alone: 151/324 patients (47%) vs. 51/315 patients (16%), P<0.0001. Eleven out of 202 patients (5%) with infected necrosis were successfully treated without any form of radiological or surgical intervention. These patients were treated with intravenous antibiotics only because, in the absence of sepsis and organ failure, their clinical condition was exceptionally good.

INTERVENTIONS FOR SUSPECTED OR CONFIRMED INFECTED NECROSIS

A radiological, endoscopic or surgical intervention for suspected or confirmed infected necrosis was performed in 208/639 patients (33%). Details on disease severity at the time of intervention are given in TABLE 18.3. Median time between onset of symptoms and intervention was 28 days (IQR 22-41). The cultures of the first intervention were positive in 185/208 patients, leading to a rate of documented infected necrosis of 89%.

In these 208 patients, the primary intervention consisted of either necrosectomy or drainage. Primary necrosectomy was performed in 78/208 patients (38%) (laparotomy: n=68, VARD: n=6, and ETN: n=4) and primary drainage in 130/208 patients (63%; percutaneous drainage: n=113, endoscopic transgastric drainage: n=17).

In the 130 patients undergoing drainage as first treatment, a median of 1 drainage

TABLE 18.3. Characteristics of patients before primary intervention for suspected or confirmed infected necrosis

Characteristic	Patients undergoing primary intervention (drainage or necrosectomy, n=208)
APACHE-II score*	13.0 (9-17)
CRP level*	200 (±109)
Data missing	46 (22%)
Admitted to ICU	
At the time of intervention	75 (36%)
Anytime before intervention	140 (67%)
Organ failure	
At the time of intervention	76 (37%)
Anytime before intervention	113 (54%)
Multiple organ failure	
At the time of intervention	46 (22%)
Anytime before intervention	84 (40%)
Infected necrosis confirmed by culture	185 (89%)

Continuous variables are mean (±SD) or median (interquartile range)
* Based on the maximal values 24 hours before intervention
APACHE stands for Acute Physiology And Chronic Health Evaluation

procedure (IQR 1-2) was performed per patient: 58% of patients underwent 1 drainage procedure, 32% underwent 2 drainage procedures and 10% had more than 2 drainage procedures. Forty-five out of the 130 patients (34%) who underwent primary drainage were treated without the need for further necrosectomy. There were 76/130 patients (58%) who underwent additional necrosectomy (laparotomy: n=24, VARD: n=23, ETN: n=9) after primary drainage. Median time between the first drainage and necrosectomy was 10 days (IQR 5-22). Nine of 130 patients (7%) treated with primary drainage died without undergoing any other intervention. Necrosectomy was not performed in these patients because at the time of percutaneous drainage and thereafter, they were not considered candidates for surgery due to their clinical condition and co-morbidity.

In total, 169 patients underwent one or more necrosectomies (laparotomy: n=104, VARD: n=54, endoscopic transgastric necrosectomy [ETN]: n=11) with or without prior percutaneous or endoscopic drainage. Median time from admission to necrosectomy was 35 days (IQR 25-52). 105/169 patients (62%) underwent 1 necrosecto-

my, 38/169 patients (23%) had 2 necrosectomies and 26 patients (15%) underwent 3 or more necrosectomies.

COMPLICATIONS AFTER INTERVENTION FOR SUSPECTED OR CONFIRMED INFECTED NECROSIS

Of the 208 patients undergoing a first intervention (i.e., drainage or necrosectomy) for suspected or documented infected necrosis, 104 patients (50%) suffered from one or more complications. New-onset organ failure occurred in 40% of patients, intra-abdominal bleeding in 16%, and enterocutaneous fistula or perforation of a visceral organ in 17%.

The longer the time between admission and first intervention, the lower the risk of complications: 0-14 days; 72%, 14-29 days; 57%, and >29 days; 39%, P=0.007. There was no association between the presence of organ failure at the time of first intervention and complications (P=0.99).

Fewer complications occurred in patients who underwent drainage as the first intervention than in patients who underwent primary necrosectomy: 42% vs. 64% respectively, P=0.003.

Of the 169 patients who underwent necrosectomy (with or without previous drainage), 105/169 patients (62%) developed one or more complications. New-onset multiple organ failure occurred in 27% of patients, intraabdominal bleeding in 22%, and enterocutaneous fistula or perforation of a visceral organ in 21%.

Considering the different techniques for the first necrosectomy, the number of patients that developed complications was greater after laparotomy than after VARD and ETN: 71%, 56% and 9% respectively, P<0.0001.

MORTALITY

TABLE 18.4 presents the mortality in several possible subgroups of necrotising pancreatitis. In the entire group mortality was 15%. Mortality was greater in patients with pancreatic necrosis than in patients with peripancreatic necrosis alone: 20% vs. 9%, P<0.0001.

In the 242 patients that needed any form of intervention, mortality was 27%. The longer the time between admission and need for intervention, the lower the risk of mortality: 0-14 days; 56%, 14-29 days; 26% and >29 days; 15%, P<0.001.

In the group of 208 patients undergoing a first intervention for suspected or confirmed infected necrosis, there was no significant difference in mortality between those patients who underwent drainage as primary intervention and those who underwent primary necrosectomy: 18% vs. 20%, P=0.86. Mortality did not differ significantly between the three techniques of necrosectomy: laparotomy: 27%, VARD: 22% and ETN: 9%, P=0.38.

Of the 93 patients who died, 41 (44%) had primary infected necrosis and 85 (91%) suffered from organ failure. Of the remaining 52 patients who died (56% of mortality in entire patient cohort), 11 (12%) had secondary infected necrosis after previous emergency laparotomy (n=9) and drainage (n=2), and 41 died (44%) without documented infected necrosis. The vast majority of these 52 patients (91%) died of organ failure, which mostly occurred in the first week of admission (85%). Mortality was higher in patients with organ failure in the first week of admission as compared to patients with organ failure after the first week of admission: 41% vs. 28%, P=0.04.

DISCUSSION

This is the largest study on patients with necrotising pancreatitis who underwent either conservative treatment or an intervention. Compared to most of the earlier studies, this study was prospective, included a large number of patients in a relatively short study period, was conducted in a nationwide multicentre setting and covered the entire clinical spectrum of necrotising pancreatitis.

Our study shows that overall mortality in necrotising pancreatitis remains as high as 15%. We confirmed that around half of the patients with necrotising pancreatitis who die have sterile necrosis with multiple organ failure, which mostly occurs in the first week of admission.[6,7] There is currently no effective treatment to improve outcome in these patients. Invasive intervention is generally contra-indicated early in the course of disease.[3] However, in 32 patients (5%) in the current study an early emergency laparotomy was performed because it was felt that the patient would die if intervention was withheld. Mortality after emergency laparotomy was exceptionally high (78%). Fifteen of these patients were suspected of having an abdominal compartment syndrome. There are only a few other studies reporting on emergency laparotomy for abdominal compartment syndrome early in the course of acute pancreatitis.[34-36] These studies were retrospective series with 3 to 8 patients, in whom

TABLE 18.4. Mortality in the different subgroups of the 639 patients with necrotising pancreatitis

Subgroups	Mortality
All patients with necrotising pancreatitis	93/639 (15%)
Peripancreatic necrosis alone	28/315 (9%)
Pancreatic necrosis	64/324 (20%)
Organ failure	
At any time during admission	85/240 (35%)
At any time during admission, persistent	78/214 (36%)
In the first week of admission	57/141 (40%)
Multiple organ failure	
At any time during admission	79/194 (41%)
At any time during admission, persistent	66/161 (41%)
In the first week of admission	44/94 (47%)
Infected or sterile necrosis	
Primary infected necrosis	41/202 (20%)
Sterile necrosis	52/437 (12%)
Conservative treatment or intervention	
Conservative treatment	28/397 (7%)
Any intervention (i.e., emergency laparotomy, drainage, necrosectomy)	65/242 (27%)
Emergency laparotomy	25/32 (78%)
Drainage or necrosectomy as first intervention for suspected or confirmed infected necrosis	40/208 (19%)
Drainage as first intervention	26/130 (20%)
Necrosectomy as first intervention	14/78 (18%)
Necrosectomy (with or without previous drainage or emergency laparotomy)	41/169 (24%)
Any operation (i.e., necrosectomy or emergency laparotomy)	56/187 (30%)

mortality varied from 30 to 75%. It is therefore questionable if an early emergency laparotomy for suspected abdominal compartment syndrome in acute pancreatitis should be performed. Notably, a 2007 international consensus conference recommended percutaneous decompression of intra-abdominal fluid as the initial step to decrease intra-abdominal pressure in patients with abdominal compartment syndrome in general.[37] This strategy in acute pancreatitis is currently being evaluated in a randomised trial (ClinicalTrials.gov identifier NCT00793715).

Organ failure occurred in 38% of patients and was associated with 35% mortality. This is in line with a recent meta-analysis of 14 cohort studies of patients with both interstitial and necrotising pancreatitis, showing overall mortality after organ failu-

re of 30%.[38] Several studies have suggested that early persisting organ failure rather than transient organ failure drives mortality in acute pancreatitis.[5,6,39] Interestingly, in the current study, the vast majority of patients with organ failure (89%) or multiple organ failure (83%) had persistent organ failure (i.e., lasting for more than 48 hours). As expected, mortality in patients with organ failure in the first week was significantly higher than for patients with organ failure occurring after the first week (41% vs. 28%). This supports the theory that organ failure early in the course of acute pancreatitis, which is associated with systemic release of cytokines and SIRS, is a different clinical entity than organ failure as a result of sepsis from infected necrosis at a later stage in the disease. We suggest that future studies on the role of organ failure in acute pancreatitis make a clear distinction between these different forms of organ failure.

Over a third of patients with necrotising pancreatitis in our study underwent an intervention (i.e., radiological, endoscopic or surgical), which was associated with 27% mortality. Several guidelines[3,9,15] now advise to withhold intervention to around 2-3 weeks after onset of symptoms, although there is only limited evidence from previous studies in support of this advice. A randomised study from 1997 suggested that delaying surgical intervention beyond the first 12 days, as compared to intervention as early as in the first 72 hours of admission, reduces mortality.[13] Two retrospective studies[14,16] previously suggested that postponing surgery to around 4 weeks further improves outcome. The current study yields further important evidence in favour of delaying intervention, as we found that both mortality and complications decreased considerably if intervention was performed later in the course of disease.

Infection of necrosis occurred in around 30% of patients with necrotising pancreatitis. This suggests that the incidence of infected necrosis has remained fairly constant over the last 20 years.[9] This is not surprising, as there are currently no effective strategies to prevent infected necrosis. Mortality in patients with primary infected necrosis in our study was 20%. This seems to be lower than the mortality of around 30% for infected necrosis reported in reviews of the literature of the last two decades.[9,38] However, our results are difficult to compare with the literature because most published reports present only selected subgroups of patients with infected necrosis (e.g., only those who underwent necrosectomy, excluding emergency laparotomy). Moreover, large, prospective, unselected cohort-studies on infected necrosis are rare.[40]

Of the entire cohort of 639 patients, 33% underwent an intervention for suspected or confirmed infected necrosis. Around a third of patients with infected necrosis were successfully managed with simple drainage only. A median of 1 drainage procedure with normal sized (i.e., 12-14 French) drains was sufficient. In these patients, decompression of the infected collection with fluid and necrosis seems to be enough for full recovery, meaning that major abdominal surgery (i.e., necrosectomy) is not necessary. Patients that were treated with drainage as first intervention also had fewer complications than patients treated with primary necrosectomy. These results are in line with our recent multicentre PANTER trial.[24] We advise that, whenever possible, all patients with suspected or confirmed infected necrosis are treated with percutaneous drainage first.

In the patients undergoing necrosectomy, minimally invasive surgical and endoscopic techniques were associated with fewer complications than open necrosectomy. This seems to confirm the hypothesis that minimally invasive necrosectomy may reduce morbidity by inducing less surgical stress (i.e., a pro-inflammatory immune response) in these already critically ill patients. There are only few other studies that directly compared patients undergoing minimally invasive necrosectomy with open necrosectomy.[22,41] In a retrospective case-matched study in 30 patients, minimally invasive retroperitoneal necrosectomy was associated with a marked reduction in postoperative multiple organ failure.[41] In a recent important study from Liverpool, Raraty, et al. retrospectively compared 137 patients who underwent minimally invasive retroperitoneal necrosectomy with 52 patients who underwent open necrosectomy.[22] Complications (including postoperative multiple organ failure) and mortality were significantly lower after minimally invasive retroperitoneal necrosectomy than after open necrosectomy: 55% vs. 81% and 19% vs. 38%, respectively. However, these studies, in contrast to the current study, both compared patient groups from different time periods which may have introduced hidden confounding factors.

Mortality in the subgroup of patients undergoing an intervention for suspected or confirmed infected necrosis in our study was 19%. Mortality in patients undergoing necrosectomy was 24%. It has been suggested that recent mortality rates of necrosectomy in North-American hospitals is lower than mortality in European centres.[42,43] Variation in case-mix probably explains these differences in mortality. Most importantly, the rate of documented infected necrosis in patients that underwent

intervention in our study was 89%, which is somewhat higher compared to the two recent North-American series on necrosectomy with infected necrosis rates of 72% to 74%.[28,29] We suggest that future studies should report the outcome of patients that underwent intervention for suspected or confirmed infected necrosis, rather than on the group of patients that underwent necrosectomy or any other form of intervention for various indications.

In our study, 5% of patients with documented infected necrosis were successfully managed without any form of intervention. This has been previously reported in some case reports and small case series.[44-47] Although our data confirm that a very small subset of patients with infected necrosis can be treated with antibiotics alone, infected necrosis should still be considered an indication for intervention in the overwhelming majority of patients. We recommend close monitoring of patients who have an extraordinarily good clinical condition that might justify conservative treatment.

