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Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis (Protocol)

Tse F, Yuan Y

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[Intervention Protocol]

Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis

Frances Tse[1], Yuhong Yuan[1]

[1]Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Canada

Contact address: Frances Tse, Department of Medicine, Division of Gastroenterology, McMaster University, 1200 Main Street West, 2F53, Hamilton, Ontario, L8N 3Z5, Canada. tsef@mcmaster.ca.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The project aims to assess the clinical effectiveness of early routine ERCP in acute gallstone pancreatitis by systematic review and meta-analysis of randomized controlled trials (RCTs).

The objectives of this review are two-fold:

1. to assess whether early routine ERCP shows any overall benefit in reducing adverse clinical outcomes including mortality, and local and systemic complications in unselected patients with acute gallstone pancreatitis by systematically reviewing all studies in which the strategy of early routine ERCP has been directly compared with the strategy of early conservative management with or without delayed or selective use of ERCP;
2. to identify any subgroups of patients that may benefit from early routine ERCP.

BACKGROUND

Description of the condition

Gallstone disease is the most common cause of acute pancreatitis in many Western and Asian countries, accounting for approximately 35% to 60% of cases (Frey 2001; Huang 2009; Imamura 2004; Thomson 1987; Toh 2000). While most cases are self limiting with a benign course, approximately 25% of patients develop severe pancreatitis associated with multi-organ failure, local complications of the pancreas (necrosis, abscess, or pseudocyst), or both (Bradley 1993; Kelly 1988). The mortality is approximately 4% to 7% for all cases, and 20% to 30% for severe cases (Bank 2002; Banks 2006; Pitchumoni 2005). About half of the deaths occur within the first two weeks and are mainly attributable to multi-organ failure; deaths after this interval are generally caused by complications associated with necrotizing pancreatitis (Johnson 2004; Mutinga 2000).

Acute gallstone pancreatitis is thought to be caused by transient obstruction of the ampulla (pancreatic and bile ducts) during passage of gallstones, which causes reflux of bile and duodenal content into the pancreatic duct, increased pressure in the pancreatic duct, or both (Acosta 1980). This in turn leads to unregulated activation of pancreatic enzymes and pancreatic auto-digestion (Acosta 1974; Wang 2009). Many theories (common channel theory, duodenal reflux theory, pancreatic duct obstruction theory) have been proposed about the pathogenesis of acute gallstone pancreatitis, but the exact mechanism by which passage of gallstones induces pancreatitis remains unknown (Acosta 1980; Wang 2009).

In clinical practice, as recommended by current guidelines (Banks 2006; Forsmark 2007; UK guidelines 2005), acute pancreatitis is diagnosed by the presence of two of the following three features:

1. abdominal pain typical of acute pancreatitis;
2. greater than or equal to three-fold elevation in amylase or lipase; and
3. computed tomography (CT) evidence of pancreatitis.

However, the diagnosis of gallstone as a cause of acute pancreatitis is not always straightforward. Currently, no consensus exists regarding the diagnostic criteria in predicting a biliary origin of acute pancreatitis. Gallstone can be suspected as a cause of acute pancreatitis when there are elevations of liver function tests and visualization of gallstones on imaging studies, in the absence of other etiology such as alcohol (Banks 2006). A meta-analysis found that a greater than or equal to three-fold elevation of serum alanine aminotransferase (ALT) in the presence of acute pancreatitis has a positive predictive value of 95% in diagnosing a biliary cause of acute pancreatitis (Tenner 1994). However, 15% to 20% of patients with gallstone pancreatitis present with normal liver function tests (Dholakia 2004). Therefore, a biliary etiology cannot be excluded solely on the basis of normal liver function tests. This is complicated by the relatively low sensitivity (67% to 87%) of ultrasound in detecting gallbladder stones in the setting of acute pancreatitis due to ileus and bowel distension (Neoptolemos 1984a; Neoptolemos 1984b). For the detection of common bile duct (CBD) stones and biliary tract dilatation, the sensitivity of ultrasound is even lower (27% to 50%) (Chak 1999; Makary 2005; Sugiyama 1998). Nevertheless, the combination of elevated liver function tests and gallbladder stones on ultrasound yields a sensitivity of 95% to 98% and specificity of 100% in the diagnosis of acute gallstone pancreatitis (Ammori 2003; Wang 1988).

Description of the intervention

Conservative medical management of acute gallstone pancreatitis

In brief, medical management of acute gallstone pancreatitis as outlined in current guidelines includes general supportive care, consisting of fluid resuscitation, supplemental oxygen as required, correction of electrolyte and metabolic abnormalities, pain control, and nutritional support (AGA statement 2007; Banks 2006; UK guidelines 2005). The notion that fluid resuscitation supports pancreatic microcirculation and prevents necrotizing pancreatitis was inferred from experimental studies and observational data suggesting that patients who received inadequate fluid replacement (as evident by a rise in hematocrit at 24 hours) were more likely to develop necrotizing pancreatitis. Clinical guidelines recognize the importance of fluid resuscitation in acute pancreatitis, but they do not provide explicit guidance on the exact amounts and rates due to insufficient evidence. Nutritional support is not required in mild pancreatitis as oral intake is usually restored within a few days. In severe pancreatitis, current guidelines recommend early enteral (within the first three to four days of illness) rather than parenteral feeding. In a recent Cochrane review, enteral nutrition was found to significantly reduce mortality, multi-organ failure, systemic infections, and the need for operative interventions compared to parenteral nutrition in patients with predicted severe acute pancreatitis (Al-Omran 2010). With respect to the use of prophylactic antibiotics against infection of pancreatic necrosis, there remains no consensus among guidelines (AGA statement 2007; Banks 2006; UK guidelines 2005). A Cochrane review suggested that patients who received prophylactic antibiotics had a lower risk of death, but no difference in the rates of infected pancreatic necrosis or surgery (Villatoro 2006). In spite of the overall lower death rate observed in the meta-analysis, the prophylactic use of antibiotics in acute pancreatitis remains controversial due to the lack of data on adverse effects and the concern of resistant bacterial or fungal infections.

