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Patient selection for urgent endoscopic retrograde cholangio-pancreatography by endoscopic ultrasound in predicted severe acute biliary pancreatitis (APEC-2) a multicentre prospective study

Hallensleben, N.D.; Stassen, P.M.C.; Schepers, N.J.; Besselink, M.G.; Anten, M.P.G.F.; Bakker, O.J.; ... ; Dutch Pancreatitis Study Grp

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Original research

Patient selection for urgent endoscopic retrograde cholangio-pancreatography by endoscopic ultrasound in predicted severe acute biliary pancreatitis (APEC-2): a multicentre prospective study

Nora D Hallensleben ,[1,2] Pauline M C Stassen,[3] Nicolien J Schepers,[1,2] Marc G Besselink ,[4,5] Marie-Paule G F Anten,[6] Olaf J Bakker,[7] Thomas L Bollen,[8] David W da Costa,[8] Sven M van Dijk,[4] Hendrik M van Dullemen,[9] Marcel G W Dijkgraaf,[10,11] Brechje van Eijck,[12] Casper H J van Eijck,[13] Willemien Erkelens,[14] Nicole S Erler,[15,16] Paul Fockens,[17] Erwin-Jan M van Geenen,[18] Janneke van Grinsven,[19] Wouter L Hazen,[20] Robbert A Hollemans,[21] Jeanin E van Hooft,[17,22] Jeroen M Jansen,[23] Frank J G M Kubben,[24] Sjoerd D Kuiken,[25] Alexander C Poen,[26] Rutger Quispel,[27] Rogier J de Ridder,[28] Tessa E H Römkens,[29] Erik J Schoon,[30] Matthijs P Schwartz,[31] Tom C J Seerden,[32] Xavier J N M Smeets,[18] B W Marcel Spanier,[33] Adriaan C I T L Tan,[34] Willem J Thijs,[35] Robin Timmer,[2] Devica S Umans,[2,17] Niels G Venneman,[36] Robert C Verdonk,[2] Frank P Vleggaar,[37] Wim van de Vrie,[38] Roy L J van Wanrooij,[17] Ben J Witteman,[39] Hjalmar C van Santvoort,[40] Stefan A W Bouwense,[41] Marco J Bruno,[1] for the Dutch Pancreatitis Study Group

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For numbered affiliations see end of article.

Correspondence to
Nora D Hallensleben, Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam 3000 CA, The Netherlands; n.hallensleben@antoniusziekenhuis.nl

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ABSTRACT

Objective Routine urgent endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic biliary sphincterotomy (ES) does not improve outcome in patients with predicted severe acute biliary pancreatitis. Improved patient selection for ERCP by means of endoscopic ultrasonography (EUS) for stone/sludge detection may challenge these findings.

Design A multicentre, prospective cohort study included patients with predicted severe acute biliary pancreatitis without cholangitis. Patients underwent urgent EUS, followed by ERCP with ES in case of common bile duct stones/sludge, within 24 hours after hospital presentation and within 72 hours after symptom onset. The primary endpoint was a composite of major complications or mortality within 6 months after inclusion. The historical control group was the conservative treatment arm (n=113) of the randomised APEC trial (Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment, patient inclusion 2013–2017) applying the same study design.

Results Overall, 83 patients underwent urgent EUS at a median of 21 hours (IQR 17–23) after hospital presentation and at a median of 29 hours (IQR 23–41) after start of symptoms. Gallstones/sludge in the bile ducts were detected by EUS in 48/83 patients (58%), all of whom underwent immediate ERCP with ES. The primary endpoint occurred in 34/83 patients (41%) in the urgent EUS-guided ERCP group. This was not different from the 44% rate (50/113 patients) in the historical conservative treatment group (risk ratio (RR)

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The APEC trial has shown that patients with predicted severe acute biliary pancreatitis do not benefit from routine urgent endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES).
⇒ Biliary decompression using ERCP with ES might be beneficial in a subselection of patients with proven common bile duct stones.
⇒ Endoscopic ultrasonography (EUS) is one of the most sensitive diagnostic tools to detect bile duct stones and sludge; it prevents an ERCP in patients in whom stones have already passed into the duodenum spontaneously.
⇒ It is unclear if a targeted approach with EUS-guided ERCP with ES improves outcomes in patients with a predicted severe acute biliary pancreatitis.

WHAT THIS STUDY ADDS

⇒ In patients with predicted severe acute biliary pancreatitis without cholangitis, urgent EUS-guided ERCP within 24 hours after hospital admission does not reduce severe complications or mortality compared with a conservative treatment strategy.

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In patients with predicted acute severe biliary pancreatitis, there is no need for early ERCP, not even in case of proven choledocholithiasis.

⇒ In patients with predicted acute severe biliary pancreatitis, a conservative strategy should be adopted with ERCP only in case of concomitant cholangitis (urgent indication) and persistent choledocholithiasis (elective indication).

0.93, 95% CI 0.67 to 1.29; p=0.65). Sensitivity analysis to correct for baseline differences using a logistic regression model also showed no significant beneficial effect of the intervention on the primary outcome (adjusted OR 1.03, 95% CI 0.56 to 1.90, p=0.92).

Conclusion In patients with predicted severe acute biliary pancreatitis without cholangitis, urgent EUS-guided ERCP with ES did not reduce the composite endpoint of major complications or mortality, as compared with conservative treatment in a historical control group.

Trial registration number ISRCTN15545919.

