University of Groningen

Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC)

Dutch Pancreatitis Study Group; Schepers, Nicolien J; Hallensleben, Nora D L; Besselink, Marc G; Anten, Marie-Paule G F; Bollen, Thomas L; da Costa, David W; van Delft, Foke; van Dijk, Sven M; van Dullemen, Hendrik M

Published in:
The Lancet

DOI:
[10.1016/S0140-6736\(20\)30539-0](https://doi.org/10.1016/S0140-6736(20)30539-0)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Dutch Pancreatitis Study Group, Schepers, N. J., Hallensleben, N. D. L., Besselink, M. G., Anten, M-P. G. F., Bollen, T. L., da Costa, D. W., van Delft, F., van Dijk, S. M., van Dullemen, H. M., Dijkgraaf, M. G. W., van Eijck, C. H. J., Erkelens, G. W., Erler, N. S., Fockens, P., van Geenen, E. J. M., van Grinsven, J., Hollemans, R. A., van Hooft, J. E., ... Bruno, M. J. (2020). Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. *The Lancet*, 396(10245), 167-176. [https://doi.org/10.1016/S0140-6736\(20\)30539-0](https://doi.org/10.1016/S0140-6736(20)30539-0)

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial

Nicolien J Schepers, Nora D L Hallensleben, Marc G Besselink, Marie-Paule G F Anten, Thomas L Bollen, David W da Costa, Foke van Delft, Sven M van Dijk, Hendrik M van Dullemen, Marcel G W Dijkgraaf, Casper H J van Eijck, G Willemien Erkelens, Nicole S Erler, Paul Fockens, Erwin J M van Geenen, Janneke van Grinsven, Robbert A Hollemans, Jeanin E van Hooft, Rene W M van der Hulst, Jeroen M Jansen, Frank J G M Kubben, Sjoerd D Kuiken, Robert J F Laheij, Rutger Quispel, Rogier J J de Ridder, Marno C M Rijk, Tessa E H Römkens, Carola H M Ruigrok, Erik J Schoon, Matthijs P Schwartz, Xavier J N M Smeets, B W Marcel Spanier, Adriaan C I T L Tan, Willem J Thijs, Robin Timmer, Niels G Venneman, Robert C Verdonk, Frank P Vleggaar, Wim van de Vrie, Ben J Witteman, Hjalmar C van Santvoort, Olaf J Bakker, Marco J Bruno, on behalf of the Dutch Pancreatitis Study Group

Summary

Background It remains unclear whether urgent endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy improves the outcome of patients with gallstone pancreatitis without concomitant cholangitis. We did a randomised trial to compare urgent ERCP with sphincterotomy versus conservative treatment in patients with predicted severe acute gallstone pancreatitis.

Methods In this multicentre, parallel-group, assessor-masked, randomised controlled superiority trial, patients with predicted severe (Acute Physiology and Chronic Health Evaluation II score ≥ 8 , Imrie score ≥ 3 , or C-reactive protein concentration >150 mg/L) gallstone pancreatitis without cholangitis were assessed for eligibility in 26 hospitals in the Netherlands. Patients were randomly assigned (1:1) by a web-based randomisation module with randomly varying block sizes to urgent ERCP with sphincterotomy (within 24 h after hospital presentation) or conservative treatment. The primary endpoint was a composite of mortality or major complications (new-onset persistent organ failure, cholangitis, bacteraemia, pneumonia, pancreatic necrosis, or pancreatic insufficiency) within 6 months of randomisation. Analysis was by intention to treat. This trial is registered with the ISRCTN registry, ISRCTN97372133.

Findings Between Feb 28, 2013, and March 1, 2017, 232 patients were randomly assigned to urgent ERCP with sphincterotomy (n=118) or conservative treatment (n=114). One patient from each group was excluded from the final analysis because of cholangitis (urgent ERCP group) and chronic pancreatitis (conservative treatment group) at admission. The primary endpoint occurred in 45 (38%) of 117 patients in the urgent ERCP group and in 50 (44%) of 113 patients in the conservative treatment group (risk ratio [RR] 0.87, 95% CI 0.64–1.18; $p=0.37$). No relevant differences in the individual components of the primary endpoint were recorded between groups, apart from the occurrence of cholangitis (two [2%] of 117 in the urgent ERCP group vs 11 [10%] of 113 in the conservative treatment group; RR 0.18, 95% CI 0.04–0.78; $p=0.010$). Adverse events were reported in 87 (74%) of 118 patients in the urgent ERCP group versus 91 (80%) of 114 patients in the conservative treatment group.

Interpretation In patients with predicted severe gallstone pancreatitis but without cholangitis, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality, compared with conservative treatment. Our findings support a conservative strategy in patients with predicted severe acute gallstone pancreatitis with an ERCP indicated only in patients with cholangitis or persistent cholestasis.

Funding The Netherlands Organization for Health Research and Development, Fonds NutsOhra, and the Dutch Patient Organization for Pancreatic Diseases.

Copyright © 2020 Elsevier Ltd. All rights reserved.

Introduction

Acute pancreatitis is among the most common gastrointestinal diagnoses for acute inpatient hospital admission, and its incidence is increasing worldwide because of increased rates of obesity and gallstones.^{1,2} Gallstones are the most common cause of acute

pancreatitis.^{3,4} The initiating event is impaction of gallstone stones or sludge in the common bile duct and ampulla.^{5,6} Patients with gallstone pancreatitis can develop cholangitis, organ failure, and other life-threatening complications.^{7–9} During endoscopic retrograde cholangiopancreatography (ERCP), retained gallstones are

Lancet 2020; 396: 167–76

See [Comment](#) page 144

Department of Gastroenterology and Hepatology (N J Schepers MD, N D L Hallensleben MD, Prof M J Bruno PhD), Department of Surgery (Prof C H J van Eijck PhD), and Department of Biostatistics (N S Erler PhD), Erasmus MC University Medical Center, Rotterdam, Netherlands; Department of Gastroenterology and Hepatology (N J Schepers, N D L Hallensleben, R Timmer PhD, R C Verdonk PhD), Department of Radiology (T L Bollen PhD, D W da Costa PhD), and Department of Surgery (S M van Dijk MD, R A Hollemans MD, H C van Santvoort PhD, O J Bakker PhD), St Antonius Hospital, Nieuwegein, Netherlands; Department of Surgery (Prof M G Besselink PhD, J van Grinsven PhD), Department of Gastroenterology and Hepatology (F van Delft PhD, Prof P Fockens PhD, J E van Hooft PhD), and Department of Clinical Epidemiology, Biostatistics, and Bioinformatics (Prof M G W Dijkgraaf PhD), Amsterdam Gastroenterology and Metabolism, Amsterdam UMC, University of Amsterdam, Netherlands; Department of Gastroenterology and Hepatology, Franciscus and Vlietland Hospital, Rotterdam, Netherlands (M-P G F Anten MD);

Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, Netherlands (H M van Dullemen PhD); Department of Gastroenterology and Hepatology, Gelre Hospital, Apeldoorn, Netherlands (G W Erkelens PhD); Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands (E J M van Geenen PhD, X J N M Smeets PhD); Department of Gastroenterology and Hepatology, Spaarne Hospital, Haarlem, Netherlands (R W M van der Hulst PhD); Department of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands (J M Jansen PhD, S D Kuiken PhD); Department of Gastroenterology and Hepatology, Maasstad Hospital, Rotterdam, Netherlands (F J G M Kubben PhD); Department of Gastroenterology and Hepatology, Elisabeth-TweeSteden Hospital, Tilburg, Netherlands (R J F Laheij PhD); Department of Gastroenterology and Hepatology, Reinier de Graaf Group, Delft, Netherlands (R Quispel PhD, C H M Ruigrok); Department of Gastroenterology and Hepatology, Maastricht University Medical Center, Maastricht, Netherlands (R J J de Ridder PhD); Department of Gastroenterology and Hepatology, Amphia Hospital, Breda, Netherlands (M C M Rijk PhD); Department of Gastroenterology and Hepatology, Jeroen Bosch Hospital, Den Bosch, Netherlands (T E H Römkens PhD); Department of Gastroenterology and Hepatology, Catharina Hospital, Eindhoven, Netherlands (E J Schoon PhD); Department of Gastroenterology and Hepatology, Meander Medical Center, Amersfoort, Netherlands (M P Schwartz PhD); Department of

Research in context

Evidence before this study

Patients with gallstone pancreatitis frequently undergo endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy to remove obstructing gallstones with the intention to ameliorate the disease course. Before initiation of this trial, we searched PubMed, Embase, the Cochrane Library, and the NHS Economic Evaluation Database for studies published in English up to May 22, 2012, with the terms “ERCP” and “gallstone” and “pancreatitis”. Six trials fulfilled the inclusion criteria. Findings from this systematic review suggested that ERCP did not reduce mortality but did reduce complications in patients with gallstone pancreatitis at high risk for developing complications. However, these trials had substantial shortcomings, such as heterogeneous patient populations, ERCPs performed late after hospital admission, no routine sphincterotomy, no separate assessment of patients with cholestasis, and use of various endpoint definitions. More importantly, the pooled sample size of patients with predicted severe gallstone pancreatitis without cholangitis was too small to detect differences in endpoints such as major complications or mortality between urgent ERCP and

conservative treatment. As widely agreed, it therefore remains unclear whether ERCP truly improves outcome in these patients.

Added value of this study

This trial answers the question of whether urgent ERCP with biliary sphincterotomy should be done in patients with predicted severe acute gallstone pancreatitis, with or without cholestasis, but without cholangitis. Our findings suggest that urgent ERCP with biliary sphincterotomy did not reduce the composite endpoint of major complications or mortality compared with conservative treatment. Although cholangitis occurred more often in patients treated conservatively, this had no negative impact on overall outcome.

Implications of all the available evidence

Urgent ERCP with biliary sphincterotomy should not be done routinely in patients with predicted severe acute gallstone pancreatitis and is indicated only in patients with concomitant cholangitis. With this strategy, around two-thirds of patients are spared an invasive procedure from which they gain no benefit but could have procedure-associated complications.

visualised, biliary sphincterotomy is done, and gallstones are extracted.

Guidelines recommend urgent ERCP in patients with gallstone pancreatitis with concomitant cholangitis and suggest that ERCP might be beneficial in patients with cholestasis but without cholangitis.^{8,10–12} In patients with gallstone pancreatitis without cholangitis and without significant cholestasis, it is unclear whether urgent ERCP is beneficial. Nevertheless, observational studies have shown that in as much as half of such patients an ERCP is performed.^{13,14} Unfortunately, previous randomised trials on this subject have substantial shortcomings. First, patients with concomitant cholangitis, patients with a predicted mild disease course, and even patients with a non-gallstone aetiology were included.^{15–19} Second, in most trials ERCP was done up to 3 days after hospital admission. Presumably, for biliary decompression to be effective in preventing complications, ERCP needs to be done as early as possible after onset of the disease—ie, after onset of symptoms.^{15,17,20} Third, in previous trials only a small proportion of patients had a biliary sphincterotomy.^{16,17,19,21} Because microlithiasis can easily be missed on cholangiogram during ERCP, and as small gallstones in particular are known to cause pancreatitis, this limitation is particularly relevant.^{22,23} Performing sphincterotomy routinely during ERCP is also supported by a previous study showing that sphincterotomy reduced complications irrespective of the presence of gallstones on cholangiogram.¹³ Furthermore, biliary sphincterotomy decompresses the biliary tract, which potentially ameliorates the disease course.^{5,24–27} In return, ERCP with sphincterotomy is an invasive procedure that

is associated with complications in up to 10% of patients.^{28,29} Finally, the study populations of the individual trials and of subsequent meta-analyses were too small to detect an effect of ERCP in the group of patients with gallstone pancreatitis with a predicted severe disease course. It therefore remains unclear whether urgent ERCP with biliary sphincterotomy is beneficial in patients with predicted severe acute gallstone pancreatitis, with and without cholestasis, but without cholangitis.

We did a multicentre randomised controlled trial to investigate whether urgent ERCP with sphincterotomy is superior to conservative treatment in patients with predicted severe acute gallstone pancreatitis.

Methods

Study design and participants

The APEC (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus Conservative treatment) trial was a multicentre, parallel-group, assessor-masked, randomised controlled superiority trial done in 26 hospitals in the Netherlands. The trial was done according to the previously published trial protocol (appendix pp 27–40).³⁰ All adult patients presenting to the emergency department with acute gallstone pancreatitis were assessed for eligibility by the local physician. Acute pancreatitis was defined as the presence of at least two of the following criteria: upper abdominal pain; serum amylase or lipase concentration more than three times the upper serum limit of normal; or features of acute pancreatitis on imaging.¹² Patients with a predicted severe disease course were eligible for randomisation on the basis of an Acute Physiology and Chronic Health Evaluation (APACHE-II)

score of eight or more, Imrie (or modified Glasgow) score of three or more, or serum C-reactive protein concentration higher than 150 mg/L within 24 h of admission.^{31–35} Gallstone pancreatitis was defined by either biliary sludge or gallstones on imaging, a dilated common bile duct on imaging (>8 mm in patients aged ≤75 years or >10 mm in patients aged >75 years), or an alanine aminotransferase concentration of more than twice the upper limit of normal.^{8,12,36–38} Exclusion criteria included cholangitis, pancreatitis due to other causes, a previous sphincterotomy or needle knife precut, or a history of chronic pancreatitis (see appendix p 3 for additional inclusion and exclusion criteria). Cholangitis was defined as fever in combination with either common bile duct stones, a dilated common bile duct, or (progressive) cholestasis (see appendix p 7 for detailed definition). Written informed consent was obtained from each participant. The APEC trial was done in accordance with the Declaration of Helsinki and the Dutch law regarding research involving human participants. The ethical committee of the Erasmus MC University Medical Center in Rotterdam, Netherlands, approved the trial protocol.