Patients with pancreatic parenchymal necrosis had significantly higher mortality than patients with peripancreatic necrosis alone: 20% vs. 9%. There is only one other study that previously compared these two subgroups of acute pancreatitis, and it showed similar mortality rates.[48] Although the outcome of patients with parenchymal necrosis was substantially worse, patients with peripancreatic necrosis alone still had a considerable risk of organ failure (24%), infected necrosis (16%), and need for intervention (23%). The subgroup of patients with acute pancreatitis in whom CT shows normally enhancing pancreatic parenchyma but signs of peripancreatic necrosis should therefore also be monitored carefully in clinical practice.

This study has several potential shortcomings. First, during the study period, CT was performed in patients admitted with acute pancreatitis by discretion of the treating physician (with the exception for the 296 patients randomised in the PROPATRIA study who underwent CT per protocol). Hence, there may be a very small group of patients in whom CT was not performed because either their clinical condition was exceptionally good or they were too ill to undergo CT. These patients may have been missed for inclusion. Second, selection bias may have occurred for the comparative analyses regarding the different type of interventions and timing of intervention, as this study had an observational character rather than a randomised design. Third, we classified patients as having 'peripancreatic necrosis alone' if the

highest CT severity index[32] measured during admission was 3 or 4. One can argue that this definition is not 100% accurate, especially as it is has been suggested that peripancreatic necrosis can not reliably be diagnosed by CT.[49,50] However, several studies demonstrated a good correlation between peripancreatic findings on CECT and the presence of fat necrosis at operation or autopsy.[51-53] Moreover, the median time between onset of symptoms and the last CT in our study was 14 days. If a patient demonstrates a heterogeneous peripancreatic collection on CT (i.e., which corresponds to a CT severity index of 3-4) two weeks into the disease, this should be considered as fat necrosis until proven otherwise.[50] Notably, in all patients with signs of peripancreatic necrosis alone on CT in whom necrosectomy was performed, peripancreatic fat necrosis was found during operation.

In conclusion, this large and prospective multicentre study demonstrated that mortality in necrotising pancreatitis remains high. Although the outcome of infected necrosis seems to improve with postponement of intervention and the use of minimally invasive techniques, patients with sterile necrosis still suffer from considerable mortality in case of multiple organ failure and the need for emergency laparotomy early in the course of disease.

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PART V

Obtaining medical ethical approval for a Dutch multicentre study

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PART V

CHAPTER 19

Obtaining medical ethical approval for a multicentre, randomised study: a prospective evaluation of a ponderous process

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ABSTRACT

BACKGROUND

The aim of this prospective study was to evaluate the procedure to obtain medical ethical approval for a multicentre study in the Netherlands.

METHODS

The application procedure for medical ethical approval of a nationwide randomised multicentre trial (the 'Pancreatitis: surgical necrosectomy versus step-up approach' [PANTER]-trial) from the medical ethics committees (MEC) of 19 Dutch hospitals during 2004-2007, was prospectively evaluated. Several predefined variables regarding the duration of the ethical review process, the time invested and material and the type of queries raised by the MECs in all centres were collected.

RESULTS

Primary approval by the central MEC of the coordinating hospital was obtained after 192 days. The duration of the review process for each of the 18 local participating centres was 105 days (range 35-361). The maximum review term of 30 days, as defined in the national guideline, was reached by only one centre. It took two years to obtain approval for all participating centres. A median of 14 different documents (range 5-23) were submitted to the MEC of each participating centre. A total of 8314 A4 size papers (about 42 kg) were sent by post, 172 telephone calls were made and 136 e-mail messages were sent by the research fellow coordinating the application procedure. Of the local MECs in the participating centres, 95% requested additional revision of the patient information sheet and 78% requested changes in the informed consent form.

CONCLUSION

Obtaining medical ethical approval for this multicentre trial in the Netherlands was a long and inefficient process, requiring a considerable investment of time and resources. Streamlining the application procedure may lead to a substantial reduction in the current unnecessary delay of starting a multicentre study.

INTRODUCTION

The Netherlands is a small and densely populated country with a growing willingness for academic and non-academic hospitals to cooperate and an excellent reputation for randomised multicentre trials.[1] Before a multicentre study can be initiated, approval has to be obtained from an accredited medical ethics committee (MEC), as specified in the Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen [WMO]; available at www.ccmo-online.nl). Previously, it was customary that the MEC of every participating hospital had to review and approve the study protocol. According to the 2004 'External Review Directive' (Richtlijn Externe Toetsing) of the Central Committee on Research Involving Human Subjects (CCMO), nowadays, only a single MEC is responsible for making a decision on the protocol of a multicentre study.[2] This so called 'central MEC' then requests a 'local feasibility declaration' for the study from the management or board of directors of each of the participating hospitals. The local MEC may advise the board of directors of the local hospital in their decision. The declaration should be 'issued within a reasonable length of time' (the explanation of the directive states 30 days) and local feasibility should be judged only on the basis of expertise, competence and experience of the local researchers and the suitability of the local facilities. Based on the local feasibility declaration, the central MEC then approves participation of the centre in the study.

During the time when the CCMO External Review Directive appeared in 2004, we submitted the study protocol of the 'Probiotics prophylaxis in predicted severe acute pancreatitis' (PROPATRIA) trial[3] to the MECs of 15 participating hospitals of the Dutch Pancreatitis Study Group. We experienced the application procedure to be a long process characterised by bureaucracy, inefficiency and miscommunication.

In 2005, six months after the appearance of the CCMO directive, the Dutch Pancreatitis Study Group began preparations for a second multicentre study: the 'Pancreatitis: maximal necrosectomy versus a minimally invasive step-up approach' (PANTER) trial[4] on the optimal intervention strategy in infected necrotising pancreatitis.

The aim of the current study was to systematically evaluate the application procedure for medical ethical approval of the nationwide PANTER trial in the Netherlands. The emphasis was on the following questions: What is the duration of

the assessment period? How much time and funds are invested in the review process? Do the local MECs restrict themselves to the criteria for local feasibility?

METHODS

We performed a prospective evaluation of the submission of the protocol of the PANTER trial[5] to the MECs of 19 Dutch hospitals, including all University Medical Centres.

STEPS IN THE SUBMISSION PROCESS

FIGURE 19.1 shows the different steps in the submission process. The following parties were involved in the process:

- *Central MEC*: the MEC of the coordinating centre that reviews the protocol and gives the final decision on approval;
- *Local MEC*: the MEC of the participating centre who advises the local board of directors on the local feasibility declaration;
- *Local principal investigator*: the specialist ultimately responsible for the study in each participating centre;
- *Coordinating investigator*: the research fellow who, in cooperation with the local principal investigator, submits the study to the central and local MECs.

DURATION OF ASSESSMENT PERIODS

We first evaluated the application procedure of the central MEC. Subsequently, the procedure for adding each participating centre to the study group was evaluated. A distinction was made in three separate assessment periods:

- *Assessment period for advice on local feasibility*: this is the time in days between submitting the protocol to the local METC, and positive advice on local feasibility of the local board of directors;
- *Assessment period for the protocol amendment of adding a local centre to the study group*: this is the time in days between the local feasibility declaration of the local board of directors and approval by the central MEC of the protocol amendment to add the participating centre to the study group;
- *Overall assessment period*: this is the sum of the two abovementioned assessment periods.

TABLE 19.1. An overview of the different types of documents that have to be submitted in multiple copies to medical ethics committee for approval of a multicentre study[a]

Type of document	Explanation
Study protocol	Outlines the study background and the methods including in- and exclusion criteria, primary and secondary outcome measures and statistical analysis
Summary study protocol on 1 A4	A short summary of the study protocol
Patient information letter	A letter that is handed to the patient with information on the background of the study, the advantages and disadvantages of participation, how patient complaints are handled and with details on the patient insurance policy etc.
Patient informed consent form	The form signed by patient (or legal representative) to declare that he/she formally provides consent to participate and is sufficiently informed about the study (informed consent).
Patient insurance policy	A certificate of the patient insurance policy
General Assessment and Registration form (ABR formulier)	The 23-page standardized form of the CCMO for medical-ethical review and registration that should be completed on www.ccmo-online.nl
List of participating centres	A list of all participating centres with the names and contact details of all local principal investigators
Local addendum	A different form for each centre covering agreements relating to the local administrative and financial responsibility of all departments involved in the study
Curriculum Vitae (CV)	Full CV's with recent publication lists of 1) the principal investigator 2) the local principal investigator(s) and 3) the independent physician(s)
Approval of the central MEC[b]	The letter of approval of the coordinating MEC
Request for local feasibility declaration[b]	The letter from the central MEC in which the local board of directors/ MEC is requested to give a local feasibility declaration
Approved study amendments[b]	Any amendments to the study protocol (e.g., minor changes in the designs, sub studies)

a= There are two types of review: central review of the study protocol by the central MEC, and review for an advice on local feasibility by the local MEC of a participating centre

b= Only when submitting a request for a local feasibility declaration to a local MEC

CCMO stands for Central Committee on Research Involving Human Subjects

TABLE 19.2. Results of the prospective evaluation of the submission procedure for medical ethical approval and advice on local feasibility for a nationwide randomised multicenter trial in 19 Dutch hospitals

MEC	No. of rounds of submitting documents	No. of different documents submitted	No. of copies of documents submitted	Total no. of A4 papers sent	Assessment period for advice on local feasibility (days)	Overall assessment period[b] (days)
1[a]	5	14	4	468	Not relevant	192
2	2	23	4	324	44	64
3	2	22	2	163	49	99
4	2	18	14	713	88	133
5	2	13	15	679	88	115
6	4	17	4	408	215	237
7	2	14	6	304	71	95
8	4	10	15	683	106	142
9	2	15	12	536	81	116
10	2	5	1	13	59	89
11	2	15	9	633	83	93
12	2	10	7	364	56	63
13	3	13	10	670	233	241
14	3	19	2	198	133	361
15	2	9	3	331	71	88
16	2	10	5	265	29	35
17	2	21	15	853	78	112
18	2	11	11	520	34	76
19	3	11	4	189	258	294

a= central MEC
b= Assessment period for an advice on local feasibility plus the subsequent assessment by the central METC for the amendment of adding the local centre to study group

DATA COLLECTION

For each centre the following data were assessed: **a**. the number of rounds of submitting documents to the MEC, **b**. the number of meetings of the MEC, **c**. the number of different types of documents requested, **d**. the number of copies in which the documents were submitted in the first round, **e**. the number of A4 papers sent, **f**. the number of telephone calls, **g**. the number of e-mails, and **h**. time (in hours) that the coordinating research fellow spent on the whole submission process. Furthermore, the requested changes and comments from each local MEC after the first round of submission were evaluated.

RESULTS

In TABLE 19.1, the documents that were needed for the application procedure to each local MEC are presented. TABLE 19.2 summarizes the results of the submission procedure for the central MEC and the 18 local MECs.

THE REVIEW BY THE CENTRAL MEC

The study protocol was submitted to the central MEC on November 30, 2004 and approved on June 9, 2005. There were 5 rounds of submitting documents, carrying out adjustments and resubmitting the documents (these 5 rounds correspond to the second box of FIGURE 19.1). The review process took 192 days. From these 192 days, 51 were used by the researchers, among others, to answer queries raised by the MEC and to make adjustments.

ADDING PARTICIPATING CENTRES TO THE STUDY GROUP: ADVICE ON LOCAL FEASIBILITY

The assessment period for advice on local feasibility in the 18 local MECs was median 80 days (range 29-258). To add a participating centre to study group, the central MEC judged the local feasibility declaration of each local board of directors. This assessment period for the protocol amendment of adding the local centre to the study group for each centre was median 29 days (range 6-228). The overall assessment period for each centre was median 105 days (range 35-361). It took a total of 2 years before medical ethical approval was obtained for all local participating centres.

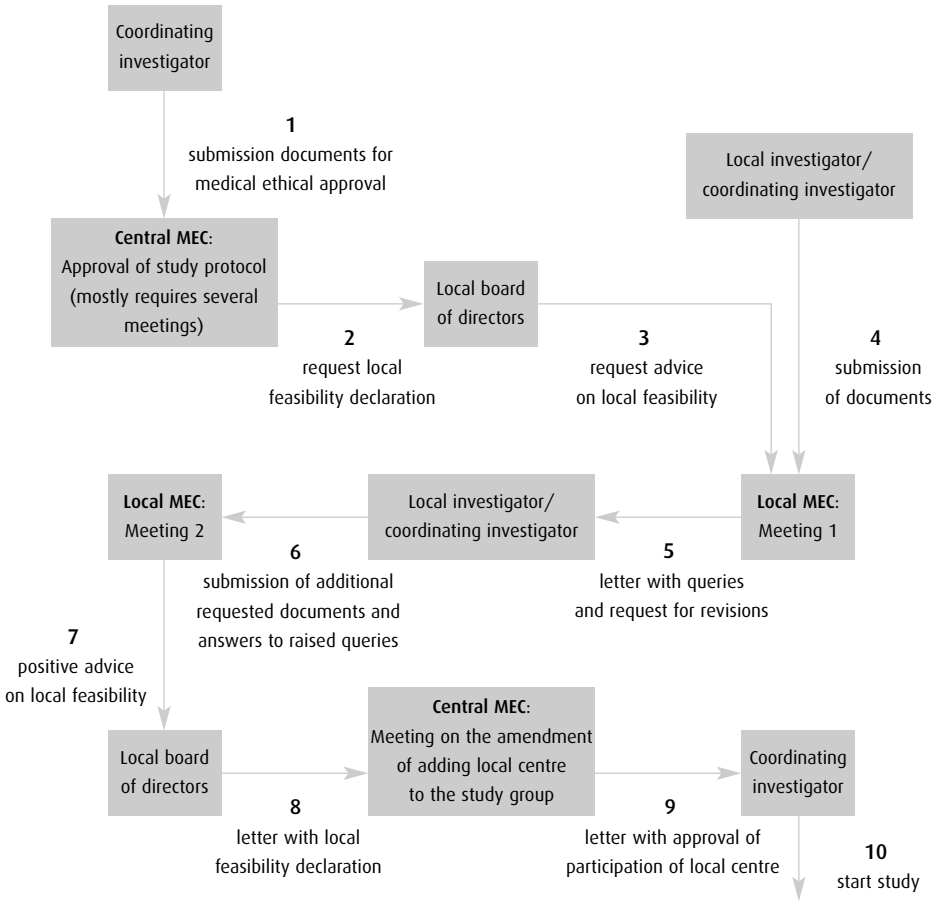

FIGURE 19.1. 10 steps to obtain medical ethical approval for a multicentre study in the Netherlands. The flowchart is an estimation of the most common situation. The various rounds that the central MEC needs for first approval of the study protocol is not shown here. Local MECs in some cases need more than 2 meetings to provide an advice to the board of directors on local feasibility (step 4, 5, 6 and 7). For approval of adding a local centre to the study group, the central MEC may also need more than one meeting (step 8 and 9).