INTRODUCTION

With an increasing incidence throughout the years, acute pancreatitis is one of the most common gastrointestinal diseases requiring acute hospital admission.[1 2] Acute biliary pancreatitis (ABP) is caused by gallstones/sludge obstructing the ampulla of Vater, creating a transient obstruction of the pancreatic duct.[3 4] The duration of the pancreatic duct obstruction appears related to the severity of inflammation of the pancreas.[5] Consequently, in an attempt to ameliorate the disease course, it seems attractive to decompress the pancreatic duct by removing bile duct stones/sludge with endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) as early as possible. Recent guidelines state that urgent ERCP with ES is warranted in patients with ABP and concomitant cholangitis and not recommended in patients with a predicted mild disease course but provide limited guidance on the indication of urgent ERCP with ES in patients with a predicted severe disease course.[6–8]

The recently published Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment (APEC) trial investigated whether urgent biliary decompression using ERCP with ES is beneficial in patients with predicted severe ABP (PSABP) without cholangitis.[9] In this trial, 232 patients were randomised between conservative treatment and urgent ERCP with ES. 'Urgent' was defined as within 24 hours after hospital presentation and within 72 hours after symptom onset. Urgent biliary decompression with ERCP with ES did not reduce the composite endpoint of major complications or mortality as compared with conservative treatment.[9] In the APEC trial, however, the probability for a biliary origin and the indication for ERCP was based on common bile duct (CBD) dilation, an increase in serum alanine-aminotransferase (ALT) or sludge or stones on imaging (located in the gallbladder or CBD). Studies have shown that elevated liver enzymes and radiological signs of CBD stones are poorly correlated to the actual presence of CBD stones/sludge during ERCP.[10 11] This was confirmed in the APEC trial, where 55% of the patients in the urgent ERCP group did not show CBD stones/sludge during ERCP. After spontaneous stone passage into the duodenum, biliary decompression is no longer necessary, and ERCP with ES may even be harmful (eg, haemorrhage and aggravation of pancreatitis).[12] The most sensitive modality for diagnosing CBD stones/sludge is endoscopic ultrasonography (EUS).[13 14] When EUS is performed immediately before an intended ERCP with ES, it allows to perform ERCP exclusively in patients with confirmed stones/sludge in the CBD who are most likely to benefit.

The APEC trial showed that urgent ERCP with ES had no benefit over a conservative approach in PSABP without cholangitis when inclusion was based on biochemical tests and transabdominal ultrasound. This is supported by a recent meta-analyses that also included the APEC trial.[15] Yet, it remains unclear whether urgent ERCP with ES is beneficial in patients with confirmed bile duct stones/sludge on EUS. Therefore, in this prospective multicentre study, we assessed whether a strategy with urgent EUS followed by urgent ERCP with ES in the case of CBD stones/sludge reduces major complications or mortality in patients with PSABP (APEC-2).

METHODS

Study design and participants

This multicentre, prospective cohort study was performed in 15 Dutch hospitals. The outcomes of this study were compared with the outcomes of the conservative treatment group of the APEC trial.[9 16] In the APEC-2 study, the 15 participating centres were selected based on their high inclusion rates during the APEC trial and their ability to organise EUS and consecutive ERCP with ES within 24 hours after hospital presentation. We adhered to the protocol used in the APEC trial, except for the EUS procedure performed prior to ERCP in all included patients.[16] Inclusion and exclusion criteria for this study were identical to those in the original APEC trial.[9] Inclusion for this study commenced after the recruitment period of the APEC trial. A detailed description of the study design inclusion and exclusion criteria, the conservative and investigational treatment, data collection, outcome measures and management of missing data can be found in online supplemental appendix part 1 and part 2.

Investigational treatment

In the current study, we assessed a strategy with urgent EUS followed by urgent ERCP with ES in the case of CBD stones/sludge ('urgent EUS-guided ERCP'). EUS needed to be performed within 72 hours after symptom onset and within 24 hours after presentation at the emergency department. If gallstones/sludge in the CBD were detected during EUS, ERCP with ES was performed subsequently. EUS was considered positive when persistent echogenic intraluminal material was seen in the CBD or common hepatic duct, with or without posterior acoustic shadow. If no gallstones/sludge were detected during EUS or when the bile ducts could not be visualised during EUS, the patient was treated conservatively. EUS and ERCP were both carried out by, or under the direct supervision of, an experienced endosonographist and interventional endoscopist.

Outcomes

The primary endpoint was a composite endpoint of major complications or mortality occurring within 6 months after inclusion. Major complications included: bacteraemia, cholangitis, new onset persistent organ failure (>48 hours or <48 hours and leading to death), pancreatic parenchymal necrosis, pneumonia and pancreatic endocrine or exocrine insufficiency (online supplemental appendix part 3). Secondary endpoints included: the incidence of the individual components of the primary endpoint, occurrence of new onset organ failure (transient=<48 hours or persistent>48 hours, single or multiorgan),

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ERCP-related complications (definitions in online supplemental appendix part 4), length of hospital stay, intensive care unit (ICU) admission, length of ICU stay, number of interventions (ie, endoscopic, radiological or surgical), readmission for biliary events (ie, recurrent biliary pancreatitis, cholecystitis, biliary colic, cholangitis and choledocholithiasis) and quality of life. Quality of life was measured using the SF-36 questionnaire. The follow-up of this study was 6 months.

Patient and public involvement

The Dutch Pancreatitis Study Group (DPSG) has close ties with the Dutch Patient Association for Pancreatic Diseases. This association was actively involved in the design of the APEC trial and also partially funded the trial. This APEC-2 study was an additional part of the APEC trial and as such the design was discussed during DPSG meetings that included representation of the patient association. Once the trial has been published, participants will be informed of the results through the DPSG website.