Endoscopic retrograde cholangiopancreatography (ERCP)

For many years, open cholecystectomy with choledochotomy or sphincteroplasty and clearing of the bile duct were the gold standard to treat both symptomatic gallbladder stones and CBD stones (Beal 1984). Over the past decade, laparoscopic cholecystectomy with intraoperative cholangiography (with or without laparoscopic exploration of the CBD) has largely replaced open cholecystectomy in the treatment of gallbladder stones and CBD stones (Williams 2008). However, laparoscopic exploration of the CBD is technically difficult and requires both experience and facilities which are only available in advanced laparoscopic centers.

Endoscopic retrograde cholangiopancreatography (ERCP) was introduced in the 1970s and rapidly evolved into a diagnostic and therapeutic technique for CBD stones (Classen 1973; Classen 1974). This technique involves passage of a side-viewing endoscope into the duodenum and cannulation of the CBD with a device (sphincterotome or catheter). Contrast can then be injected in a retrograde manner into the biliary tree. If a CBD stone is identified on fluoroscopy, a sphincterotomy (a small incision in the ampulla) can be performed to facilitate extraction of the stone. ERCP has now become a standard treatment option for patients with CBD stones,

with a success rate of over 85% to 90%. However, large prospective series have found overall complication rates of 5% to 10% and mortality rates of 0.02% to 0.5% after ERCP (Freeman 1996). The most common complication is post-ERCP pancreatitis. Despite the concern of aggravation of pancreatitis, prospective studies have found ERCP to be safe in the setting of acute gallstone pancreatitis (Neoptolemos 1986; Neoptolemos 1989).

How the intervention might work

Early routine ERCP strategy

If acute gallstone pancreatitis is triggered by duct obstruction caused by a stone, it would be reasonable to suggest that early ERCP with removal of any residual stones might reduce the severity of pancreatitis. The strategy of early ERCP is strongly supported by results from experimental studies and human studies, which show that the duration of biliary obstruction is a major factor in determining the severity of pancreatitis and that decompression of the biliary system can prevent progression of the disease (Acosta 1997; Hirano 1993; Runzi 1995a; Runzi 1995b; Senninger 1986). In addition, patients with severe pancreatitis tended to have stones impacted in the ampulla, and early (within 48 hours) surgical decompression of the obstruction has been shown to decrease mortality rates from 16% to 2% in a retrospective case-control study (Acosta 1978). These observations lend support to the theory of using early ERCP to remove obstructing stones in acute gallstone pancreatitis.

Early conservative management with or without delayed or selective use of ERCP strategy

Proponents of early conservative management with delayed or selective use of ERCP argue that early routine ERCP may lead to many unnecessary ERCPs in the majority of patients as the offending gallstone has often passed before the diagnosis of pancreatitis is made. Also, it remains unclear whether early ERCP improves the prognosis of acute gallstone pancreatitis. The severity of the pancreatitis may be determined at its inception and may not be dependent on the duration of duct obstruction. Furthermore, performing ERCP in the setting of acute pancreatitis can be technically difficult because of swollen ampulla and duodenal wall. Thus, it may be prudent to identify patients with persistent duct obstruction who would benefit from ERCP after a period of conservative medical management in order to avoid unnecessary negative ERCPs.

Numerous studies have tried to define predictive criteria for persistent CBD stones in patients with acute gallstone pancreatitis (Chan 2008; Chang 1998; Cohen 2001; van Santvoort 2011). Rising liver function tests and persistent dilatation of the common bile duct, in particular, were found to be highly predictive of persistent CBD stones in the setting of acute gallstone pancreatitis (Chang 1998; Chang 2000; Cohen 2001). Nevertheless, even with the application of these clinical predictors, only 37% to 42% of patients undergoing ERCP were found to have CBD stones (Chang 1998; Chang 2000; Cohen 2001). Therefore, other non-invasive (or minimally invasive) imaging techniques, such as endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP), have been used to select patients for therapeutic ERCP to minimize the risk of complications associated with unnecessary diagnostic ERCPs. Both EUS and MRCP have been confirmed in meta-analyses to be highly accurate for the diagnosis of CBD stones (Romagnuolo 2003; Tse 2008). However, MRCP can miss small CBD stones (less than 5 mm). Moreover, EUS and MRCP are highly operator-dependent techniques and may not be available in many centers. Despite the fact that most stones pass spontaneously, establishing a biliary etiology is extremely important because there is a high risk of recurrent pancreatitis (33% to 60%) if the gallstone disease is not treated (Frei 1986; Mayer 1984; Paloyan 1975).