For each MEC documents were submitted median 2 times (range 1-4). The local MECs needed median two meetings (range 1-3) to come to a positive advice on local feasibility. Of the 18 local MECs, 3 had meetings 4 times per month, 7 met twice a month and 3 did so only once a month.

TABLE 19.3. Requested revisions and queries raised by local MECs after the patient information sheets and consent forms had already been approved by central METC

Requested revisions and queries regarding	No. of local MECs
Patient information letter*	17
Informed consent form*	14
Local addendum	2
Curriculum vitae local investigator	2
Study protocol	1

* After adjustments to local conditions (e.g., local principal investigator's name) were already made

INVESTED RESOURCES AND TIME

Per centre median 14 different types of documents (range 5-23) were submitted in median 6-fold (range 1-15). This amounted to a median of 408 A4 pages (range 12-853) per centre. To all 19 centres, a total of 8314 A4 pages (approximately 42 kg) were sent by the coordinating research fellow. For each centre, the coordinating research fellow made a median of 9 telephone calls (range 3-18) and sent median 5 e-mails (range 1-22). A total of 172 telephone calls were made and 136 e-mails were sent. The time involved in preparing and submitting the documents, answering queries and comments from the MECs and discussing the protocol with the MEC in each centre was median 255 minutes per centre (range 55-1345). In total, 5994 minutes (nearly 100 hours) were invested to obtain approval in 19 centres.

REQUESTED CHANGES AND COMMENTS FROM LOCAL MECS

The requested changes and comments from local MEC are summarized in TABLE 19.3. The vast majority of MECs requested adjustments to the patient information and consent forms, after they were already adapted to local conditions (e.g., local principal investigator name, telephone numbers). These adjustments were often not related to the local situation, for example the addition of background information about acute pancreatitis, changing the word 'research' to 'study' and the word 'random' to 'lottery'. There were many adjustments required and questions raised with regard to the patient insurance policy. For example, there was a difference of opinion between the central MEC and local MEC about who was responsible for arranging the patient insurance policy and the costs for the policy (approximately 125

euro's). Other comments and requested changes were were related to the curriculum vitae of the local principal investigator (e.g., this was not detailed enough according to the local MEC) and, contrary to the CCMO directive, once with regard to the study protocol (i.e., the MEC requested that an extra passage be added on safeguarding patient privacy).

DISCUSSION

This prospective evaluation showed that the application procedure for ethical approval of a multicentre study in the Netherlands demands a large investment of time and resources. The maximum review term of 30 days, as defined by the CCMO, was reached by only one out of 18 local centres, and was often greatly exceeded. Moreover, local MECs often did not confine themselves to criteria for local feasibility. In our experience, the introduction of the CCMO External Review Directive did not lead to a more efficient and effective review process for multicentre studies.

We emphasize that our analysis was only carried out to evaluate a complex procedure and, if necessary, to identify areas that need improvement. We did not intend to criticize individual members of the MECs of the participating centres. It is commonly known that medical specialists and other health care workers, in addition to their busy daily activities, invest a lot of time in ethical review of study protocols.

POSSIBLE EXPLANATIONS

There are several possible explanations for our findings. First, the application procedure is complicated and time consuming because of the large number of different people involved in the process (see FIGURE 19.1). Delay frequently occurred, because people who had to sign certain documents were temporarily absent from work or replaced by other people not yet aware of the procedure.

The complexity of the procedure may cause serious administrative and communication errors. For instance, local MECs sometimes did not send important correspondence to the person responsible for the application procedure, but to another person involved in the investigation (e.g., the local principal investigator). Because the local principal investigator, often a medical specialist, does not have time in daily practice to delve into the complex application procedure and to handle the admini-

strative load, the coordinating investigator usually takes on this task. This investigator, usually a research fellow, is available full time, well motivated and knows the details of the procedure. On the other hand, he or she does not have the network of specialists, heads of departments, managers, MECs, and so on, to independently circulate all the internal documents quickly and effectively.

Completely contrary to the External Review Directive, almost every MEC requested revisions of the patient information letter and informed consent forms, which had no relation with the local situation. Because each MEC has its own local guideline, 19 different versions of the patient information letter and consent form for the PANTER-trial are currently circulating in the Netherlands. The vast majority of MECs reviewed the submitted documents only if the patient information letter was printed on the hospital's official letter paper. Therefore, the coordinating investigator had to first collect large quantities of official letter paper from each participating centre.

The fact that the central MEC has additional meetings to discuss adding a local centre after a local feasibility declaration is issued also led to delays. On several occasions, the central MEC did not accept the local feasibility declaration because the letter of approval from the local MEC was addressed to the board of directors of the coordinating hospital (this is correct), instead of the central MEC, or because the revised patient information letters were not forwarded by the local MEC. This illustrates that the local MEC and the central MEC often follow different procedures, although the correct procedure is clearly explained in the CCMO directive.

SIMILAR RESEARCH IN THE NETHERLANDS AND OTHER COUNTRIES

In 2006 Ooms et al reported on their experience with the procedure of submitting the protocol of a multicentre trial to 12 centres.[6] In a similar analysis they showed that only 2 of the 11 local participating centres reached the maximal assessment term which at that time was 6 weeks. In each centre, an average delay in the start of the study of 13 weeks occurred. Studies from Britain, Spain and Germany showed a similar inefficiency in the review process of multicentre studies leading to delay and high costs.[7-9]

IMPLICATIONS

The lengthy application process has a demoralising effect on the researchers involved. Even worse is the delay in the start of the study. In the situation where a severe disease with low incidence is studied, a delay of several months has a significant impact on the progress of inclusion. The PANTER-trial included patients with infected necrotising pancreatitis. In an average Dutch hospital only 2 or 3 of these patients are treated each year. From the moment the central MEC approved the study, it took another two years before approval was obtained for participation of all other centres. This means that a relatively large number of 'rare' patients were missed for inclusion during the review process. In a time when funding agencies pose strict regulations on the inclusion progress, study delay can lead to early termination of the study by the grant provider.

CONCLUSION

Obtaining medical-ethical approval for a multicentre trial in the Netherlands is a long and difficult process that leads to considerable delay. To increase the efficiency of the process and to reduce the risk of administrative and communication errors, we have the following recommendations:

- National guidelines are needed for the patient information letter and the informed consent form to replace the current local guidelines used by MECs;
- The procedure and the forms for administrative and financial arrangements between local departments about the study protocol (i.e., the local addendum) should be standardised;
- It should be decided on a national level if either the coordinating centre or each local participating centre is responsible for arranging the patient insurance policies;
- If the board of directors of a local participating centre issues a local feasibility declaration, the central METC should approve participation of the centre without further review;
- The board of directors of every hospital should ensure that their MEC follows the CCMO External Review Directive, and that no requests beyond local feasibility are made.

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PART V

CHAPTER 20

Summary and general discussion

SUMMARY

Acute pancreatitis is an acute inflammation of the pancreas mostly caused by gallstones and alcohol abuse.[1] Around 15 to 20% of patients show a severe clinical course, which is characterised by multiple organ failure and necrosis of the pancreatic parenchyma and/ or peripancreatic fat tissue.[2-4] In around 30% of patients with necrotising pancreatitis, secondary infection of necrosis occurs,[3,5] probably due to bacterial translocation from the patient's own gut.[6,7] Infected necrosis is an indication for intervention and is associated with 30% mortality.[3,8]

There are relatively few prospective studies on acute pancreatitis. This is probably explained by the fact that acute pancreatitis is a complicated disease with a relatively low incidence in the severe form. Even international high volume expert centres do not treat enough patients with necrotising pancreatitis to, individually, perform adequately powered prospective studies. Therefore, inter-institutional collaboration is the key. In 2002, we formed the Dutch Pancreatitis Study Group, with the aim to improve outcome of patients with acute (necrotising) pancreatitis through centralisation, consultation and multicentre research. The Dutch Pancreatitis Study Group now comprises over 20 hospitals, including all Dutch University Medical Centres, in which many surgeons, gastroenterologists, radiologists and other specialists actively participate.

This thesis presents much of the clinical research performed by the Dutch Pancreatitis Study Group in the period of 2004-2010. We conducted studies on four main topics in acute pancreatitis that will be summarized in the coming sections.

PART I: DEFINING ACUTE PANCREATITIS AND ITS COMPLICATIONS

There is a need for correct terminology and standardized definitions to ensure adequate communication on acute pancreatitis and its complications, both in daily practice, and in clinical research. The widely used 1992 Atlanta Classification[4] (TABLE 1.2, page 16) suffers from several shortcomings. In CHAPTER 2, we summarized the first interobserver agreement study on the Atlanta Classification. Five Dutch radiologists categorized peripancreatic collections on computed tomography (CT) from 70 patients operated for acute necrotising pancreatitis using the Atlanta definitions for 'acute fluid collection', 'pseudocyst', 'pancreatic abscess', or 'pancreatic necrosis'. The interobserver agreement was poor (κ 0.144; standard deviation,

0.095). In only 3 cases (4%), all radiologists chose the same definition.

In CHAPTER 3, we describe a systematic literature review to assess whether the Atlanta definitions are accepted in the literature, and to evaluate the extent of variation in interpretation of these definitions. We assessed 447 articles on acute pancreatitis, including 12 guidelines and 82 reviews. Alternative definitions of predicted severity of acute pancreatitis, actual severity and organ failure were used in more than half of the studies. There was a large variation in the interpretation of the Atlanta definitions of local complications, especially relating to the content of peripancreatic collections. We concluded that the Atlanta Classification definitions are often used inappropriately, and alternative definitions are frequently applied.

CHAPTER 4 presents a new set of descriptive, morphological terms to categorize peripancreatic collections on CT that we designed in collaboration with the departments of Surgery and Radiology of the University of Washington Medical Center. The criteria, referred to as PANCODE, were subsequently tested for interobserver agreement among 7 gastrointestinal surgeons, 2 gastroenterologists and 8 radiologists in 3 US and 5 European tertiary referral hospitals. Agreement was good to excellent for the terms 'collection', 'relation with pancreas', 'content', 'shape', 'mass effect', 'loculated gas bubbles', and 'air-fluid level'. Agreement was moderate for 'extent of pancreatic nonenhancement' and 'encapsulation'. Overall, interobserver agreement for the new set of morphological terms to describe peripancreatic collections in acute pancreatitis was good to excellent.

PART II: PREVENTING INFECTIONS IN ACUTE PANCREATITIS

It is thought that the vast majority of patients who die from acute pancreatitis suffer from infectious complications.[5,9] Infected necrosis alone is responsible for at least half the deaths in acute pancreatitis. Strategies to prevent infections in acute pancreatitis are therefore highly needed. In CHAPTER 5, we summarized an observational cohort study that assessed the timing and impact of infections in acute pancreatitis. We retrospectively analysed a prospective cohort of 731 patients with acute pancreatitis who were admitted to 15 hospitals of the Dutch Pancreatitis Study Group in 2004-2007. The initial infection (i.e., bacteraemia, pneumonia, or infected necrosis) in 173 patients (24%) was diagnosed at a median of 8 days after admission. Of the 61 patients who died, 80% had an infection. In 98 patients with infected

necrosis, bacteraemia was associated with higher mortality (40% vs. 16%, P=0.014). This study showed that infections occur early in acute pancreatitis, and have a significant impact on mortality, especially bacteraemia.

A strategy to prevent infections in acute pancreatitis might be the administration of enteral nutrition.[10,11] CHAPTER **6** is a summary of a systematic review and meta-analysis of 5 randomised controlled trials comparing enteral nutrition with parenteral nutrition in terms of infections and death in 202 patients with predicted severe acute pancreatitis. Enteral nutrition (n=107) significantly reduced the risk of infectious complications (risk ratio [RR], 0.47; 95% confidence interval [CI], 0.28-0.77), pancreatic infections (RR 0.48; 95% CI 0.26-0.91), and mortality (RR 0.32; 95% CI 0.11-0.98).

Another strategy to prevent infections in acute pancreatitis may be prophylactic administration of probiotics.[12,13] In CHAPTER **7**, we present an overview of the proposed mechanisms of action of probiotics in preventing infections in surgical patients and the current clinical evidence. Probiotics are thought to exert beneficial effects at the 3 pathophysiological levels that drive bacterial translocation: **1**. at the level of the intestinal lumen, probiotics may prevent bacterial overgrowth of potential pathogens by direct antimicrobial effects and competitive growth[14,15]; **2**. at the level of the intestinal epithelium, probiotics may preserve or reinforce the mucosal gastrointestinal barrier function[16,17]; **3**. at the level of the immune system, probiotics may induce production of the anti-inflammatory cytokines and decrease the production of pro-inflammatory cytokines.[18,19] From 14 randomised controlled trials that studied the effects of prophylactic probiotics in a variety of surgical patient populations, 9 studies showed a significant reduction in total infectious complications in patients receiving probiotics. However, methodological quality of these studies was often poor.