Statistical analyses

The sample size calculation of this study was based on data from the interim analysis of the APEC trial since full trial results were not yet available. Cholestasis or bile duct stones on transabdominal ultrasound in the conservative group were used as a proxy for bile duct obstruction. In the APEC trial, the prevalence of the composite endpoint in the patients in the conservative study group with cholestasis or bile duct stones was 45%. In the ERCP with ES group, the composed endpoint was seen in 29% of patients that had CBD stones during ERCP that were successfully removed. As a result, in case of bile duct obstruction, a reduction of 16 percentage points in the composite endpoint was achieved after ERCP with ES. To account for the possibility of missed small stones in the conservative group and intention bias (ie, actors perceive a greater motivation to complete a task when the underlying indication to perform the procedure is supposedly more scientifically based), an additional 5 percentage points reduction of the primary endpoint was expected in the group that would be treated with urgent EUS-guided ERCP with ES. Using a χ^2 test without continuity correction, we established that with an expected reduction of 21 percentage points in the composite endpoint, a two-sided significance level of 5 and a 1% dropout rate, a total of 78 patients needed to be included to have a power of 80%. Patients in whom the composed primary endpoint could not be assessed due to withdrawal of informed consent were replaced. Furthermore, to provide a total of 78 *evaluable* patients for the per-protocol analysis, additional patients were added to replace patients that did not undergo EUS or in whom EUS was incomplete and patients in whom ERCP was not successful. The adjudication committee was only allowed to exclude patients before the statistical analyses were performed; these patients were not replaced but were excluded from the analyses. The composite primary endpoint and the individual components of the primary endpoint were analysed according to the intention-to-treat principle. A per-protocol analysis that only included the patients that underwent urgent EUS was also performed. All other secondary endpoints were analysed according to the intention-to-treat principle.

Continuous data were compared with the Mann-Whitney U test, dichotomous data with the Pearson's χ^2 test or Fisher's exact test. A two-sided p value of <0.05 was considered statistically significant. Results are presented as risk ratios (RRs) with their corresponding 95% CI.

The analyses of the primary endpoint and the quality of life analyses were performed by an independent statistician (NE). As this study comprised a prospective cohort series and a historic comparison group, logistic regression models were used for sensitivity analyses to investigate the influence of potential confounders on the primary outcome. In this model, we included clinically relevant potential confounders including age, sex, ASA classification, organ failure at baseline and the study arm to investigate the effect of these factors on our primary outcome. For statistical analysis, IBM SPSS Statistics V.25 and R V.4.1.3 (2022-03-10) were used.

RESULTS

Between 15 August 2017 and 21 August 2019, 522 patients with ABP were assessed for eligibility. Figure 1 shows the inclusion flow chart. Most eligible patients did not meet the inclusion criteria due to a predicted mild disease course. Eighty-seven patients with a predicted severe disease course were included in

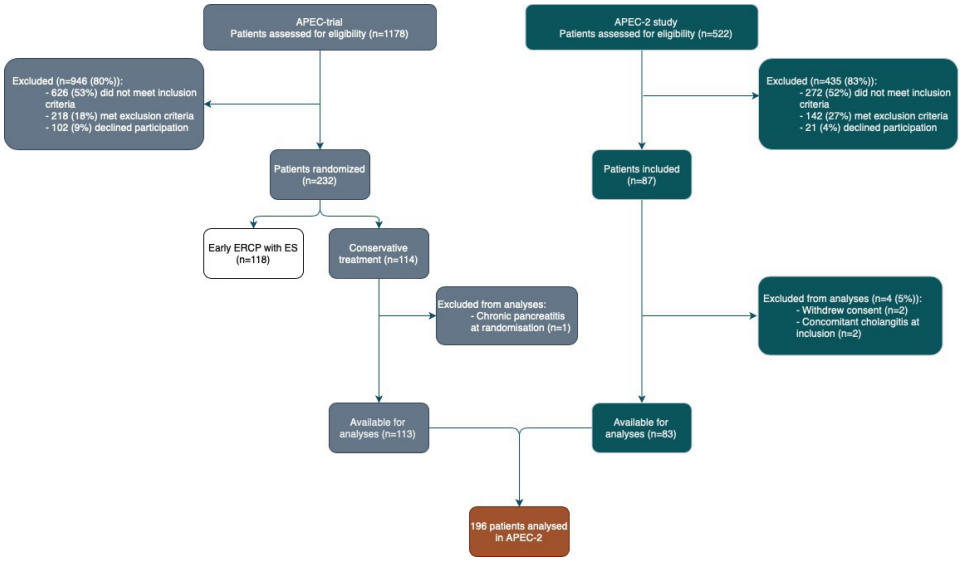

Figure 1 Inclusion flow chart of the APEC trial and APEC-2 patients. APEC, Acute biliary Pancreatitis: urgent ERCP with sphincterotomy versus conservative treatment.

