

# Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis (Review)

Ayub K, Slavin J, Imada R



**THE COCHRANE  
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3

<http://www.thecochranelibrary.com>



---

Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis (Review)  
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	3
METHODS . . . . .	3
RESULTS . . . . .	6
DISCUSSION . . . . .	7
AUTHORS' CONCLUSIONS . . . . .	8
ACKNOWLEDGEMENTS . . . . .	8
REFERENCES . . . . .	8
CHARACTERISTICS OF STUDIES . . . . .	9
DATA AND ANALYSES . . . . .	13
Analysis 1.1. Comparison 1 Early ERCP+/-ES versus Conservative Mx, Outcome 1 Mortality stratified by severity of GAP. . . . .	13
Analysis 1.2. Comparison 1 Early ERCP+/-ES versus Conservative Mx, Outcome 2 Complications stratified by severity of GAP. . . . .	14
WHAT'S NEW . . . . .	15
HISTORY . . . . .	15
CONTRIBUTIONS OF AUTHORS . . . . .	15
DECLARATIONS OF INTEREST . . . . .	15
INDEX TERMS . . . . .	15

[Intervention Review]

# Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis

Khurram Ayub<sup>1</sup>, John Slavin<sup>2</sup>, Regina Imada<sup>3</sup>

<sup>1</sup>Adderbury, UK. <sup>2</sup>Surgery, Mid Cheshire Hospitals NHS Trust, Crewe, UK. <sup>3</sup>Endoscopy Unit, Santa Casa School of Medicine, São Paulo, Brazil

Contact address: Khurram Ayub, 6 Griffin Close, Adderbury, Oxfordshire, OX17 3HR, UK. [ayubkhurram@aol.com](mailto:ayubkhurram@aol.com). (Editorial group: Cochrane Upper Gastrointestinal and Pancreatic Diseases Group.)

*Cochrane Database of Systematic Reviews*, Issue 3, 2009 (Status in this issue: *Unchanged*)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DOI: 10.1002/14651858.CD003630.pub2

**This version first published online:** 19 July 2004 in Issue 3, 2004.

**Last assessed as up-to-date:** 22 March 2004. (Help document - [Dates and Statuses](#) explained)

**This record should be cited as:** Ayub K, Slavin J, Imada R. Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No.: CD003630. DOI: 10.1002/14651858.CD003630.pub2.

## ABSTRACT

### Background

Early endoscopic retrograde cholangio-pancreatography with or without endoscopic sphincterotomy (ERCP+/-ES) has been advocated to reduce complications in patients presenting with a severe attack of gallstone-associated acute pancreatitis (GAP). However, a recent trial has reported contradictory results. Importantly, patients with acute cholangitis were excluded suggesting it may be a major confounding factor affecting previous studies.

### Objectives

To assess the effectiveness of early ERCP+/-ES compared to conservative management stratified according to severity of disease, concealment of randomisation, acute cholangitis and bilirubin level in the reduction of mortality, morbidity, length of hospitalisation and cost in adults suspected of having GAP.

### Search strategy

We searched - Cochrane Library (Issue 4 2003), Medline (1966-2004), EMBASE (1980-2004) and LILACS. 'Grey literature' was sought by looking at cited references and hand searched to identify further relevant trials. Conference proceedings of United European Gastroenterology Week (published in *Gut*) and Digestive Disease Week (published in *Gastroenterology*) were also hand searched.

### Selection criteria

Randomized controlled trials (RCT) of adult patients, from 15 years old or greater, presenting with gallstone-associated acute pancreatitis (GAP) comparing ERCP +/- ES versus Conservative management within 72 hours of admission.

### Data collection and analysis

Data were assessed for quality independently by two reviewers. Wherever appropriate, results were pooled together and sub-grouped by predicted severity of disease. Fixed and random effects models were applied. Sensitivity analysis was performed to test the fragility of results.

### Main results

---

**Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis (Review)**  
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

Three trials, involving 511 patients, met inclusion criteria. The test for heterogeneity yielded statistically non-significant results ( $p$ -value 0.1 to 0.63) suggesting all comparisons were above the established threshold for combinability ( $p < 0.1$ ). Fixed effect and random effect meta-analyses gave identical results. Early ERCP +/- ES was associated with non-significant effect on reduction of mortality in predicted mild (OR = 0.62, 95% CI = 0.27 to 1.41) and severe GAP (OR = 0.62, 95% CI = 0.27 to 1.41). Reduction in complications was non-significant in predicted mild (OR = 0.89, 95% CI = 0.53 to 1.49), but significant in severe GAP (OR = 0.27, 95% CI = 0.14 to 0.53). There was insufficient evidence to draw any conclusions about hospital stay and cost.

### Authors' conclusions

Odds of having complications are reduced in predicted severe disease by early ERCP +/- ES. This effect was however, non-significant in predicted mild disease and for reduction of mortality in either predicted mild or severe disease. These results are controlled for confounding due to associated acute cholangitis and are robust for clinical and statistical heterogeneity.

## PLAIN LANGUAGE SUMMARY

### Patients with a predicted severe attack of gallstone-associated acute pancreatitis need early endoscopic retrograde cholangiopancreatography

Patients presenting with acute pancreatitis may benefit from treatment to reduce complications and mortality. Early endoscopic retrograde cholangio-pancreatography with or without sphincterotomy has been advocated for acute pancreatitis associated with gallstones since the late 1980s. A more recent multicentre trial, however has suggested that it may be associated with an increased mortality and was stopped at interim analyses. The effect of confounding factors such as acute cholangitis, that is an independent indication for urgent endoscopic retrograde cholangio-pancreatography, has been the major issue in this controversy. This systematic review controls for this confounding effect and shows that early endoscopic retrograde cholangiopancreatography can decrease complications in a predicted severe attack of acute pancreatitis associated with gallstones.

## BACKGROUND

Gallstone-associated acute pancreatitis (GAP) is defined as acute pancreatitis in association with gallstones and in the absence of other known causes. It is the commonest cause and accounts for between 35% and 60% of cases of acute pancreatitis depending upon the population studied (Mergener 1999; Toh 2000; Howard 1987). The clinical presentation of GAP is similar to other causes of acute pancreatitis: abdominal pain, nausea and vomiting. Most cases are self-limiting with a benign course. However, approximately 25% of patients develop a severe and life-threatening illness (Frakes 1999; Bhatia 2000) resulting in multiorgan failure and possible death. The overall mortality of acute pancreatitis ranges from 5-10% (Lowham 1999, Mergener 1999, Toh 2000, McKay 1999). Between 4 and 8% of patients with gallstones will develop GAP secondary to migratory gallstones (Howard 1987). In patients who do not undergo cholecystectomy or endoscopic sphincterotomy a second attack occurs in 30% with a median delay of 180 days (Paloyan 1975).

The association of gallstones with pancreatitis was first proposed by Bernard in 1856. In 1901 Opie performed an autopsy on a patient who had died of severe pancreatitis and found a gallstone impacted at the ampulla of Vater (Opie 1901). He postulated that

the acute inflammatory reaction was induced by reflux of bile into the pancreatic duct as a result of obstruction at the ampulla. Other theories have tried to explain the association of gallstones with pancreatitis (duodenal reflux theory, common-channel theory), but the exact mechanism by which passage of gallstone through the ampulla of Vater initiates inflammation of the pancreas remains unclear (Uomo 1998). Interestingly, an increased serum nitric oxide activity was found in patients presenting with acute pancreatitis (Ayub 1999). Studies in animal models of acute pancreatitis suggest that a number of aetiological factors converge upon a single common ischaemia-reperfusion injury pathway resulting in induction of inducible nitric oxide synthase and consequent tissue damage due to rapid accumulation of reactive oxygen species (Ayub 2001, Vollmar 2003). That the gallstone passage occurs during an attack of pancreatitis is not in doubt; stones can be recovered from the faeces of recuperating patients (Acosta 1974). The "two phases theory" postulates that in the first phase small migrating stones initiate an attack of AP; patency of the ampulla of Vater following stone passage allows egress of activated enzymes and leads to a mild attack. In the second phase, persisting stones or the repeated passage of small stones results in relative (intermittent or continuous) obstruction to both the main bile duct (MBD)

and pancreatic duct with an accumulation of activated pancreatic enzymes and the development of a severe attack (Neoptolemos 1989). The increased incidence of persisting MBD stones in the more severe forms of GAP, in patients who die, and in patients with pancreatic necrosis supports this theory (Neoptolemos 1989; Wilson 1988). These concepts provide a rational basis for the use of early biliary decompression in patients with GAP.

Prior to the introduction of endoscopic retrograde cholangio-pancreatography (ERCP) two prospective randomised studies investigated the effect of surgical biliary decompression at the time of urgent cholecystectomy on the outcome of GAP. Stone et al randomized 65 patients to transduodenal sphincteroplasty and decompression within 72 hours of admission, or delayed surgery until the patient was in remission. Of 36 patients undergoing urgent surgery, complications occurred in 11% with one death (3%), compared to 11% and 7% respectively in the patients that had surgery whilst in remission. These differences were not statistically significant (Stone 1981). In 1988 Kelly and Wagner reported on a randomised prospective study of 165 patients stratified according to Ranson's prognostic criteria. Although there was no overall difference in outcome, patients with a predicted severe attack who underwent urgent (within 48 hours of admission) supraduodenal bile duct decompression, had a higher morbidity (83% vs. 18%) and mortality (48% vs. 11%) than those undergoing delayed surgery (Kelly 1988). This study persuaded many in the surgical community that early open surgical intervention in these patients was unwise. A major flaw however was the use of supraduodenal bile duct exploration; this is not the functional equivalent of a sphincteroplasty and does not decompress the pancreatic duct.

ERCP was introduced in 1968 as a diagnostic procedure, but the subsequent development of endoscopic sphincterotomy (ES) allowed treatment of main bile duct calculi. Endoscopic sphincterotomy with MBD stone extraction certainly offers an attractive alternative to surgical biliary decompression but during early 1980s both acute pancreatitis and cholangitis were considered to be the main contraindications to ERCP and ES. This view however changed rapidly since late 1980s and the worldwide experience of ERCP and ES for GAP is associated with a mean morbidity rate of 8% and a mortality rate of 2.4% (reviewed in Uomo 1998). Since the late 1980s early ERCP has been used to manage GAP, two randomised controlled trials (RCTs) have provided support for this approach (Fan 1993; Neoptolemos 1988), a more recent RCT (Fölsch 1997) reported conflicting results and was stopped at interim analysis. The latest study excluded patients with acute cholangitis. Since acute cholangitis is an indication for urgent ERCP, doubts have been raised with regard to the role of early ERCP for patients with a severe attack of GAP without associated acute cholangitis.

How far were the differences observed in the previous RCTs caused by confounding due to associated acute cholangitis and does early ERCP +/- sphincterotomy benefit patients without cholangitis?

This question is of obvious clinical importance but a meta-analysis has not been conducted to address it. A previous attempt at overall meta-analysis (Sharma 1999) failed to reach any meaningful conclusions due to missing data in reports of these trials. Interestingly, as has been the case in many other conventional reviews and guidelines on this subject, this report also erroneously included a study (Nowak 1995) on a related subject.

## OBJECTIVES

The aim of this systematic review was to compare early (within 72 Hs of admission) ERCP +/- ES with conservative management, to determine whether early ERCP reduced morbidity and mortality in patients with GAP

Subgroup analysis was planned to determine whether the results differed by:

- i. severity of disease (mild and severe)
- ii. grade of concealment of randomization
- iii. acute cholangitis
- iv. bilirubin

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Only randomized, controlled trials (RCT) were accepted to guarantee control of selection bias. Studies that on closer scrutiny were determined to be quasi-randomised, or cross-over studies were excluded.

#### Types of participants

Adult patients, from 15 years old or greater, presenting with acute pancreatitis as evidenced by the presence of at least two of the following: compatible clinical presentation (i.e. abdominal pain, nausea, vomiting); amylase greater than 3 times of the upper limit of normal; Ultrasound (US) or abdominal CT evidence of pancreatitis, and gallstones on the basis of US/Magnetic Resonance Cholangio-Pancreatography (MRCP); elevated liver enzymes or past ERCP.

#### Types of interventions

ERCP +/- ES versus Conservative management within 72 hours of admission.

## Types of outcome measures

Primary outcome:

- Overall mortality, evaluated at hospital discharge, if this information was available, otherwise mortality at day-n was considered.

Secondary outcomes:

If mortality is equal, other outcomes become important such as:

- Systemic complications (Bradley 1993)
- Pancreatic complications (Bradley 1993)
- Length of hospitalization in survivors
- Cost

## Search methods for identification of studies

The search was conducted independently by the UGPD search co-ordinator and updated at yearly intervals to identify any studies made available during the process of this systematic review. The standard methods of The Cochrane UGPD Review Group were employed. There were no restrictions regarding language, date of publication or publication status. Searches were conducted to identify all published and unpublished randomised controlled trials (RCTs).

Trials were identified by searching the following electronic databases - The Cochrane Library (Issue 4 2003) Medline (1966-2004) Embase (1980-2004) and LILACS.

MEDLINE search strategy

The following search strategy was constructed by using a combination of subject headings and text words relating to the use of ERCP in the treatment of patients with gallstone-associated acute pancreatitis.

randomized controlled trial.pt.

controlled clinical trial.pt.

randomized controlled trials.sh.

random allocation.sh.

double blind method.sh.

single-blind method.sh.

or/1-6

(animal not human).sh.

7 not 8

clinical trial.pt.

exp clinical trials/

(clin\$ adj25 trial\$).ti,ab.

((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 blind\$).mp. or mask\$.ti,ab. [mp=title, abstract, cas registry/ec number word, mesh subject heading]

placebos.sh.

placebo\$.ti,ab.

random\$.ti,ab.

research design.sh.

or/10-17

18 not 8

19 not 9

comparative study.sh.

exp evaluation studies/

follow up studies.sh.

prospective studies.sh.

(control\$ or prospectiv\$).mp. or volunteer\$.ti,ab. [mp=title, abstract, cas registry/ec number word, mesh subject heading]

or/21-25

26 not 8

27 not (9 or 20)

9 or 20 or 28

exp pancreatitis/

pancreatitis.tw.

(acut\$ adj5 pancrea\$).tw.

(biliar\$ adj5 pancrea\$).tw.

(gallstone\$ adj5 pancrea\$).tw.

exp Cholangiopancreatography, Endoscopic Retrograde/

(endoscop\$ adj3 retrograd\$ adj3 cholangiopancreatograph\$).tw.

exp Sphincterotomy, Endoscopic/

(endoscop\$ adj5 sphincterot\$).tw.

exp cholecystectomy/

cholecystect\$.tw.

exp Cholecystectomy, Laparoscopic/

(laparoscop\$ adj5 cholecystect\$).tw.

or/30-34

or/35-42

43 and 44

45 and 29

EMBASE search strategy

1.exp randomized controlled trial/

2. randomized controlled trial.mp.

3. randomized controlled trial\$.tw.

4. exp randomization/

5. exp single blind method/

6. exp double blind method/

7. or/1-6

8. animal.hw.

9. human.hw.

10. 8 not (8 and 9)

11. 7 not 10

12. exp clinical trial/

13. clinical trial.mp.

14. (clin\$ adj3 (stud\$ or trial\$)).ti,ab,tw.

15. (clin\$ adj3 trial\$).ti,ab,tw.

16. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj3 (blind\$ or mask\$)).ti,ab,tw.

17. exp placebo/

18. placebo\$.ti,ab,tw.

19. random.ti,ab,tw.

20. (crossover\$ or cross-over\$).ti,ab,tw.

21. or/12-20

22. 21 not 10

23. 22 not 11

24. exp comparative study/  
 25. exp evaluation studies/  
 26. exp prospective studies/  
 27. exp controlled study/  
 28. (control\$ or prospective\$ or volunteer\$).ti,ab,tw.  
 29. or/24-28  
 30. 29 not 10  
 31. 30 not (11 or 23)  
 32. 11 or 23 or 31  
 33. exp pancreatitis/  
 34. pancreatitis.tw.  
 35. (acut\$ adj5 pancrea\$).tw.  
 36. (biliar\$ adj5 pancrea\$).tw.  
 37. (gallstone\$ adj5 pancrea\$).tw.  
 38. exp Cholangiopancreatography, Endoscopic Retrograde/  
 39. (endoscop\$ adj3 retrograd\$ adj3 cholangiopancreato-  
 graph\$).tw.  
 40. exp Sphincterotomy, Endoscopic/  
 41. (endoscop\$ adj5 sphincterot\$).tw.  
 42. exp cholecystectomy/  
 43. cholecystect\$.tw.  
 44. exp Cholecystectomy, Laparoscopic/  
 45. (laparoscop\$ adj5 cholecystect\$).tw.  
 46. or/33-37  
 47. or/38-45  
 48. 46 and 47  
 49. 48 and 32  
 Cochrane Library search strategy  
 #1.PANCREATITIS single term (MeSH) 402  
 #2.pancreatitis\* 867  
 #3.(acut\* near pancrea\*) 431  
 #4.(biliar\* near pancrea\*) 169  
 #5.(gallstone\* near pancrea\*) 31  
 #6.(#1 or #2 or #3 or #4 or #5) 1003  
 #7.SPINCTEROTOMY ENDOSCOPIC single term (MeSH)  
 70  
 #8.(endoscop\* near sphincterot\*) 128  
 #9.CHOLECYSTECTOMY single term (MeSH) 592  
 #10.cholecystect\* 1453  
 #11.CHOLECYSTECTOMY LAPAROSCOPIC single term  
 (MeSH) 427  
 #12.(laparoscop\* near cholecystect\*) 675  
 #13.CHOLANGIOPANCREATOGRAPHY ENDOSCOPIC  
 RETROGRADE single term (MeSH) 227  
 #14.(endoscop\* near retrograd\* near cholangiopancreatograph\*)  
 309  
 #15.ercp\* 41  
 #16.(#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)  
 1789  
 #17.(#6 and #16) 205  
 LILACS search terms entered  
 Pancrea\$ AND ERCP OR endoscopic retrograde cholangiopan-

creatography.

Reference lists from trials selected by electronic searching were hand searched to identify further relevant trials. Published abstracts from conference proceedings from the United European Gastroenterology Week UEGW 1993 -2003 (published in Gut) and Digestive Disease Week DDW 1997-2003 (published in Gastroenterology) were also hand searched.

## Data collection and analysis

The standard methods of The Cochrane UGPD Review Group were employed. Assessment of methodology and extraction of data were performed by two independent reviewers (KA and JS) with resolution of differences at each stage with the help of third reviewer (RI) until unanimous agreements were reached. Trials published only as abstracts were reviewed, if enough details were included or available from the trialists. In case of duplicate publications, only the most comprehensive report was included.

### CRITICAL APPRAISAL OF STUDIES

The quality of each trial was judged by whether or not the study design had minimized bias within the scope of the clinical context. The biases examined were selection, performance, attrition and detection. Level of agreement of reviewers was recorded.

External validity criteria were also examined:

-baseline comparability of treatment groups (Severity score)

-presence of inclusion and exclusion criteria

-intervention described in detail

-definition of outcomes

-stated time for outcome assessment

-stated indications for further interventions

### DATA COLLECTION

The data were extracted using a data extraction and quality assessment form. Recorded data were cross-checked by reviewers. The software package (Review Manager 4.2.3) provided by the Cochrane Collaboration was used for analysis. Clinical homogeneity was assessed by examination of severity scores and demographic data such as age and sex to ensure the studies are from similar populations.

### CONTROL FOR CONFOUNDING DUE TO ASSOCIATED ACUTE CHOLANGITIS

Confounding due to associated acute cholangitis has been a major concern from the earliest RCT to assess this treatment (Neopteleomos 1988) and all three trialists had different approaches to this problem. This however precluded combinability of the overall data reported for each study. In view of the overriding clinical importance of this issue, it was unanimously agreed that overall combination with no control for confounding for associated acute cholangitis would be misleading. Instead a solution to control for confounding was proposed (KA) and was accepted unanimously. This approach meant that data on all intended outcomes was traded off for a complete data set stratified according to severity of disease on primary (mortality) and the more important secondary outcome

(complications) with least confounding due to associated acute cholangitis. The approach reasoned that least confounded data would either be for participants without associated acute cholangitis or participants with associated acute cholangitis but all patients diagnosed to have acute cholangitis in the conservative management group to have had an urgent ERCP.

For the UK trial, the protocol required ERCP to be withheld for 5 days among the conservative management group and it would have confounded the outcomes as reasoned above. However, the trialists had reported data for patients without associated acute cholangitis in the original report and some missing aspects could be deduced and verified from statements and tables. For the German trial, associated acute cholangitis patients were excluded. However, data stratified according to severity were mentioned to have been studied albeit not available in the report. These were made available by the trialists. The Hong Kong trial had included patients with associated acute cholangitis but had provided urgent ERCP for associated acute cholangitis in the conservative management group. Hence, overall data from this study were used. The extracted data were combined by calculating a pooled estimate of the odds ratio using the method of Mantel-Haenszel, the relative risk and risk difference and their 95% confidence interval for dichotomous data. Both a fixed-effect and random-effect model were used.

#### DATA ANALYSIS AND PRESENTATION

All RCTs comparing endoscopic interventions versus no treatment for acute gallstone pancreatitis and separated into subgroups according to predicted mild and severe disease with control for confounding due to associated acute cholangitis. Wherever appropriate, results were pooled together and sub-group analyses were performed according to predicted severity of disease.

For the individual trial results, odds ratio, with 95% confidence intervals (CI), and number needed to treat were calculated for categorical outcomes. After clinical exploration of all important sources of variation, and formal exploration of heterogeneity using statistical test of non-combinability, meta-analysis was performed using fixed and random effects model.

For the meta-analysis, odds ratios (OR) and 95% confidence intervals (CI) were reported for categorical outcomes. Publication bias was explored using a plot of study sample size against relative risk (funnel plot).

Sensitivity analysis was performed limited to: the fragility of results by determining the effect of small shifts in the number of events between intervention and control groups.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Five studies were examined further after an initial assessment of study eligibility criteria. Three studies ([Fan 1993](#); [Fölsch 1997](#); [Neoptolemos 1988](#)) met the study inclusion criteria and were assessed for methodological quality (See 'Characteristics of Included Studies'). Two studies were excluded on closer scrutiny ([Nowak 1995](#); [Pezelli 1998](#)) (See 'Characteristics of Excluded Studies'). Two included studies ([Fan 1993](#); [Neoptolemos 1988](#)) were from single centre and one was multi centre ([Fölsch 1997](#)). The total number of patients randomized in each study varied from 121 ([Neoptolemos 1988](#)) to 238 ([Fölsch 1997](#)). All studies included GAP patients. The age at randomization ranged from 15 ([Fölsch 1997](#)) to 96 ([Neoptolemos 1988](#)).

In all the trials the severity of the disease was assessed by combining several prognostic variables into a severity score (Ranson's or modified Glasgow criteria), which provides initial risk stratification for patients with acute pancreatitis (See 'Table of included studies').

Delivery of interventions of each trial varied mainly in the treatment of patients with associated acute cholangitis.

Not all the considered outcomes were reported in each study. Mortality was reported but other secondary outcomes considered relevant for this review were not reported in all the studies.

### Risk of bias in included studies

Methodological quality assessments was performed unblinded. Cochrane components were used to evaluate the methodological quality of each study. The results were used for sensitivity analysis and not as exclusion criteria. When a discrepancy occurred, another reviewer was asked for an opinion in order to reach consensus.

#### Randomisation and allocation concealment

None of the reports of the trials included a statement as to allocation concealment.

#### Blinding

These trials are examples of a complex, interventional therapy being used where complete blinding is not possible. Attempts to blind participants may be made either by designing an appropriate placebo or partially concealing (within ethical boundaries) the purpose of trial from participants ([Miller 2003](#)). Neither was done in these trials. Obviously, in an interventional procedure it is not possible to blind the health care workers (unlike a drug trial when an identical placebo will blind the carer as well as the participant). Outcome assessment (determining rates of death and rates and cause of admission) was performed blinded in one trial ([Fölsch 1997](#)) only.

#### Loss to follow up

All randomized patients were accounted for in all studies. However, data used from the UK study for patients without associated acute cholangitis are not on intention-to-treat basis.

## Effects of interventions

Since statistical tests for heterogeneity have low power especially when there are not many studies, the possibility of a type II (false negative) error must be considered and a thorough attempt was made to identify clinical heterogeneity or sources of bias. The data set were chosen as to control for confounding due to associated acute cholangitis. This approach did not affect the data for mortality but meant that separate data set for systemic and pancreatic complications were not available for all studies. However, data for total complications were available. Hence, total complications was used as a 'surrogate' secondary outcome measure. Analyses assessing the hospital stay in survivors and cost were not performed as insufficient data were available.

Grade of concealment of randomization was unclear in all studies. Stratification according to bilirubin and associated cholangitis was not possible due to insufficient data.

Total number of randomized patients was 511. Globally, when considering mortality in mild GAP, the results from the trials clustered between odds ratio not-estimable and 4.64, overlapping confidence intervals. For mortality in severe GAP, the results from the trials clustered between odds ratio of 0.09 and 2.7, with overlapping confidence intervals. For complications in mild GAP, the results from the trials clustered between an odds ratio of 0.7 and 1.44, with overlapping confidence intervals. For complications in severe GAP, the results from the trials clustered between an odds ratio of 0.12 and 0.81, with overlapping confidence intervals.

The test for heterogeneity yielded statistically non-significant results (p-value 0.1 to 0.63) suggesting all comparisons were above the established threshold for combinability ( $p < 0.1$ ). Fixed effect and random effect meta-analyses gave identical results suggesting that important statistical heterogeneity was unlikely.

Funding source and level of support was mentioned for only one study (Fölsch 1997). One study (Fölsch 1997) was rated (3/5 points) to be of high quality and two studies (Fan 1993; Neoptolemos 1988) were rated (2/5 points each) to be of low quality.

### PUBLICATION BIAS

The small numbers of trials precluded an assessment of publication bias and should suggest a cautious interpretation.

### META-ANALYSIS OF PRIMARY OUTCOMES

Mortality Mild GAP (OR (95% CI))

fixed effect model 4.64 (0.22 to 98.12) test for heterogeneity not applicable

random effects model 4.64 (0.22 to 98.12)

Mortality Severe GAP

fixed effect model 0.62 (0.27 to 1.41) test for heterogeneity  $p = 0.10$  (df=2)

random effects model 0.64 (0.13 to 3.14)

### META-ANALYSIS OF SECONDARY OUTCOMES

Complications Mild GAP (OR (95% CI))

fixed effect model 0.89 (0.53 to 1.49) test for heterogeneity  $p = 0.63$  (df=2)

random effects model 0.89 (0.53 to 1.49)

Complications Severe GAP (OR (95% CI))

fixed effect model 0.27 (0.14 to 0.53) test for heterogeneity  $p = 0.11$  (df=2)

random effects model 0.28 (0.10 to 0.79)

### SUBGROUP ANALYSIS

We intended to carry out subgroup analysis of complications into pancreatic and systemic complications but data with control for confounding were not available for all studies.

### OTHER SECONDARY OUTCOMES

We intended to carry out assessments of cost and length of stay in survivors but due to missing data in reports and our decision to extract data controlled for confounding precluded assessments of these outcomes.

## DISCUSSION

In patients with severe GAP an early ERCP +/- ES reduced the odds of having complications by 73% of what they were in the control group. Another way of looking at this is to estimate the number needed to treat (NNT). For reducing complications if we provided early ERCP +/- ES for 100 patients with severe GAP 30 patients will benefit who would have not benefited if given conservative management. Approximately we will need to treat 4 patients with early ERCP +/- ES to help prevent complications in one patient.

Globally, the effect of early ERCP +/- ES on overall mortality and complications in GAP patients was not significant. Subgroup analyses stratified according to predicted severity were planned 'a priori' in the protocol to minimise bias. The stable results already shown by the similar fixed and random effects model were also confirmed by testing the 'fragility of the results'.

The overall estimate was of statistical significance for complications in predicted severe GAP patients and when using the fixed effect and the random effects, reflected stable conclusion. The studies were well matched, equally weighted and the meta-analyses were not dominated by any single trial.

Among the secondary outcomes complete data set were available for total complications for all the studies. Other secondary outcomes relevant for this review were inadequately reported.

The concerns about clinical heterogeneity of trials were:

Mainly due to confounding due to associated acute cholangitis and was controlled for in this review.

Mortality was the main endpoint, but the cut-off point was not clear and may be varied.

The German trial (Fölsch 1997) reported the lowest mortality rate in the control group presumably reflecting a lower baseline risk.

Inclusion criteria were very similar or even identical across studies, whereas exclusion criteria were slightly different.

Some questions still remain open:

The effect of treatment for pancreatic and systematic complications may be varied. This issue could not be explored in this systematic review of aggregate data.

The definition of early (within 72 hours of admission) is arbitrary, and is based on practical considerations.

The effects of posture and sedation during ERCP were not an issue tackled in the studies.

Early ERCP +/- ES in predicted severe GAP can be very effective for short term complications, but its impact on the long term recovery is still uncertain.

It may be interesting to sub-analyse patients with 'gallstones only' to gauge the effect of future improvements in our diagnostic ability due to non-invasive modalities such as magnetic resonance cholangiopancreatography that can accurately exclude patients without gallstones. This aspect may be of interest if an IPD analyses is contemplated in future updates of this review.

Finally, these trials were conducted before the effects of antibiotic prophylaxis became widely known. Since patients having ERCP may have received prophylactic antibiotics as part of the ERCP procedure. In the absence of any information to the contrary the

possibility of a confounding effect on outcome can not be ruled out.

## AUTHORS' CONCLUSIONS

### Implications for practice

The odds of having complications are reduced in predicted severe disease by early ERCP +/- ES. However, the effect was non-significant in predicted mild disease and for clinically relevant reduction of mortality in either predicted mild or severe disease. There was insufficient evidence to draw any conclusion about other outcomes.

### Implications for research

A systematic review that uses individual patient data (IPD), may provide an opportunity to:

Analyse other important outcomes by sub-group analyses.

Ensure the appropriateness of analysis.

## ACKNOWLEDGEMENTS

Thanks to Iris Gordon UGPD search co-ordinator for contributions to search methods and conduct of the searches. Dr Uri Fölsch German trial co-ordinator for providing additional data.

## REFERENCES

### References to studies included in this review

#### Fan 1993 *{published data only}*

Fan S, Lai E. C. S, Mok F. P. T, Lo C, Zheng S, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *The New England Journal of Medicine* 1993;**28**:228–232.

#### Fölsch 1997 *{published and unpublished data}*

Fölsch U. R, Nitsche R, Lüdtke R, Hilgers R. A, Creutzfeldt E. Early ERCP and Papillotomy compared with conservative treatment for acute biliary pancreatitis. *The New England Journal of Medicine* 1997; **23**(4):237–242.

#### Neoptolemos 1988 *{published data only}*

Neoptolemos J. P, Carr-Locke D. L, London N. J, Bailey I. A, James D, Dfossard D. P. Controlled Trial of Urgent Endoscopic Retrograde Cholangiopancreatography and Endoscopic Sphincterotomy versus Conservative Treatment for Acute Pancreatitis Due to Gallstones. *The Lancet* 1988;**October**:979–983.

### References to studies excluded from this review

#### Nowak 1995 *{published data only}*

Nowak A, Nowkowska-Dulawa E, Marek TA, Rybicka J. Final results of the prospective, randomised, controlled study on endoscopic sphincterotomy versus conventional management in acute biliary pancreatitis. *Gastroenterology* 1995;**108**:A380 (abstract).

#### Pezelli 1998 *{published data only}*

Pezelli R, Billi P, Barakat D, Barocini D, D'Inferio N, Miglio F. Effect of early ductal decompression in human biliary pancreatitis. *Pancreas* 1998;**16**(2):165–168.

### Additional references

#### Acosta 1974

Acosta JM, Ledesma CL. Gallstone migration as a cause of acute pancreatitis. *N Engl J Med* 1974;**290**:484–7.

#### Ayub 1999

Ayub K, Al-Mufti RA, Williamson RCN, Mathie RT. Increased nitric oxide activity in acute pancreatitis. *Hepato-Gastroenterology*. 1999; Vol. 46(suppl. II):1480(Abstract).

**Ayub 2001**

Ayub K, Serracino-Inglott F, Williamson RC, Mathie RT. Expression of inducible nitric oxide synthase contributes to the development of pancreatitis following pancreatic ischaemia and reperfusion. *Br J Surg* 2001;**88**(9):1189–93.

**Bhatia 2000**

Bhatia M, Brady M, Shokuhi S, Christmas S, Neoptolemos JP, Slavin J. Inflammatory mediators in acute pancreatitis. *Journal of Pathology* 2000;**190**(2):117–125.

**Bradley 1993**

Bradley EL. A clinically based classification system for acute pancreatitis. *Archives of Surgery* 1993;**128**:586–590.

**Frakes 1999**

Frakes J. T. Biliary Pancreatitis: A review. *Journal Clinical of Gastroenterology* 1999;**28**(2):97–109.

**Howard 1987**

Howard JM. Gallstone pancreatitis. In: Howard JM, Jordan GL, Reber HA editor(s). *Surgical diseases of the pancreas*. Philadelphia: Lea and Febiger, 1987:265–283.

**Kelly 1988**

Kelly TR, Wagener DS. Gallstone pancreatitis; a prospective randomised trial of the timing of surgery. *Surgery* 1988;**104**:424–428.

**Lowham 1999**

Lowham A, Lavelle J, Leese T. Mortality from Acute Pancreatitis. *International Journal of Pancreatology* 1999;**25**(2):103–106.

**McKay 1999**

McKay CJ, Evans S, Sinclair M, Carter CR, Imrie CW. High early mortality rate from acute pancreatitis in Scotland, 1984–1995. *British Journal of Surgery* 1999;**86**(10):1302–1305.

**Mergener 1999**

Mergener K, Baillie J. Endoscopic Treatment for Acute Biliary Pancreatitis. When and in Whom?. *Gastroenterology Clinics of North America* 1999;**28**(3):601–613.

**Miller 2003**

Miller FG. Sham surgery: an ethical analysis. *Am J Bioeth* 2003;**3**(4):41–8.

**Neoptolemos 1989**

Neoptolemos JP. The theory of 'persisting' common bile duct stones in severe gallstone pancreatitis. *Annals of the Royal College of Surgeons of England* 1989;**71**(5):326–31.

**Opie 1901**

Opie EL. The aetiology of acute haemorrhagic pancreatitis. *Bull Johns Hopkins Hosp* 1901;**12**:182–188.

**Paloyan 1975**

Paloyan D, Simonowitz D, Skinner DB. The timing of biliary tract operations in patients with pancreatitis associated with gallstones. *Surg Gynecol Obstet* 1975;**141**:737–9.

**Sharma 1999**

Sharma VK, Howden CW. Metaanalysis of randomized controlled trials of endoscopic retrograde cholangiography and endoscopic sphincterotomy for the treatment of acute biliary pancreatitis. *Am J Gastroenterol* 1999;**94**(11):3211–4.

**Stone 1981**

Stone HH, Fabian TC, Dunlop WE. Gallstone pancreatitis: Biliary tract pathology in relation to time of operation.. *Ann Surg* 1981;**194**:305–310.

**Toh 2000**

Toh S.K. C, Johnson C. D. A Prospective audit against national standards of the presentation and management of acute pancreatitis in the South of England. *Gut* 2000;**46**:239–243.

**Uomo 1998**

Uomo G, Slavin J. Endoscopic sphincterotomy for acute pancreatitis: arguments in favour. *Italian Journal of Gastroenterology and Hepatology* 1998;**30**(5):557–561.

**Vollmar 2003**

Vollmar B, Menger MD. Microcirculatory dysfunction in acute pancreatitis. A new concept of pathogenesis involving vasomotion-associated arteriolar constriction and dilation. *Pancreatology* 2003;**3**(3):181–90.

**Wilson 1988**

Wilson C, Imrie CW, Carter D. Fatal acute pancreatitis. *Gut* 1988;**29**:782–8.

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Fan 1993

Methods	Generation of allocation sequences: unclear. Study duration: September 1988 - December 1991. Blinding: patient - not stated, provider-not stated, assessor-not stated. Intent to treat: yes.	
Participants	Single centre (Hong Kong): 195 adults, Age range: 17-94 Sex: 80 males, 115 females. Included: suspected GAP stratified into mild and severe according to Ranson's criteria.	
Interventions	Randomization: ERCP+/-ES within 24 hours of admission (experimental arm) or conservative management including urgent ERCP if acute cholangitis developed (control arm).	
Outcomes	Primary: in-hospital mortality. Secondary: complications.	
Notes	Powered for 26 patients with severe disease in each group. Data for all patients from original report have been used.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

#### Fölsch 1997

Methods	Generation of allocation sequences: stratified block procedure. Study duration: November 1989 - February 1994. Blinding: patient-not stated, provider-not stated, assessor-no. Intent to treat: yes.	
Participants	22 centres (Germany): 238 adults, Age range: 15-93 Sex: 96 males, 142 females. Included: suspected GAP stratified into mild and severe according to modified Glasgow criteria. Excluded after randomization: 32 patients (16 each group) had incomplete data.	
Interventions	Randomization: ERCP+/-ES within 72 hours of admission (experimental arm) or conservative management including urgent ERCP if acute cholangitis developed (control arm).	
Outcomes	Primary: mortality within 3 months of admission. Secondary: complications.	

Fölsch 1997 (Continued)

Notes	Powered for 190 patients in each group. Stopped early because of increased mortality in the experimental group (second planned interim analysis). Original report does not show data for participants according to severity; further breakdown data have been provided by the trialists.
-------	---

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

**Neoptolemos 1988**

Methods	Generation of allocation sequences: unclear. Study duration: 1983 - 1987. Blinding: patient-not stated, provider-not stated, assessor-not stated. Intent to treat: no.
---------	---

Participants	Single centre (Leicester, UK): 121 adults, Age range: 20-96 Sex: 52 males, 69 females. Included: suspected GAP stratified according to modified Glasgow criteria. Excluded after randomization: 10 patients (6 experimental arm; 4 control arm) due to alternative diagnosis.
--------------	---

Interventions	Randomization: ERCP+/-ES within 72 hours of admission (experimental arm) or conservative management including withheld ERCP for initial 5 days of admission (control arm).
---------------	--

Outcomes	Primary: mortality. Secondary: complications.
----------	--

Notes	Powered for 26 patients with severe disease in each group. To minimize effect of withholding ERCP on participants with associated acute cholangitis data from original report for participants without acute cholangitis have been used.
-------	---

*Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

### Characteristics of excluded studies *[ordered by study ID]*

Nowak 1995	Allocation: randomized. Participants: patients undergoing duodenoscopy for suspected GAP and found to have normal papilla, not those presenting with GAP. Interventions: papillotomy (experimental group) versus no papillotomy (“conservative” Mx group).
Pezelli 1998	Allocation: not randomized, case-control study.

## DATA AND ANALYSES

### Comparison 1. Early ERCP+/-ES versus Conservative Mx

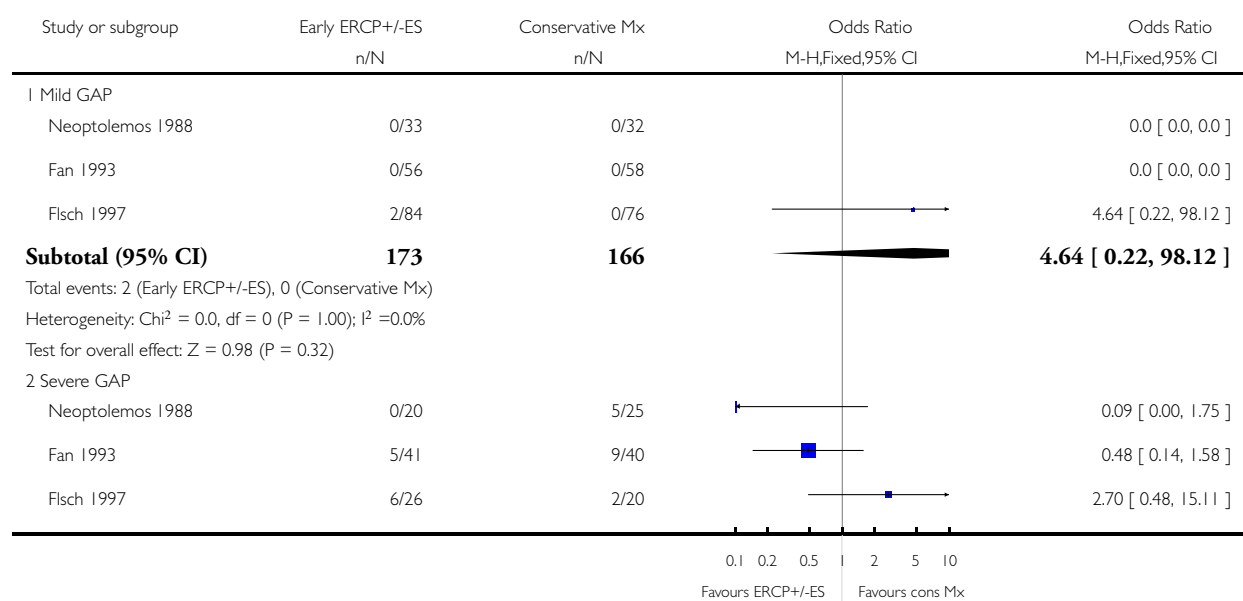
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality stratified by severity of GAP	3	511	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.62]
1.1 Mild GAP	3	339	Odds Ratio (M-H, Fixed, 95% CI)	4.64 [0.22, 98.12]
1.2 Severe GAP	3	172	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.27, 1.41]
2 Complications stratified by severity of GAP	3	511	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.38, 0.83]
2.1 Mild GAP	3	339	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.53, 1.49]
2.2 Severe GAP	3	172	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.14, 0.53]

#### Analysis 1.1. Comparison 1 Early ERCP+/-ES versus Conservative Mx, Outcome 1 Mortality stratified by severity of GAP.

Review: Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis

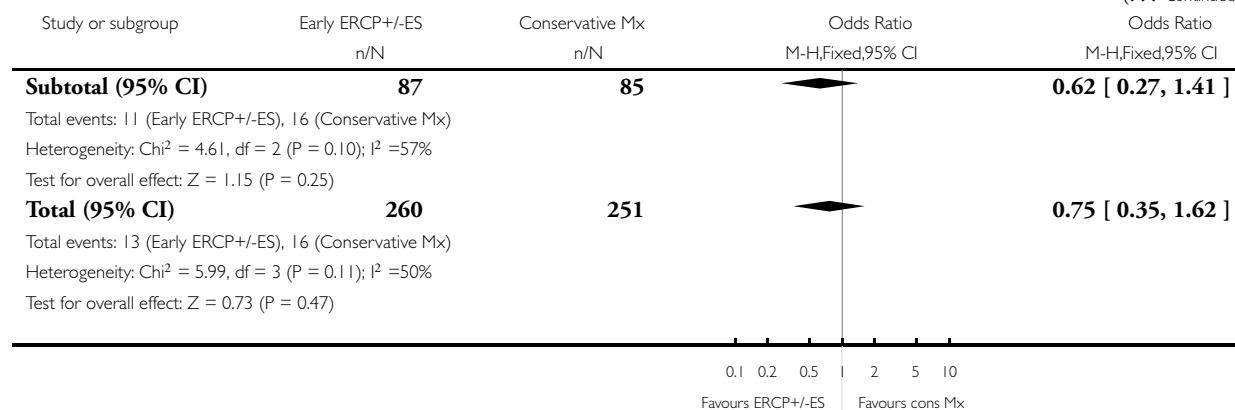
Comparison: 1 Early ERCP+/-ES versus Conservative Mx

Outcome: 1 Mortality stratified by severity of GAP



(Continued ...)

(... Continued)

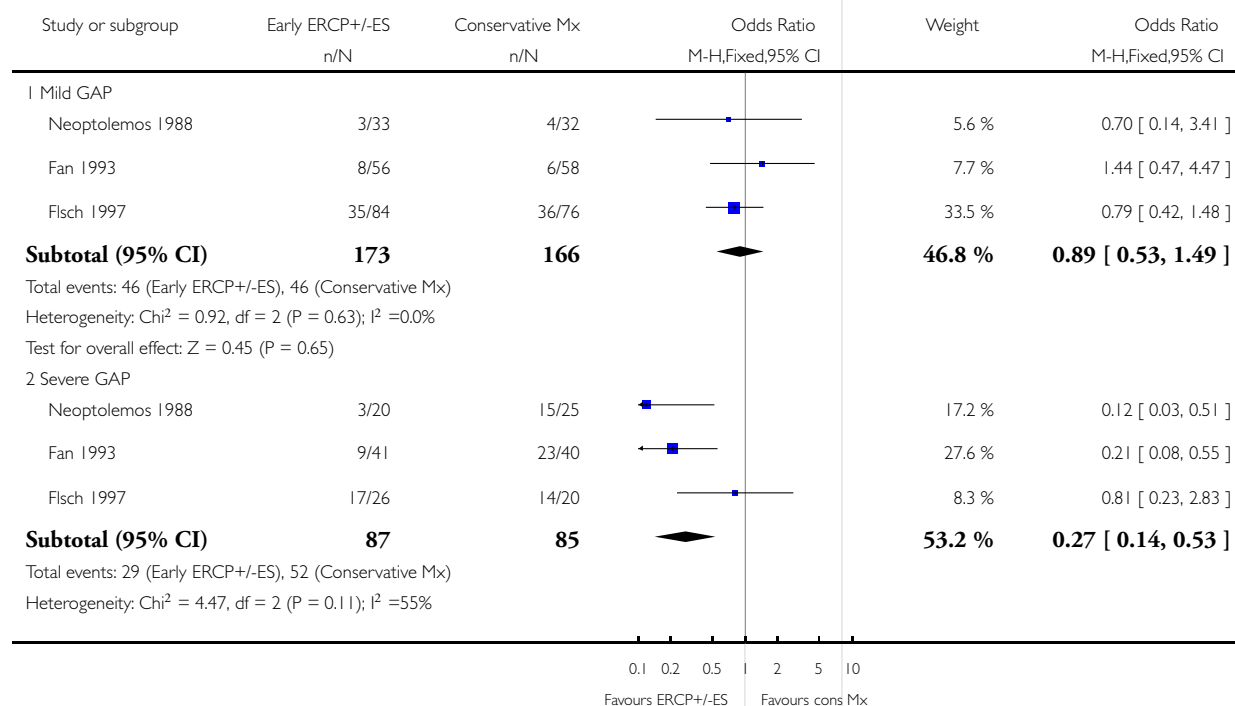


### Analysis 1.2. Comparison 1 Early ERCP+/-ES versus Conservative Mx, Outcome 2 Complications stratified by severity of GAP.

Review: Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis

Comparison: 1 Early ERCP+/-ES versus Conservative Mx

Outcome: 2 Complications stratified by severity of GAP



(Continued ...)

Study or subgroup	Early ERCP+/-ES	Conservative Mx	Odds Ratio M-H,Fixed,95% CI	Weight	(... Continued) Odds Ratio M-H,Fixed,95% CI
	n/N	n/N			
Test for overall effect: Z = 3.86 (P = 0.00011)					
<b>Total (95% CI)</b>	<b>260</b>	<b>251</b>	<b>◆</b>	<b>100.0 %</b>	<b>0.56 [ 0.38, 0.83 ]</b>
Total events: 75 (Early ERCP+/-ES), 98 (Conservative Mx)					
Heterogeneity: Chi <sup>2</sup> = 12.68, df = 5 (P = 0.03); I <sup>2</sup> = 61%					
Test for overall effect: Z = 2.86 (P = 0.0042)					
			0.1 0.2 0.5   2 5 10		
			Favours ERCP+/-ES	Favours cons Mx	

## WHAT'S NEW

Last assessed as up-to-date: 22 March 2004.

30 October 2008	Amended	Converted to new review format.
-----------------	---------	---------------------------------

## HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 4, 2004

## CONTRIBUTIONS OF AUTHORS

Protocol: RI, KA & JS - Manuscript; RI - Contact reviewer; RI, KA & JS - Post peer review editing; KA - Re-submission & comments for referees; All reviewers reviewed and approved the final version.

Review: KA & JS - Selection of studies; KA - Confounding control methodology; JS - Trialist liaison; KA - Data extraction; JS - Double data entry; RI - arbitration; KA - analyses & manuscript; JS & RI - Edit and comments; KA - Contact reviewer; KA - Revision & comments for referees; JS & RI review and approval peer referee's comments and final version.

## DECLARATIONS OF INTEREST

None known

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

\*Cholangiopancreatography, Endoscopic Retrograde; \*Sphincterotomy, Endoscopic; Acute Disease; Gallstones [complications; \*surgery]; Pancreatitis [etiology; mortality; \*surgery]; Randomized Controlled Trials as Topic

### **MeSH check words**

Humans