CHAPTER **8** describes the **PRO**biotics in **PA**ncreatitis **TRIA**l (PROPATRIA). In this randomised, double-blind, placebo-controlled, multicentre trial, we randomly assigned 296 patients with predicted severe acute pancreatitis to receive a multispecies probiotic preparation (n=152) or placebo (n=144) within 72 hours after onset of symptoms. The primary endpoint of infectious complications occurred in 46 patients (30%) in the probiotics group and in 41 patients (28%) in the placebo group (RR 1.06; 95% CI 0.75-1.51). Surprisingly, 24 patients (16%) in the probiotics group

died, compared with only nine patients (6%) in the placebo group (RR 2.53; 95% CI 1.22-5.25). Nine patients in the probiotics group developed bowel ischemia (eight with fatal outcome), compared with none in the placebo group (P=0.004). Our study showed that prophylactic probiotics do not reduce infections in acute pancreatitis. More importantly, for the first time ever, probiotics were shown to have adverse effects in critically ill patients. In CHAPTER **9** we summarized a study in which we assessed intestinal barrier function in 141 out of 296 patients from the PROPATRIA study. We measured excretion of intestinal fatty acid binding protein (IFABP, a parameter for enterocyte damage), recovery of polyethylene glycols (PEGs, a parameter for intestinal permeability), and excretion of nitric oxide (NOx, a parameter for bacterial translocation) in urine. IFABP concentrations in the first 72 hours were higher in patients who developed bacteraemia (P=0.03), infected necrosis (P=0.01), and organ failure (P=0.008). PEG 4000 recovery was higher in patients who developed bacteraemia (P=0.001), organ failure (P<0.001), or died (P=0.009). Probiotic prophylaxis was associated with an increase in IFABP (median 362 vs. 199 pg/mL; P=0.02), most evidently in patients with organ failure (P=0.01), and did not influence intestinal permeability. Overall, probiotics decreased NOx (P=0.02), but, in patients with organ failure, probiotics increased NOx (P=0.002). We concluded that bacteraemia, infected necrosis, organ failure, and mortality are all associated with intestinal barrier dysfunction early in the course of acute pancreatitis. Overall, probiotic prophylaxis seems to reduce bacterial translocation, but is associated with increased bacterial translocation and enterocyte damage in patients with organ failure.

PART III: EARLY ENDOSCOPIC INTERVENTION FOR BILIARY PANCREATITIS

Early endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy has been suggested to reduce complications and death in patients with acute biliary pancreatitis.[20,21] This procedure is preferably only performed in patients with a high risk of stones in the common bile duct (CBD). In CHAPTER **10**, we evaluated whether commonly used radiological and biochemical predictors (i.e., increased liver functions) for CBD stones in a general patient population[22] are also reliable early in the course of acute biliary pancreatitis. In 167 patients with acute biliary pancreatitis undergoing early ERCP (<72 hours after onset of symptoms), CBD

stones were found in 53%. All studied parameters showed poor positive predictive value (ranging from 0.53 to 0.69) and poor negative predictive value (ranging from 0.46 to 0.67) for CBD stones. We concluded that commonly used biochemical and radiological predictors for CBD stones during the earliest stages of acute biliary pancreatitis are probably unreliable.

It is unclear if early ERCP with sphincterotomy reduces complications and death in patients with acute biliary pancreatitis.[2,3,20,21] In CHAPTER **11**, we performed a meta-analysis of 3 randomised studies that compared early ERCP with conservative treatment in 450 patients with acute biliary pancreatitis without cholangitis. There was no significant effect of ERCP (n=230) on complications (RR 0.76; 95% CI 0.41-1.04) or mortality (RR 1.13; 95% CI 0.23-5.63). Results were similar in the subgroup of patients with predicted severe acute biliary pancreatitis (n=129). This meta-analysis does not provide a definitive answer on the role of ERCP in acute biliary pancreatitis for several reasons. First, the pooled data comprised of relatively few patients with predicted severe acute biliary pancreatitis, which is the group of patients most at risk for complications. Second, the trials included different subgroups of patients with varying incidence of cholestasis. Third, sphincterotomy was only performed in 53% of patients and there was considerable variation in the timing of ERCP. A new study evaluating the clinical effect of ERCP in patients solely with predicted severe acute biliary pancreatitis was needed. CHAPTER **12** is a prospective, observational, multicentre study that compared early ERCP (within 72 hours after onset of symptoms) with conservative treatment in 153 patients with predicted severe acute biliary pancreatitis without cholangitis. Patients without and with cholestasis, defined as bilirubin >2.3 mg/dL and/or dilated CBD on imaging, were analysed separately. Due to great variation in the indication for ERCP in the 15 participating hospitals, the patients undergoing early ERCP (n=81) and patients undergoing conservative treatment (n=72) were highly comparable at baseline. Cholestasis was present in 78 patients (51%). In patients with cholestasis, ERCP (n=52), as compared to conservative treatment (n=26), was associated with fewer complications (25% vs. 54%, P=0.02). This included fewer patients with >30% pancreatic necrosis (8% vs. 31%, P=0.01). In patients without cholestasis, ERCP (n=29) was not associated with reduced complications (45% vs. 41%, P=0.814). These results suggest that early ERCP is associated with fewer complications in predicted

severe acute biliary pancreatitis if cholestasis is present.

PART IV: INTERVENTION FOR NECROTISING PANCREATITIS

The main indication for intervention in necrotising pancreatitis is infected necrosis.[2] The traditional method of intervention is primary open necrosectomy by laparotomy, which is associated with an extraordinary high risk of complications (34 to 95%) and death (11 to 39%).[23-28] As an alternative, minimally invasive techniques are increasingly performed. These techniques include percutaneous drainage,[29] endoscopic transgastric drainage and necrosectomy,[30] and minimally invasive retroperitoneal necrosectomy.[27,31,32]

CHAPTER **13** is a summary of a systematic review on the role of percutaneous drainage for infected necrosis or symptomatic sterile pancreatic necrosis. A total of 11 studies with a pooled population of 384 patients were included. Infected necrosis was proven in 71% of patients. In 56% of patients, no additional surgical necrosectomy was required after percutaneous drainage. Overall mortality was 17%. These results suggest that a considerable number of patients can be treated with percutaneous drainage, without the need for surgical necrosectomy.

CHAPTER **14** is a technical report of video-assisted retroperitoneal debridement (VARD). VARD is a form of minimally invasive retroperitoneal necrosectomy that can be considered a hybrid between sinus tract endoscopy[31] and classic open retroperitoneal necrosectomy.[33] As demonstrated in FIGURE 20.1, a 5 cm subcostal incision is placed in the left flank, close to the exit point of the preoperatively placed percutaneous drain. With the CT images and using the drain as a guide, the retroperitoneum is entered. After the first necrosis is removed under direct vision, the remaining loosely adherent necrosis is carefully removed with videoscopic assistance. Continuous postoperative lavage is performed through two large bore drains.

In CHAPTER **15**, we summarize a study on the feasibility of minimally invasive techniques in necrotising pancreatitis. Peripancreatic collections on preoperative CT scans of 80 consecutive patients operated for necrotising pancreatitis were classified according to their distance from the left abdominal wall. Five experienced radiologists individually evaluated accessibility for drain placement. In 55 patients (69%), the lateral border of the collection was less than 5 cm from the left abdominal wall. Placement of a drain was deemed feasible in 67 patients (84%). The interobserver

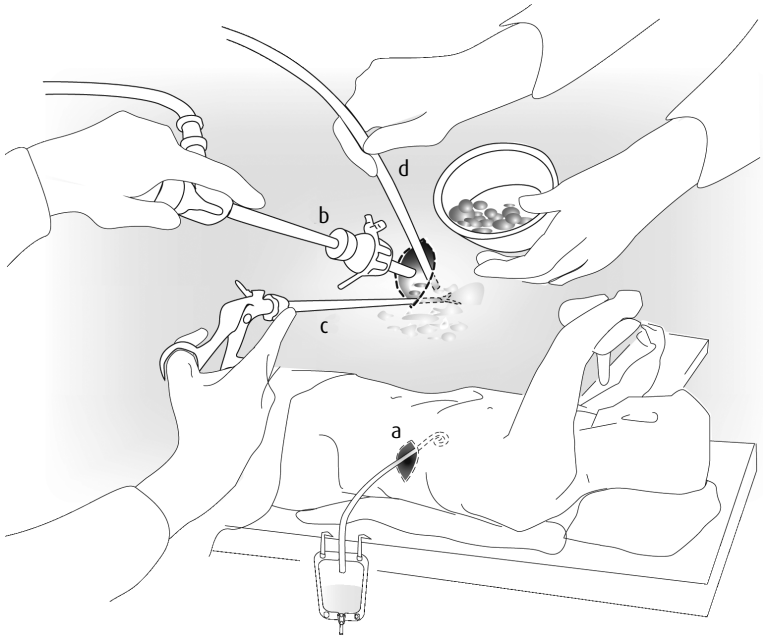

FIGURE 20.1 Video-assisted retroperitoneal debridement.
The preoperatively placed retroperitoneal percutanaous drain is used as a guide to open the peripancreatic collection through a 5 cm subcostal incision. **a**. After the first necrosis is removed with a forceps under direct vision, the collection is inspected with a videoscope through a trocar placed in the edge of the incision **b**. Additional necrosectomy is performed with a laparoscopic forceps (**c**) and a suction device (**d**)

agreement for accessibility was moderate (mean κ 0.43 $\pm$ 0.09). In 45 of these 67 patients (67%), it was thought a drain could be placed through the left retroperitoneum. These results demonstrate that most peripancreatic collections in necrotising pancreatitis are accessible to a minimally invasive approach.

CHAPTER **16** is a summary of the first study to perform a head-to-head comparison of minimally invasive retroperitoneal necrosectomy with open necrosectomy. We matched 15 patients undergoing VARD with 15 patients undergoing open necrosectomy, in 2 hospitals between 2001 and 2005, for the presence of preoperative organ failure, status of infection, timing of surgery, age, and CT severity index. In addition to all matched preoperative characteristics, there were no significant differences in sex, preoperative intensive care admission, APACHE-II scores, and pre-

operative multiple organ failure. We found that postoperative new-onset multiple organ failure occurred in 10 patients in the open necrosectomy group vs. 2 patients in the VARD group (P=0.008). Six patients died in the open necrosectomy group vs. 1 patient in the VARD group (P=0.08). These findings point to a benefit of the minimally invasive retroperitoneal necrosectomy over open necrosectomy.

On the basis of the aforementioned preparative studies, we designed the study presented in CHAPTER **17**: the **PA**ncreatitis, maximal **N**ecrosectomy versus minimally invasive s**TE**p up app**R**oach (PANTER)-trial. This was a randomised, controlled multicentre trial to establish the preferred surgical strategy in infected necrotising pancreatitis in terms of clinical outcomes, health care resource utilisation, and costs. A total of 88 patients with suspected or confirmed infected necrosis were randomly assigned to undergo primary open necrosectomy or a step-up approach of minimally invasive techniques. The step-up approach consisted of percutaneous drainage followed, if necessary, by VARD. The primary end point was a composite of major complications (new-onset multiple organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding) or death. The primary end point occurred in 31 of 45 patients (69%) assigned to open necrosectomy and in 17 of 43 patients (40%) assigned to the step-up approach (RR with the step-up approach, 0.57, 95% CI 0.38-0.87). Of the patients assigned to the step-up approach, 35% were treated with percutaneous drainage only. New-onset multiple organ failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% vs. 40%, P=0.002). Patients assigned to the step-up approach had a lower rate of incisional hernias (7% vs. 24%, P=0.03), new-onset diabetes (16% vs. 38%, P=0.02) and need for pancreatic enzyme suppletion (7% vs. 33%, P=0.002). Mean total costs per patient during admission and 6 months follow-up were €10,839 lower (12%) with the step-up approach.

The literature on necrotising pancreatitis of the past 25 years consists mainly of small, retrospective series, from single expert centres, covering long time periods and mostly reporting on patients that underwent intervention. New data from large prospective multicentre studies are therefore needed, to serve as a standard reference for recent outcome of necrotising pancreatitis. CHAPTER **18** is a prospective observational cohort study that analysed the outcome of conservative treatment and intervention in 639 patients with necrotising pancreatitis who were screened for eli-

gibility for the PROPATRIA and PANTER studies during 2004-2008. Mortality in all 639 patients was 15%. Organ failure occurred in 240 patients (38%), with 35% mortality. Conservative treatment was performed in 397 patients (62%), with 7% mortality. An intervention was performed in 242 patients (38%), with 27% mortality. The longer the time between admission and intervention, the lower the risk of mortality (P<0.001). An emergency laparotomy very early in the course of disease was performed in 32 patients (5%), with 78% mortality. An intervention for suspected or confirmed infected necrosis was performed in 204 patients (32%), with 19% mortality. The longer the time between admission and first intervention for infected necrosis, the fewer the complications (P=0.007). Primary percutaneous drainage was performed in 63% of 204 patients undergoing an intervention: 35% of these patients were successfully treated without the need of further necrosectomy. In total, 106 patients underwent necrosectomy, with mortality of 24%. Complications occurred more often after laparotomy (n=104) than after VARD (n=54) and ETN (n=11): 71%, 56% and 9% respectively, P<0.0001. We concluded that mortality in necrotising pancreatitis remains high. Outcome of infected necrosis seems to improve with postponement of intervention and the use of minimally invasive techniques. Patients with sterile necrosis still suffer from considerable mortality in case of multiple organ failure and emergency laparotomy early in the course of disease.

PART V: OBTAINING MEDICAL ETHICAL APPROVAL FOR A DUTCH MULTICENTRE STUDY

In the final part of this thesis, we studied a topic other than acute pancreatitis: the application procedure for medical ethical approval for a multicentre study in the Netherlands. According to the 2004 'External Review Directive'[34] of the Central Committee on Research Involving Human Subjects (CCMO) - the committee that oversees al Dutch medical ethics committees (MECs) -, the protocol of a multicentre study should only be approved by the MEC of the coordinating centre. For the other participating centres the local boards of directors are requested to sign a 'local feasibility declaration'.[34] This declaration is only based on expertise, competence and experience of the local researchers and the suitability of the local facilities. The Dutch Pancreatitis Study Group felt that the CCMO directive was often not followed by the MECs, which resulted in a bureaucratic and inefficient process.