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Table 1 Baseline characteristics

Characteristic	Urgent EUS±ERCP with ES (n=83)	Conservative treatment (n=113)	P value
Age in years – mean (SD)	70 (11)	71 (12)	0.65
Female sex - n (%)	37 (45)	53 (47)	0.75
ASA score, n (%)			*0.03*
Healthy status	16 (19)	16 (14)	
Mild systemic disease	52 (63)	57 (50)	
Severe systemic disease	15 (18)	40 (35)	
BMI (kg/m²), mean (SD)	29 (5)	29 (6)	0.58
Severity of disease on admission			
APACHE-II score, median (IQR)	10 (9–13)	10 (8–13)	0.87
Modified Glasgow score, median (IQR)	2 (2-3)	2 (1-3)	0.24
CRP, median (IQR)	78 (28–164)	38 (11–104)	*0.003*
SIRS, n (%)	45 (54)	61 (54)	0.97
Organ failure, n (%)	7 (8)	25 (22)	*0.01*
Biliary aetiology, n (%)			
Gallstones on imaging	57 (69)	88 (78)	0.19
Dilated common bile duct on imaging	18 (22)	32 (28)	0.32
Serum ALT >2 times the upper limit of normal	77 (93)	93 (82)	*0.03*
Serum ALT >2 times the upper limit of normal in absence of other biliary criteria	23 (28)	18 (16)	0.05
Cholestasis, n (%)			
Bilirubin (>40 µmol/L, >2.3 mg/dL)	46 (55)	51 (45)	0.16
Dilated common bile duct on imaging	18 (22)	31 (27)	0.36
Time from onset of symptoms to presentation at emergency department in hours, median	11 (5–20)	9 (5-18)	0.38

ALT, alanine aminotransferase; APACHE-II, Acute Physiology and Chronic Health Evaluation II; ASA score, American Society of Anaesthesiologists' (ASA) classification of Physical Health ; BMI, body mass index; CBD, common bile duct; CRP, C reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; SIRS, Systemic Inflammatory Respons Syndrome Score.

this study, of whom four were excluded due to either withdrawal of consent (n=2) or cholangitis at inclusion (n=2). Subsequently, 83 patients were included in the analyses. In the urgent EUS-guided ERCP group, 81 patients (98%) underwent EUS. In two patients, EUS and ERCP were cancelled after inclusion by the treating physician, due to rapidly developing organ failure. The patients from this prospective cohort were compared with a cohort of the APEC randomised trial, consisting of 113 patients with PSABP that were treated conservatively.[9] Both a per-protocol analysis and intention-to-treat analysis were performed. Full results and the inclusion flow chart of the per-protocol analysis can be found in the online supplemental appendix part 5.

Baseline characteristics

Baseline characteristics are shown in table 1. In the urgent EUS-guided ERCP group fewer patients were included with severe systemic disease and organ failure (defined as a Modified Marshall Score of 2 or higher, which could indicate either single or multi organ failure) at baseline.[17] In this group, baseline CRP levels were higher. Cholestasis was present in 53 out of 83 patients (64%) in the urgent EUS group and in 67 out of 113 patients (59%) in the conservative treatment group.

Primary and secondary endpoints

The primary composite endpoint of major complications or mortality occurred in 34 out of 83 patients (41%) in the urgent EUS group compared with 50 out of 113 patients (44%) in the conservative treatment group (RR 0.93, 95% CI 0.67 to 1.29, p=0.65). Apart from a difference in the occurrence of pancreatic exocrine insufficiency (PEI), no other differences were found in the individual components of the primary endpoint. PEI was observed in nine patients (11%) in the urgent EUS group and in two patients (2%) in the conservative group (RR 6.13, 95% CI 1.36 to 27.62, p=0.01). Exocrine insufficiency was defined by a low faecal elastase at 3 months after inclusion and the use of enzyme replacement therapy at 6 months after inclusion. By using a faecal elastase level of <200 mg/g, irrespective of replacement therapy, the difference remained significant between groups (23 patients (33%) vs 13 patients (18%), respectively (RR 1.82, 95% CI of RR 1.01–3.30, p=0.04)).

Five patients (6%) died in the in the urgent EUS group versus 10 patients (9%) in the conservative group (RR 0.68, 95% CI 0.24 to 1.91, p=0.46). An overview of the primary and secondary endpoints is presented in table 2. In online supplemental appendix part 6, the data of the urgent ERCP with ES group of the APEC trial are added to online supplemental appendix table 1 (S5), online supplemental appendix table 2 (S6) and online supplemental appendix table 5 (S7) for a more detailed overview.

Sensitivity analyses were used to investigate the effect of both the baseline differences between groups and other relevant clinical parameters on the primary outcome (table 3). Logistic regression analysis showed no significant relation between sex, ASA grade or organ failure at baseline and the effect of urgent EUS-guided ERCP on the primary endpoint (adjusted OR 1.03, 95% CI 0.56 to 1.90, p=0.92). The ASA score did not have a significant effect (OR 0.70, 95% CI 0.26 to 1.84 and OR 0.70, 95% CI 0.34 to 1.41), neither did organ failure (OR 1.79, 95% CI 0.80 to 4.00), although in the latter case, a possible effect could not be ruled out completely. Age did show a significant effect (table 3).

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Table 2 Primary and secondary endpoints: intention-to-treat analysis

