

## Early ERCP in Acute Gallstone Pancreatitis without Cholangitis: A Meta-analysis

Manley C Uy, Ma Lourdes O Daez, Peter P Sy, Virgilio P Banez,  
Wendell Z Espinosa, Marilyn C Talingdan-Te

Section of Gastroenterology, Department of Medicine, Philippine General Hospital,  
University of the Philippines. Manila, Philippines

### ABSTRACT

**Context** Early ERCP was reported to result in recovery from acute gallstone pancreatitis. To date, several RCTs comparing it to conservative treatment have yielded different results. **Objective** We conducted a meta-analysis to determine the effect of early ERCP on the morbidity and mortality of acute gallstone pancreatitis without cholangitis. **Methods** We searched the following databases up to January 11<sup>th</sup>, 2008: the Cochrane Library, MEDLINE, EMBASE, the Australasian Medical Index, Latin American Caribbean Health Sciences Literature, and the Health Research and Development Information Network. References were scrutinized. Authors were contacted. There were no restrictions regarding language, publication date or publication status. **Results** Seven RCTs were retrieved, but only two RCTs involving 177 treated patients and 163 control patients were included. A meta-analysis on morbidity was inconclusive (RR=0.95, 95% CI: 0.74-1.22). Meta-analysis on mortality only showed a trend in favor of conservative management (RR=1.92, 95% CI: 0.86-4.32) for both mild and severe pancreatitis. **Conclusions** There is a trend towards more mortality from early ERCP with or without sphincterotomy in the setting of acute gallstone pancreatitis without cholangitis. However, more studies are needed. In the meantime, early ERCP should not be carried out unless there is at least a slight suspicion of cholangitis or persistent ampullary obstruction.

### INTRODUCTION

Persistent ampullary obstruction by an impacted stone or by ampullary edema following stone passage may result in pancreatic edema, inflammation [1], hemorrhage and necrosis with a mortality rate of 13-50% [2]. Accordingly, early relief of the obstruction is believed to halt the progression of severe attacks as well as prevent the evolution of mild attacks [1]. Early surgical removal of gallstones has been advocated [2]; however, a 1979 study by Ranson showed that surgery within one week of admission in severe pancreatitis was associated with a mortality rate of 67%. This was confirmed by the 1988 randomized controlled trial (RCT) of Kelly and Wagner on 165 patients which showed that surgery within 48 h of admission in severe pancreatitis was associated with a mortality rate of 47.8% as compared to 11.8% with delayed surgery [3]. This led to the abandonment of early surgery. The

alternative, endoscopic retrograde cholangiopancreatography with or without endoscopic sphincterotomy, was demonstrated by Classen *et al.* in 1978 to result in the complete removal of bile duct stones and recovery from pancreatitis in 17 patients [4].

However, difficult cannulation and pancreatic contrast injection during ERCP may potentially worsen pancreatitis. So the question is: would ERCP with or without endoscopic sphincterotomy for biliary obstruction from retained stones or ampullary edema benefit patients with gallstone acute pancreatitis without cholangitis? The results of 7 RCTs comparing early ERCP with or without endoscopic sphincterotomy with conservative treatment yielded contradictory results [1, 2, 5, 6, 7, 8, 9]. We conducted a meta-analysis to determine the effect of early ERCP with or without endoscopic sphincterotomy on the morbidity and mortality of gallstone acute pancreatitis without cholangitis, the latter being an independent indication for early ERCP.

### METHODS

#### Identification and Selection of Studies

Relevant studies were identified and selected by searching the following databases: the Cochrane Library, MEDLINE, EMBASE, the Australasian Medical Index (AMI), Latin American Caribbean

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**Correspondence** Manley C Uy

Gastrointestinal Clinic, 1<sup>st</sup> floor, Central Block, Philippine General Hospital, Taft Avenue, Ermita 1000, Manila, Philippines

Phone: +63-2.567.2983; Fax: +63-2.567.2983

E-mail: sutzeran@yahoo.com

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Health Sciences Literature (LILACS), and the Health Research and Development Information Network (HERDIN) up to January 11<sup>th</sup>, 2008 using the search strategy "Gallstone" OR "Gallstone [MESH]" AND "Pancreatitis" OR "Pancreatitis [MESH]" AND "endoscopic retrograde cholangiopancreatography" OR "endoscopic retrograde cholangiopancreatography [MESH]" AND "randomized controlled trial" OR "randomized controlled trial [MESH]" AND "cholangitis" OR "cholangitis [MESH]" where applicable. We also did a full manual search from the reference lists of the trials selected. Authors of the trials retrieved were also contacted for information concerning any trials and relevant unpublished materials. There were no restrictions regarding language, publication date or publication status. The following selection criteria were applied: 1) study population: gallstone acute pancreatitis patients without cholangitis; 2) intervention: early ERCP with or without endoscopic sphincterotomy vs. conservative treatment within at most 72 h of admission; 3) outcome measures: incidence of morbidity and mortality; 4) study design: randomized controlled trial to guarantee control of selection bias. Papers identified by the searches were evaluated and any papers unrelated to this review were excluded. Decisions at this stage were made based upon the title and abstract. Inclusion decisions were guided by eligibility criteria.

**Data Extraction**

The following relevant information was also extracted and recorded: country of origin, inclusion and exclusion criteria used, baseline comparability between treatment groups, comparison of types of treatment and number of patients in each arm, drop-outs reported and their reasons, incidence of mortality and morbidity, treatment carried out, and adverse events. In some studies, the reported overall incidence was not used as

we had to account for those with baseline cholangitis. One study (Fölsch *et al.*) [6] did not report mortality and morbidity data according to the severity of baseline pancreatitis. Data reported by the meta-analysis of Ayub *et al.* [10] as provided by Fölsch *et al.* were used. Data were entered into Review Manager software (RevMan 4.2, Cochrane Collaboration, Oxford, England, United Kingdom; <http://www.cc-ims.net/RevMan>).

**Quality of Methodology**

The methodological quality of the studies included in the meta-analysis was scored using the Jadad composite scale. This is a 5-point quality scale, with low-quality studies having a score of less than 3 and high-quality studies having a score  $\geq 3$ . Each study was given an overall quality score based on the above criteria, which was then used to rank the studies.

**STATISTICS**

The data analysis was carried out using the fixed-effect model with the meta-analysis Review Manager software (RevMan 4.2, Cochrane Collaboration, Oxford, England). The dichotomous mortality and morbidity data were expressed as relative risks (RR), together with 95% confidence intervals (95% CI). The relative risk of adverse events was used for 3 reasons: 1) there is empirical evidence that relative effect measures are, on the average, more consistent than absolute measures; 2) there is also empirical evidence that risk ratios of the adverse outcome are more consistent than ratios of the non-event and 3) it is a concept more familiar to patients and health professionals, and its interpretation is less complicated than for odds. We tested inconsistency between trials with the  $I^2$  statistic which describes the percentage of the variability in effect estimates which is due to heterogeneity rather than sampling error (chance), with a value greater than 50% considered as substantial

**Table 1.** Characteristics of trials initially included in the meta-analysis.

	Neoptolemos <i>et al.</i> , 1988 [7]	Fölsch <i>et al.</i> , 1997 [6]	Oría <i>et al.</i> , 2007 [1]
<b>Methods</b>	121 patients. Single center (Leicester Royal Infirmary, Leicester, UK)	238 patients. 22 centers (Germany). Intention-to-treat	103 patients. Single center (Cosme Argerich Hospital, Argentina). Intention-to-treat
<b>Participants</b>	Gallstone acute pancreatitis. Gender: 52 M, 69 F. Age: 20-96 years. Reported according to presence/absence of cholangitis.	Gallstone acute pancreatitis with/without obstructive jaundice. Gender: 96 M, 142 F. Age: 15-93 years	Gallstone acute pancreatitis with distal CBD $\geq 8$ mm and total serum bilirubin $\geq 20$ $\mu$ mol/L. Gender: 29 M, 73 F. Age: $\geq 18$ years. Excluded acute cholangitis as defined by Charcot's triad
<b>Interventions</b>	ERCP $\pm$ endoscopic sphincterotomy within 72h of admission vs. conventional Rx $\pm$ ERCP $\pm$ endoscopic sphincterotomy after the 5 <sup>th</sup> day of admission	ERCP $\pm$ endoscopic sphincterotomy within 72h of symptom onset vs. conservative management $\pm$ ERCP within 3 weeks for signs of biliary obstruction or sepsis	ERCP $\pm$ endoscopic sphincterotomy $\pm$ biliary stent within 48 h of symptom onset vs. conservative management. Elective surgery during the same admission once gallstone acute pancreatitis subsided.
<b>Outcomes</b>	Local and systemic complications, death. Overall cannulation success: 90%; stone extraction 100%	Mortality due to pancreatitis, complications. Overall mortality. Overall cannulation success: 94%; stone extraction: 98%	Changes in organ failure score and CT severity index during 1 <sup>st</sup> week of admission. Local complications. Morbidity and mortality. Overall cannulation success: 92%; stone extraction 94%
<b>Notes</b>	Routine antibiotics. Modified Glasgow criteria (<3 mild)	Antibiotics for T>39C. Gallstone acute pancreatitis severity classified before treatment by modified Glasgow criteria (<3 mild)	Routine antibiotics (ciprofloxacin plus metronidazole) for acute cholangitis. APACHE II score (>6 severe)

**Table 2.** Characteristics of trials excluded from the meta-analysis.

Study	Reason for exclusion
Fan <i>et al.</i> , 1993 [3]	Did not explicitly exclude cholangitis. Included pancreatitis from other causes, such as alcohol and hyperlipidemia
Nowak <i>et al.</i> , 1995 [8]	Reported only in abstract form. Not known whether cholangitis excluded
Zhou <i>et al.</i> , 2002 [9]	Did not explicitly exclude cholangitis
Acosta <i>et al.</i> , 2006 [5]	Excluded only those with severe cholangitis

heterogeneity. Funnel plots to address whether there exists publication bias could not be done due to the small number of studies.

## RESULTS

### Description of Selected Studies

The search strategy yielded 7 studies. Initially, 3 were included (Table 1) and 4 were excluded (Table 2). In general, the studies included involved patients with gallstone acute pancreatitis without cholangitis. Fölsch *et al.* [6] and Oría *et al.* [1] specifically excluded acute cholangitis, Neoptolemos *et al.* [7] provided the information according to the presence or absence of cholangitis.

The methodological quality scores of the 3 RCTs included ranged from 2-3 (Table 3): Neoptolemos *et al.* [7] got a 2 as they did not mention their method of randomization, Fölsch *et al.* [6] and Oría *et al.* [1] both got 3. None of them were double blinded. We decided to go ahead with the meta-analyses as ERCP is a complex invasive intervention not amenable to complete blinding. Follow-up and exclusion data are complete. There are no concerns regarding selective reporting.

### Meta-Analyses of Clinical Events

Using a fixed effects model, an overall meta-analysis on the effect of early ERCP with or without endoscopic

sphincterotomy on morbidity of acute pancreatitis was inconclusive (RR=0.82, 95% CI: 0.64-1.04). Morbidity meta-analyses for mild and severe pancreatitis were also inconclusive (Table 4).

As for mortality, an overall meta-analysis was also inconclusive (RR 1.22, 95% CI: 0.61-2.45). Separate meta-analyses according to the severity of the pancreatitis were also inconclusive for both mild and severe pancreatitis (Table 4).

Tests of heterogeneity using the I<sup>2</sup> test revealed that the majority of the meta-analyses carried out were heterogeneous. This could be due to the various enrollment criteria of the studies included, i.e., the endoscopic community is hampered by a lack of a strict definition of biliary pancreatitis [3]. A review of these RCTs revealed that the study of Neoptolemos *et al.* [7] had a relatively lower methodological quality. Furthermore, this study recruited patients “n” hours after admission while the other two studies recruited patients “n” hours after symptom onset. As those who had onset of symptoms long before admission may already have had subsiding gallstone acute pancreatitis, the eventual benefit of ERCP with or without endoscopic sphincterotomy in the study of Neoptolemos *et al.* may be ascribed to relief of the biliary obstruction, not pancreatitis [1]. This could have biased the outcome in favor of ERCP with or without the endoscopic sphincterotomy group. Therefore, a sensitivity analysis with deselection of the study of Neoptolemos *et al.* was carried out. Not surprisingly, this yielded more homogenous meta-analyses and different results (Figures 1, 2, 3, 4, 5, 6). Although, overall morbidity meta-analyses were still inconclusive, an overall mortality meta-analysis appeared to be in favor of conservative management. The same applied for meta-analyses performed according to pancreatitis severity.

## DISCUSSION

There have been several meta-analyses on the subject. The 1999 meta-analysis of Sharma *et al.* [4] concluded

**Table 3.** Jadad quality score of trials included in the meta-analysis.

	Neoptolemos <i>et al.</i> , 1988 [7]	Fölsch <i>et al.</i> , 1997 [6]	Oría <i>et al.</i> , 2007 [1]
<b>Randomization method</b>	1 (not mentioned)	2 (stratified block procedure)	2 (sealed envelopes)
<b>Double blinding</b>	0	0	0
<b>Withdrawals/dropouts</b>	1	1	1
<b>Total</b>	2	3	3

**Table 4.** Initial meta-analyses of morbidity and mortality (fixed-effects model).

	Studies	Patients	RR	95% CI	I <sup>2</sup>
<b>Morbidity</b>					
Combined	3	450	0.82	0.64-1.04	65.3%
Mild pancreatitis	3	289	0.87	0.62-1.21	0%
Severe pancreatitis	3	129	0.80	0.57-1.13	76.6%
<b>Mortality</b>					
Combined	3	450	1.22	0.61-2.45	53.7%
Mild pancreatitis	3	289	4.53	0.22-92.88	Not applicable
Severe pancreatitis	3	129	1.13	0.45-2.83	56.3%

The discrepancy in the number of patients in the combined and the summation of the mild and severe pancreatitis is due to the study of Fölsch *et al.* [6] where some patients were classified as having pancreatitis of undefined severity if at least 2 of the criteria were met, but not all the values were available.

Review: Urgent ERCP in acute gallstone pancreatitis  
 Comparison: 01 ERCP vs conservative Rx for acute gallstone pancreatitis  
 Outcome: 01 morbidity

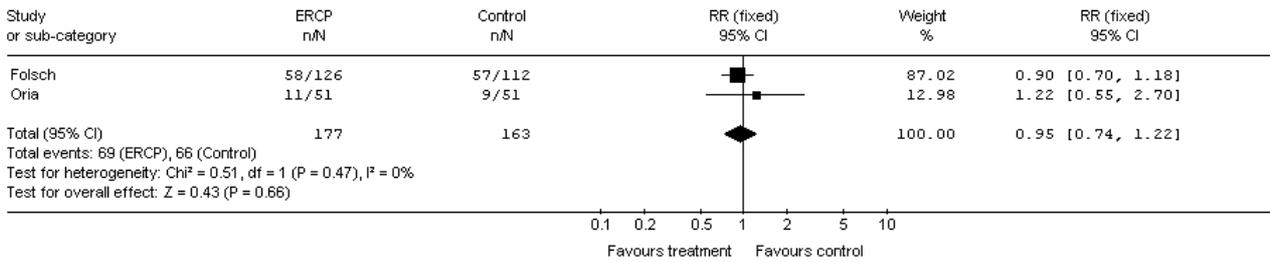


Figure 1. Meta-analysis on morbidity of ERCP with or without ES vs. conservative treatment in acute gallstone pancreatitis.

Review: Urgent ERCP in acute gallstone pancreatitis  
 Comparison: 01 ERCP vs conservative Rx for acute gallstone pancreatitis  
 Outcome: 02 mortality

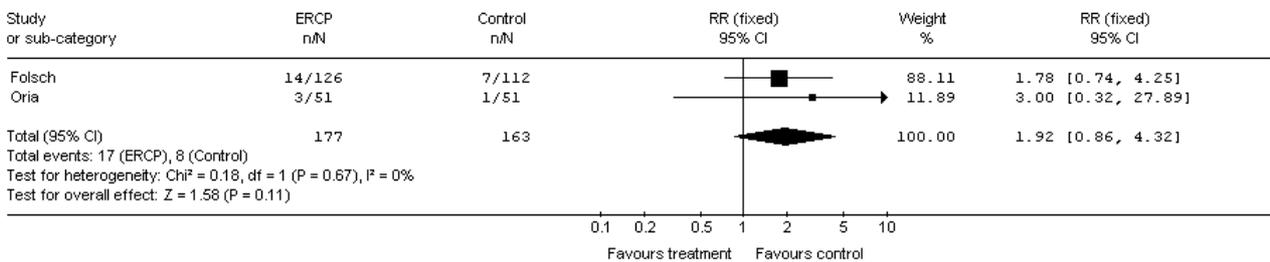


Figure 2. Meta-analysis on mortality of ERCP with or without ES vs. conservative treatment in acute gallstone pancreatitis.

Review: Urgent ERCP in acute gallstone pancreatitis  
 Comparison: 02 ERCP vs conservative Rx for mild acute gallstone pancreatitis  
 Outcome: 01 morbidity

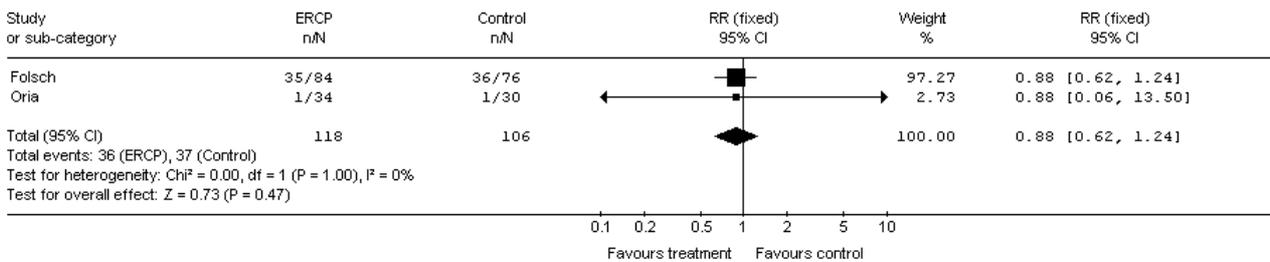


Figure 3. Meta-analysis on morbidity of ERCP with or without ES vs. conservative treatment in mild acute gallstone pancreatitis.

Review: Urgent ERCP in acute gallstone pancreatitis  
 Comparison: 02 ERCP vs conservative Rx for mild acute gallstone pancreatitis  
 Outcome: 02 mortality

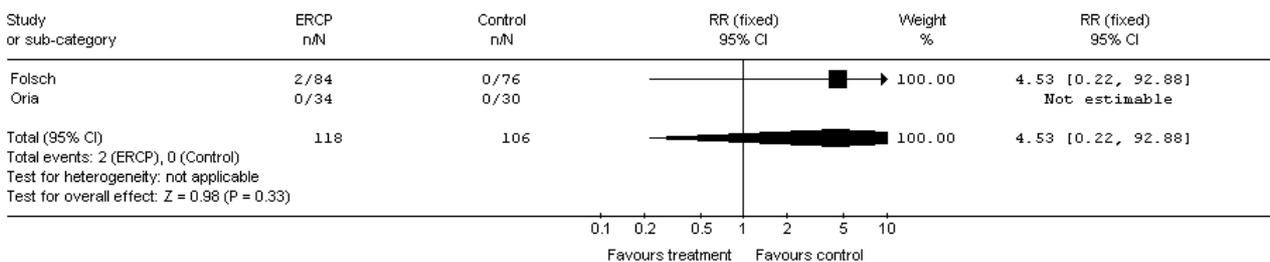


Figure 4. Meta-analysis on mortality of ERCP with or without ES vs. conservative treatment in mild acute gallstone pancreatitis.

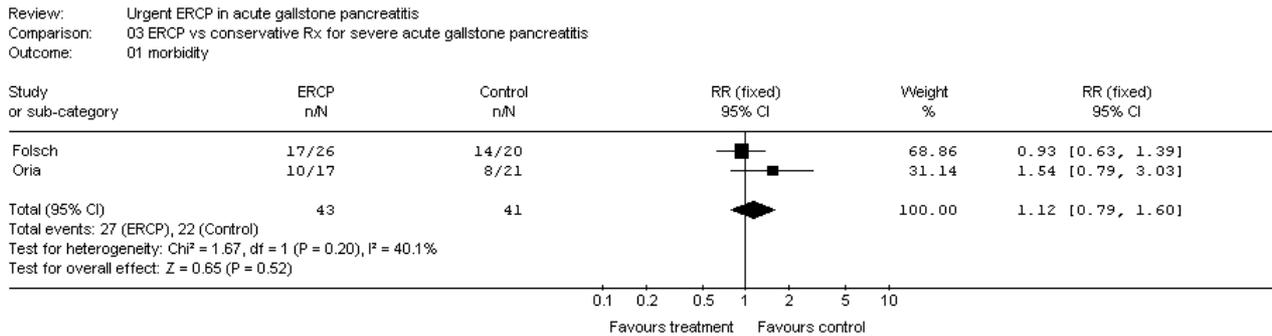


Figure 5. Meta-analysis on morbidity of ERCP with or without ES vs. conservative treatment in severe acute gallstone pancreatitis.

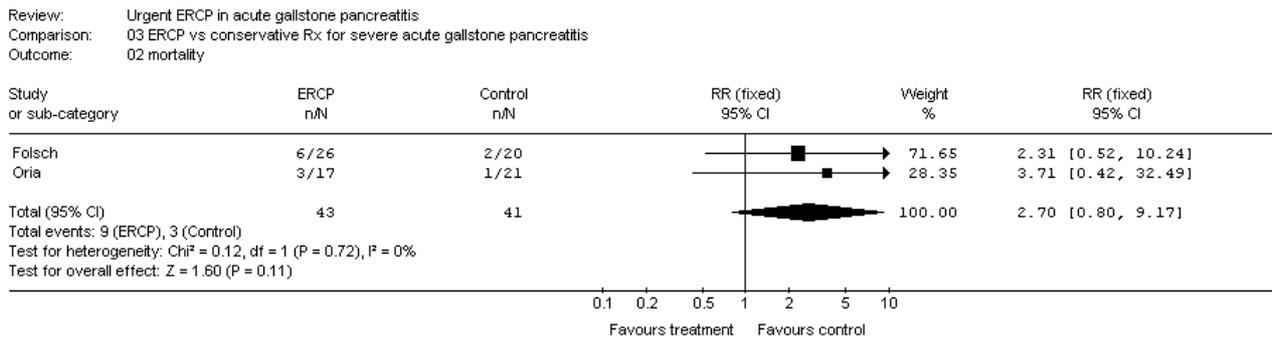


Figure 6. Meta-analysis on mortality of ERCP with or without ES vs. conservative treatment in severe acute gallstone pancreatitis.

that ERCP with or without endoscopic sphincterotomy reduces morbidity and mortality in gallstone acute pancreatitis. However, this meta-analysis included the studies of Fan *et al.* [2] and Nowak *et al.* [8]. The 2004 meta-analysis of Ayub *et al.* [10] for Cochrane and the recent 2008 meta-analysis of Moretti *et al.* [11] both concluded that early ERCP with or without endoscopic sphincterotomy may reduce the odds of having complications in predicted severe gallstone acute pancreatitis, but both also included the study of Fan *et al.* [2]. Moretti *et al.* [8] also included the studies of Neoptolemos *et al.* [7] and Zhou *et al.* [9]. Moreover just recently in 2008, Petrov *et al.* [12] reported a meta-analysis which concluded that early ERCP with or without endoscopic sphincterotomy did not reduce complications and mortality of gallstone acute pancreatitis. However, they also included the study of Neoptolemos *et al.* [7]. The result of this latter meta-analysis was similar to our initial meta-analysis (prior to sensitivity analysis).

The results of our present meta-analysis were different in that they not only suggested that early ERCP with or without endoscopic sphincterotomy might be unnecessary but also that it might possibly lead to higher mortality in both mild and severe gallstone acute pancreatitis. This was not in alignment with current guidelines on the management of gallstone acute pancreatitis which recommend early ERCP for severe gallstone acute pancreatitis [13, 14, 15, 16, 17]. Although this is only a trend (P>0.05), it is worth noting that a recent audit revealed that a low compliance of 48% with the UK guideline for 100% ERCP with or

without endoscopic sphincterotomy for severe gallstone acute pancreatitis did not increase the complication or mortality rates from severe acute pancreatitis [18].

The following should be considered in the interpretation of the results of this meta-analysis.

First, individual patient data were not used.

Second, the cumulative study population is relatively small at 340. The inconclusiveness of the meta-analyses may be due to type II error.

Third, the studies included did not have a placebo group.

Fourth, only about half of the patients in the studies included (Fölsch *et al.* 46% [6], Oría *et al.* 66% [1]) who underwent a successful ERCP were found to have choledocholithiasis. Indeed, by not excluding patients without choledocholithiasis, these studies may have skewed the possibility of detecting the benefits of early ERCP with or without endoscopic sphincterotomy. Fan *et al.* [2] showed that, in the presence of confirmed biliary stones, the morbidity rates in the group undergoing early ERCP with or without endoscopic sphincterotomy were significantly lower than those in the conservative-treatment group (P=0.03). They also showed that the mortality rate was lower (P=0.09). The study of Acosta *et al.* [5] on patients with gallstone acute pancreatitis with ampullary obstruction showed that limiting the duration of the obstruction to not longer than 48 hours by ERCP with or without endoscopic sphincterotomy decreased morbidity. Unfortunately, they did not exclude those with mild cholangitis. In relation to this, the low proportion of

patients with confirmed choledocholithiasis reflects the fact that the present definitions of gallstone acute pancreatitis aim to diagnose gallstone acute pancreatitis and not choledocholithiasis. In addition, gallstone acute pancreatitis as we all know, is more often associated with small stones which can transiently obstruct the common bile duct, cause pancreatitis or papillary edema, and pass into the duodenum. Therefore, we need a reliable way of detecting the presence of choledocholithiasis. A recent RCT comparing EUS with or without ERCP with endoscopic sphincterotomy (in the case of choledocholithiasis) to ERCP with or without endoscopic sphincterotomy in 140 patients with gallstone acute pancreatitis showed a more successful examination of the biliary tree with comparable morbidity and mortality risks in patients undergoing EUS with or without ERCP with endoscopic sphincterotomy. Thus, by identifying persistent ampullary obstruction, EUS may spare those who have already passed their stones from an unnecessary invasive procedure, thus preventing the potential risk of ERCP-associated complications [19]. This result was confirmed by Polkowski *et al.* [20] and Lee *et al.* [21]. These studies support the recommendations of the British Society of Gastroenterology guidelines that EUS or MR be used to confirm the presence of choledocholithiasis taking into account accessibility and local expertise. They perform better than ultrasound or CT scan [17]. Fifth, the two studies selected included different types of gallstone acute pancreatitis patients. Fölsch *et al.* [6] excluded all patients with obstructive jaundice while Oría *et al.* [1] excluded patients with cholangitis, but included those with obstructive jaundice. The fact that, in terms of mortality, the study of Fölsch *et al.* [6] has more of a trend in favor of the control group than does the study of Oría *et al.* [1] does could be due to the absence of the need for ERCP with or without endoscopic sphincterotomy in patients without obstructive jaundice. Finally, it should be noted that gallstone acute pancreatitis by itself may also present with signs of cholangitis-like right upper quadrant pain, fever and jaundice [22]. Moreover, the diagnosis of cholangitis is often problematic because signs and symptoms pointing to the biliary tract as the source of sepsis are often absent in the critical early period of the disease. More importantly, of all the complications of gallstones, cholangitis kills the most swiftly [23]. Adequately powered randomized placebo-controlled multicenter studies using patients diagnosed with a standardized definition of gallstone acute pancreatitis plus confirmed choledocholithiasis but without obstructive jaundice and/or acute cholangitis presenting within a clearly defined period after onset of the disease should be carried out in the future in order to explore the effect of early ERCP or EUS on specific local and systemic complications of gallstone acute pancreatitis. Alternatively, a meta-analysis using individual patient data may provide an opportunity to

analyze this. In the meantime, it might be prudent not to carry out early ERCP with or without endoscopic sphincterotomy in patients with gallstone acute pancreatitis unless there is at least a slight suspicion of cholangitis or persistent ampullary obstruction.

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**Potential conflict of interest** None known

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