Therefore, we performed the study in CHAPTER **19**: a prospective evaluation of the application procedure for medical ethical approval for the PANTER trial in 19 hospitals. Several predefined variables regarding the duration of the ethical review process, the time invested and material and the type of queries raised by the MECs were collected. Primary approval by the central MEC of the coordinating hospital was obtained after 192 days. The duration of the review process for each of the 18 local participating centres was median 105 days (range 35-361). The maximum review term of 30 days, as defined in CCMO directive, was reached by only one centre. It took two years to obtain approval for all participating centres. A median of 14 different documents (range 5-23) were submitted to the MEC of each participating centre. A total of 8314 A4 size papers (about 42 kg) were sent by post, 172 telephone calls were made and 136 e-mail messages were sent by the research fellow coordinating the application procedure. Of the local MECs in the participating centres, 95% requested additional revision of the patient information sheet and 78% requested changes in the informed consent form. The application procedure for medical ethical approval for a multicentre trial in the Netherlands seems to be a long and inefficient process, requiring a considerable investment of time and resources.

CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis provides answers to several important clinical questions on diagnosis and treatment of acute pancreatitis (TABLE 20.1). In the following paragraphs, we present the conclusions and implications for clinical practice and further research in each of the main topics that were studied.

PART I: DEFINING ACUTE PANCREATITIS AND ITS COMPLICATIONS

We showed that the 1992 Atlanta definitions[4] for acute pancreatitis are often used inappropriately in the literature, and alternative definitions are frequently applied. The interobserver agreement for the Atlanta Classification to describe CT findings is very poor. This illustrates that these definitions should no longer be used in radiological reports. The proposed alternative of objective, descriptive terms for CT findings showed good to excellent interobserver agreement. Therefore, these descriptive, morphological terms will be incorporated in a revised version of the Atlanta Classification. An international working group, which includes two members of the

TABLE 20.1. The main study questions and answers of this thesis

Chapter	Study questions and answers
2	**What is the interobserver agreement among radiologists for the Atlanta Classification to describe computed tomography findings in acute pancreatitis?** The interobserver agreement among radiologists for the Atlanta Classification to describe computed tomography findings in acute pancreatitis is poor.
3	**Are the definitions of the Atlanta Classification consistently used and interpreted in the literature?** The definitions of the Atlanta Classification are often used and interpreted inappropriately in the literature, and alternative definitions are frequently applied.
4	**What is the interobserver agreement among radiologists and clinicians from different parts of the world for a newly designed set of morphological criteria to describe computed tomography findings in acute pancreatitis?** Objective, morphologic terms to describe computed tomography findings in acute pancreatitis show good to excellent interobserver agreement.
5	**What is the time of onset and clinical impact of infections in acute pancreatitis?** Infections occur very early in acute pancreatitis and have considerable impact on mortality.
6	**Does enteral nutrition, as compared to parenteral nutrition, reduce the risk of infections and death in predicted severe acute pancreatitis?** Enteral nutrition is associated with a reduced risk of infections and death in predicted severe acute pancreatitis
7	**What are the proposed mechanisms of action of probiotics and current evidence from randomised studies, with focus on prevention of infections in surgical and critically ill patients?** Probiotics are thought to exert beneficial effects at three pathofysiological levels that drive bacterial translocation: the intestinal lumen, the intestinal epithelium and the immune system. Probiotic prophylaxis seems to reduce infections in patients undergoing elective surgery.
8	**What is the role of probiotic prophylaxis in patients with predicted severe acute pancreatitis?** Probiotic prophylaxis with a specific preparation (*Ecologic 641*) does not reduce infections in patients with predicted severe acute pancreatitis, but is associated with increased mortality.
9	**What is the association between the clinical course of acute pancreatitis and increased intestinal permeability, enterocyte damage, and bacterial translocation, and how are these processes influenced by probiotics?** Infected necrosis, organ failure and mortality are associated with increased intestinal permeability early in the course of acute pancreatitis. Generally, probiotics seem to reduce bacterial translocation but are associated with increased bacterial translocation and enterocyte damage in patients with organ failure.
10	**What is the value of radiological and biochemical predictors for choledocholithiasis early in the course of acute biliary pancreatitis?** Widely used parameters for choledocholithiasis, such as a dilated common bile duct on ultrasonography and increased liver function tests, are probably unreliable early in the course of acute biliary pancreatitis.

Chapter	Study questions and answers
11-12	**Does early ERCP, as compared to conservative treatment, improve clinical outcome in acute biliary pancreatitis?** Early ERCP is associated with fewer complications in patients with acute biliary pancreatitis, but only in predicted severe disease with signs of cholestasis.
13	**What is the role of percutaneous drainage in necrotising pancreatitis?** Over a third of patients with an indication for intervention in necrotising pancreatitis can be treated with percutaneous drainage only, and do not need surgical necrosectomy.
14	**How do you perform VARD in necrotising pancreatitis?** VARD is a minimally invasive form of necrosectomy that involves a 5 cm subcostal incision through which the percutaneous drain is followed into the retroperitoneum and the collection is carefully debrided with the assistance of a laparoscope.
15	**What is the feasibility of minimally invasive techniques in necrotising pancreatitis?** The vast majority of peripancreatic collections in necrotising pancreatitis are accessible for minimally invasive radiological, endoscopic and surgical techniques.
16	**Is VARD, as compared to open necrosectomy, associated with a better clinical outcome in necrotising pancreatitis?** VARD is associated with a lower risk of post-operative multiple organ failure in necrotising pancreatitis.
17	**Does a minimally invasive step-up approach, as compared to primary open necrosectomy, reduce the combination of major complications and death, as well as long term complications, health care utilisation, and total costs in patients with necrotising pancreatitis?** A minimally invasive step-up approach, as compared to primary open necrosectomy, reduces the combination of major complications and death, as well as long term complications, health care utilization and total costs in patients with necrotising pancreatitis.
18	**What is the recent outcome of patients from the entire clinical spectrum of necrotising pancreatitis who undergo either conservative treatment or intervention?** Mortality in necrotising pancreatitis remains high. Outcome for patients with infected necrosis seems to improve with postponement of intervention and the use of minimally invasive techniques. Patients with sterile necrosis still suffer from considerable mortality in case of multiple organ failure and emergency laparotomy early in the course of disease.
19	**How is the application procedure for medical ethical approval for a nationwide multicentre study in the Netherlands functioning, in terms of adherence to the national guideline, duration of the review process, and time and materials invested?** The national guideline for medical ethical approval of a multicentre study in the Netherlands is not followed well. Consequently, the application procedure is a long and inefficient process that requires a considerable investment of time and resources.

ERCP stands for endoscopic cholangiopancreaticography
VARD stands for video-assisted retroperitoneal debridement

Dutch Pancreatitis Study Group, is currently coordinating a global internet-based consensus statement. Several drafts of the new classification have been reviewed by members of all major international pancreatic and gastroenterological societies, and a definitive update is expected soon. New (interobserver) studies have to evaluate the revised Atlanta Classification.

PART II: PREVENTING INFECTIONS IN ACUTE PANCREATITIS

Infectious complications occur early in the course of acute pancreatitis and have a major impact on mortality. Preventive strategies should therefore focus on early intervention. Enteral nutrition, as compared to parenteral nutrition, seems to be an effective strategy to reduce infections in acute pancreatitis. The optimal time to initiate enteral nutrition remains unknown. Therefore, since late 2008, the Dutch Pancreatitis Study Group is enrolling patients in the **P**ancreatitis, very earl**Y** compared wi**TH** selective delayed start **O**f e**N**teral feeding (PYTHON) study: a randomised controlled trial that compares enteral nutrition within 24 hours after admission to a selective, delayed start of enteral nutrition (>72 hours after admission) in 208 patients with predicted severe acute pancreatitis [ISRCTN18170985].

Probiotics may be effective in preventing infections when they are administered to patients prior to elective surgery. However, in patients with severe acute pancreatitis, especially with organ failure, the specific probiotics we tested (*Ecologic 641*) do not reduce infections but are associated with an increase in enterocyte damage, bacterial translocation, bowel ischemia and mortality. Future studies should find an explanation for these adverse effects. Until then, probiotics should not be given to critically ill patients.

PART III: EARLY ENDOSCOPIC INTERVENTION FOR ACUTE PANCREATITIS

Commonly used radiological and biochemical parameters for CBD stones are probably unreliable in the earliest stages of acute biliary pancreatitis. If the decision to perform early ERCP is to be based on the likelihood of CBD stones, alternative diagnostic modalities such as endoscopic ultrasound or magnetic resonance cholangiopancreaticography might be considered. We demonstrated, however, that regardless of the presence of CBD stones, early ERCP may reduce complications in patients with predicted severe acute biliary pancreatitis and signs of cholestasis.

In order to finally answer the question if early ERCP is truly beneficial in these patients, a new randomised controlled trial is currently being designed by the Dutch Pancreatitis Study Group.

PART IV: INTERVENTION FOR NECROTISING PANCREATITIS

We demonstrated that the preferred treatment strategy for patients with infected necrosis, from both a clinical and an economic point of view, is a minimally invasive step-up approach consisting of percutaneous drainage followed, if necessary, by VARD. More than one third of patients is successfully treated with percutaneous drainage and does not require major abdominal surgery. Percutaneous drainage and VARD are feasible in the overwhelming majority of patients.

It remains unknown which exact method for necrosectomy is optimal in patients who do not improve after percutaneous drainage. Endoscopic transgastric necrosectomy may further reduce morbidity. The Dutch Pancreatitis Study Group recently finished the **P**ancreatitis, **EN**doscopic trans**G**astric vers**U**s pr**I**mary **N**ecrosectomy in patients with infected necrosis (PENGUIN) study: a randomised controlled pilot study in 20 patients focusing primarily on the post-procedural pro-inflammatory immune response (ISRCTN07091918). The results are eagerly awaited. Preparations are underway for a nationwide randomised controlled trial with a clinical primary endpoint: the **T**ransluminal **E**ndoscopic step-up approach versus mi**N**imally invasive **S**urg**I**cal step-up appr**O**ach in patients with infected pancreatic **N**ecrosis (TENSION) trial.

The outcome of infected necrosis seems to improve with postponement of intervention and the introduction of minimally invasive techniques. However, patients with sterile necrosis and early multiple organ failure still have a very high risk of mortality. Future studies should investigate means to mitigate early organ failure and improve treatment of abdominal compartment syndrome in acute pancreatitis.

PART V: OBTAINING MEDICAL ETHICAL APPROVAL FOR A DUTCH MULTICENTRE STUDY

We showed that the 2004 CCMO 'External Review Directive' is not followed well. Consequently, the application procedure for medical ethical approval for a multicentre study in the Netherlands is a long and inefficient process that requires great

investment of time and resources. Following the publication of our study, the CCMO sent a letter to the MEC and board of directors of every Dutch hospital to once more explain the correct procedure and responsibilities of the hospital management and other parties involved. The CCMO also published an example 'local feasibility declaration'[35] to improve the efficiency of the approval process. Future studies need to evaluate whether these actions have had an effect.

This thesis has presented 6 years of Dutch clinical research on acute pancreatitis. New frontiers were boldly explored and important discoveries were made. However, the horizon of pancreatology is constantly shifting and there are always new territories to chart. Much work remains to be done. The Dutch Pancreatitis Study Group is preparing several new randomised controlled trials and various international collaborative projects are underway.

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D U T C H S U M M A R Y

Nederlandse
samenvatting
en conclusies

SAMENVATTING

De alvleesklier, in het Latijn 'pancreas' (uit het Grieks παν = 'alles' en κρεαζ = 'vlees'), ligt diep in de buik, gedeeltelijk achter de maag en de twaalf-vingerige darm. Het pancreas is een orgaan met belangrijke functies in de spijsvertering en de stofwisseling. Het produceert sappen met enzymen die in het darmkanaal voedsel afbreken, en enzymen die de bloedsuikerspiegel reguleren (bv. insuline).

Acute pancreatitis is een acute ontsteking van het pancreas die meestal wordt veroorzaakt door galstenen of overmatig alcoholgebruik.[1] Bij ongeveer 15 tot 20% van de patiënten heeft de ziekte een ernstig beloop, dat gepaard kan gaan met orgaanfalen en met necrose ('afsterven') van pancreasweefsel en het omliggende vetweefsel. We spreken dan van necrotiserende pancreatitis.[2-4] Bij ongeveer 30% van de patiënten met necrotiserende pancreatitis treedt een secundaire infectie van de necrose op,[3,5] waarschijnlijk veroorzaakt door bacteriën vanuit de darm van de patiënt zelf.[6,7] Geïnfecteerde necrose is een indicatie voor interventie en gaat gepaard met een kans op overlijden van rond de 30%.[3,8]

Er zijn relatief weinig prospectieve studies naar acute pancreatitis gepubliceerd. Dit wordt waarschijnlijk verklaard door het feit dat acute pancreatitis een complexe ziekte is met een relatief lage incidentie in de ernstige vorm. Zelfs internationale gespecialiseerde hoog-volume centra behandelen niet genoeg patiënten met necrotiserende pancreatitis om, individueel, prospectieve studies met voldoende patiënten uit te voeren. De oplossing is samenwerking tussen verschillende ziekenhuizen. In 2002 werd de Pancreatitis Werkgroep Nederland opgericht. Het doel van deze werkgroep is de behandeling van acute (necrotiserende) pancreatitis te verbeteren door een combinatie van centralisatie, consultatie en multicentrisch onderzoek. De Pancreatitis Werkgroep Nederland bestaat nu uit meer dan 20 ziekenhuizen, waaronder alle Universitair Medische Centra, waarin chirurgen, gastroenterologen, radiologen en andere specialisten actief participeren.

In dit proefschrift wordt het klinisch onderzoek beschreven dat de Pancreatitis Werkgroep Nederland heeft uitgevoerd in de periode 2004-2010. Wij hebben studies verricht naar vier onderwerpen binnen acute pancreatitis, die in deze samenvatting achtereenvolgens aan bod zullen komen.