Why it is important to do this review

The role and timing of ERCP in acute gallstone pancreatitis remains controversial. A number of clinical trials and meta-analyses have provided conflicting results (Moretti 2008; Petrov 2008a; Petrov 2008b; Sharma 1999; Uy 2009). Although current clinical guidelines differ in their recommendations, there is general consensus that: (1) early ERCP is not indicated in patients with mild gallstone pancreatitis and (2) concomitant cholangitis or biliary obstruction is an indication for urgent ERCP. However, the early use of ERCP in the setting of severe gallstone pancreatitis without cholangitis or biliary obstruction continues to be an issue of debate. The American College of Gastroenterology guidelines suggest urgent ERCP (preferably within 24 hours) for those with severe gallstone pancreatitis complicated by organ failure (Banks 2006). The UK practice guidelines advocate early ERCP (within 72 hours) in all patients with predicted or actual severe acute gallstone pancreatitis (UK guidelines 2005). However, the American Gastroenterology Association Guidelines found insufficient evidence to support this aggressive approach (AGA statement 2007). Compliance with these guidelines with respect to the indications for and timing of ERCP is highly variable (Aly 2002; Barnard 2002; Foitzik 2007; Lankisch 2005; Pezzilli 2007). In an audit of adherence to the UK guidelines, early ERCP was performed in only 48% of patients with severe gallstone pancreatitis (Barnard 2002). These results might be explained by lack of confidence in the validity of the guidelines or conflict with individual practitioners' values and beliefs. Nevertheless, this poor compliance did not appear to result in increased mortality (Barnard 2002).

Acute gallstone pancreatitis is a common clinical problem and carries significant morbidity and mortality. We conducted this systematic review to evaluate the relative merits of these two different management strategies. The findings of this review are relevant to patients, physicians and to healthcare systems.

OBJECTIVES

The project aims to assess the clinical effectiveness of early routine ERCP in acute gallstone pancreatitis by systematic review and meta-analysis of randomized controlled trials (RCTs).

The objectives of this review are two-fold:

1. to assess whether early routine ERCP shows any overall benefit in reducing adverse clinical outcomes including mortality, and local and systemic complications in unselected patients with acute gallstone pancreatitis by systematically reviewing all studies in which the strategy of early routine ERCP has been directly compared with the strategy of early conservative management with or without delayed or selective use of ERCP;
2. to identify any subgroups of patients that may benefit from early routine ERCP.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs comparing early routine ERCP versus early conservative management with or without delayed or selective use of ERCP strategies in patients with suspected acute gallstone pancreatitis. At least one of the following outcomes had to be reported: mortality and/or local and/or systemic complications of pancreatitis. Trials that permitted other concomitant therapies are eligible, as long as they were administered to both the intervention and control arms. We will not include trials that employed non-random methods of allocation such as judgment of the clinician or preference of the participant, results of a laboratory test or series of tests, or availability of the intervention, as the allocation was not truly random. We will consider published and unpublished studies, full articles, and abstracts for inclusion in this review.

Types of participants

Trials are eligible for inclusion in the review if they recruited men and women aged at least 18 years presenting to the hospital with acute pancreatitis suspected to be biliary in origin on the basis of a combination of clinical features, biochemical tests, and imaging studies. The patients are required to have had:

1. symptoms consistent with acute pancreatitis (upper abdominal pain);
2. elevation of serum amylase or lipase levels;
3. findings of gallstones on imaging studies or elevation of abnormal liver function tests;
4. no other causes of pancreatitis including alcoholism, hypercalcemia, hyperlipidemia, and post-ERCP pancreatitis.

We will include studies in which the population with acute gallstone pancreatitis was a subgroup within a larger group of patients. However, studies needed to report mortality (primary outcome) and/or local and/or systemic complications related to pancreatitis (secondary outcomes) in the acute gallstone pancreatitis cohort to be eligible for inclusion in the review.

We will include studies involving only a selected subgroup of patients with acute gallstone pancreatitis (mild or severe pancreatitis) only in subgroup analyses. We will not include their results in the main analyses as the primary objective of the main analyses is to determine if early routine ERCP compared to early conservative management with or without delayed or selective use of ERCP strategies had any benefit in an unselected group of patients with suspected acute gallstone pancreatitis.

Types of interventions

Early routine ERCP strategy

Routine ERCP with or without endoscopic sphincterotomy (ES) in all patients with acute gallstone pancreatitis within 72 hours of admission. This will be combined with conservative medical management. Although early ERCP in our review is defined as within 72 hours, we accept that the duration of conservative management prior to early routine ERCP (time to ERCP) may be variable between studies. We will explore the differences in timing of ERCP in subgroup analysis.

Early conservative management with or without delayed or selective use of ERCP strategy

Initial conservative management may include replacement of fluid, monitoring of hemodynamic status, nutritional support, and pharmacological treatment with antibiotics. This may be followed by delayed or selective use of ERCP with or without ES as indicated based on symptoms or signs suggestive of cholangitis or persistent biliary obstruction or positive findings of CBD stones or persistent biliary obstruction on non-invasive (or minimally invasive) tests such as ultrasound, CT, MRCP, or EUS. We accept that the duration of conservative management prior to consideration of delayed or selective use of ERCP (time to ERCP) may be highly variable between studies.

Concomitant therapies will be permitted, as long as they were administered to both the intervention and the control arms.

Types of outcome measures

Primary outcomes

The primary outcome measure in this review will be all-cause mortality, defined as any death occurring during hospitalization for acute gallstone pancreatitis.

Secondary outcomes

The secondary outcome measures are as follows:

1. Complications related to pancreatitis as defined by the Atlanta Classification (Bradley 1993)
   a. Local complications (necrosis, abscess, pseudocyst)
   b. Systemic complications (organ failure including shock, pulmonary insufficiency, renal failure, and gastrointestinal bleeding; disseminated intravascular coagulation or severe metabolic disturbances)
2. Complications related to pancreatitis as defined by authors:
   a. Local pancreatic complications (excluding biliary complications such as cholecystitis or cholangitis)
   b. Systemic complications (excluding death)
3. ERCP-related complications:
   a. Bleeding
   b. Perforation
   c. Post-ERCP cholangitis
   d. Post-ERCP pancreatitis defined as a rise in amylase or lipase level compared to pre-ERCP level and worsening of abdominal pain

Complications based on the Atlanta Classification are determined as the most important secondary outcomes because studies have used variable definitions for complications. The outcomes as defined by the Atlanta Classification would serve to standardize the definitions for complications and allow comparability between trials.