Outcome	Urgent EUS±ERCP with ES (n=83)	Conservative treatment (n=113)	Risk ratio (95% CI)	P value
Primary composite endpoint				
Major complications or mortality	34 (41)	50 (44)	0.93 (0.67 to 1.29)	0.65
Secondary endpoints				
Death	5 (6)	10 (9)	0.68 (0.24 to 1.91)	0.46
New-onset persistent organ failure	14 (17)	17 (15)	1.12 (0.59 to 2.14)	0.73
Single organ failure (any duration)	12 (15)	18 (16)	0.91 (0.46 to 1.78)	0.78
Persistent single organ failure	8 (10)	9 (8)	1.21 (0.49 to 3.00)	0.68
Multiple organ failure (any duration)	7 (8)	13 (12)	0.73 (0.31 to 1.76)	0.48
Persistent multiple organ failure	5 (6)	8 (7)	0.85 (0.29 to 2.51)	0.77
Cholangitis	6 (7)	11 (10)	0.74 (0.29 to 1.92)	0.54
Bacteraemia	13 (16)	25 (22)	0.71 (0.39 to 1.30)	0.26
Pneumonia	7 (8)	10 (9)	0.95 (38 to 2.40)	0.92
Pancreatic parenchymal necrosis	19 (23)	18 (16)	1.47 (0.81 to 2.56)	0.22
Pancreatic endocrine or exocrine insufficiency	9 (11)	3 (3)	4.08 (1.14-14-63)	*0.02*
Endocrine insufficiency	3 (4)	2 (2)	2.04 (0.35 to 11.95)	0.42
Exocrine insufficiency*	9 (11)	2 (2)	6.13 (1.36 to 27.62)	*0.01*
Hospital stay in days	11 (6–22)	14 (10–26)	–	*0.03*
ICU admission	14 (17)	13 (12)	1.48 (0.74 to 2.99)	0.27
ICU stay in days	9 (5-21)	8 (4-35)	–	0.91
Readmission for biliary complication	6 (7)	24 (21)	0.34 (0.15 to 0.80)	*0.01*
Recurrent biliary pancreatitis	2 (2)	10 (9)	0.27 (0.06 to 1.21)	0.06
Cholangitis	1 (1)	3 (3)	0.46 (0.05 to 4.29)	0.48
Cholecystitis	3 (4)	7 (6)	0.58 (0.16 to 2.19)	0.42
Biliary colic	1 (1)	7 (6)	0.19 (0.02 to 1.56)	0.08
Choledocholithiasis	0 (0)	7 (6)	–	*0.02*

Data are presented as n (%) or median (IQR).
*Data on faecal elastase levels in stool were missing for 43 patients (22%); details on medication use for pancreatic insufficiency was available for all patients.
ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; EUS, endoscopic ultrasonography; ICU, intensive care unit.

Hospital stay was shorter in the urgent EUS group versus the conservative treatment group, with a median of 11 days (IQR 6–22) and 14 days (IQR 10–26), respectively (p=0.03). ICU admission was required in 14 patients (17%) in the urgent EUS group compared with 13 (12%) the conservative group (RR 1.48, 95% CI 0.74 to 2.99, p=0.27).

The results from the per-protocol analysis, including 75 patients, did not differ meaningfully from the intention-to-treat analysis (online supplemental appendix part 5).

Biliary complications and adverse events

Biliary complications occurred less often in the urgent EUS group; 6 patients (7%) in the urgent EUS group versus 24 patients (21%) in the conservative treatment group (RR 0.34, 95% CI 0.15 to 0.80, p=0.01) including recurrent biliary pancreatitis (2% vs 9%, p=0.06) and choledocholithiasis (0% vs 6%, p=0.02) (table 2).

In total, 24 (12%) patients had a cholecystectomy before inclusion. Out of the remaining 172 patients, 100 patients (58%) underwent cholecystectomy at a median of 59 days (IQR 25–96) after inclusion. In the conservative treatment arm, the median time to cholecystectomy was 75 days (IQR 45–109) and in the urgent EUS group 42 days (IQR 11–87), which was longer in the conservative group (p=0.02).

Out of 138 patients that did not have pancreatic necrosis, 14 underwent same admission cholecystectomy, 10 of whom were part of the EUS-guided ERCP group. More patients in the urgent EUS-guided ERCP group underwent same admission cholecystectomy compared with the conservative group (p=0.01). As previously reported, 10 patients (9%) in the conservative group were readmitted with recurrent biliary pancreatitis. Of these, four patients had a cholecystectomy prior to randomisation, four patients had a mild disease course but did not undergo same-admission cholecystectomy, one patient had a severe disease course and did not undergo a cholecystectomy and one patient had pancytopaenia leading to delayed cholecystectomy.[9] In the urgent EUS-guided ERCP group, two patients (2%) were readmitted for recurrent biliary pancreatitis, of whom one had a cholecystectomy prior to inclusion and one underwent cholecystectomy between the initial pancreatitis episode and the recurrent episode.

Table 3 Logistic regression model of predicting factors for the primary endpoint of severe complications or death

Variable	OR	95% CI for OR	Wald	P value
Study arm	1.03	0.56 to 1.90	0.01	0.92
Age	0.97	0.94 to 0.99	6.02	0.01
Female sex	0.73	0.41 to 1.32	1.09	0.27
Organ failure at baseline	1.79	0.80 to 4.00	1.99	0.16
ASA classification			1.04	0.59
ASA classification (1)	0.70	0.26 to 1.84	0.53	0.47
ASA classification (2)	0.70	0.34 to 1.42	1.00	0.32
Constant	10.36		3.82	0.05

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Table 4 Characteristics of first EUS procedure

Study group*	Urgent EUS±ERCP with ES (n=83)
EUS performed	81 (98)
Time from onset symptoms to first EUS (hours)	29 (23–42)
Time from presentation to first EUS (hours)	21 (17–23)
Duration of first EUS procedure (min)	14 (8–18)
First EUS performed by trainee under direct supervision	0 (0)
Papilla visualised	71 (86)
Gallstones or sludge in papilla (n=71)	17 (24)
Common bile duct visualised	80 (96)
Diameter of common bile duct (n=78)	7 (5-9)
Gallstones or sludge in common bile duct	47 (59)
Cystic duct visualised	35 (42)
Gallstones or sludge in cystic duct	5 (14)
Proximal biliary tract visualised	59 (71)
Gallstones or sludge in proximal biliary tract	1 (1)
Stones visualised on EUS	48 (58)

Data are presented as n (%) or median (IQR).
*No EUS procedures were performed in the conservative group.
ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; EUS, endoscopic ultrasonography.