Randomisation and masking

Patients were randomly assigned (1:1) by the central study coordinators to urgent ERCP with biliary sphincterotomy or conservative treatment with a web-based randomisation module with randomly varying block sizes. At randomisation, patients were stratified according to the presence of cholestasis and for the region of the hospital (appendix p 3). Cholestasis was defined as a serum bilirubin of more than 2·3 mg/dL (40 μmol/L) or a dilated common bile duct (>8 mm in patients aged ≤75 years or >10 mm in patients aged >75 years) at randomisation. Because of the invasive nature of the intervention, participants and physicians were not masked to treatment assignment.

Procedures

Urgent ERCP with biliary sphincterotomy needed to be done within 24 h after presentation at the emergency department and within 72 h after symptom onset. Biliary sphincterotomy was done irrespective of whether common bile duct stones were confirmed. ERCP was performed by, or under the direct supervision of, an experienced endoscopist (defined as >400 ERCPs in his or her lifetime and >50 ERCPs annually on average in the previous 3 years). If the common bile duct could not be cannulated, even after precut sphincterotomy, urgent ERCP was abandoned and the patient was treated conservatively.

In the conservative treatment group, patients were managed according to a supportive treatment regimen (appendix pp 3–4). On-demand ERCP with biliary sphincterotomy was done when a patient developed cholangitis. If the attending clinician doubted whether ERCP should be done, the trial coordinator presented the

case to a multidisciplinary expert panel, which provided treatment advice within 24 h. An elective ERCP was done in the event of persistent cholestasis or retained bile duct stones when the patient had recovered from the initial pancreatitis episode. A CT scan was done 5–7 days after hospital admission for assessment of pancreatic necrosis.

Data were collected by local physicians using a standardised case record form. In-hospital use of health care was registered as part of the data collection. Out-of-hospital use of health care was documented by self-administered questionnaires. All CT scans were reassessed by one experienced radiologist (TLB) masked to treatment allocation. An independent monitor assessed the study documents and compared these with the source documents.

Outcomes

The primary endpoint was a composite of major complications or mortality occurring within 6 months after randomisation. Major complications were defined as new-onset persistent organ failure, pancreatic parenchymal necrosis, bacteraemia, cholangitis, pneumonia, or pancreatic endocrine or exocrine insufficiency (for definitions, see appendix p 7). Secondary endpoints included the need and length of intensive care admission, the length of hospital stay, readmissions for gallstone-related events, quality of life, and societal costs (including health-care costs and out-of-pocket expenses by patients) in the first 180 days after randomisation (see appendix p 31 for full list of secondary endpoints).

A masked adjudication committee of gastroenterologists and surgeons assessed all potential endpoints individually. Disagreements were resolved in a consensus meeting.

An independent Data Safety Monitoring Committee (DSMC) assessed protocol adherence, patient recruitment, and patient safety. Adverse events were reported by treating clinicians to the coordinating investigator, who subsequently reported the events to the Dutch Central Committee for Research Involving Human Subjects. All events were reported unblinded to the DSMC per consecutive group of 60 patients. A continuous sequential safety analysis on death was also done to ensure patients' safety throughout the trial (Pest software, version 4.4).³⁹

Statistical analysis

The sample size calculation was based on an expected reduction of the primary endpoint from 46% in the conservative treatment group to 32% in the urgent ERCP with sphincterotomy group, as reported in a nationwide observational study.¹³ A correction factor of 2% for both percentages was used to account for the possibilities that ERCP was not done within 24 h after presentation or no sphincterotomy was performed. We calculated that 232 patients were required to detect a reduction of the primary endpoint from 48% to 30%, with a power of 80%, a two-sided significance level of 5%, and a 1% dropout rate.

Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem, Netherlands (B W M Spanier PhD); Department of Gastroenterology and Hepatology, Canisius Wilhelmina Hospital, Nijmegen, Netherlands (A C I T L Tan PhD); Department of Gastroenterology and Hepatology, Martini Hospital, Groningen, Netherlands (W J Thijs PhD); Department of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, Netherlands (N G Venneman PhD); Department of Gastroenterology and Hepatology (F P Vleggaar PhD) and Department of Surgery (H C van Santvoort), University Medical Center Utrecht, Utrecht, Netherlands; Department of Gastroenterology and Hepatology, Albert Schweitzer Hospital, Dordrecht, Netherlands (W van de Vrie PhD); and Department of Gastroenterology and Hepatology, Hospital Gelderse Vallei, Ede, Netherlands (Prof B J Witteman PhD)

Correspondence to: Dr Nicolien J Schepers, Dutch Pancreatitis Study Group, St Antonius Hospital, 3435 CM Nieuwegein, Netherlands (n.schepers@antoniusziekenhuis.nl)

See Online for appendix

Figure: Trial profile

ERCP=endoscopic retrograde cholangiopancreatography. *Logistical reasons included insufficient staff capacity (nurses, endoscopists, or anaesthetists), full (emergency) endoscopy schedule, inability to arrange ERCP within the remaining hours of the first 24 h after presentation, and failure or maintenance of devices.