Search methods for identification of studies

We constructed the search strategies by using a combination of subject headings and text words relating to the use of ERCPs for the treatment of acute pancreatitis. We will apply the standard Cochrane search strategy filter for identifying RCTs to all searches.

Electronic searches

We will conduct a comprehensive literature search to identify all published and unpublished randomized controlled trials with no language restriction. We will search the following electronic databases to identify potential studies:

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*) (Appendix 1);
- MEDLINE 1966 to January 2012 (Appendix 2);
- EMBASE 1980 to January 2012 (Appendix 3); and
- LILACS 1982 to January 2012 (Appendix 4).

Searching other resources

Two review authors (YY, FT) will handsearch the published abstracts from the conference proceedings in Digestive Disease Week (published in *Gastroenterology* and *Gastrointestinal Endoscopy*) and United European Gastroenterology Week (published in *Gut*) in the previous five years from 2007 to 2011. We will handsearch references cited in studies found by the above search to identify further relevant trials.

Data collection and analysis

Selection of studies

Two review authors (YY, FT) will independently screen titles and trial abstracts that are identified by the updated search strategy for potential inclusion in the review using pre-defined inclusion criteria and exclusion criteria. We will resolve differences by discussion and consensus. The same two authors (YY, FT) will retrieve and review the complete report of all selected articles. We will contact the authors of trial reports if they were published only as abstracts. In case of duplicate publications, we will retain only the most comprehensive report.

Data extraction and management

Two independent review authors (YY, FT) will record the following study and patient characteristics:

- setting (single or multi-centre);
- country of origin;
- enrolment period (years of study);
- year of publication, format (abstract or journal article);
- study design;
- inclusion and exclusion criteria used;
- criteria for diagnosing gallstone-associated pancreatitis;
- scoring systems used to predict severity of pancreatitis;
- endoscopists (number);
- number of patients assigned per intervention (total, predicted mild acute or severe pancreatitis based on scoring systems used to predict severity of pancreatitis);
- patient demographics and characteristics including gender, mean age, co-morbidities;
- definition and number of patients with cholangitis;
- definition and number of patients with biliary obstruction;
- conservative management strategy (indications for ERCP, use of non-invasive images to select patients for ERCP);
- number of patients receiving ERCP in the conservative management strategy;
- timing of ERCP in each group;
- number of ERCPs performed in each group;
- endoscopic interventions performed (sphincterotomy, biliary stent placement, nasobiliary-drainage catheter) in each group;
- cannulation success, stone extraction success in each group;
- complications of ERCP (post sphincterotomy bleeding, perforation, cholangitis, death) in each group;
- concomitant treatment (antibiotics, octreotide, somatostatin, others);
- surgery (same admission or post discharge);
- number of patients confirmed to have CBD stones in each group (total, predicted mild, or severe pancreatitis)
- outcomes (mortality, local complications, systemic complications, cholangitis);
- criteria used to classify severity of pancreatitis;
- drop outs or loss to follow-up; and
- study quality (generation of allocation sequence, allocation concealment, blinding, incomplete outcome data, selective reporting, other bias).

We will summarize studies and, if appropriate, undertake meta-analysis.

Assessment of risk of bias in included studies

Two review authors (YY, FT) will independently assess the methodological quality of the included studies based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess each included study regarding sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. We will resolve disagreement by discussion and consensus. We will contact the original authors for further clarification as necessary.

Random sequence generation

- Low risk, if the allocation sequence was generated by a computer or a random number table. We considered drawing of lots, tossing of a coin, shuffling of cards, or throwing dice as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomized, but the method used for generation of the allocation sequence was not described.
- High risk, if a system involving dates, names, or hospital record numbers was used for the allocation of patients.

Allocation concealment

- Low risk, if the allocation of patients involved central allocation or sequentially numbered, opaque, sealed envelopes.
- Unclear, if there is insufficient information to permit judgment of 'low risk' or 'high risk'.
- High risk, if the allocation was based on using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards, alternation, or rotation; date of birth; case record number; or any other explicitly unconcealed procedure.

Blinding of participants, personnel, outcome assessment (mortality)

- Low risk, if blinding of participants is not possible due to the nature of the interventions evaluated. Blinding of personnel and outcome assessment is possible. However, knowledge of the assigned intervention is unlikely to impact on mortality.

Blinding of participants, personnel, outcome assessment (complications related to pancreatitis)

- Low risk, blinding of participants is not possible due to the nature of the interventions evaluated. Blinding of personnel and outcome assessment is possible. However, knowledge of the assigned intervention is unlikely to impact on complications related to pancreatitis.

Incomplete outcome data

- Low risk, if no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome; missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; missing data have been imputed using appropriate methods.
- Unclear, if insufficient reporting of attrition/exclusions to permit judgment of 'low risk' or 'high risk' (e.g. number randomized not stated, no reasons for missing data provided).
- High risk, if reasons for missing outcome data are likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; the proportion of missing outcomes compared with observed event risk is enough to induce clinically relevant bias in intervention effect estimate; per-protocol analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.

Selective reporting

- Low risk, if the published reports include all expected outcomes, including those that were pre-specified.
- Unclear, if insufficient information to permit judgment of 'low risk' or 'high risk'.
- High risk, if not all of the study's pre-specified primary outcomes have been reported; if one or more primary outcomes is reported using measurements, analysis methods or subsets of the data that were not pre-specified; one or more reported primary outcomes were not pre-specified; one or more outcomes of interest were reported incompletely; or the study report failed to include results for a key outcome that would be expected to have been reported for such a study.