DEEL I: HET DEFINIËREN VAN ACUTE PANCREATITIS EN DE COMPLICATIES

Er is grote behoefte aan correcte terminologie en gestandaardiseerde definities om adequate communicatie over pancreatitis te waarborgen, zowel in de klinische praktijk als in klinisch onderzoek. De wereldwijd toegepaste Atlanta Classificatie uit 1992 (zie TABEL 1.2 op pagina 16) kent enkele grote tekortkomingen. In HOOFDSTUK **2** vatten wij een studie samen die voor het eerst de 'interobserver-overeenstemming' van de Atlanta Classificatie heeft bestudeerd. Vijf Nederlandse radiologen classificeerden peri-pancreatische collecties op CT scans van 60 patiënten die werden geopereerd voor acute necrotiserende pancreatitis, met de definities van de Atlanta Classificatie: 'acute vochtcollectie', 'pseudocyste', 'pancreasabces' of 'pancreas necrose'. De interobserver-overeenstemming was slecht (κ 0.144; standaard deviatie, 0.095). Bij slechts 3 patiënten (4%), kozen alle radiologen dezelfde definitie.

In HOOFDSTUK **3** beschrijven we een systematisch literatuuronderzoek om te beoordelen of definities van de Atlanta Classificatie geaccepteerd zijn in de literatuur, en om de variatie in interpretatie van deze definities te evalueren. Wij beoordeelden 447 artikelen over acute pancreatitis, waaronder 12 richtlijnen, en 82 overzichtsartikelen. Alternatieve definities met betrekking tot voorspelde ernst van acute pancreatitis, daadwerkelijke ernst en orgaanfalen werden in meer dan de helft van de studies gebruikt. Er was grote variatie in de interpretatie van de definities voor lokale complicaties, met name met betrekking tot de inhoud van peri-pancreatische collecties. Wij concludeerden dat de definities van de Atlanta Classificatie vaak incorrect worden gehanteerd en dat alternatieve definities veel worden toegepast.

HOOFDSTUK **4** beschrijft een nieuwe set van descriptieve, morfologische termen om peri-pancreatische collecties te classificeren op CT die wij ontwikkelden in samenwerking met de afdeling Chirurgie en Radiologie van the University of Washington Medical Center in Seattle. De criteria, met de naam PANCODE, werden vervolgens getest op hun interobserver-overeenstemming onder 7 gastroïntestinaal chirurgen, 2 gastroenterologen en 8 radiologen uit 3 Amerikaanse en 5 Europese gespecialiseerde ziekenhuizen. De overeenstemming was goed tot excellent voor de termen 'collectie', 'relatie met pancreas', 'inhoud', 'vorm', 'massawerking', 'geloculeerde gasbellen' en 'lucht-vloeistof spiegel'. De overeenstemming was

matig voor 'uitgebreidheid van niet aankleurend pancreas' en 'afkapseling'. In het algemeen was de interobserver-overeenstemming voor de nieuwe set van morfologische termen voor het beschrijven van peri-pancreatische vochtcollecties bij acute pancreatitis goed tot excellent.

DEEL II: HET VOORKOMEN VAN INFECTIES BIJ ACUTE PANCREATITIS

In het algemeen wordt aangenomen dat de grote meerderheid van patiënten die overlijden aan acute pancreatitis lijden aan infectieuze complicaties.[5,9] Geïnfecteerde necrose alleen is al verantwoordelijk voor tenminste de helft van de sterfgevallen bij acute pancreatitis. Er is dus een grote behoefte aan strategieën om infecties bij acute pancreatitis te voorkomen. In HOOFDSTUK **5** vatten wij een observationele cohort studie samen waarin het moment van optreden en de invloed van infectieuze complicaties bij acute pancreatitis werd bestudeerd. Wij analyseerden retrospectief een prospectief cohort van 731 patiënten met acute pancreatitis die werden opgenomen in 15 ziekenhuizen van de Pancreatitis Werkgroep Nederland tussen 2004 en 2007. De eerste infectie (bacteriëmie, pneumonie of geïnfecteerde necrose) werd bij 173 patiënten (24%), op mediaan 8 dagen na opname, gediagnosticeerd. Van de 61 patiënten die overleden had 80% een infectie. Bij de 98 patiënten met geïnfecteerde necrose, was bacteriëmie geassocieerd met hogere sterfte (40% vs. 16%, P=0.014). Deze studie toonde aan dat infecties vroeg optreden bij acute pancreatitis, en een significante invloed hebben op mortaliteit, met name bacteriëmie.

Een potentiële strategie om infecties bij acute pancreatitis te voorkomen is het gebruik van enterale voeding.[10,11] HOOFDSTUK **6** is een samenvatting van een systematisch literatuuronderzoek en een meta-analyse van 5 gerandomiseerde gecontroleerde studies die het effect van enterale voeding vergeleken met parenterale voeding op het optreden van infecties en sterfte bij 202 patiënten met voorspeld ernstige acute pancreatitis. Enterale voeding (n=107) reduceerde significant het risico op infectieuze complicaties (relatief risico [RR], 0.47; 95% betrouwbaarheidsinterval [BI], 0.28-0.77), pancreas infecties (RR 0.48; 95% BI 0.26-0.91), en sterfte (RR 0.32; 95% BI 0.11-0.98).

Een andere strategie om infectieuze complicaties bij acute pancreatitis te voorkomen is profylactische toediening van probiotica.[12,13] In HOOFDSTUK **7** geven we een overzicht van de veronderstelde werkingsmechanismen van probiotica ten aan-

zien van het voorkomen van infecties bij chirurgische patiënten en het huidige bewijs hiervoor op basis van klinisch onderzoek. Probiotica worden verondersteld gunstige effecten te hebben op de 3 pathosfysiologische niveaus die verantwoordelijk zijn voor bacteriële translocatie: **1**. op het niveau van het darmlumen zouden probiotica bacteriële overgroei van potentiële pathogenen voorkomen door directe antimicrobiële effecten en competitieve groei.[14,15]; **2**.) op het niveau van het darmepitheel zouden probiotica de mucosale gastroïntestinale barrière behouden of versterken[16,17]; 3) op het niveau van het immuunsysteem, zouden probiotica de productie van anti-inflammatoire cytokines stimuleren en de productie van pro-inflammatoire cytokines inhiberen.[18,19] Van de 14 gerandomiseerde gecontroleerde studies die het effect van profylactische probiotica in een verscheidenheid van chirurgische patiëntenpopulaties onderzochten toonden 9 studies een significante reductie in het totaal aantal infectieuze complicaties door probiotica. Echter, de methodologische kwaliteit van deze studies was vaak matig.

HOOFDSTUK **8** beschrijft de **PRO**biotics in **PA**ncreatitis **TRIA**l (PROPATRIA). In deze gerandomiseerde, dubbel-blinde, placebo-gecontroleerde, multicentrische studie randomiseerden wij 296 patiënten met voorspeld ernstige acute pancreatitis tussen prophylaxe met een multispeciës probiotica preparaat (n=152) of placebo (n=144), binnen 72 uur na aanvang van symptomen. Het primaire eindpunt, bestaande uit infectieuze complicaties, trad op bij 46 patiënten (30%) in de probiotica groep en bij 41 patiënten (28%) in de placebo groep (RR 1.06; 95% BI 0.75-1.51). Geheel verrassend overleden er 24 patiënten (16%) in de probiotica groep, ten opzichte van slechts negen patiënten (6%) in de placebo groep (RR 2.53; 95% BI 1.22-5.25). Negen patiënten in de probiotica groep ontwikkelden darmischemie (waarvan acht met dodelijke afloop), in vergelijking met géén patiënten in de placebo groep (P=0.004). Onze studie toonde aan dat probiotica profylaxe infecties bij acute pancreatitis niet voorkomen. Belangrijker is dat er voor het eerst werd aangetoond dat probiotica schadelijke effecten bij kritiek zieke patiënten kunnen hebben.

In HOOFDSTUK **9** vatten we een studie samen waarin wij intestinale barrière functie bij 141 van de 296 patiënten uit de PROPATRIA studie bestudeerden. We hebben in de urine de excretie gemeten van 'intestinal fatty acid binding protein' (IFABP, een parameter voor enterocytenschade), de terugvondst van 'polyethylene glycols' (PEGs, een parameter voor intestinale permeabiliteit), en de excretie van

stikstof oxide (NOx, een parameter voor bacteriële translocatie). IFABP concentraties in de eerste 72 uur waren hoger bij patiënten met bacteriëmie (P=0.03), geïnfecteerde necrose (P=0.01), en orgaanfalen (P=0.008). PEG 4000 terugvondst was hoger bij patiënten met bacteriëmie (P=0.001), orgaanfalen (P<0.001), of die overleden (P=0.009). Probiotica profylaxe was geassocieerd met een toename van IFABP (mediaan 362 vs. 199 pg/mL; P=0.02). Dit was het meest duidelijk bij patiënten met orgaanfalen (P=0.01) en had geen invloed op de intestinale permeabiliteit. In het algemeen waren probiotica geassocieerd met een vermindering van NOx (P=0.02), maar, bij patiënten met orgaanfalen waren probiotica geassocieerd met een toename van NOx (P=0.002). Wij concludeerden dat bacteriëmie, geïnfecteerde necrose, orgaanfalen en sterfte allemaal geassocieerd zijn met falen van de intestinale barrière vroeg in het beloop van acute pancreatitis. In het algemeen lijkt probiotica profylaxe de bacteriële translocatie te verminderen, maar het is geassocieerd met een toename van bacteriële translocatie en enterocytenschade bij patiënten met orgaanfalen.

DEEL III: VROEGE ENDOSCOPISCHE INTERVENTIE VOOR BILIAIRE PANCREATITIS

Het is gesuggereerd dat vroege endoscopische retrograde cholangiopancreaticografie (ERCP) met papillotomie leidt tot een reductie van complicaties en sterfte bij patiënten met acute biliaire pancreatitis.[20,21] Deze procedure wordt bij voorkeur alleen uitgevoerd bij patiënten met een hoog risico op stenen in de ductus choledochus. In HOOFDSTUK **10** evalueerden wij of veelgebruikte radiologische en biochemische predictoren (verhoogde leverfunctie testen) voor choledocholithiasis in een algemene patiëntenpopulatie[22] ook betrouwbaar zijn vroeg in het beloop van acute biliaire pancreatitis. Van 167 patiënten met acute biliaire pancreatitis die een vroege ERCP (<72 uur na aanvang van de buikpijn) ondergingen, werd in 53% van de gevallen een choledochus steen gevonden. Alle bestudeerde parameters hadden een slechte positief voorspellende waarde (uitersten: 0.53 tot 0.69) en slechte negatief voorspellende waarde (uitersten: 0.46 tot 0.67) voor choledocholithiasis. Wij concludeerden dat veelgebruikte biochemische en radiologische predictoren voor choledocholithiasis tijdens de vroege fase van of ABP waarschijnlijk niet betrouwbaar zijn.
Het is onduidelijk of vroege ERCP met papillotomie complicaties en sterfte bij patiënten met biliaire pancreatitis vermindert.[2,3,20,21] In HOOFDSTUK **11**, beschrij-

ven we een meta-analyse van 3 gerandomiseerde studies waarin vroege ERCP werd vergeleken met conservatieve behandeling bij 450 patiënten met acute biliaire pancreatitis zonder cholangitis. Er was geen significant effect van ERCP (n=230) op complicaties (RR 0.76; 95% BI 0.41-1.04) of sterfte (RR 1.13; 95% BI 0.23-5.63). De resultaten waren vergelijkbaar in de subgroep patiënten met voorspeld ernstige acute biliaire pancreatitis (n=129). Deze meta-analyse geeft geen definitief antwoord op de vraag ERCP een gunstig effect heeft bij acute biliaire pancreatitis, om verschillende redenen. Ten eerste werden er relatief weinig patiënten met voorspeld ernstige acute biliaire pancreatitis geïncludeerd, terwijl dit juist de subgroep is die het meeste risico loopt op complicaties. Ten tweede includeerden de studies verschillende subgroepen van patiënten met acute bilaire pancreatitis met een variërende incidentie van cholestasis per groep. Ten derde werd een papillotomie slechts bij 53% van de patiënten uitgevoerd en was er variatie in het tijdstip vanaf aanvang van de symptomen waarop de ERCP werd uitgevoerd. Er was een nieuwe studie nodig om het klinische effect van ERCP te bestuderen bij patiënten met alleen voorspeld ernstige acute biliaire pancreatitis. HOOFDSTUK **12** is een prospectieve, observationele, multicentrische studie die vroege ERCP (binnen 72 uur na aanvang van de buikpijn) vergelijkt met conservatieve behandeling bij 153 patiënten met voorspeld ernstige acute biliaire pancreatitis zonder cholangitis. Patiënten met en zonder cholestase, gedefinieerd als een bilirubine >2.3 mg/dL en/ of uitgezette ductus choledochus op beeldvorming, werden apart geanalyseerd. Door de grote variatie in de indicatie voor ERCP tussen de 15 participerende ziekenhuizen waren de groep patiënten die vroege ERCP (n=81) ondergingen bij baseline sterk vergelijkbaar met de groep patiënten die conservatief behandeld werden (n=72). Cholestase was aanwezig bij 78 patiënten (51%). Bij patiënten met cholestase was ERCP (n=52), in vergelijking met een conservatief beleid (n=26), geassocieerd met minder complicaties (25% vs. 54%, P=0.02). Hieronder vielen ook minder patiënten met > 30% pancreasnecrose (8% vs. 31%, P=0.01). Bij patiënten zonder cholestase, was ERCP (n=29) niet geassocieerd met minder complicaties (45% vs. 41%, P=0.814). Deze resultaten suggereren dat vroege ERCP geassocieerd is met minder complicaties bij voorspeld ernstige acute biliaire pancreatitis, als er ook sprake is van cholestase.