An interim analysis of the primary endpoint was done after 50% of patients were randomly assigned and discharged from hospital. We used a Haybittle-Peto approach to test for a beneficial effect (symmetric stopping boundaries at $p < 0.001$); there was no assessment of futility.^{40,41} The adjudication committee, masked to treatment assignment, only excluded patients before statistical analyses were done. Final analyses were based on the intention-to-treat principle, with patients being analysed according to allocated treatment group and irrespective of whether sphincterotomy was successful. Dichotomous data were compared with the Pearson's χ^2 test or Fisher's exact test and continuous data with the Mann-Whitney U test. Results are presented as risk ratios (RRs) with corresponding 95% CI. A two-sided p value of

	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)
Sex		
Men	66 (56%)	60 (53%)
Women	51 (44%)	53 (47%)
Age (years)	69 (13)	71 (12)
Basis of gallstone aetiology		
Gallstones or sludge on imaging	88 (75%)	88 (78%)
Dilated common bile duct on imaging	24 (21%)	32 (28%)
More than twice the upper limit of normal ALT	103 (88%)	93 (82%)
More than twice the upper limit of normal ALT in the absence of meeting other gallstone criteria	24 (21%)	18 (16%)
Cholestasis	63 (54%)	67 (59%)
Bilirubin >2.3 mg/dL (>40 μ mol/L)	50 (43%)	51 (45%)
Dilated common bile duct*	23 (20%)	31 (27%)
ASA class on admission		
Healthy status	21 (18%)	16 (14%)
Mild systemic disease	55 (47%)	57 (50%)
Severe systemic disease	40 (34%)	40 (35%)
Severe systemic disease with constant threat to life	1 (1%)	0
Body-mass index (kg/m ²)	28 (6)	29 (6)
Disease severity		
APACHE-II score†	11 (9–15)	10 (8–13)
Imrie score‡	2 (1–3)	2 (1–3)
C-reactive protein (mg/L)	60 (13–166)	38 (11–104)
SIRS§	76 (65%)	61 (54%)
Organ failure¶	29 (25%)	25 (22%)
Time from onset of symptoms to presentation at emergency department (h)	10 (5–22)	9 (5–18)
Time from presentation at emergency department to randomisation (h)	15 (7–20)	15 (8–20)

Data are n (%), mean (SD), or median (IQR). ERCP=endoscopic retrograde cholangiopancreatography. ALT=alanine aminotransferase. ASA=American Society of Anesthesiologists. APACHE-II=Acute Physiology and Chronic Health Evaluation. SIRS=systemic inflammatory response syndrome. *A dilated common bile duct was defined as more than 8 mm in patients 75 years or younger, or more than 10 mm in patients older than 75 years on imaging. †APACHE-II score ranges from 0 to 71, with higher scores indicating more severe disease. ‡Imrie (or modified Glasgow) score ranges from 0 to 8, with higher scores indicating more severe disease. §SIRS was defined according to the consensus conference criteria of the American College of Chest Physicians and the Society of Critical Care Medicine. ¶Organ failure was defined as a modified Marshall score of two or more (on a scale of 0 to 12, with higher scores indicating more severe disease), as proposed in the revised Atlanta classification.⁷

Table 1: Baseline characteristics

less than 0.05 was considered significant. Missing data for the primary and other secondary endpoints were categorised as no event. For other analyses, data were considered to be missing completely at random. The interim analysis and final analysis were done by an independent statistician. A predefined exploratory

subgroup analysis was done in patients with cholestasis at randomisation. Logistic regression models were used as formal tests for interaction to assess the potential size of different treatment effects among these subgroups. A post-hoc analysis was done to compare the incidence of the primary endpoint in patients with common bile duct stone extraction during ERCP versus patients in the conservative treatment group.

Results for costs, quality-adjusted life-years (QALYs), and differences between treatment groups are reported with bias-corrected and accelerated 95% CIs to account for sampling variability, based on bootstrapping of 5000 samples. The bootstrap results are reported with quadrants of the incremental costs versus the numbers of patients with poor outcome prevented or versus the numbers of QALYs gained. For statistical analysis we used IBM SPSS Statistics version 24, R version 3.6.1 (2019-07-05), and the packages epitools (version 0.5.10), survival (version 2.44.1.1), and nlme (version 3.1.140). This trial is registered with the ISRCTN registry, ISRCTN97372133. Details of the statistical analysis and the economic evaluation are provided in the appendix (pp 4–5).

Role of the funding source

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

Results

Between Feb 28, 2013, and March 1, 2017, 1178 patients with acute gallstone pancreatitis were assessed for eligibility (figure); however, most patients had a predicted mild disease course. 232 patients with a predicted severe disease course were randomly assigned to urgent ERCP with sphincterotomy or conservative treatment. The adjudication committee excluded two patients after randomisation: one patient in the urgent ERCP group with concomitant cholangitis and one patient in the conservative treatment group with chronic pancreatitis. 117 patients in the urgent ERCP group and 113 patients in the conservative treatment group were included in the intention-to-treat analyses. Baseline characteristics of the two groups are shown in table 1. Cholestasis was present in 63 (54%) of 117 patients in the urgent ERCP group and in 67 (59%) of 113 patients in the conservative treatment group.

The primary composite endpoint of major complications or mortality occurred in 45 (38%) of 117 patients in the urgent ERCP group compared with 50 (44%) of 113 patients in the conservative treatment group (RR 0·87, 95% CI 0·64 to 1·18; absolute risk difference 5·79 percentage points, 95% CI –6·93 to 18·50; $p=0\cdot37$; table 2). In a post-hoc analysis, the primary endpoint occurred in 22 (41%) of 54 patients with common bile

	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)	Risk ratio (95% CI)	p value
Primary composite endpoint				
Mortality or major complication*	45 (38%)	50 (44%)	0·87 (0·64–1·18)	0·37
Secondary endpoints				
Mortality	8 (7%)	10 (9%)	0·77 (0·32–1·89)	0·57
Major complication				
New-onset organ failure†	22 (19%)	17 (15%)	1·25 (0·70–2·23)	0·45
Single organ failure	17 (15%)	18 (16%)	0·91 (0·50–1·68)	0·77
Persistent single organ failure	14 (12%)	9 (8%)	1·50 (0·68–3·33)	0·31
Multiple organ failure	13 (11%)	13 (12%)	0·97 (0·47–1·99)	0·93
Persistent multiple organ failure	10 (9%)	8 (7%)	1·21 (0·49–2·95)	0·68
Cholangitis	2 (2%)	11 (10%)	0·18 (0·04–0·78)	0·010
Bacteraemia	17 (15%)	25 (22%)	0·66 (0·38–1·15)	0·14
Pneumonia	9 (8%)	10 (9%)	0·87 (0·37–2·06)	0·75
Pancreatic parenchymal necrosis‡	17 (15%)	18 (16%)	0·91 (0·50–1·68)	0·77
Pancreatic endocrine or exocrine insufficiency§	9 (8%)	3 (3%)	2·90 (0·81–0·43)	0·086
Other outcomes				
CT severity index score¶	3 (2–5)	3 (2–5)	NA	0·64
Hospital stay (days)	13 (9–24)	14 (10–26)	NA	0·67
Intensive care admission	24 (21%)	13 (12%)	1·78 (0·96–3·33)	0·063
Intensive care stay (days)	6 (4–17)	8 (4–35)	NA	0·67
Readmission for gallstone-related complication	14 (12%)	24 (21%)	0·56 (0·31–1·03)	0·058
Recurrent gallstone pancreatitis	0	10 (9%)	NA	0·0010
Cholangitis	1 (1%)	3 (3%)	0·32 (0·03–3·05)	0·36
Cholecystitis	10 (9%)	7 (6%)	1·38 (0·54–3·50)	0·50
Gallstone colic	4 (3%)	7 (6%)	0·55 (0·17–1·83)	0·37
Choledocholithiasis	1 (1%)	7 (6%)	0·14 (0·02–1·10)	0·033