Measures of treatment effect

Primary outcome

The primary outcome is mortality rate, defined as death during the hospitalization for acute gallstone pancreatitis. We expect dichotomous data for mortality and we will express this as risk ratio (RR) with 95% confidence intervals (CI). We will define RR as the risk of death in early routine ERCP strategy compared to early conservative management strategy with or without delayed or selective use of ERCP.

Secondary outcomes

We will express dichotomous outcomes of complications related to pancreatitis (as defined by the Atlanta Classification and by authors) as RR with 95% CI. RRs are defined as the risks of complications related to pancreatitis (or ERCP) in early routine ERCP strategy compared to early conservative management strategy with delayed or selective use of ERCP.

Unit of analysis issues

There are no issues relating to unit of analysis. All included studies are likely to be parallel-group trials.

Dealing with missing data

We will contact authors for any data missing from included studies. We will perform analyses on an intention-to-treat basis.

Assessment of heterogeneity

We will assess heterogeneity using the Chi^2 test ($P < 0.10$ = significant heterogeneity) and I^2 statistic (> 50% = substantial heterogeneity) using a random-effects model along with visual inspection of forest plots. When significant heterogeneity is found, we will investigate possible explanations by subgroup analyses and sensitivity analyses to test the robustness of the overall results. The potential sources of heterogeneity hypothesized a priori will be the following.

1. Cholangitis (inclusion versus exclusion of these patients at study level)
2. Biliary obstruction (inclusion versus exclusion of these patients at study level) as evident by clinical (jaundice), biochemical (abnormal LFTs), and imaging findings of biliary obstruction (dilated biliary tree)
3. Predicted severity of acute pancreatitis based on clinical scoring systems such as Ranson criteria, Glasgow-Imrie score, Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS), Medical Research Council Sepsis Score (MRC Sepsis Score), Multiple Organ System Score (MOSS) at patient level (mild versus severe)
4. Time to ERCP in early routine ERCP group (≤ 24 hours versus 24 to 72 hours)
5. Use of delayed or selective ERCP in conservative management group (yes versus no)
6. Risk of bias (high versus low and unclear)

Assessment of reporting biases

This review was designed to include published and unpublished studies with no language restriction. We will assess publication bias visually by examining the relationship between the treatment effects and the standard error of the estimate using a funnel plot.

Data synthesis

We will conduct a meta-analysis for the comparison of early routine ERCP (within 72 hours of admission) strategy compared with early conservative management with or without delayed or selective use of ERCP strategy for acute gallstone pancreatitis. We will perform meta-analysis only if two or more trials with similar comparisons

and outcome measures are found. Where appropriate, we will combine data using random-effects modeling (the Mantel-Haenszel method) to determine a summary estimate of the risk ratio (RR) and the 95% confidence interval (CI). We will calculate the RR of the incidence of mortality as the primary outcome. We will calculate the RRs of other dichotomous secondary outcomes including complications related to pancreatitis (as defined by the Atlanta criteria and by studies). We will include data from all studies to calculate the RRs of the secondary outcomes of ERCP related complications (bleeding, perforation, post-ERCP cholangitis, post-ERCP pancreatitis). We will use the Cochrane Review Manager 5 software (RevMan 2011) to carry out the analysis based on the intention-to-treat principle. We will present results in forest plots, using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses a priori for the outcome of **mortality** in the following categories.

1. Cholangitis (inclusion versus exclusion at study level)
2. Biliary obstruction (inclusion versus exclusion at study level) as evident by clinical (jaundice), biochemical (abnormal liver function tests), and imaging findings of biliary obstruction (dilated biliary tree)
3. Predicted severity of acute pancreatitis based on clinical scoring systems such as Ranson criteria, Glasgow-Imrie score, Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS), Medical Research Council Sepsis Score (MRC Sepsis Score), Multiple Organ System Score (MOSS) at patient level (mild versus severe)
4. Time to ERCP in early routine ERCP group (≤ 24 hours versus 24 to 72 hours)
5. Use of delayed or selective ERCP in conservative management group (Yes versus No)
6. Risk of bias (high versus low and unclear)

We will perform the following subgroup analyses for **local and systemic complications related to pancreatitis as defined by the Atlanta Criteria**:

1. Cholangitis (inclusion versus exclusion at study level)
2. Biliary obstruction (inclusion versus exclusion at study level) as evident by clinical (jaundice), biochemical (abnormal LFTs), and imaging findings of biliary obstruction (dilated biliary tree)
3. Predicted severity of acute pancreatitis based on clinical scoring systems such as Ranson criteria, Glasgow-Imrie score, Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score (SAPS), Medical Research Council Sepsis Score (MRC Sepsis Score), Multiple Organ System Score (MOSS) at patient level (mild versus severe)

We will perform tests for subgroup differences based on the fixed-effect inverse-variance method (implemented in RevMan 2011) for the above outcomes with $P < 0.05$ considered statistically significant.

Sensitivity analysis

1. Summary statistic (risk ratio versus odds ratio)
2. Meta-analysis modeling (fixed versus random-effects)
3. Per-protocol analysis (for the primary outcome of mortality in the main analysis)

In addition, an influence analysis will be performed by the exclusion of each study.

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REFERENCES

Additional references

Acosta 1974

Acosta JM, Ledesma CL. Gallstone migration as a cause of acute pancreatitis. *New England Journal of Medicine* 1974;**290**(9):484-7.

Acosta 1978

Acosta JM, Rossi R, Galli OM, Pellegrini CA, Skinner DB. Early surgery for acute gallstone pancreatitis: evaluation of a systematic approach. *Surgery* 1978;**83**(4):367-70.