De belangrijkste indicatie voor interventie bij necrotiserende pancreatitis is geïnfecteerde necrose.[2] De klassieke methode is een primaire open necrosectomie door een laparotomie (het verwijderen van de necrose door een grote buikoperatie). Dit is geassocieerd met een uitzonderlijk hoog risico op complicaties (34 tot 95%) en sterfte (11 tot 39%).[23-28] Als een alternatief voor primaire open necrosectomie worden steeds vaker zogenaamde 'minimaal invasieve technieken' gebruikt. Onder deze technieken vallen CT- of echo-geleide percutane drainage[29], endoscopisch transgastrische drainage en necrosectomie,[30] en minimaal invasieve retroperitoneale necrosectomie.[27,31,32]

HOOFDSTUK **13** is een samenvatting van een systematisch literatuuronderzoek naar de rol van percutane drainage bij geïnfecteerde necrose of symptomatische steriele pancreasnecrose. In totaal werden 11 studies met een gezamenlijke studiepopulatie van 384 patiënten geïncludeerd. Geïnfecteerde necrose werd bewezen bij 71% van de patiënten. Bij 56% van de patiënten was na percutane drainage geen aanvullende operatieve necrosectomie nodig. De mortaliteit was 17%. Deze resultaten suggereren dat een aanzienlijk deel van de patiënten behandeld kan worden met alleen percutane drainage, zonder de noodzaak tot chirurgische necrosectomie.

HOOFDSTUK **14** is een technische beschrijving van 'videoscopisch-geassisteerde retroperitoneale débridement (VARD)'. VARD is een vorm van minimaal invasieve retroperitoneale necrosectomie die kan worden gezien als een hybride tussen 'sinus tract endoscopy'[31] en een klassieke lumbotomie.[33] Zoals te zien in FIGUUR 20.1 (blz. 308), wordt er een 5 cm subcostale incisie geplaatst in de linker flank, nabij waar de preoperatief geplaatste percutane drain uitsteekt. Met de CT beelden en de drain als geleide wordt het retroperitoneum binnengegaan. Nadat de eerste necrose á vue is verwijderd wordt de resterende loszittende necrose voorzichtig verwijderd onder videoscopische assistentie. Er wordt continue postoperatieve lavage verricht door twee grote drains.

In HOOFDSTUK **15**, vatten we een studie samen naar de haalbaarheid van minimaal invasieve technieken bij necrotiserende pancreatitis. Peri-pancreatische collecties op preoperatieve CT scans van 80 opeenvolgende patiënten die waren geopereerd voor necrotiserende pancreatitis werden geclassificeerd op basis van de afstand vanaf de linker laterale buikwand. Vijf ervaren radiologen beoordeelden individueel de toe-

gangsmogelijkheid voor een drain. Bij 55 patiënten (69%), lag de laterale grens van de collectie minder dan 5 cm van de linker buikwand. Het werd haalbaar geacht een drain te plaatsen bij 67 patiënten (84%). De interobserver-overeenstemming voor een toegangsroute voor drainage was matig (gemiddelde κ 0.43 ±0.09). Bij 45 van de 67 patiënten (67%), werd het als haalbaar beoordeeld een drain te plaatsen door het linker retroperitoneum. Deze resultaten suggereren dat de meeste peri-pancreatische collecties bij necrotiserende pancreatitis toegankelijk zijn voor een minimaal invasieve benadering.

HOOFDSTUK **16** is een samenvatting van de eerste studie waarin een 'head-to-head' vergelijking wordt gemaakt tussen minimaal invasieve retroperitoneale necrosectomie en open necrosectomie. We koppelden 15 patiënten die een VARD ondergingen met 15 patiënten die open necrosectomie ondergingen, in 2 ziekenhuizen gedurende 2001 en 2005, voor aanwezigheid van preoperatief orgaanfalen, status van infectie, het tijdstip van operatie, leeftijd, en de CT severity index. Naast alle gekoppelde preoperatieve kenmerken waren er geen significante verschillen tussen de beide groepen met betrekking tot geslacht, preoperatieve intensive care opname, APACHE-II scores, en preoperatief multi-orgaanfalen. We vonden dat de postoperatief nieuw multi-orgaanfalen optrad bij 10 patiënten in de open necrosectomie groep vs. 2 patiënten in de VARD groep (P=0.008). Zes patiënten overleden in de open necrosectomie groep vs. 1 patiënt in de VARD groep (P=0.08). Deze resultaten wijzen richting een voordeel van minimaal invasieve retroperitoneale necrosectomie boven open necrosectomie.

Op basis van de bovengenoemde voorbereidende studies ontwierpen wij de studie die wordt beschreven in HOOFDSTUK **17**: de **PA**ncreatitis, maximal **N**ecrosectomy versus minimal invasive s**TE**p up app**R**oach (PANTER)-trial. Dit was een gerandomiseerd, gecontroleerd, multicentrisch onderzoek om vast te stellen welke chirurgische behandelstrategie de voorkeur heeft bij geïnfecteerde necrotiserende pancreatitis als het gaat om klinische uitkomstmaten, gebruik van gezondheidszorgmiddelen, en kosten. Er werden in totaal 88 patiënten met de verdenking op of bewezen geïnfecteerde necrose gerandomiseerd tussen primaire open necrosectomie of de zogenaamde 'step-up benadering' van minimaal invasieve technieken. De step-up benadering bestond uit percutane drainage gevolgd, mits nodig, door VARD. Het primaire eindpunt was een combinatie van grote complicaties (het nieuw ont-

staan van multi-orgaanfalen of multi-systemische complicaties, een perforatie van een hol orgaan of een enterocutane fistel, of een bloeding) of sterfte. Het primaire eindpunt trad op bij 31 van de 45 patiënten (69%) in de open necrosectomie groep en bij 17 van de 43 patiënten (40%) in de step-up benadering groep (RR 0.57, 95% BI 0.38-0.87). Van de patiënten die werden toegewezen aan de step-up benadering, was alleen percutane drainage een succesvolle behandeling in 35% van de gevallen. Nieuw ontstaan multi-orgaanfalen trad minder vaak op bij patiënten in de step-up benadering groep dan bij patiënten in de open necrosectomie groep (12% vs. 40%, P=0.002). Patiënten in de step-up benadering groep hadden minder vaak een littekenbreuk (7% vs. 24%, P=0.03), nieuw ontstane diabetes (16% vs. 38%, P=0.02) en de noodzaak tot gebruik van pancreas enzymsuppletie (7% vs. 33%, P=0.002). De gemiddelde totale kosten per patiënt gedurende opname en 6 maanden follow-up waren €10,839 lager (12%) in de step-up groep.

De literatuur over necrotiserende pancreatitis van de afgelopen 25 jaar bestaat voornamelijk uit kleine, retrospectieve series, uit enkele gespecialiseerde ziekenhuizen, die lange tijdsperioden beschrijven en meestal alleen resultaten rapporteren van patiënten die een interventie ondergingen. Nieuwe data van grote prospectieve multicentrische studies zijn dus nodig om als standaardreferentie te dienen voor de recente uitkomsten van necrotiserende pancreatitis. HOOFDSTUK **18** is een prospectieve, observationele cohort studie die de uitkomst beschrijft van conservatieve behandeling en interventie bij 639 patiënten met necrotiserende pancreatitis die werden gescreend voor eventuele inclusie in de PROPATRIA en PANTER studies, gedurende 2004-2008. De sterfte in de totale groep van 639 patiënten was 15%. Orgaanfalen trad op bij 240 patiënten (38%), met 35% sterfte. Een conservatief beleid werd gevoerd bij 397 patiënten (62%), met 7% sterfte. Een interventie werd uitgevoerd bij 242 patiënten (38%), met 27% sterfte. Hoe langer de tijd tussen opname en interventie, hoe lager het risico op sterfte (P<0.001). Een spoedlaparotomie zeer vroeg in het ziektebeloop werd uitgevoerd bij 32 patiënten (5%), met 78% sterfte. 204 patiënten (32%) ondergingen een interventie voor verdenking op of bewezen geïnfecteerde necrose, met 9% sterfte. Hoe langer de tijd tussen opname en de eerste interventie voor geïnfecteerde necrose, hoe lager de complicaties (P=0.007). Primaire percutane drainage werd verricht bij 62% van de 204 patiënten die een interventie ondergingen: 35% van deze patiënten werden succesvol behandeld zon-

der de noodzaak tot een necrosectomie. In totaal ondergingen 106 patiënten een necrosectomie, met een sterfte van 24%. Complicaties traden vaker op bij patiënten na laparotomie (n=104) dan na VARD (n=54) en ETN (n=11): respectievelijk 71%, 56% en 9%, P<0.0001. Wij concludeerden dat de sterfte bij necrotiserende pancreatitis hoog blijft. De uitkomst van geïnfecteerde necrose lijkt te verbeteren met het uitstellen van interventie en het gebruik van minimaal invasieve technieken. De sterfte onder patiënten met steriele necrose is nog steeds hoog in het geval van multi-orgaanfalen en een spoedlaparotomie vroeg in het ziektebeloop.

DEEL V: HET VERKRIJGEN VAN MEDISCH ETHISCHE GOEDKEURING VOOR EEN NEDERLANDSE MULTICENTRISCHE STUDIE

In het laatste deel van dit proefschrift bestudeerden wij een ander onderwerp dan acute pancreatitis: de procedure voor het verkrijgen van medische ethische goedkeuring voor een multicentrische studie in Nederland. Volgens de 'Richtlijn Externe Toetsing'[34] uit 2004 van de Centrale Commissie voor Mensgebonden Onderzoek (CCMO) – de commissie die toezicht houdt over alle Nederlandse Medisch Ethische Toetsingscommissies (METC's) –, hoeft het protocol van een multicentrische studie alleen goedgekeurd te worden door de METC van het coördinerende centrum. In alle andere deelnemende centra wordt de lokale Raad van Bestuur verzocht een zogenaamde 'Lokale uitvoerbaarheidverklaring' te tekenen.[34] Deze verklaring heeft slechts betrekking op deskundigheid en de bekwaamheid van de lokale hoofdonderzoekers en de infrastructuur van het eigen ziekenhuis. De Pancreatitis Werkgroep Nederland had het gevoel dat de CCMO richtlijn vaak niet werd gevolgd door de METC's, wat resulteerde in een bureaucratisch en inefficiënt proces.

Om die reden hebben wij de studie verricht die wordt beschreven in HOOFDSTUK **19**: een prospectieve evaluatie van de procedure tot het verkrijgen van medisch-ethische goedkeuring van de PANTER trial in 19 ziekenhuizen. Vooraf gedefinieerde variabelen van de beoordelingstermijn, de geïnvesteerde tijd en het benodigde materiaal werden bestudeerd, evenals de gevraagde aanpassingen en opmerkingen van METC's tijdens de toetsingsprocedure. De inhoudelijke toetsing van het studieprocotol door de centraal oordelende METC bedroeg 192 dagen. De beoordelingstermijn voor het toevoegen van 18 deelnemende centra aan de studiegroep bedroeg per centrum nog mediaan 105 dagen (uitersten: 35-361 dagen). De volgens

TABEL De belangrijkste onderzoeksvragen en antwoorden van dit proefschrift

Hoofdstuk	Onderzoeksvragen en antwoorden
2	**Wat is de interobserver-overeenstemming onder radiologen voor de Atlanta Classificatie om CT bevindingen bij acute pancreatitis te beschrijven?** De interobserver-overeenstemming onder radiologen voor de Atlanta Classificatie om CT bevindingen bij acute pancreatitis te beschrijven is slecht.
3	**Worden de definities van de Atlanta Classificatie consistent gebruikt en geïnterpreteerd in de literatuur?** De definities van de Atlanta Classificatie worden vaak onjuist gebruikt en geïnterpreteerd in de literatuur, en alternatieve definities worden vaak toegepast.
4	**Wat is de interobserver-overeenstemming onder radiologen en clinici uit verschillende delen van de wereld voor een nieuw ontworpen set van morfologische criteria om CT bevindingen bij acute pancreatitis te beschrijven?** Objectieve, morfologische termen om CT bevindingen bij acute pancreatitis te beschrijven hebben een goede tot excellente interobserver-overeenstemming.
5	**Wat is het tijdstip van ontstaan en de klinische invloed van infecties bij acute pancreatitis?** Infecties treden erg vroeg in het beloop van acute pancreatitis op en hebben een aanzienlijke invloed op de mortaliteit.
6	**Leidt enterale voeding, in vergelijking met parenterale voeding tot een reductie van infecties en sterfte bij voorspeld ernstige acute pancreatitis?** Enterale voeding is geassocieerd met een reductie van infecties en sterfte bij voorspeld ernstige acute pancreatitis.
7	**Wat zijn de veronderstelde werkingsmechanismen van probiotica en het huidige bewijs op basis van gerandomiseerde studies, als het gaat om het voorkomen van infecties bij chirurgische en kritiek zieke patiënten?** Probiotica worden verondersteld gunstige effecten uit te oefenen op de drie pathosfysiologische niveaus die verantwoordelijk zijn voor bacteriële translocatie: het intestinale lumen, het intestinale epitheel en het immuunsysteem. Profylactische probiotica lijken infecties te reduceren bij patiënten die electieve operaties ondergaan.
8	**Wat is de rol van probiotica profylaxe bij patiënten met voorspeld ernstige acute pancreatitis?** Probiotica profylaxe met een specifiek preparaat (Ecologic 641) reduceert niet het aantal infecties bij patiënten met voorspeld ernstige acute pancreatitis, maar is geassocieerd met verhoogde mortaliteit.
9	**Wat is de associatie tussen het klinisch beloop van acute pancreatitis en verhoogde darmpermeabiliteit, enterocytenschade, en bacteriële translocatie, en hoe worden deze processen beïnvloed door probiotica?** Geïnfecteerde necrose, orgaanfalen en sterfte zijn geassocieerd met verhoogde darmpermeabiliteit vroeg in het beloop van acute pancreatitis. In het algemeen lijken probiotica bacteriële translocatie te reduceren, maar zij zijn geassocieerd met verhoogde bacteriële translocatie en enterocytenschade bij patiënten met orgaanfalen.
10	**Wat is de waarde van radiologische en biochemische predictoren voor choledocholithiasis vroeg in het beloop van acute biliaire pancreatitis?** Veelgebruikte parameters voor choledocholithiasis, zoals een verwijde d. choledochus bij beeldvorming en verhoogde leverfunctietesten zijn waarschijnlijk niet betrouwbaar vroeg in het beloop van acute biliaire pancreatitis.

11, 12	**Leidt vroege ERCP, in vergelijking met een conservatief beleid, tot een verbetering in klinische uitkomsten bij acute biliaire pancreatitis?** Vroege ERCP is geassocieerd met minder complicaties bij patiënten met acute biliaire pancreatitis, maar alleen bij patiënten met voorspeld ernstige ziekte met tekenen van cholestase.
13	**Wat is de rol van percutane drainage bij necrotiserende pancreatitis?** Meer dan één derde van de patiënten met een indicatie voor interventie bij necrotiserende pancreatitis kunnen succesvol worden behandeld met alleen percutane drainage, en hoeven dus geen operatieve necrosectomie te ondergaan.
14	**Hoe verricht men een VARD bij necrotiserende pancreatitis?** VARD is een minimaal invasieve vorm van necrosectomie die bestaat uit een 5 cm kleine subcostale incisie waardoor de percutane drain wordt gevolgd tot in het retroperitoneum en de collectie voorzichtig wordt gedébrideert met de assistentie van een laparoscoop.
15	**Wat is de haalbaarheid van minimaal invasieve technieken bij necrotiserende pancreatitis?** De overgrote meerderheid van peri-pancreatische collecties bij necrotiserende pancreatitis zijn benaderbaar voor minimaal invasieve radiologische, endoscopische en chirurgische technieken.
16	**Is VARD, in vergelijking met open necrosectomie, geassocieerd met betere klinische uitkomsten bij necrotiserende pancreatitis?** VARD is geassocieerd met een lager risico op postoperatief multi-orgaanfalen bij necrotiserende pancreatitis.
17	**Reduceert een minimaal invasieve step-up benadering, in vergelijking met primaire open necrosectomie, de combinatie van grote complicaties en sterfte, alsook de lange termijn complicaties, het gebruik van gezondheidszorgmiddelen en de totale kosten, bij patiënten met necrotiserende pancreatitis?** Een minimaal invasieve step-up benadering, in vergelijking met primaire open necrosectomie, reduceert de combinatie van grote complicaties en sterfte, alsook de lange termijn complicaties, het gebruik van gezondheidszorgmiddelen en de totale kosten, bij patiënten met necrotiserende pancreatitis.
18	**Wat is de recente uitkomst van patiënten uit het gehele klinische spectrum van necrotiserende pancreatitis die conservatief of met een interventie worden behandeld?** De sterfte als gevolg van necrotiserende pancreatitis blijft hoog. De uitkomsten voor patiënten met geïnfecteerde necrose lijken te verbeteren met het uitstellen van interventie en minimaal invasieve technieken. Patiënten met steriele necrose hebben nog steeds een aanzienlijke kans te overlijden in geval van multi-orgaanfalen en een spoedlaparotomie vroeg in het ziektebeloop.
19	**Hoe functioneert de procedure tot het verkrijgen van medisch-ethische goedkeuring voor een landelijke multicentrische studie in Nederland, met betrekking tot het volgen van de richtlijnen, de duur van het beoordelingsproces en de tijd en middelen die worden geïnvesteerd?** De landelijke richtlijnen voor het medisch-ethische toetsing van een multicentrische studie in Nederland wordt niet goed gevolgd. Als gevolg hiervan is er sprake van een lang en inefficiënt proces dat vraagt om een aanzienlijke investering van tijd en middelen.

CT staat voor computed tomography
ERCP staat voor endoscopische retrograde cholangiopancreaticografie
VARD staat voor videoscopisch-geassisteerd retroperitoneale débridement

de CCMO richtlijn maximale lokale beoordelingstermijn van 30 dagen werd maar 1 maal gehaald. Het duurde 2 jaar voordat er in alle centra toestemming was. Er werden mediaan 14 verschillende soorten documenten (uitersten: 5-23) bij iedere METC ingediend. In totaal werden 8314 A4'tjes (circa 42 kg) verstuurd, 172 telefoongesprekken gevoerd en 136 e-mailberichten verstuurd door de arts-onderzoeker die de indieningsprocedure coördineerde. Van de METC's van de deelnemende centra vroeg 95% een wijziging in de patiënteninformatiebrief en 78% een wijziging in het toestemmingsformulier. Het verkrijgen van medisch-ethische goedkeuring voor dit multicentrisch onderzoek in Nederland was tot voor kort een inefficiënt en langdurig proces dat gepaard ging met een grote investering van tijd en middelen.

CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Dit proefschrift geeft antwoorden op enkele belangrijke klinische vragen met betrekking tot de diagnose en behandeling van acute pancreatitis (zie TABEL). In de volgende paragrafen presenteren wij de conclusies en implicaties voor de klinische praktijk en toekomstig onderzoek voor ieder van de onderwerpen die werden bestudeerd.

DEEL I: HET DEFINIËREN VAN ACUTE PANCREATITIS EN DE COMPLICATIES

Wij toonden aan dat de definities van de Atlanta Classificatie uit 1992[4] voor acute pancreatitis vaak verkeerd worden gebruikt in de literatuur, en alternatieve definities veelvuldig worden toegepast. De interobserver-overeenstemming voor de Atlanta Classificatie om CT bevindingen te beschrijven is erg slecht. Dit illustreert dat deze definities niet langer moeten worden gebruikt in radiologische verslagen. Het voorgestelde alternatief van objectieve, beschrijvende termen voor CT bevindingen had een goede tot excellente interobserver-overeenstemming. Deze descriptieve, morfologische termen zullen worden opgenomen in de gereviseerde versie van de Atlanta Classificatie. Een internationale werkgroep, waaronder twee leden van de Pancreatitis Werkgroep Nederland, coördineert op dit moment een mondiale internet-consensus richtlijn. Meerdere versies van de nieuwe classificatie zijn inmiddels voorgelegd aan de leden van alle grote internationale pancreatologische en gastroenterologische verenigingen. Een definitieve revisie van de Atlanta Classificatie wordt binnenkort verwacht. Nieuwe (interobserver) studies zullen deze gereviseerde classificatie moeten evalueren.

DEEL II: HET VOORKOMEN VAN INFECTIES BIJ ACUTE PANCREATITIS

Infectieuze complicaties treden vroeg op in het beloop van acute pancreatitis en hebben een grote negatieve invloed op sterfte. Profylactische strategieën moet zich daarom richten op vroege interventie. Enterale voeding, in vergelijking met parenterale voeding, lijkt een effectieve strategie om infecties bij acute pancreatitis te voorkomen. Het optimale tijdstip om enterale voeding te starten is echter nog niet duidelijk. Om die reden is de Pancreatitis Werkgroep Nederland eind 2008 gestart met de **P**ancreatitis, very earl**Y** compared wi**TH** selective delayed start **O**f e**N**teral feeding (PYTHON) studie: een landelijk, gerandomiseerd, gecontroleerd onderzoek waarin enterale voeding binnen 24 uur na opname wordt vergeleken met een selectieve, latere start van enterale voeding (>72 uur na opname) bij 208 patiënten met voorspeld ernstige acute pancreatitis [ISRCTN18170985].

Probiotica lijken effectief te zijn in het voorkomen van infecties als zij worden toegediend aan patiënten voordat deze een electieve operaties ondergaan. Echter, bij patiënten met ernstige acute pancreatitis, met name in geval van orgaanfalen, bleek het specifieke probiotica preparaat dat wij onderzochten (*Ecologic 641*) niet effectief in het verminderen van infecties. Het was echter geassocieerd met een toename in enterocytenschade, bacteriële translocatie, darmischemie en sterfte. Toekomstige studies moeten een verklaring vinden voor deze schadelijke effecten. Tot die tijd dienen probiotica niet te worden toegediend bij ernstig zieke patiënten.

DEEL III: VROEGE ENDOSCOPISCHE INTERVENTIE VOOR BILIAIRE PANCREATITIS

Veelgebruikte radiologische en biochemische parameters voor choledocholithiasis zijn waarschijnlijk niet betrouwbaar in de vroege fase van acute biliaire pancreatitis. Als men de beslissing om een ERCP te verrichten wil baseren op waarschijnlijkheid van choledocholithiasis, dan zouden alternatieve diagnostische modaliteiten zoals endoscopische echografie of magnetische resonantie cholangiopancreaticografie (MRCP) overwogen kunnen worden. Wij lieten echter wel zien dat, onafhankelijk van de aanwezigheid van choledocholithiasis, vroege ERCP complicaties zou kunnen reduceren bij patiënten met voorspeld ernstige acute biliaire pancreatitis en tekenen van cholestase. Om een definitief antwoord te krijgen op de vraag of vroege ERCP werkelijk voordelig is bij deze patiënten wordt er op dit moment

een nieuwe landelijke gerandomiseerde studie ontworpen door de Pancreatitis Werkgroep Nederland.

DEEL IV: INTERVENTIE VOOR NECROTISERENDE PANCREATITIS

Wij toonden aan dat het de voorkeur heeft om patiënten met geïnfecteerde necrose, zowel vanuit klinisch als economisch oogpunt, te behandelen met een minimaal invasieve step-up benadering, bestaande uit percutane drainage gevolgd, mits nodig, door VARD. Meer dan één derde van de patiënten kan succesvol worden behandeld met alleen percutane drainage, en hoeft dus geen grote buikoperatie te ondergaan. Percutane drainage en VARD zijn technisch mogelijk bij de overgrote meerderheid van de patiënten.

Het blijft onduidelijk welke methode voor necrosectomie de voorkeur heeft bij patiënten die na percutane drainage geen klinische verbetering tonen. Endoscopisch transgastrische necrosectomie zou de morbiditeit verder kunnen reduceren. De Pancreatitis Werkgroep Nederland heeft recent de **P**ancreatitis, **EN**doscopic trans**G**astric vers**U**s pr**I**mary **N**ecrosectomy in patients with infected necrosis (PENGUIN) studie afgerond. PENGUIN is een gerandomiseerde, gecontroleerde pilot-studie onder 20 patiënten die zich toespitst op de post-procedurele, pro-inflammatoire immuunresponse (ISRCTN07091918). De resultaten worden binnenkort verwacht. Op dit moment worden ook de voorbereidingen getroffen voor een landelijk gerandomiseerd, gecontroleerd onderzoek met een klinisch primair eindpunt: the **T**ransluminal **E**ndoscopic step-up approach versus mi**N**imally invasive **S**urg**I**cal step-up appr**O**ach in patients with infected pancreatis **N**ecrosis (TENSION) trial.

De uitkomst van geïnfecteerde necrose lijkt te verbeteren met het uitstellen van interventie en de introductie van minimaal invasieve technieken. Patiënten met steriele necrose en vroeg multi-orgaanfalen hebben echter nog steeds een zeer hoog risico te overlijden. Toekomstige studies moeten de mogelijkheden onderzoeken om vroeg orgaanfalen te verminderen en de behandeling van het abdominaal compartiment syndroom bij acute pancreatitis te verbeteren.

DEEL V: HET VERKRIJGEN VAN MEDISCH ETHISCHE GOEDKEURING VOOR EEN NEDERLANDSE MULTICENTRISCHE STUDIE

Wij hebben aangetoond dat de CCMO 'Richtlijn Externe Toetsing'[34] uit 2004 niet goed gevolgd werd. Het gevolg is dat de indieningsprocedure voor medisch ethische goedkeuring van een multicentrische studie in Nederland een lang en inefficiënt proces is, dat een grote investering van tijd en middelen vraagt. Naar aanleiding van de publicatie van deze resultaten heeft de CCMO een brief verstuurd naar alle METC's en Raden van Bestuur van iedere Nederlands ziekenhuis, om nogmaals de correcte procedure en verantwoordelijkheden van het ziekenhuismanagement en andere betrokken partijen onder de aandacht te brengen.[35] De CCMO heeft tevens een model 'Lokale uitvoerbaarheidverklaring'[36] gepubliceerd om de efficiëntie van het indieningsproces te verbeteren. Toekomstige studies zullen moeten uitwijzen of deze stappen effect hebben gehad.

In dit proefschrift beschreven wij 6 jaar Nederlands klinisch onderzoek naar acute pancreatitis. Er werden grenzen verlegd en belangrijke ontdekkingen gedaan. In de pancreatologie verandert de horizon echter voortdurend, en zijn er altijd nieuwe gebieden te verkennen. Er is nog veel werk te verzetten. De Pancreatitis Werkgroep Nederland is verschillende nieuwe gerandomiseerde onderzoeken aan het voorbereiden en is betrokken bij meerdere internationale samenwerkingsprojecten.

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CURRICULUM VITAE

HJALMAR VAN SANTVOORT was born on the 12th of October in 1979. He spent most of his childhood in Amersfoort where he graduated from the Stedelijk Gymnasium Johan van Oldenbarnevelt in 1998. In the following two years he was not selected for Medical School due to the numerus fixus. He therefore worked and travelled in Australia, New Zealand and Indonesia for seven months (1998-1999) and earned his propaedeuse degree in Biology at the Utrecht University (1999-2000).

In 2000 he started Medical School at the University Medical Center Utrecht. As a student in 2004, he joined the research group of Prof.dr. H.G. Gooszen and Prof.dr. L.M.A. Akkermans at the department of Surgery, University Medical Center Utrecht, to do clinical research on acute pancreatitis. He coordinated the Dutch Pancreatitis Study Group and the nationwide PROPATRIA and PANTER studies from July 2005 to January 2008. During this period, he was involved in organizing an international research collaboration with institutions including the University of Washington Medical Center (Seattle), Mayo Clinic (Rochester), Harvard Medical School (Boston) and the University of Heidelberg, and also graduated from Medical School (November 2006).

In January 2008, he started his training in General Surgery at the St. Antonius Hospital in Nieuwegein (Dr. P.M.N.Y.H. Go), which he will continue at the University Medical Center Utrecht in July 2011 (Prof.dr. I.H.M. Borel Rinkes).

Hjalmar van Santvoort is (co-)author of over 40 peer-reviewed articles and book-chapters and has won several awards, including 'the National Pancreas Foundation Award of the American Pancreatic Association' (2008), 'the Research prize for best abstract in acute pancreatitis of the European Pancreatic Club' (2010), and 'the award for best presentation of the Dutch Surgical Association meeting' (2008 and 2010).