Data are n (%) or median (IQR), unless otherwise stated. Risk ratios are for urgent ERCP with sphincterotomy compared with conservative treatment. ERCP=endoscopic retrograde cholangiopancreatography. NA=not applicable. *The same patient may have had multiple events; this was considered as one endpoint. †New-onset organ failure was defined as organ failure that was not present at randomisation. Persistent organ failure was defined as organ failure that lasted more than 48 h. Multiple organ failure was defined as failure of two or more organs at the same time. ‡A contrast-enhanced CT scan was done 5–7 days after hospital admission for assessment of pancreatic necrosis. 11 (9%) of 117 patients in the urgent ERCP group and ten (9%) of 113 patients in the conservative treatment group did not have a CT scan. §Pancreatic insufficiency (endocrine and exocrine) was assessed 6 months after randomisation. ¶CT severity index scores range from 0 to 10, with higher scores indicating more extensive pancreatic parenchymal or extrapancreatic necrosis.

Table 2: Primary and secondary endpoints

duct stone extraction during ERCP compared with 50 (44%) of 113 patients in the conservative treatment group (RR 0·96, 95% CI 0·77 to 1·18; $p=0\cdot67$). No relevant differences in the individual components of the primary endpoint were found between groups, apart from the occurrence of cholangitis: two (2%) patients in the urgent ERCP group developed cholangitis compared with 11 (10%) patients in the conservative treatment group (RR 0·18, 95% CI 0·04 to 0·78; $p=0\cdot010$; table 2). Eight (7%) patients in the urgent ERCP group died, compared with ten (9%) patients in the conservative treatment group (RR 0·77, 95% CI 0·32 to 1·89; $p=0\cdot57$).

In the urgent ERCP group, 24 (21%) of 117 patients were admitted to the intensive care unit, compared with 13 (12%) of 113 patients in the conservative treatment group (RR 1.78, 95% CI 0.96–3.33; $p=0.063$; appendix p 6). New-onset pulmonary organ failure developed in 20 (17%) patients in the urgent ERCP group, compared with 13 (12%) patients in the conservative treatment group (RR 1.61, 95% CI 0.83–3.14; $p=0.16$). 14 (12%) patients in the urgent ERCP group were readmitted for gallstone-related events, compared with 24 (21%) patients in the conservative treatment group (RR 0.56, 95% CI 0.31–1.03; $p=0.058$). No patients were readmitted for recurrent gallstone pancreatitis in the urgent ERCP group, compared with ten (9%) patients in the conservative treatment group ($p=0.0010$). In four of ten patients admitted for recurrent gallstone pancreatitis, cholecystectomy was performed before their first pancreatitis episode. No cholecystectomy was performed during the initial admission in six of ten patients: four had a mild disease course but no same-admission cholecystectomy, one patient had a severe disease course of the pancreatitis, and in one patient cholecystectomy was not performed because of pancytopenia. There was no evidence for a difference in quality of life between study groups (appendix pp 9–12).

In the urgent ERCP group, 112 (96%) of 117 patients underwent ERCP a median of 3 h (IQR 1–5) after randomisation, a median of 20 h (12–23) after presentation at the emergency department, and a median of 29 h (22–44) after onset of symptoms (table 3). Five (4%) patients did not undergo urgent ERCP (details are provided in the appendix p 5). Successful biliary cannulation was achieved in 91 (81%) of 112 patients, all of whom had biliary sphincterotomy. In three of 21 patients, biliary cannulation was not possible because the papilla was situated in a diverticula, and seven of 21 patients had complications of the pancreatitis during urgent ERCP, such as papillary oedema and respiratory insufficiency.

In the conservative treatment group, ERCP was done in 35 (31%) of 113 patients a median of 8 days (IQR 3–34) after randomisation. Biliary sphincterotomy was done in 30 (86%) of 35 patients. The indication for ERCP was cholangitis in 13 patients and persistent cholestasis in 21 patients.

A total of 128 ERCPs were done in the urgent ERCP group compared with 44 in the conservative treatment group (absolute reduction 66%). An ERCP-related complication (see appendix p 8 for definitions) occurred in three (3%) of 112 patients in the urgent ERCP group compared with one (3%) of 35 patients in the conservative treatment group.

In 130 patients with cholestasis at randomisation, the primary composite endpoint occurred in 20 (32%) of 63 patients in the urgent ERCP group, compared with 29 (43%) of 67 patients in the conservative treatment group (RR 0.73, 95% CI 0.47–1.16; $p=0.18$; table 4). Logistic regression showed no evidence of an interaction between the subgroups with and without cholestasis at baseline and the effect of urgent ERCP on the primary endpoint (odds ratio 0.594, 95% CI 0.20–1.72; $p=0.34$).

Adverse events were reported in 87 (74%) of 118 patients in the urgent ERCP group versus 91 (80%) of 114 patients in the conservative treatment group (see appendix pp 20–26 for full list of adverse events).

Utilisation of health-care resources did not differ between treatment groups, apart from the mean number of ERCPs, which were done more than twice as often in the urgent ERCP group compared with the conservative treatment group (mean difference 0.62; bias-corrected accelerated [BCa] 95% CI 0.36 to 0.81; appendix p 14). The mean societal care costs per patient were €24627 (US\$27892) in the urgent ERCP group compared with €24595 (\$27856) in the conservative treatment group; a mean difference of €32 (\$36) in favour of the conservative treatment group (BCa 95% CI –13 030 to 10 845; $p=0.994$; appendix pp 13–15). Although there was a mean difference of €112 (\$127) in favour of the urgent ERCP group from a health-care perspective (€23 746 [\$26 894] in the urgent ERCP group vs €23 859 [\$27 022] in the conservative treatment group), higher out-of-pocket expenses for the urgent ERCP group did not result in a notable overall cost difference from a societal perspective. Details regarding