Acosta 1980

Acosta JM, Pellegrini CA, Skinner DB. Etiology and pathogenesis of acute biliary pancreatitis. *Surgery* 1980;**88**(1):118-25.

Acosta 1997

Acosta JM, Rubio Galli OM, Rossi R, Chinellato AV, Pellegrini CA. Effect of duration of ampullary gallstone obstruction on severity of lesions of acute pancreatitis. *Journal of the American College of Surgeons* 1997;**184**(5):499-505.

AGA statement 2007

American Gastroenterological Association (AGA) Institute on "Management of Acute Pancreatitis" Clinical Practice and Economics Committee, AGA Institute Governing Board. AGA Institute medical position statement on acute pancreatitis. *Gastroenterology* 2007;**132**(5):2019-21.

Al-Omran 2010

Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD002837.pub2]

Aly 2002

Aly EA, Milne R, Johnson CD. Non-compliance with national guidelines in the management of acute pancreatitis in the United Kingdom. *Digestive Surgery* 2002;**19**(3):192-8.

Ammori 2003

Ammori BJ, Boreham B, Lewis P, Roberts SA. The biochemical detection of biliary etiology of acute pancreatitis on admission: a revisit in the modern era of biliary imaging. *Pancreas* 2003;**26**(2):e32-5.

Bank 2002

Bank S, Singh P, Pooran N, Stark B. Evaluation of factors that have reduced mortality from acute pancreatitis over the past 20 years. *Journal of Clinical Gastroenterology* 2002;**35**(1):50-60.

Banks 2006

Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *American Journal of Gastroenterology* 2006;**101**(10):2379-400.

Barnard 2002

Barnard J, Siriwardena AK. Variations in implementation of current national guidelines for the treatment of acute pancreatitis: implications for acute surgical service provision. *Annals of the Royal College of Surgeons of England* 2002;**84**(2):79-81.

Beal 1984

Beal JM. Historical perspective of gallstone disease. *Surgery, Gynecology and Obstetrics* 1984;**158**(2):181-9.

Bradley 1993

Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Archives of Surgery* 1993;**128**(5):586-90.

Chak 1999

Chak A, Hawes RH, Cooper GS, Hoffman B, Catalano MF, Wong RC. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. *Gastrointestinal Endoscopy* 1999;**49**(5):599-604.

Chan 2008

Chan T, Yaghoubian A, Rosing D, Lee E, Lewis RJ, Stabile BE, et al. Total bilirubin is a useful predictor of persisting common bile duct stone in gallstone pancreatitis. *American Surgeon* 2008;**74**(10):977-80.

Chang 1998

Chang L, Lo SK, Stabile BE, Lewis RJ, de Virgilio C. Gallstone pancreatitis: a prospective study on the incidence of cholangitis and clinical predictors of retained common bile duct stones. *American Journal of Gastroenterology* 1998;**93**(4):527-31.

Chang 2000

Chang L, Lo S, Stabile BE, Lewis RJ, Toosie K, de Virgilio C. Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate gallstone pancreatitis: a prospective randomized trial. *Annals of Surgery* 2000;**231**(1):82-7.

Classen 1973

Classen M, Demling L. Retrograde cholangiography in obstructive jaundice [Retrograde cholangiographie beim verschlussikterus]. *Radiologe* 1973;**13**(1):35-40.

Classen 1974

Classen M, Demling L. Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct [Endoskopische sphinkterotomie der papilla vateri und steinextraktion aus dem ductus choledochus]. *Deutsche Medizinische Wochenschrift* 1974;**99**(11):496-7.

Cohen 2001

Cohen ME, Slezak L, Wells CK, Andersen DK, Topazian M. Prediction of bile duct stones and complications in gallstone pancreatitis using early laboratory trends. *American Journal of Gastroenterology* 2001;**96**(12):3305-11.

Dholakia 2004

Dholakia K, Pitchumoni CS, Agarwal N. How often are liver function tests normal in acute biliary pancreatitis?. *Journal of Clinical Gastroenterology* 2004;**38**(1):81-3.

Foitzik 2007

Foitzik T, Klar E. (Non-)compliance with guidelines for the management of severe acute pancreatitis among German surgeons. *Pancreatology* 2007;**7**(1):80-5.

Forsmark 2007

Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology* 2007;**132**(5):2022-44.

Freeman 1996

Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. *New England Journal of Medicine* 1996;**335**(13):909-18.

Frei 1986

Frei GJ, Frei VT, Thirlby RC, McClelland RN. Biliary pancreatitis: clinical presentation and surgical management. *American Journal of Surgery* 1986;**151**(1):170-5.

Frey 2001

Frey CF, Zhou H, Harvey DJ, White RH. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994-2001. *Pancreas* 2006;**33**(4):336-44.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hirano 1993

Hirano T, Manabe T. A possible mechanism for gallstone pancreatitis: repeated short-term pancreaticobiliary duct obstruction with exocrine stimulation in rats. *Proceedings of the Society for Experimental Biology and Medicine* 1993;**202**(2):246-52.

Huang 2009

Huang J, Chang CH, Wang JL, Kuo HK, Lin JW, Shau WY, et al. Nationwide epidemiological study of severe gallstone disease in Taiwan. *BMC Gastroenterology* 2009;**9**:63.

Imamura 2004

Imamura M. Epidemiology of acute pancreatitis--incidence by etiology, relapse rate, cause of death and long-term prognosis. *Nihon Rinsho* 2004;**62**(11):1993-7.

Johnson 2004

Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. *Gut* 2004;**53**(9):1340-4.