Table 5 Characteristics of first ERCP procedure

Study group	Urgent EUS±ERCP with ES (n=83)	Conservative treatment (n=113)
ERCP performed	53 (64)	35 (31)
Total number of ERCPs performed	65	44
ERCPs per patient	1 (1–1)	0 (0–1)
Total number of first ERCPs performed based on EUS results	48 (58)	0
Time from onset symptoms to first ERCP (hour)	31 (24–48)	216 (99–832)
Time from presentation to first ERCP (hour)	22 (19–24)	211 (75–815)
Time between EUS and ERCP (min)*	10 (5–33)	–
Duration of first ERCP procedure (min)†	24 (16–43)	25 (17–50)
Indication for first ERCP		
Study related	48	0
Progressive cholestasis and/or suspicion of common bile duct stones	3	21
Cholangitis according to treating physician	1	5
Cholangitis according to study criteria	–	8
Endoprosthesis placement	1	1
Main bile duct stones or sludge on cholangiography‡	42 (79)	23 (66)
Common bile duct cannulation‡	48 (91)	32 (91)
Pancreatic duct cannulation‡	27 (51)	12 (34)
Precut sphincterotomy‡	16 (30)	6 (17)
Sphincterotomy‡	48 (91)	30 (86)
Stone extraction‡	45 (85)	25 (71)
Incomplete‡	1 (2)	1 (3)
ERCP-related complications	1 (2)	1 (3)

Data are no. (%) or median (IQR), unless otherwise stated.
*Data on time between EUS and ERCP were missing in one patient.
†Data on the duration of the ERCP procedure was missing in four patient in the urgent EUS group and in 13 patients in the conservative treatment group.
‡Denominators are the number of patients who had ERCP (ie, 53 in the urgent EUS group and 35 in the conservative treatment group).
§ERCP-related complications included bleeding, perforation, respiratory insufficiency and cardiovascular complications. Definitions are provided in the online supplemental appendix part 4.
ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; EUS, endoscopic ultrasonography.

Adverse events occurred in 63 out of 83 patients (76%) in the EUS group versus 90 out of 113 patients (80%) in the conservative treatment group (RR 0.95, 95% CI 0.82 to 1.11, p=0.53). All adverse events are presented in online supplemental appendix part 7.

Procedural characteristics of EUS and ERCP

In the urgent EUS group, 81 patients (98%) underwent EUS at a median of 29 hours (IQR 23–42) after symptom onset and 21 hours (IQR 17–23) after presentation at the emergency department (table 4). In two patients, EUS and ERCP were cancelled after inclusion by the treating physician due to rapidly developing organ failure. EUS was positive in 48 patients (58%), all of whom underwent immediate ERCP. Median time between EUS and ERCP was 10 min (IQR 5–33). In the group with a positive EUS, 14 out of 48 patients (29%) had only sludge/microlithiasis in the bile ducts and 34 (71%) had one or multiple stones.

In the urgent EUS group, 53 patients (64%) underwent ERCP with ES. In 48 patients, performance of ERCP was based on urgent EUS findings. ALT levels at baseline did not differ between patients with and without stones and/or sludge in the CBD (237 U/L (IQR 122–401) vs 237 U/L (IQR 148–443), p=0.77).

In five patients (6%), the initial EUS investigation during admission was negative, but these patients underwent ERCP at a later stage. Three patients had progressive cholestasis, and CBD stones were found and removed during ERCP (9 days, 22 days and 2 months after the initial EUS, respectively). One patient had cholangitis due to a CBD stenosis due to pancreatitis. The fifth patient had intraabdominal biliary leakage secondary to a liver abscess for which a biliary stent was placed. ERCP characteristics of all first ERCP procedures, including these five patients, are shown in table 5.

In the conservative group, an ERCP was performed in 35 of 113 (31%) patients, a median of 8 days (IQR 3–34) after inclusion. Sphincterotomy was performed in 30 of 35 patients (86%). The indication for ERCP was persistent cholestasis in 21 patients (19%) and cholangitis in 13 patients (12%); in 25 patients (71%) stones were found and extracted. In each group one patient had a procedural complication, in the urgent EUS group a patient developed post sphincterotomy bleeding 9 days after the initial procedure and in the conservative group one patient had a cardiovascular complication.

In the current APEC-2 study, 30 different endoscopists performed the ERCP procedures, of whom 16 (53%) also performed ERCP procedures for the APEC trial. Out of these 30 endoscopists, 20 (67%) also performed the EUS procedures; for the other 10 endoscopists, a colleague performed the EUS.

In patients in whom ERCP was performed based on EUS, biliary cannulation was achieved in 43 out of 48 patients (90%) (table 6). Unintentional pancreatic duct cannulation was seen in 50% of patients. Out of 24 patients that underwent an urgent ERCP based on EUS results and had PD cannulation, eight developed pancreatic necrosis (33%). In the remaining 23 patients in whom the PD was not cannulated, five (22%) developed pancreatic necrosis. This difference was not statistically significant (p=0.37). When looking at infected necrosis, results are similar: 3 out of 24 (13%) patients in the PD cannulation group

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Table 6 Characteristics of ERCP procedures performed based on EUS results

Study group	Urgent EUS and ERCP with ES (n=48)
Total number of ERCPs performed – no. of procedures	56
ERCPs per patient	1 (1–1)
Time from onset symptoms to first ERCP (hours)	31 (24–48)
Time from presentation to first ERCP (hours)	22 (19–24)
Time from EUS to ERCP (minutes)	10 (5–33)
Duration of first ERCP procedure (minutes)	24 (15–45)
First ERCP performed by trainee under direct supervision	0
Common bile duct stones or sludge on cholangiography*	40 (83)
Common bile duct cannulation	43 (90)
Pancreatic duct cannulation	24 (50)
Precut sphincterotomy	15 (33)
Sphincterotomy	43 (90)
Stone extraction	42 (88)†
Incomplete	1 (2)‡
ERCP-related complications	1 (2)

Data are no. (%) or median (IQR), unless otherwise stated.
*Cholangiography data was not available in five patients.
†In one patient, stones had passed between EUS and ERCP.
‡A pancreatic duct stent was placed.
ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography.

developed infected necrosis versus 3 out of 23 (13%) in the no PD cannulation group, p=0.96.