	Urgent ERCP with sphincterotomy (n=117)	Conservative treatment (n=113)
Patients who had ERCP	112 (96%)	35 (31%)
Total number of ERCPs performed	128	44
ERCPs per patient	1 (1–1)	0 (0–1)
Time from onset of symptoms to first ERCP (h)	29 (22–44)	216 (99–832)
Time from presentation to first ERCP (h)	20 (12–23)	211 (75–815)
Time from randomisation to first ERCP (h)	3 (1–5)	187 (67–807)
Duration of first ERCP procedure (min)*	25 (15–40)	25 (17–50)
Indication for first ERCP		
Trial-related	112	0
Persistent cholestasis	0	21
Cholangitis according to treating physician	0	5
Cholangitis according to trial criteria	0	8
Endoprosthesis placement	0	1
Main bile duct stones or sludge†	48 (43%)	23 (66%)
Common bile duct cannulation†	91 (81%)	32 (91%)
Pancreatic duct cannulation (unintentional)†	40 (36%)	12 (34%)
Precut sphincterotomy†	24 (21%)	6 (17%)
Sphincterotomy†	91 (81%)	30 (86%)
Stone extraction†	54 (48%)	25 (71%)
Incomplete†	0	1 (3%)
ERCP-related complications ††	3 (3%)	1 (3%)

Data are n (%) or median (IQR), unless otherwise stated. ERCP=endoscopic retrograde cholangiopancreatography. *Data on the duration of the ERCP procedure was missing in one patient in the urgent ERCP group and in 13 patients in the conservative treatment group. †Denominators are the number of patients who had ERCP (ie, 112 in the urgent ERCP group and 35 in the conservative treatment group). ‡ERCP-related complications included bleeding, perforation, respiratory insufficiency, and cardiovascular complications. Definitions are provided in the appendix p 8.

Table 3: ERCP characteristics

	Patients with cholestasis (n=130)				Patients without cholestasis (n=100)			
	Urgent ERCP with sphincterotomy (n=63)	Conservative treatment (n=67)	Risk ratio (95% CI)	p value	Urgent ERCP with sphincterotomy (n=54)	Conservative treatment (n=46)	Risk ratio (95% CI)	p value
Primary endpoint: mortality or major complication	20 (32%)	29 (43%)	0.73 (0.47–1.16)	0.18	25 (46%)	21 (46%)	1.01 (0.66–1.55)	0.95
Mortality	2 (3%)	7 (10%)	0.30 (0.07–1.41)	0.17	6 (11%)	3 (7%)	1.70 (0.45–6.44)	0.50
New-onset organ failure	9 (14%)	9 (13%)	1.06 (0.45–2.51)	0.89	13 (24%)	8 (17%)	1.38 (0.63–3.04)	0.41
Pancreatic parenchymal necrosis	7 (11%)	14 (21%)	0.53 (0.23–1.23)	0.13	10 (19%)	4 (9%)	2.13 (0.72–6.34)	0.16
Bacteraemia	8 (13%)	14 (21%)	0.61 (0.27–1.35)	0.21	9 (17%)	11 (24%)	0.70 (0.32–1.53)	0.37
Cholangitis	1 (2%)	6 (9%)	0.18 (0.02–1.43)	0.12	1 (2%)	5 (11%)	0.17 (0.02–1.41)	0.092
Pneumonia	4 (6%)	6 (9%)	0.71 (0.21–2.40)	0.75	5 (9%)	4 (9%)	1.07 (0.30–3.73)	1.00
Pancreatic endocrine or exocrine insufficiency	2 (3%)	1 (2%)	2.13 (0.20–22.88)	0.61	7 (13%)	2 (4%)	2.98 (0.65–13.65)	0.17

Data are n (%), unless otherwise stated. ERCP=endoscopic retrograde cholangiopancreatography.

Table 4: Outcome according to cholestasis subgroup

QALYs and the incremental cost-effectiveness analysis are shown in the appendix (pp 5–6 and pp 16–19, respectively).

Discussion

This multicentre randomised trial in patients with predicted severe acute gallstone pancreatitis found no evidence that urgent ERCP with biliary sphincterotomy reduces the composite endpoint of major complications or mortality, compared with conservative treatment. Although cholangitis occurred more often in patients treated conservatively, this had no measurable negative impact on the overall outcome. We did not observe a notable overall cost difference between treatment groups from a societal perspective. With a conservative strategy and use of ERCP with sphincterotomy only in patients with cholangitis or persistent cholestasis, about two-thirds of patients did not need to undergo ERCP. Our results showed a benefit of urgent ERCP in the number of readmissions for recurrent gallstone pancreatitis or choledocholithiasis. Recurrent gallstone pancreatitis occurred in ten patients treated conservatively, of whom four had a mild pancreatitis initially but no cholecystectomy during the initial admission. Cholecystectomy within the same admission might have prevented recurrent gallstone pancreatitis in these patients.⁴²

With 232 enrolled patients, this is the largest trial on ERCP in patients with predicted severe acute gallstone pancreatitis without cholangitis. Our trial differs from previous trials studying ERCP in gallstone pancreatitis for several reasons.

First, in previous trials only a proportion of patients (19%,¹⁹ 37%,²⁰ 44%,¹⁷ and 46%¹⁶) had a predicted severe disease course at admission. In patients at low risk for complications, urgent ERCP with sphincterotomy is not beneficial.⁴³ In the current trial, we only included patients with a predicted severe disease course, which is reflected by the high prevalence of organ failure (23%) at randomisation. Nonetheless, we did not find a benefit of urgent ERCP with sphincterotomy.

Second, gallstones or biliary sludge are thought to initiate and aggravate pancreatitis, hence the hypothesis that urgent biliary decompression ameliorates the disease course. In previous trials, ERCP was done between 24 h and 72 h after admission.^{15–17,20} In our trial, ERCP was done very early, after a median of 3 h after randomisation, 20 h after presentation to the emergency department, and 29 h after the start of symptoms. Furthermore, when ERCP is done later in the disease course, successful biliary cannulation might be hampered even further by more mucosal and papillary oedema due to the ongoing pancreatic inflammation.

Third, small gallstones and sludge can be easily missed on cholangiography during ERCP and microscopic examination is required to rule out microlithiasis.^{23,44,45} This issue is particularly relevant because small gallstones cause acute gallstone pancreatitis.²² In a post-hoc analysis of our trial, comparing only patients with common bile duct stone extraction during ERCP (n=54) and patients treated conservatively (n=113), we found no difference in the primary endpoint. In previous trials, sphincterotomy was done in only 38–74% of all patients.^{16,20} By comparison, in our trial sphincterotomy was done in all patients in the urgent ERCP group in whom biliary cannulation succeeded (81%). Biliary cannulation was unsuccessful in 21 (19%) patients, of whom seven had complications of the pancreatitis during ERCP, such as papillary oedema.

Fourth, a previous trial suggested that ERCP was associated with increased respiratory complications.¹⁹ In severely ill patients these respiratory complications might be triggered by conscious sedation and potential aspiration or by temporarily reduced oxygenation associated with sedation. We observed more intensive care admissions in the urgent ERCP group than in the conservative treatment group, but no difference in new-onset respiratory failure or duration of intensive care stay.

Fifth, patients with concomitant cholangitis were included in previous studies.^{15–17} Because cholangitis is an already established indication for urgent ERCP in acute

gallstone pancreatitis, this leads to an overestimation of the beneficial effects of ERCP. In our trial, we excluded patients with acute cholangitis at admission.

Finally, our trial included a predefined subgroup analysis of 130 patients with acute pancreatitis and cholestasis. These patients may theoretically benefit most from urgent ERCP with sphincterotomy.^{13,43} Previous studies included only a small number of patients at high risk for complications with concurrent cholestasis. Moreover, various diagnostic criteria for biliary obstruction were used and no separate analyses of patients with biliary obstruction were provided.^{15–18,20} We did not observe a significant effect of urgent ERCP in the 130 patients with cholestasis, although a type II error in this subgroup cannot be ruled out.

A possible explanation why urgent ERCP with sphincterotomy within 24 h did not show an advantage over conservative treatment could be that the opportunity to positively influence the disease course had already passed at the time of the ERCP despite the fact that it was performed early. Animal models have shown that trypsinogen activation within the pancreas occurs within 10 min after chemically inducing pancreatitis.⁴⁶ It is well known that most bile duct stones in patients with gallstone pancreatitis cause only temporary obstruction and pass spontaneously into the duodenum.^{47,48} This temporary obstruction already initiates pancreatitis and data from animal models show that this includes intrapancreatic trypsin activation, rupturing of vacuoles releasing active trypsin, and pancreatic autodigestion.⁴⁹ In the current trial, urgent ERCP was done after a median 29 h after onset of symptoms and common bile duct stones were found in 43% of patients. Even this narrow time window might already be too long to prevent pancreatitis from deteriorating by performing an urgent ERCP with sphincterotomy.

The results of this trial should be interpreted in view of some limitations. First, diagnosis of concomitant cholangitis can be challenging because gallstone pancreatitis by itself can cause fever. We therefore applied more stringent diagnostic criteria for the diagnosis of cholangitis than the international diagnostic criteria for cholangitis.⁵⁰ Consequently, we might have included patients with cholangitis and gallstone pancreatitis. Nevertheless, such bias, if present, would be in favour of the urgent ERCP group because of the clear therapeutic effect of ERCP in patients with cholangitis. Because we did not find any difference between groups, the effect of ERCP is not overestimated by this potential bias. Second, a well known limitation of trials involving patients with acute pancreatitis is the moderate positive predictive value of clinical scoring systems for disease severity.⁵¹ Current scoring systems inevitably lead to the inclusion of patients who at presentation are classified as high risk for developing complications, but who eventually develop a mild pancreatitis. Nonetheless, at the time of randomisation, 60% of patients in our trial had systemic inflammatory response

syndrome and 23% of patients had organ failure. Third, we used biochemical and radiological tests for diagnosis of common bile duct stones or sludge rather than endoscopic ultrasound, which has the highest diagnostic accuracy.⁵² Endoscopic ultrasound might have identified a subgroup of patients without common bile duct stones or sludge. These patients would potentially not have profited from urgent ERCP with sphincterotomy. Therefore, a promising approach might be to perform urgent ERCP only in those patients in whom gallstones or sludge are confirmed by endoscopic ultrasound. However, endoscopic ultrasound is not uniformly available worldwide (especially not during out-of-office hours) and therefore at the time of initiation of this trial, we chose not to include endoscopic ultrasound.

In conclusion, urgent ERCP with sphincterotomy did not reduce the composite endpoint of major complications or mortality in patients with predicted severe gallstone pancreatitis, compared with conservative treatment. These findings support a conservative strategy with an ERCP indicated only in patients with cholangitis or persistent cholestasis. With this conservative strategy, about two-thirds of patients did not need to undergo ERCP.

Contributors

MJB supervised the study. NJS and NDLH coordinated the trial during inclusion. NJS did the statistical analysis. NSE did the quality of life and survival analyses. NDLH and NSE checked the statistical analysis. NJS and MGWD did the economic evaluation. NJS drafted the manuscript. OJB, MJB, MGB, NDLH, and HCvS co-authored the writing of the manuscript. All authors critically assessed the study design, included patients in the study, edited the manuscript, and approved the final manuscript.

Declaration of interests

NJS reports grants from ZonMw and Fonds NutsOhra, during the conduct of the study. PF reports grants from Boston Scientific, and personal fees from Olympus, Cook, and Ethicon Endosurgery, outside the submitted work. MJB reports grants from ZonMw and Fonds NutsOhra, during the conduct of the study; and personal fees from Boston Scientific, Cook Medical, Pentax Medical, and Mylan, and grants from Boston Scientific, Cook Medical, Pentax Medical, 3M, and Mylan, outside the submitted work. All other authors declare no competing interests.

Data sharing

Requests for data can be made to the corresponding author and will be discussed during a meeting of the Dutch Pancreatitis Study Group. Individual participant data that underlie the results reported in this Article, after de-identification, will be shared after approval by the Dutch Pancreatitis Study Group. Related documents, such as the trial protocol and statistical analysis plan, will be available online immediately following publication without an end date to anyone who wishes to access the data.

Acknowledgments

This trial was funded by the Netherlands Organization for Health Research and Development (Health Care Efficiency Research programme, grant number 837002008), Fonds NutsOhra (grant number 1203-052), and the Dutch Patient Organization for Pancreatic Diseases.

References

- 1 Cruz-Monserrate Z, Conwell DL, Krishna SG. The impact of obesity on gallstone disease, acute pancreatitis, and pancreatic cancer. *Gastroenterol Clin North Am* 2016; 45: 625–37.
- 2 Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; 143: 1179–87.e3.