Kelly 1988

Kelly TR, Wagener DS. Gallstone pancreatitis: a prospective randomized trial of the timing of surgery. *Surgery* 1988;**104**(4):600-5.

Lankisch 2005

Lankisch PG, Weber-Dany B, Lerch MM. Clinical perspectives in pancreatology: compliance with acute pancreatitis guidelines in Germany. *Pancreatology* 2005;**5**(6):591-3.

Makary 2005

Makary MA, Duncan MD, Harmon JW, Freeswick PD, Bender JS, Bohlman M. The role of magnetic resonance cholangiography in the management of patients with gallstone pancreatitis. *Annals of Surgery* 2005;**241**(1):119-24.

Mayer 1984

Mayer AD, McMahon MJ, Benson EA, Axon AT. Operations upon the biliary tract in patients with acute pancreatitis: aims, indications and timing. *Annals of the Royal College of Surgeons of England* 1984;**66**(3):179-83.

Moretti 2008

Moretti A, Papi C, Aratari A, Festa V, Tanga M, Koch M, et al. Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. *Digestive and Liver Disease* 2008;**40**(5):379-85.

Mutinga 2000

Mutinga M, Rosenbluth A, Tenner SM, Odze RR, Sica GT, Banks PA. Does mortality occur early or late in acute pancreatitis?. *International Journal of Pancreatology* 2000;**28**(2):91-5.

Neoptolemos 1984a

Neoptolemos JP, Goodman AJ, Salter ND, Carr-Locke DL, Fossard DP. Problem of identifying patients with gallstone-induced pancreatitis based on biochemical and/or clinical criteria. *Annals of Surgery* 1984;**200**(5):680-2.

Neoptolemos 1984b

Neoptolemos JP, Hall AW, Finlay DF, Berry JM, Carr-Locke DL, Fossard DP. The urgent diagnosis of gallstones in acute pancreatitis: a prospective study of three methods. *British Journal of Surgery* 1984;**71**(3):230-3.

Neoptolemos 1986

Neoptolemos JP, London N, Slater ND, Carr-Locke DL, Fossard DP, Moosa AR. A prospective study of ERCP and endoscopic sphincterotomy in the diagnosis and treatment of gallstone acute pancreatitis. A rational and safe approach to management. *Archives of Surgery* 1986;**121**(6):697-702.

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.

Paloyan 1975

Paloyan D, Simonowitz D, Skinner DB. The timing of biliary tract operations in patients with pancreatitis associated with gallstones. *Surgery, Gynecology and Obstetrics* 1975;**141**:737-9.

Petrov 2008a

Petrov MS, van Santvoort HC, Besselink MGH, van der Heijden GJMG, van Erpecum KJ, Gooszen HG. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis. A meta-analysis of randomized trials. *Annals of Surgery* 2008;**247**(2):250-7.

Petrov 2008b

Petrov MS, Uchugina AF, Kukosh MV. Does endoscopic retrograde cholangiopancreatography reduce the risk of local pancreatic complications in acute pancreatitis? A systematic review and metaanalysis. *Surgical Endoscopy* 2008;**22**(11):2338-43.

Pezzilli 2007

Pezzilli R, Uomo G, Gabbrielli A, Zerbi A, Frulloni L, De Rai P, et al. A prospective multicentre survey on the treatment of acute pancreatitis in Italy. *Digestive and Liver Disease* 2007;**39**(9):838-46.

Pitchumoni 2005

Pitchumoni CS, Patel NM, Shah P. Factors influencing mortality in acute pancreatitis: can we alter them?. *Journal of Clinical Gastroenterology* 2005;**39**(9):798-814.

RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Romagnuolo 2003

Romagnuolo J, Bardou M, Rahme E, Joseph L, Reinhold C, Barkun AN. Magnetic resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. *Annals of Internal Medicine* 2003;**139**(7):547-57.

Runzi 1995a

Runzi M, Raptopoulos V, Saluja AK, Kaiser AM, Nishino H, Gerdes D. Evaluation of necrotizing pancreatitis in the opossum by dynamic contrast-enhanced computed tomography: correlation between radiographic and morphologic changes. *Journal of the American College of Surgeons* 1995;**180**(6):673-82.

Runzi 1995b

Runzi M, Saluja A, Kaiser A, Gerdes D, Sengupta A, Steer ML. Biochemical and morphological changes that characterise recovery from necrotising biliary pancreatitis in the opossum. *Gut* 1995;**37**(3):427-33.

Senninger 1986

Senninger N, Moody FG, Coelho JC, Van Buren DH. The role of biliary obstruction in the pathogenesis of acute pancreatitis in the opossum. *Surgery* 1986;**99**(6):688-93.

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. *American Journal of Gastroenterology* 1999;**94**(11):3211-4.

Sugiyama 1998

Sugiyama M, Atomi Y. Acute biliary pancreatitis: the roles of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography. *Surgery* 1998;**124**(1):14-21.

Tenner 1994

Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *American Journal of Gastroenterology* 1994;**89**(10):1863-6.

Thomson 1987

Thomson SR, Hendry WS, McFarlane GA, Davidson AI. Epidemiology and outcome of acute pancreatitis. *British Journal of Surgery* 1987;**74**(5):398-401.

Toh 2000

Toh SK, Phillips S, Johnson CD. A prospective audit against national standards of the presentation and management of acute pancreatitis in the South of England. *Gut* 2000;**46**(5):239-43.

Tse 2008

Tse F, Liu L, Barkun AN, Armstrong D, Moayyedi P. EUS: a meta-analysis of test performance in suspected choledocholithiasis. *Gastrointestinal Endoscopy* 2008;**67**(2):235-44.

UK guidelines 2005

Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut* 2005;**54**(Suppl 3):iii1-9.