In five patients, biliary cannulation could not be achieved; in three patients, there was an inflammatory stenosis of the duodenum that could either not be passed or prohibited adequate exposure of the papilla, and in two patients, biliary cannulation failed. Complete stone extraction was achieved at the initial ERCP in 42 patients (88%). In one patient, stone extraction was incomplete, and a biliary stent was placed.

Quality of life analysis and costs

The association between treatment strategy and quality of life over time was investigated using linear mixed models. There was no significant difference in quality of life as measured with the SF-36 questionnaire, between study groups at 1 month, 3 months and 6 months after inclusion (online supplemental appendix part 8). During the study period, data on utilisation of healthcare were registered. However, we have decided to omit the cost-effectiveness analysis as the health intervention in this study was not beneficial. An interesting finding that bares economical relevance is that patients who underwent EUS spend a median of 3 days less (11 (IQR 6–22) versus (14 (IQR 10-26) in hospital compared with patients who did not undergo EUS. This translates to a saving of €1428 based on the average unit cost of an inpatient hospital day at the general ward in the Netherlands.[18]

DISCUSSION

This prospective multicentre APEC-2 cohort study found that urgent EUS in patients with PSABP, followed by urgent ERCP with ES in the case of bile duct stones/sludge, did not reduce the composite endpoint of major complications or mortality as compared with the conservative arm of the APEC randomised trial. In 58% of patients, bile duct stones/sludge were found with urgent EUS within 24 hours after presentation at the emergency department and within 72 hours of start of symptoms. Immediate ERCP with ES was performed successfully in 90% of patients with a low complication rate (2%).

Anderloni *et al*[11] performed a prospective study on early EUS-guided ERCP with ES (within 48 hours after admission) in 71 patients with ABP with a predominantly predicted mild disease course. CBD stones were found in 31 patients (44%), all of whom underwent ERCP. Clinical outcomes of the pancreatitis episode and rates of recurrent biliary events were not reported. In addition, De Lisi *et al* performed a meta-analysis comparing EUS-guided ERCP with ERCP in ABP including seven studies with a total of 545 patients of whom 188 had a severe ABP. An EUS-guided strategy prevented 57%–74% of ERCP procedures. However, clinical superiority could not be established.[13] In contrast to our study, most patients included in this meta-analysis had a predicted mild disease course. Moreover, we identified more CBD stones (58% vs 29%), presumably because we included patients very early in their disease course, leaving less time for stones to migrate into the duodenum spontaneously.

With regard to the individual components of the primary endpoint, we only found that PEI occurred more frequently in the intervention group. The occurrence of endocrine insufficiency did not differ between groups, and patients in the urgent EUS-guided ERCP group had the same level of pancreatic parenchymal necrosis as the conservatively treated patients. We believe that this is not an actual effect but an incidental finding.

Readmission for recurrent biliary events, especially recurrent biliary pancreatitis, was more frequent in the conservative treatment group compared with the urgent EUS-guided ERCP group. Cholecystectomy is the most effective strategy to prevent recurrent biliary events after ABP, both in the case of a mild and a severe disease course.[19 20] In case of a mild disease course, cholecystectomy should be performed during the same admission. In the conservative treatment group, however, 4 out of 10 patients had a mild disease course but did not undergo a same-admission cholecystectomy. In those patients, the chance of recurrent biliary pancreatitis might have been reduced if a same-admission cholecystectomy was performed. Therefore, we cannot recommend urgent EUS-guided ERCP in the acute phase of biliary pancreatitis to prevent recurrent biliary events.

There are some limitations of our study that need consideration. First, this study was not a randomised trial but composed of a prospective cohort series that was compared with the control group from a recently published randomised controlled trial, the APEC trial, which means that bias cannot be excluded.[9] To minimise the risk of bias in the current study, we used the same protocol (eg, eligibility criteria and endpoints) as in the original trial with an preprocedural EUS to the urgent ERCP with ES arm. Consecutive patients were included in the same group of hospitals; they were followed closely and treated by experienced endoscopists with a documented track record in doing both the EUS and ERCP with ES procedures. Most endoscopists were also involved in the original APEC trial. Some differences in baseline characteristics were observed between the groups, such as fewer patients with organ failure at baseline in the urgent EUS-guided ERCP group, despite similar APACHE-II scores, modified Glasgow scores and Systemic Inflammatory Respons Syndrome Score. Sensitivity analyses confirmed that these differences did not have an impact on the primary outcome of this study.

Based on this evidence, we believe that early EUS-guided ERCP is not indicated in patients with PSABP that do not have cholangitis. Only a randomised controlled trial will yield a higher level of evidence. A potentially more practical and feasible approach would be a stepped-wedge cluster randomised trial in which at random and sequential crossover of hospitals/clusters from

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control (no ERCP) to intervention (early EUS-guided ERCP) takes place until all clusters are exposed.

In conclusion, the combined results of the current prospective APEC-2 study and the original APEC trial show that in patients with a PSABP without cholangitis, urgent ERCP with ES, even when guided by EUS, does not reduce major complications or mortality. Therefore, we recommend a conservative treatment strategy in patients with a PSABP, with an ERCP only in case of concomitant cholangitis (urgent indication) and symptomatic and/or persistent choledocholithiasis (elective indication).

Author affiliations
[1]Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands
[2]Department of Gastroenterology and Hepatology, Sint Antonius Hospital, Nieuwegein, The Netherlands
[3]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands
[4]Department of Surgery, Amsterdam UMC Locatie AMC, Amsterdam, North Holland, The Netherlands
[5]Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, Noord-Holland, The Netherlands
[6]Department of Gastroenterology and Hepatology, Sint Franciscus Vlietland Groep, Rotterdam, Zuid-Holland, The Netherlands
[7]Department of Surgery, Sint Antonius Hospital, Nieuwegein, The Netherlands
[8]Department of Radiology, Sint Antonius Hospital, Nieuwegein, The Netherlands
[9]Department of Gastroenterology, Universtiy of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
[10]Department of Epidemiology and Data Science, Amsterdam UMC Locatie AMC, Amsterdam, North Holland, The Netherlands
[11]Methodology department, Amsterdam Public Health Research Institute, Amsterdam, North Holland, The Netherlands
[12]Department of Gastroenterology and Hepatology, Spaarne Gasthuis, Haarlem, Noord-Holland, The Netherlands
[13]Department of Surgery, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands
[14]Department of Gastroenterology and Hepatology, Gelre Hospitals, Apeldoorn, Gelderland, The Netherlands
[15]Department of Biostatistics, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands
[16]Department of Epidemiology, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands
[17]Department of Gastroenterology and Hepatology, Amsterdam UMC Locatie AMC, Amsterdam, North Holland, The Netherlands
[18]Gastroenterology and Hepatology, Radboudumc, Nijmegen, Gelderland, The Netherlands
[19]Department of Surgery, University of Amsterdam, Amsterdam, The Netherlands
[20]Department of Gastroenterology and Hepatology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, Noord-Brabant, The Netherlands
[21]Department of Surgery, University Medical Center Utrecht, Utrecht, The Netherlands
[22]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands
[23]Department of Gastroenterology, OLVG, Amsterdam, Noord-Holland, The Netherlands
[24]Department of Gastroenterology, Maasstad Hospital, Rotterdam, The Netherlands
[25]Department of Gastroenterology and Hepatology, OLVG, Amsterdam, Noord-Holland, The Netherlands
[26]Department of Gastroenterology and Hepatology, Isala Hospital, Zwolle, Overijssel, Netherlands
[27]Department of Gastroenterology and Hepatology, Reinier de Graaf Gasthuis, Delft, Zuid-Holland, The Netherlands
[28]Department of Gastroenterology and Hepatology, Maastricht UMC+, Maastricht, Limburg, The Netherlands
[29]Department of Gastroenterology and Hepatology, Jeroen Bosch Ziekenhuis, Den Bosch, Noord-Brabant, The Netherlands
[30]Gastroenterology, Catharina Hospital, Eindhoven, The Netherlands
[31]Department of Internal Medicine and Gastroenterology, Meander Medical Center, Amersfoort, The Netherlands
[32]Department of Gastroenterology and Hepatology, Amphia Hospital, Breda, The Netherlands
[33]Department of Gastroenterology and Hepatology, Rijnstate Hospital, Arnhem, The Netherlands
[34]Canisius Wilhelmina Hospital, Nijmegen, The Netherlands
[35]Department of Gastroenterology and Hepatology, Martini Hospital, Groningen, Groningen, The Netherlands
[36]Department of Gastroenterology and Hepatology, Medical Spectrum Twente, Enschede, The Netherlands
[37]Department of Gastroenterology, University Medical Center Utrecht, Utrecht, The Netherlands
[38]Department of Gastroenterology and Heptatology, Albert Schweitzer Hospital, Dordrecht, Zuid-Holland, The Netherlands
[39]Department of Gastroenterology, Gelderse Vallei Hospital, Ede, The Netherlands
[40]Department of Surgery, Dutch Acute Pancreatitis Study Group, University Medical Center Utrecht, Utrecht, The Netherlands
[41]Department of Surgery, Maastricht Universitair Medisch Centrum+, Maastricht, Limburg, The Netherlands

Twitter Marc G Besselink @marcbesselink

Contributors All authors contributed to the conceptualisation and methodology. The investigation was performed by NDH and PMCS. MB, MGB, M-PGFA, OJB,TLB, DWdC, SMvD, HMvD, BvE, CvE, WE, PF, E-JvG, JvG, WLH, RAH, JEvH, JMJ, FJGMK, SK, ACP, RQ, RJdR, TCJS, TR, EJS, MPS, XJNMS, MPS, AT, WT, RT, DSU, NGV, RCV, FV, WvdV, RLJvW and BJMW contributed to patient recruitment, investigational treatment and the acquisition of data. TLB assessed the imaging. The formal analysis was performed by NDH, PMCS and NS. The manuscript was drafted by NDH. SAWB, MB, MGB, NJS, PMCS and HvS coauthored the writing. All authors have critically appraised the manuscript. MJB was the guarantor that supervised the study.

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ORCID iDs
Nora D Hallensleben http://orcid.org/0000-0002-7433-0200
Marc G Besselink http://orcid.org/0000-0003-2650-9350

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