- 3 Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006; 33: 323–30.
- 4 Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology* 2013; 144: 1252–61.
- 5 Lerch MM, Saluja AK, Runzi M, Dawra R, Saluja M, Steer ML. Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum. *Gastroenterology* 1993; 104: 853–61.
- 6 Opie EL. The aetiology of acute haemorrhagic pancreatitis. *Bull Johns Hopkins Hosp* 1901; 12: 182–88.
- 7 Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62: 102–11.
- 8 Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; 108: 1400–15.
- 9 Kimura Y, Takada T, Kawarada Y, et al. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo guidelines. *J Hepatobiliary Pancreat Surg* 2007; 14: 15–26.
- 10 Arvanitakis M, Dumonceau JM, Albert J, et al. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. *Endoscopy* 2018; 50: 524–46.
- 11 Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on initial management of acute pancreatitis. *Gastroenterology* 2018; 154: 1096–101.
- 12 Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatol* 2013; 13 (suppl 2): e1–15.
- 13 van Santvoort HC, Besselink MG, de Vries AC, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. *Ann Surg* 2009; 250: 68–75.
- 14 Lee HS, Chung MJ, Park JY, et al. Urgent endoscopic retrograde cholangiopancreatography is not superior to early ERCP in acute biliary pancreatitis with biliary obstruction without cholangitis. *PLoS One* 2018; 13: e0190835.
- 15 Chen P, Hu B, Wang C, Kang Y, Jin X, Tang C. Pilot study of urgent endoscopic intervention without fluoroscopy on patients with severe acute biliary pancreatitis in the intensive care unit. *Pancreas* 2010; 39: 398–402.
- 16 Fan ST, Lai EC, Mok FP, Lo CM, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med* 1993; 328: 228–32.
- 17 Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988; 2: 979–83.
- 18 Zhou MQ, Li NP, Lu RD. Duodenoscopy in treatment of acute gallstone pancreatitis. *Hepatobiliary Pancreat Dis Int* 2002; 1: 608–10.
- 19 Folsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeldt W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med* 1997; 336: 237–42.
- 20 Oria A, Cimmino D, Ocampo C, et al. Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. *Ann Surg* 2007; 245: 10–17.
- 21 Acosta JM, Katkhouda N, DeBian KA, Groshen SG, Tsao-Wei DD, Berne TV. Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomized clinical trial. *Ann Surg* 2006; 243: 33–40.
- 22 Venneman NG, Buskens E, Besselink MG, et al. Small gallstones are associated with increased risk of acute pancreatitis: potential benefits of prophylactic cholecystectomy? *Am J Gastroenterol* 2005; 100: 2540–50.
- 23 Kim HS, Moon JH, Choi HJ, et al. The role of intraductal US in the management of idiopathic recurrent pancreatitis without a definite cause on ERCP. *Gastrointest Endosc* 2011; 73: 1148–54.
- 24 Acosta JM, Rubio Galli OM, Rossi R, Chinellato AV, Pellegrini CA. Effect of duration of ampullary gallstone obstruction on severity of lesions of acute pancreatitis. *J Am Coll Surg* 1997; 184: 499–505.
- 25 Runzi M, Saluja A, Lerch MM, Dawra R, Nishino H, Steer ML. Early ductal decompression prevents the progression of biliary pancreatitis: an experimental study in the opossum. *Gastroenterology* 1993; 105: 157–64.
- 26 Senninger N, Moody FG, Coelho JC, Van Buren DH. The role of biliary obstruction in the pathogenesis of acute pancreatitis in the opossum. *Surgery* 1986; 99: 688–93.
- 27 Stone HH, Fabian TC, Dunlop WE. Gallstone pancreatitis: biliary tract pathology in relation to time of operation. *Ann Surg* 1981; 194: 305–12.
- 28 Andriulli A, Loperfido S, Napolitano G, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; 102: 1781–88.
- 29 Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; 335: 909–18.
- 30 Schepers NJ, Bakker OJ, Besselink MG, et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. *Trials* 2016; 17: 5.
- 31 Barreto SG, Rodrigues J. Comparison of APACHE II and Imrie scoring systems in predicting the severity of acute pancreatitis. *World J Emerg Surg* 2007; 2: 33.
- 32 Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. *Gut* 1984; 25: 1340–46.
- 33 Corfield AP, Cooper MJ, Williamson RC, et al. Prediction of severity in acute pancreatitis: prospective comparison of three prognostic indices. *Lancet* 1985; 2: 403–07.
- 34 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818–29.
- 35 Werner J, Hartwig W, Uhl W, Muller C, Buchler MW. Useful markers for predicting severity and monitoring progression of acute pancreatitis. *Pancreatol* 2003; 3: 115–27.
- 36 Ammori BJ, Boreham B, Lewis P, Roberts SA. The biochemical detection of biliary etiology of acute pancreatitis on admission: a revisit in the modern era of biliary imaging. *Pancreas* 2003; 26: e32–35.
- 37 Liu CL, Fan ST, Lo CM, et al. Clinico-biochemical prediction of biliary cause of acute pancreatitis in the era of endoscopic ultrasonography. *Aliment Pharmacol Ther* 2005; 22: 423–31.
- 38 Moolla Z, Anderson F, Thomson SR. Use of amylase and alanine transaminase to predict acute gallstone pancreatitis in a population with high HIV prevalence. *World J Surg* 2013; 37: 156–61.
- 39 Whitehead J. The design and analysis of sequential clinical trials. Chichester, UK: Wiley, 1997.
- 40 Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol* 1971; 44: 793–97.
- 41 Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer* 1976; 34: 585–612.
- 42 da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet* 2015; 386: 1261–68.
- 43 Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev* 2012; 5: CD009779.
- 44 Gurusamy KS, Gilja V, Takwoingi Y, et al. Endoscopic retrograde cholangiopancreatography versus intraoperative cholangiography for diagnosis of common bile duct stones. *Cochrane Database Syst Rev* 2015; 2: CD010339.
- 45 Buscail L, Escourrou J, Delvaux M, et al. Microscopic examination of bile directly collected during endoscopic cannulation of the papilla. Utility in patients with suspected microlithiasis. *Dig Dis Sci* 1992; 37: 116–20.
- 46 Grady T, Saluja A, Kaiser A, Steer M. Edema and intrapancreatic trypsinogen activation precede glutathione depletion during caerulein pancreatitis. *Am J Physiol* 1996; 271: G20–26.

- 47 Acosta JM, Ledesma CL. Gallstone migration as a cause of acute pancreatitis. *N Engl J Med* 1974; **290**: 484–87.
- 48 Acosta JM, Pellegrini CA, Skinner DB. Etiology and pathogenesis of acute biliary pancreatitis. *Surgery* 1980; **88**: 118–25.
- 49 Steer ML. Pathogenesis of acute pancreatitis. *Digestion* 1997; **58** (suppl 1): 46–49.
- 50 Kiriya S, Kozaka K, Takada T, et al. Tokyo guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci* 2018; **25**: 17–30.
- 51 Mounzer R, Langmead CJ, Wu BU, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology* 2012; **142**: 1476–82.
- 52 Giljaca V, Gurusamy KS, Takwoingi Y, et al. Endoscopic ultrasound versus magnetic resonance cholangiopancreatography for common bile duct stones. *Cochrane Database Syst Rev* 2015; **2**: CD011549.