Uy 2009

Uy MC, Daez ML, Sy PP, Banez VP, Espinosa WZ, Talingdan-Te MC. Early ERCP in acute gallstone pancreatitis without cholangitis: a meta-analysis. *JOP: Journal of the Pancreas* 2009;**10**(3):299-305.

van Santvoort 2011

van Santvoort HC, Bakker OJ, Besselink MG, Bollen TL, Fischer K, Nieuwenhuijs VB, et al. Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis. *Endoscopy* 2011;**43**(1):8-13.

Villatoro 2006

Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD002941.pub3]

Wang 1988

Wang SS, Lin XZ, Tsai YT, Lee SD, Pan HB, Chou YH. Clinical significance of ultrasonography, computed tomography, and

biochemical tests in the rapid diagnosis of gallstone-related pancreatitis: a prospective study. *Pancreas* 1988;**3**(2):153-8.

Wang 2009

Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. *World Journal of Gastroenterology* 2009;**15**(12):1427-30.

Williams 2008

Williams EJ, Green J, Beckingham I, Parks R, Martin D, Lombard M. Guidelines on the management of common bile duct stones (CBDS). *Gut* 2008;**57**(7):1004-21.

APPENDICES

Appendix 1. CENTRAL search strategy

1. (Pancreatitis) and (acute)
2. MeSH descriptor Pancreatitis, explode all trees
3. (#1 OR #2)
4. MeSH descriptor Cholangiopancreatography, Endoscopic Retrograde explode all trees
5. MeSH descriptor Sphincterotomy, Endoscopic explode all trees
6. (endoscop* near sphincterotom*)
7. endoscopic retrograde cholangiopancreatography:ti,ab,kw
8. (ERCP):ti,ab,kw
9. (papillotomy):ti,ab,kw
10. (#4 OR #5 OR #6 OR #7 OR #8 OR #9)
11. (#3 AND #10)
12. random*
13. (#11 AND#12)

Appendix 2. MEDLINE search strategy

1. ERCP.mp. or exp endoscopic retrograde cholangiopancreatography/
2. (endoscop$ adj3 retrograd$ adj3 cholangiopancreatograph$).tw.
3. exp Sphincterotomy, Endoscopic/
4. (endoscopic adj3 sphincterotom$).mp.
5. papillotomy.mp.
6. or/1-5
7. exp Pancreatitis, Acute Necrotizing/ or exp Pancreatitis/
8. Pancreatitis.mp.
9. or/7-8
10. (acute or billar$ or gallstone$ or stones).mp.
11. 6 and 9 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. random$.mp.
15. (trial or groups).ab.
16. placebo.ab.
17. drug therapy.fs.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 10 and 18
20. animals/ not (human/ and animals/).sh.
21. 19 not 20

References to other published versions of this review

Ayub 2004

Ayub K, Imada R, Slavin J. Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD003630.pub3]

Appendix 3. EMBASE search strategy

1. ERCP.mp. or exp endoscopic retrograde cholangiopancreatography/
2. (endoscop$ adj3 retrograd$ adj3 cholangiopancreatograph$).tw.
3. exp Sphincterotomy, Endoscopic/
4. (endoscop$ adj3 sphincterotom$).mp.
5. papillotomy.mp.
6. or/1-5
7. hemorrhagic pancreatitis/ or acute hemorrhagic pancreatitis/
8. acute pancreatitis/
9. exp pancreatitis/ or pancreatitis.mp.
10. or/7-19
11. (acute or billar$ or gallstone$ or stone$).mp.
12. 6 and 10 and11
13. exp clinical trial/ or clin$ trial$.mp. or clinial trial.pt.
14. exp Randomized controlled trial/
15. exp Randomization/
16. Single-Blind Method/
17. Double-Blind Method/
18. Cross-Over Studies/ or (crossover$ or cross-over$).tw.
19. exp Random Allocation/
20. RCT.tw.
21. random$.mp.
22. (Single blind$ or Double blind$ or ((treble or triple) adj blind$)).tw.
23. comparative study/
24. controlled study/
25. placebo/ or placebo$.tw.
26. or/13-25
27. (animal not (humans and animal)).sh.
28. 26 not 27
29. 12 and 28

Appendix 4. LILACS search strategy

1. ERCP [Words] and
2. C06.689.750 [DeCS Category exploded] and
3. ((PT:"randomized controlled trial" OR PT:"controlled clinical trial" OR PT:"multicenter study" OR MH:"randomized controlled trials as topic" OR MH:"controlled clinical trials as topic" OR MH:"multicenter study as topic" OR MH:"random allocation" OR MH:"double-blind method" OR MH:"single-blind method") OR ((ensaio$ OR ensayo$ OR trial$) AND (azar OR acaso OR placebo OR control$ OR aleat$ OR random$ OR enmascarado$ OR simpleciego OR ((simple$ OR single OR duplo$ OR doble$ OR double$) AND (cego OR ciego OR blind OR mask))) AND clinic$)) AND NOT (MH:animals OR MH:rabbits OR MH:rats OR MH:primates OR MH:dogs OR MH:cats OR MH:swine OR PT:"in vitro") [Words]

CONTRIBUTIONS OF AUTHORS

All authors participated in the design of this review.

All authors reviewed and accepted the final version of the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- McMaster University, Canada.

External sources

- No sources of support supplied

NOTES

This protocol is based on a review published by Ayub et al (Ayub 2004). The protocol has been redone and republished as the review is being redone as opposed to being updated due to changes in methodology and scope.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Cholangiopancreatography, Endoscopic Retrograde [adverse effects] [*methods] [mortality]; Cholestasis [complications]; Gallstones [*complications]; Pancreatitis [mortality] [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans