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Pharmacological interventions for acute pancreatitis (Review)

Moggia E, Koti R, Belgaumkar AP, Fazio F, Pereira SP, Davidson BR, Gurusamy KS

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[Intervention Review]

Pharmacological interventions for acute pancreatitis

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ABSTRACT

Background

In people with acute pancreatitis, it is unclear what the role should be for medical treatment as an addition to supportive care such as fluid and electrolyte balance and organ support in people with organ failure.

Objectives

To assess the effects of different pharmacological interventions in people with acute pancreatitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2016, Issue 9), MEDLINE, Embase, Science Citation Index Expanded, and trial registers to October 2016 to identify randomised controlled trials (RCTs). We also searched the references of included trials to identify further trials.

Selection criteria

We considered only RCTs performed in people with acute pancreatitis, irrespective of aetiology, severity, presence of infection, language, blinding, or publication status for inclusion in the review.

Data collection and analysis

Two review authors independently identified trials and extracted data. We did not perform a network meta-analysis as planned because of the lack of information on potential effect modifiers and differences of type of participants included in the different comparisons, when information was available. We calculated the odds ratio (OR) with 95% confidence intervals (CIs) for the binary outcomes and rate ratios with 95% CIs for count outcomes using a fixed-effect model and random-effects model.

Main results

We included 84 RCTs with 8234 participants in this review. Six trials (N = 658) did not report any of the outcomes of interest for this review. The remaining 78 trials excluded 210 participants after randomisation. Thus, a total of 7366 participants in 78 trials contributed to one or more outcomes for this review. The treatments assessed in these 78 trials included antibiotics, antioxidants, aprotinin, atropine, calcitonin, cimetidine, EDTA (ethylenediaminetetraacetic acid), gabexate, glucagon, iniprol, lexipafant, NSAIDs

(non-steroidal anti-inflammatory drugs), octreotide, oxyphenonium, probiotics, activated protein C, somatostatin, somatostatin plus omeprazole, somatostatin plus ulinastatin, thymosin, ulinastatin, and inactive control. Apart from the comparison of antibiotics versus control, which included a large proportion of participants with necrotising pancreatitis, the remaining comparisons had only a small proportion of patients with this condition. Most trials included either only participants with severe acute pancreatitis or included a mixture of participants with mild acute pancreatitis and severe acute pancreatitis (75 trials). Overall, the risk of bias in trials was unclear or high for all but one of the trials.

Source of funding: seven trials were not funded or funded by agencies without vested interest in results. Pharmaceutical companies partially or fully funded 21 trials. The source of funding was not available from the remaining trials.

Since we considered short-term mortality as the most important outcome, we presented only these results in detail in the abstract. Sixty-seven studies including 6638 participants reported short-term mortality. There was no evidence of any differences in short-term mortality in any of the comparisons (very low-quality evidence). With regards to other primary outcomes, serious adverse events (number) were lower than control in participants taking lexipafant (rate ratio 0.67, 95% CI 0.46 to 0.96; N = 290; 1 study; very low-quality evidence), octreotide (rate ratio 0.74, 95% CI 0.60 to 0.89; N = 770; 5 studies; very low-quality evidence), somatostatin plus omeprazole (rate ratio 0.36, 95% CI 0.19 to 0.70; N = 140; 1 study; low-quality evidence), and somatostatin plus ulinastatin (rate ratio 0.30, 95% CI 0.15 to 0.60; N = 122; 1 study; low-quality evidence). The proportion of people with organ failure was lower in octreotide than control (OR 0.51, 95% CI 0.27 to 0.97; N = 430; 3 studies; very low-quality evidence). The proportion of people with sepsis was lower in lexipafant than control (OR 0.26, 95% CI 0.08 to 0.83; N = 290; 1 study; very low-quality evidence). There was no evidence of differences in any of the remaining comparisons in these outcomes or for any of the remaining primary outcomes (the proportion of participants experiencing at least one serious adverse event and the occurrence of infected pancreatic necrosis). None of the trials reported heath-related quality of life.

Authors' conclusions

Very low-quality evidence suggests that none of the pharmacological treatments studied decrease short-term mortality in people with acute pancreatitis. However, the confidence intervals were wide and consistent with an increase or decrease in short-term mortality due to the interventions. We did not find consistent clinical benefits with any intervention. Because of the limitations in the prognostic scoring systems and because damage to organs may occur in acute pancreatitis before they are clinically manifest, future trials should consider including pancreatitis of all severity but power the study to measure the differences in the subgroup of people with severe acute pancreatitis. It may be difficult to power the studies based on mortality. Future trials in participants with acute pancreatitis should consider other outcomes such as complications or health-related quality of life as primary outcomes. Such trials should include health-related quality of life, costs, and return to work as outcomes and should follow patients for at least three months (preferably for at least one year).

PLAIN LANGUAGE SUMMARY

Medical treatment for people with acute pancreatitis (sudden inflammation of the pancreas)

Background

The pancreas is an organ in the abdomen (tummy) that secretes several digestive enzymes (substances that enable and speed up chemical reactions in the body) into the pancreatic ductal system before it empties into the small bowel. It also contains the Islets of Langerhans, which secrete several hormones including insulin (helps regulate blood sugar). Acute pancreatitis is life-threatening illness characterized by sudden inflammation of the pancreas, which can lead to failure of other organs, such as the lungs and kidneys. There is a lot of research into different medical treatments for the treatment of acute pancreatitis, but it is not clear what benefits each treatment has, or indeed if any medical treatment is beneficial apart from supportive treatment. This care includes body hydration and intensive care treatment for people with organ failure (to support the failing organs). We sought to resolve this issue by searching for existing studies on the topic. We included all randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) whose results were reported to 7 October 2016.

Study characteristics

We included 84 RCTs with 8234 participants in this review. Six trials (658 participants) did not report any of the outcomes of interest for this review. In the remaining 78 trials, 210 participants were excluded after randomisation. Thus, a total of 7366 participants in 78 trials contributed to one or more outcomes for this review. Apart from the comparison of whether antibiotics should be used, the

other comparisons included only a small percentage of people with pancreatic necrosis (an extremely severe form of pancreatitis, which results in pancreatic destruction). Most trials included only the severe form of acute pancreatitis or included both mild and severe forms of pancreatitis.

Source of funding: seven trials were not funded or were funded by agencies without vested interest in results. Twenty-one trials were partly or fully funded by pharmaceutical companies. The source of funding was not available from the remaining trials.

Quality of the evidence

The overall quality of evidence was low for all the measures because the trials were at unclear or high risk of bias (a systematic error or deviation from the truth that affects the results, favouring one treatment over another) and were small trials. As a result, further studies are required on this topic.

Key results

Sixty-seven studies including 6638 participants reported short-term deaths. Overall, an average 12% of people who received only supportive care died. There was no evidence that any of the treatments decreased short-term deaths. There was evidence that various treatments might be beneficial in a number of outcomes; however, these results were not consistent, and we cannot make any conclusions as to whether any of the treatments may be beneficial. None of the trials reported health-related quality of life.

In conclusion, based on low quality evidence, there is no evidence that any drug treatment added on to supportive care decreases short-term deaths. Future trials in participants with acute pancreatitis should include health-related quality of life, costs, and return to work as outcomes and should follow patients for at least three months (preferably for at least one year).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Pharmacological interventions for treatment of acute severe pancreatitis (mortality)

Patient or population: people with acute pancreatitis
Settings: secondary or tertiary setting
Intervention: various treatments
Control: inactive control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Inactive control	Corresponding risk Various treatments			
Short-term mortality Follow-up: up to 3 months	**Antibiotics**		**OR 0.81** (0.57 to 1.15)	1058 (17 studies)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**99 per 1000** (72 to 135)			
	Antioxidants		**OR 2.01** (0.53 to 7.56)	163 (4 studies)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**215 per 1000** (68 to 508)			
	Aprotinin		**OR 0.68** (0.40 to 1.14)	651 (7 studies)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**85 per 1000** (52 to 135)			
	Calcitonin		**OR 0.55** (0.15 to 2.00)	125 (2 studies)	⊕◯◯◯ **Very low**[1,2,3]
	120 per 1000	**69 per 1000** (20 to 214)			
	Cimetidine		**OR 1.00** (0.06 to 17.18)	40 (1 study)	⊕◯◯◯ **Very low**[a,b,c]

120 per 1000	**120 per 1000** (8 to 701)			
EDTA		**OR 0.94** (0.12 to 7.08)	64 (1 study)	⊕◯◯◯ **Very low**[1,2,3]
120 per 1000	**113 per 1000** (17 to 491)			
Gabexate		**OR 0.79** (0.48 to 1.30)	576 (5 studies)	⊕◯◯◯ **Very low**[a,b,c]
120 per 1000	**98 per 1000** (62 to 151)			
Glucagon		**OR 0.97** (0.51 to 1.87)	409 (5 studies)	⊕◯◯◯ **Very low**[1,2,3]
120 per 1000	**117 per 1000** (65 to 203)			
Iniprol		**OR 0.14** (0.01 to 1.67)	24 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
120 per 1000	**19 per 1000** (2 to 185)			
Lexipafant		**OR 0.55** (0.30 to 1.01)	423 (3 studies)	⊕◯◯◯ **Very low**[1,2,3]
120 per 1000	**70 per 1000** (40 to 121)			
Octreotide		**OR 0.76** (0.47 to 1.23)	927 (6 studies)	⊕◯◯◯ **Very low**[a,b,c]
120 per 1000	**94 per 1000** (60 to 143)			
Probiotics		**OR 1.70** (0.87 to 3.30)	358 (2 studies)	⊕◯◯◯ **Very low**[a,b,c,d]

	120 per 1000	**188 per 1000** (106 to 310)			
	Activated protein C		**OR 8.56** (0.41 to 180.52)	32 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**539 per 1000** (52 to 961)			
	Somatostatin		**OR 0.57** (0.29 to 1.10)	493 (6 studies)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**72 per 1000** (39 to 130)			
	Somatostatin plus omeprazole		**OR 0.23** (0.05 to 1.11)	140 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**30 per 1000** (6 to 132)			
	Somatostatin plus ulinastatin		**OR 0.43** (0.15 to 1.23)	122 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**55 per 1000** (20 to 144)			
	Thymosin		**Not estimable**	24 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**not estimable**			
	Ulinastatin		**OR 0.45** (0.12 to 1.72)	132 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]
	120 per 1000	**58 per 1000** (16 to 190)			
Long-term mortality Follow-up: 1 year	None of the trials with inactive treatment in the control group reported long-term mortality				

*The basis for the **assumed risk** is the average control group proportion across all comparisons. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence intervals; **OR**: odds ratio; **EDTA**: ethylenediaminetetraacetic acid.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a] Risk of bias: downgraded by one level.
[b] Imprecision: downgraded one level for wide confidence intervals.
[c] Imprecision: downgraded one level for small sample size.
[d] Heterogeneity: downgraded one level for lack of overlap of confidence intervals and high I^2.

BACKGROUND

Description of the condition

The pancreas is an abdominal organ that secretes several digestive enzymes into the pancreatic ductal system before it empties into the small bowel. The pancreas also lodges the Islets of Langerhans, which secrete several hormones including insulin (NCBI 2014). Acute pancreatitis is a sudden inflammatory process in the pancreas, with variable involvement of nearby organs or other organ systems (Bradley 1993). The annual incidence of acute pancreatitis ranges from 5 to 30 per 100,000 population (Roberts 2013; Yadav 2006). There has been an increase in the incidence of acute pancreatitis in the last 10 to 20 years in the UK and USA (Roberts 2013; Yang 2008). Acute pancreatitis is the commonest gastrointestinal (digestive tract) cause of hospital admission in the USA (Peery 2012), and gallstones and alcohol are the two main causes. Approximately, 50% to 70% of acute pancreatitis is caused by gallstones (Roberts 2013; Yadav 2006); these slip into the common bile duct and obstruct the ampulla of Vater (a common channel formed by the union of common bile duct and pancreatic duct), resulting in obstruction to the flow of pancreatic enzymes and leading to activation of trypsinogen within the pancreas and acute pancreatitis (Sah 2013).

Advanced age, male sex, and lower socioeconomic class are associated with higher incidence of acute pancreatitis (Roberts 2013). Clinicians generally diagnose acute pancreatitis when at least two of the following three features are present (Banks 2013).

1. Acute onset of a persistent, severe, epigastric pain, often radiating to the back.
2. Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal.
3. Characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography.

Depending upon the type of inflammation, acute pancreatitis can be classified into interstitial oedematous pancreatitis (diffuse (widespread) or occasionally localised enlargement of the pancreas due to inflammatory oedema as seen on CECT) or necrotising pancreatitis (necrosis involving either the pancreas, peripancreatic tissues, or both) (Banks 2013). Approximately 90% to 95% of people with acute pancreatitis have interstitial oedematous pancreatitis, while the remainder have necrotising pancreatitis (Banks 2013). Necrotising pancreatitis may be sterile or infected (Banks 2013). Various theories exist as to how pancreatic and peripancreatic tissues get infected. These include spread from blood circulation, lymphatics, bile, and the small bowel (duodenum) through the pancreatic duct, as well as movement (translocation) through the large bowel wall (Schmid 1999).

Local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled-off necrosis (Banks 2013). The systemic complications of acute pancreatitis include worsening of pre-existing illnesses such as heart or chronic lung disease (Banks 2013). The mortality rates following an attack of acute pancreatitis are between 6% and 20% (Roberts 2013; Yadav 2006), according to severity. Acute pancreatitis can be classified as mild, moderate, or severe, depending on the presence of local or systemic complications, transient organ failure involving one of more of lungs, kidneys, and cardiovascular system (heart and blood vessels) lasting up to 48 hours, or persistent failure of these organs lasting beyond 48 hours. Mild pancreatitis has the best prognosis, and there are no local or systemic complications or organ failure. In moderately severe acute pancreatitis, there may be local or systemic complications or transient organ failure. Severe acute pancreatitis carries the worst prognosis in terms of mortality, and there is persistent organ failure (Banks 2013).

The clinical manifestation of acute pancreatitis is believed to be caused by activation of inflammatory pathways either directly by the pathologic insult or indirectly by activation of trypsinogen (an enzyme that digests protein or a protease), resulting in formation of trypsin, a protease that can break down the pancreas (Sah 2013). This activation of inflammatory pathways manifests clinically as systemic inflammatory response syndrome (SIRS) (Banks 2013; Sah 2013; Tenner 2013). Systemic inflammatory response syndrome is characterised by two or more of the following criteria (Bone 1992).

1. Temperature of less than 36°C or more than 38°C.
2. Heart rate less than 90 beats/minute.
3. Respiratory rate more than 20/min or PCO_2 less than 32 mm Hg.
4. White blood cell count more than 12,000/mm^3, less than 4000/mm^3, or more than 10% immature (band) forms.

See Appendix 1 for a glossary of terms.

Description of the intervention

The main purpose of treatment is to decrease the mortality and morbidity associated with acute pancreatitis. The various pharmacological interventions that have been evaluated in the treatment of acute pancreatitis include agents such as somatostatin or octreotide that decrease pancreatic secretions; protease inhibitors such as gabexate mesilate, aprotinin, ulinastatin, and nafamostat; antioxidants such as vitamin C and selenium; platelet activating factor such as lexipafant; other agents that modulate the inflammatory pathway such as steroids and tumour necrosis factor-alpha (TNF-α) antibody; probiotics; and antibiotics (Bang 2008; Neumann 2011; Rada 2011; Yang 2011). We included any pharmacological intervention aimed at the treatment of acute pancreatitis.

We did not cover endoscopic sphincterotomy for the treatment of common bile duct stones (Ayub 2010), nor did we focus on

endoscopic, radiology-guided percutaneous treatments or surgical treatments for treatment of complications of acute pancreatitis (Tenner 2013). Furthermore, we did not cover the use of non-steroidal anti-inflammatory drugs (NSAIDs) or other drugs such as somatostatin analogues for preventing postendoscopic retrograde cholangiopancreatography (post-ECRP)-induced pancreatitis (Elmunzer 2012; Zhang 2009).

How the intervention might work

Somatostatin and its analogues decrease pancreatic secretion (Bang 2008). Since autodigestion (breakdown of pancreas) due to trypsinogen activation is one of the mechanisms believed to cause acute pancreatitis, decreasing pancreatic secretion can decrease the amount of trypsinogen. Inhibition of trypsin by protease inhibitors may result in decreased damage to the pancreas (Neumann 2011). Antioxidants, platelet-activating factor inhibitors, steroids, and TNF-α antibody are all aimed at decreasing the inflammatory response or at mitigating the damage resulting from the inflammatory response (Bang 2008). Probiotics decrease the bacterial colonisation of the gut, and antibiotics have antibacterial actions (Bang 2008).

Why it is important to do this review

Despite various pharmacological interventions being evaluated in acute pancreatitis, none is currently recommended in the treatment of acute pancreatitis, with the exception of antibiotics in infected necrotising pancreatitis (Tenner 2013). Systematic reviews and meta-analyses increase the precision of the treatment effects (i.e. they provide a narrower range of the average treatment effect) (Higgins 2011), and so decrease the risk of a type II error (concluding that there is no difference between treatments when there is actually a difference). Systematic reviews also help in identifying the differences in the treatment effects between studies and allow exploration of the reasons behind these differences. Many studies have compared these interventions with placebo or with no treatment. It is therefore not possible to obtain accurate information on how one treatment compares with another treatment. Multiple treatment comparisons or a network meta-analysis allow comparison of several treatments simultaneously and provide information on the relative effect of one treatment versus another, even when there is no direct comparison. There is no Cochrane Review or network meta-analysis on this topic. So, we planned to perform a network meta-analysis if the type of participants were included across all the comparisons. This systematic review will identify the relative effects of different treatments and identify any research gaps.

OBJECTIVES

To assess the effects of different pharmacological interventions in people with acute pancreatitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs). We included studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

We included adults with acute pancreatitis irrespective of the severity (mild, moderately severe, or severe acute pancreatitis) or the type of acute pancreatitis (acute interstitial oedematous pancreatitis or necrotising pancreatitis).

Types of interventions

We included trials comparing any pharmacological interventions mentioned above with another, with placebo, or with no intervention, provided that the only difference between the randomised groups was the pharmacological intervention or interventions being assessed. Some of the interventions that we included are listed below.

- Activated protein C.
- Antibiotics.
- Antioxidants.
- Aprotinin.
- Calcitonin.
- Cimetidine.
- EDTA (ethylenediaminetetraacetic acid).
- Gabexate.
- Glucagon.
- Iniprol.
- Lexipafant.
- Octreotide.
- Omeprazole.
- Probiotics.
- Somatostatin.
- Thymosin.
- Ulinastatin.

We did not combine the different somatostatin analogues (such as somatostatin or octreotide) as a single treatment in order to avoid further clinical heterogeneity. We assessed a combination of drugs as a separate treatment.

Types of outcome measures

Primary outcomes

1. Mortality.
   i) Short-term mortality (in-hospital mortality or mortality within six months).
   ii) Long-term mortality (at maximum follow-up).
2. Serious adverse events (within six months). We accepted the definition of serious adverse events from the International Conference on Harmonisation - Good Clinical Practice guideline (ICH-GCP 1997): any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability/incapacity. Wealso accepted other variations of ICH-GCP classifications such as Food and Drug Administration (FDA) classification (FDA 2006), Medicines and Healthcare products Regulatory Agency (MHRA) classification (MHRA 2013).
   i) Proportion of people who developed serious adverse events (i.e. the percentage of people who developed one or more serious adverse events) and the number of serious adverse events (i.e. the total number of serious adverse events in each group regardless of the number of people in whom the serious adverse events developed).
   ii) Organ failure (however reported by authors).
   iii) Infected necrotising pancreatitis (cytology or positive culture).
   iv) Sepsis (however reported by authors).
3. Health-related quality of life (using any validated scale).
   i) Short-term (four weeks to three months).
   ii) Medium-term (three months to one year).
   iii) Long-term (more than one year).
4. Health-related quality of life (using any validated scale).
   i) Short-term (four weeks to three months).
   ii) Medium-term (three months to one year).
   iii) Long-term (more than one year).

Secondary outcomes

1. Adverse events (within six months). We accepted all adverse events reported by the trial authors, irrespective of the severity of the adverse event.
2. Measures of decreased complications and earlier recovery (within six months).
   i) Length of hospital stay (including the index admission for acute pancreatitis and any disease-related or intervention-related readmissions including those for recurrent episodes).
   ii) Length of intensive care unit (ICU) stay (including the index admission for acute pancreatitis and any disease- or intervention-related readmissions).
   iii) Requirement for additional invasive intervention such as necrosectomy for pancreatic necrosis, endoscopic or radiological drainage of collections.
   iv) Time to return to normal activity (return to pre-acute pancreatitis episode mobility without any additional caregiver support).
   v) Time to return to work (in those who were employed previously).
3. Costs (within six months).

We chose the above clinical outcomes based on the necessity to assess whether the pharmacological interventions were effective in decreasing complications, thereby decreasing the length of ICU and hospital stay, decreasing any additional interventions, and resulting in earlier return to normal activity and work as well as improvement in quality of life. The costs provide an indication of resource requirement.

We did not regard the reporting of the outcomes listed here as an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We conducted a literature search to identify all published and unpublished randomised controlled trials. The literature search identified potential studies in all languages. We translated the non-English language papers and fully assessed them for potential inclusion in the review as necessary.

We searched the following electronic databases for identifying potential studies.

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9, 2016; searched 7 October 2016; Appendix 2).
- MEDLINE (1966 to 7 October 2016; Appendix 3).
- Embase (1988 to 7 October 2016; Appendix 4).
- Science Citation Index (1982 to 7 October 2016; Appendix 5).

We also conducted a search of ClinicalTrials.gov (Appendix 6) and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (Appendix 8) on 7 October 2016.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and asked them to identify any other published and unpublished studies.

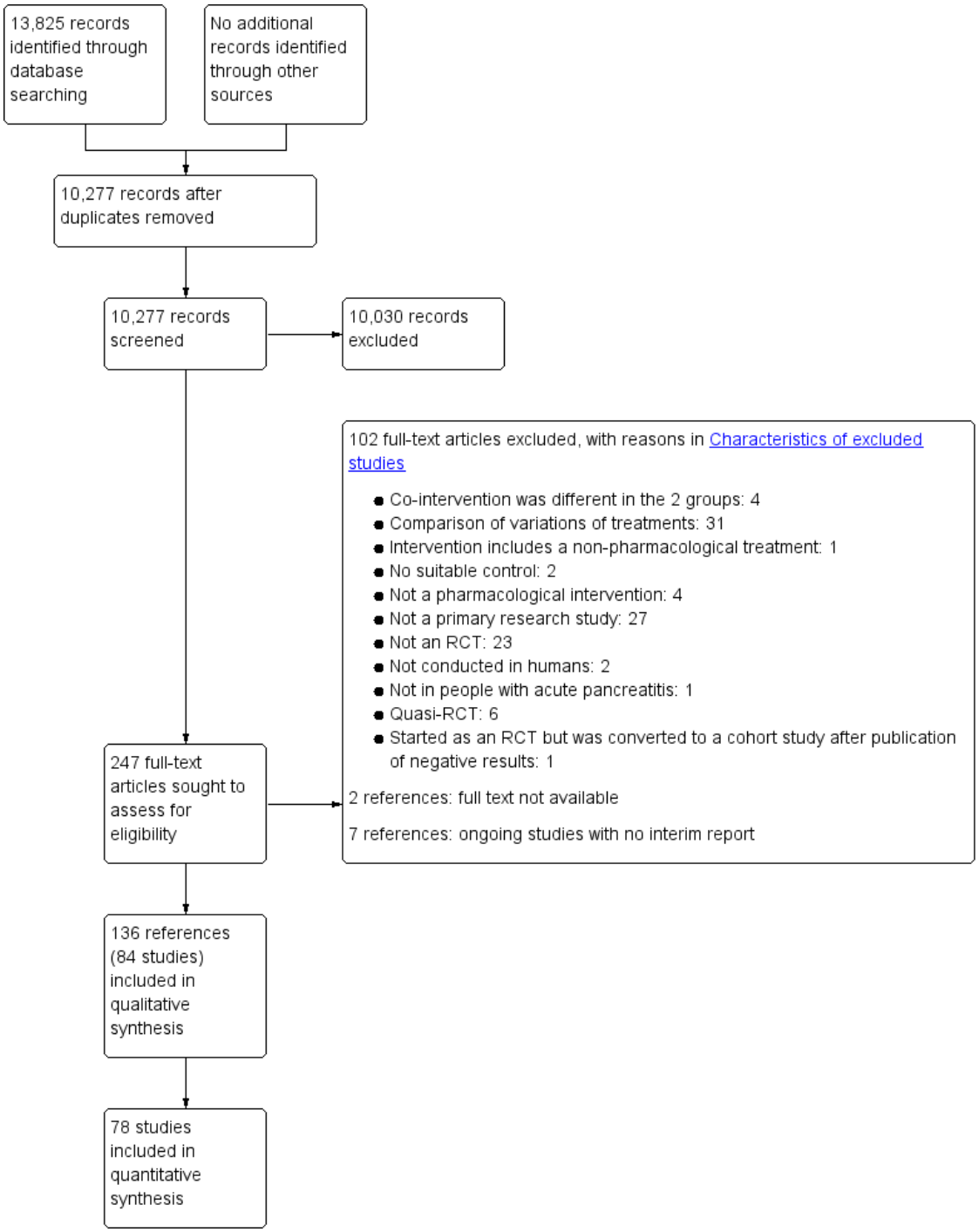
We searched for errata or retractions from eligible trials on www.ncbi.nlm.nih.gov/pubmed on 7 October 2016.

Data collection and analysis

Selection of studies

Two review authors (KG and AB) independently screened titles and abstracts of all the potential studies that we identified through the searches and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports, and two review authors (KG and RK or EM) independently screened them and identified studies for inclusion; we identified and recorded reasons for exclusion of the ineligible studies. We resolved any disagreement through discussion. We identified and excluded duplicates and collated multiple reports of the same study so that each study rather than each report was the unit of interest in the review. We planned to contact the investigators of trials of unclear eligibility. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and a 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram.



Data extraction and management

We used a standard data collection form for study characteristics and outcome data, which had been piloted on three studies in the review. Two review authors (KG and RK or EM) independently extracted the following study characteristics.

1. Methods: study design, total duration study and run-in, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: number (N), mean age, age range, sex, severity and type of acute pancreatitis, inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, co-interventions, number of participants randomised to each group.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported. For binary outcomes, we obtained the number of participants with events and the number of participants included in the analysis in each group. For continuous outcomes, we obtained the unit or scale of measurement, mean, standard deviation, and the number of participants included in the analysis for each group. For count outcomes, we obtained the number of events and number of participants included in the analysis in each group. For time-to-event outcomes, we obtained the proportion of people with events, the average duration of follow-up of participants in the trial, and the number of participants included in the analysis for each group.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (KG and RK or EM) independently extracted outcome data from included studies. If outcomes were reported at multiple time points, we planned to extract the data for all time points. We obtained information on the number of participants with adverse events (or serious adverse events) and the number of such events where applicable. We planned to extract all information on costs using the currency reported by the trial authors and planned to convert this to USD at the conversion rates on the day of the analysis. We extracted data for every trial arm that was an included intervention. If studies reported outcome data in an unusable way, we attempted to contact the trial authors and tried to obtain usable data. If we were unable to obtain usable data despite this, we planned to summarise the unusable data in an appendix. We resolved disagreements by consensus. One review author (EM) copied across the data for 'Characteristics of included studies' and 'Characteristics of excluded studies' from the data collection form into the Review Manager 5 (RevMan 5) file (RevMan 2014). One review author (KG) copied across the data for 'Data and analyses' from the data collection form into the RevMan 5 file. We double-checked that the data were entered correctly by comparing the study reports with how the data were presented in the systematic review.

Assessment of risk of bias in included studies

Two review authors (KG and RK or EM) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Bias due to funding source.
8. Other potential bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' tables. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary, for example, for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale. Where information on risk of bias relates to unpublished data or to correspondence with a trial author, we planned to note this in the 'Risk of bias' table. We presented the risk of bias in each pair-wise comparison in Table 1. When considering treatment effects, we took into account the risk of bias for the studies that contribute to that outcome by a sensitivity analysis.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in the 'Differences between protocol and review' section of this review.

Measures of treatment effect

For dichotomous variables (short-term mortality, proportion of participants with adverse events, requirement for additional interventions), we calculated the odds ratio (OR) with 95% confidence interval (CI). For continuous variables, such as length of hospital stay, ICU stay, time to return to normal activity, time to return to work, and costs, we planned to calculate the mean difference (MD) with 95% CI. We planned to use standardised mean difference (SMD) with 95% CI for quality of life if different scales were

used. For count outcomes such as the number of adverse events, we calculated the rate ratio with 95% CIs. For time-to-event data, such as long-term mortality, we planned to use the hazard ratio (HR) with a 95% CI. However, only one trial reported mortality beyond 3 months and presented the number of deaths at two years. We analysed this information as binary data.

A common way that trial authors indicate when they have skewed data is by reporting medians and interquartile ranges. When we encountered this, we reported the difference in means or medians in a table.

Unit of analysis issues

The unit of analysis was individual participants with acute pancreatitis. As anticipated, we did not find any cluster-randomised trials for this comparison.

In multi-arm trials, the models account for the correlation between trial-specific treatment effects from the same trial.

Dealing with missing data

We attempted to contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). For binary, count, and time-to-event outcomes, we performed an intention-to-treat analysis whenever possible (Newell 1992). Since this was not possible, we performed an available-case analysis but planned to assess the impact of 'best-best', 'best-worst', 'worst-best', and 'worst-worst' scenario analyses on the results for binary outcomes. For continuous outcomes, we planned to perform an available-case analysis. If we were unable to obtain the information from the investigators or study sponsors, we planned to impute the mean from the median (i.e. consider the median as the mean) and the standard deviation from the standard error, interquartile range, or P values according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), but we planned to assess the impact of including such studies as indicated in a sensitivity analysis. If we were unable to calculate the standard deviation from the standard error, interquartile range, or P values, we planned to impute the standard deviation as the highest standard deviation in the remaining trials included in the outcome, being fully aware that this method of imputation would decrease the weight of the studies in the meta-analysis of mean difference and shift the effect estimate towards no effect for standardised mean difference. We planned to assess the impact of including such studies by sensitivity analysis.

Assessment of heterogeneity

We assessed the heterogeneity in each pair-wise comparison by assessing the Higgins I^2 (Higgins 2003), the Chi^2 test with significance set at a P value less than 0.10, and by visual inspection.

Assessment of reporting biases

We attempted to contact trial authors, asking them to provide missing outcome data. Where this was not possible, and if we thought that the missing data may introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis**.**

If we were able to pool more than 10 trials for a specific comparison, we created and examined a funnel plot to explore possible publication biases. We used Egger's test to determine the statistical significance of the reporting bias (Egger 1997). We considered a P value of less than 0.05 to indicate statistically significant reporting bias.

Data synthesis

We undertook meta-analyses only where this was meaningful (i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense). In general, we favoured performing a meta-analysis and clearly highlighted the reason for not performing one if we decided against it. We used both the fixed-effect and random-effects model, reporting the fixed-effect model when the choice of models did not alter the conclusion and the random-effects model when it did. We did not perform a network meta-analysis as planned because of the lack of information on potential effect modifiers and differences of type of participants included in the different comparisons, when information was available (i.e. the transitivity assumption was not satisfied).

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses regardless of heterogeneity.

1. Different types of acute pancreatitis (acute interstitial oedematous pancreatitis or necrotising pancreatitis).
2. Different severity of acute pancreatitis (mild pancreatitis versus moderate or severe acute pancreatitis).
3. Presence of persistent organ failure (mild or moderate acute pancreatitis versus severe acute pancreatitis).
4. Presence of infection (infected necrotising pancreatitis versus non-infected necrotising pancreatitis).

We planned to calculate the test for subgroup differences to identify differences between subgroups.

Sensitivity analysis

We planned to perform the following sensitivity analyses defined a priori to assess the robustness of our conclusions.

1. Excluding trials at unclear or high risk of bias (one or more of the 'Risk of bias' domains classified as unclear or high).
2. Excluding trials in which either the mean or the standard deviation or both were imputed.

3. Imputation of binary outcomes under 'best-best', 'best-worst', 'worst-best', and 'worst-worst' scenarios.

'Summary of findings' table

Although we planned to create a 'Summary of findings' table using all the outcomes, this would have resulted in a incomprehensible table. So, we presented the 'Summary of findings' table for the primary outcomes only. We used the five GRADE considerations (study limitations, inconsistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it related to the studies contributing data to the meta-analyses for the prespecified outcomes. We justified all decisions to down- or upgrade the quality rating of studies using footnotes, making comments to aid the reader's understanding of the review where necessary. We considered whether there was any additional outcome information that we were not able to incorporate into meta-analyses and planned to note this in the comments, stating whether it supported or contradicted the information from the meta-analyses.

Reaching conclusions

We based our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We have avoided making recommendations for practice, and our implications for research give the reader a clear sense of where the focus of any future research in the area should be and what the remaining uncertainties are.

RESULTS

Description of studies

Results of the search

We identified a total of 13,825 references through electronic searches of CENTRAL (1345 records), MEDLINE (5649 records), Embase (4102 records), Science Citation Index Expanded (2604 records), World Health Organization International Clinical Trials Registry Platform (78 records) and ClinicalTrials.gov (47 records). After removing 3548 duplicates, we obtained 10,277 references. We then excluded 10,030 clearly irrelevant references through screening titles and reading abstracts. We sought 247 references for further assessment but could not obtain 2 (Hansen 1966; Perez 1980). Seven references were ongoing trials, suspended trials, or completed trials identified from clinical registers with no interim reports available (ChiCTR-IPR-16008301; EUCTR2014-004844-37-ES; NCT01132521; NCT02025049; NCT02212392; NCT02692391; NCT02885441). We did not identify any new trials by scanning reference lists of the identified randomised trials. We excluded 102 references for the reasons listed under the table 'Characteristics of excluded studies'. In total, 136 references (84 trials) met the inclusion criteria. The reference flow is summarised in the study flow diagram (Figure 1).

Included studies

A total of 8234 participants were included in these 84 trials. Six trials (N = 658) did not report any of the outcomes of interest for this review (Birk 1994; Chooklin 2007; Marek 1999; Moreau 1986; Plaudis 2010; Wang 2013b). The remaining 78 trials excluded 210 participants after randomisation. Thus, a total of 7366 participants in 78 trials contributed to one or more outcomes for this review.

One trial included only participants with acute interstitial oedematous pancreatitis (Chen 2002a); 12 trials included only participants with acute necrotising pancreatitis (Barreda 2009; Chen 2002b; Delcenserie 2001; Dellinger 2007; Frulloni 1994; Garcia-Barrasa 2009; Llukacaj 2012; Nordback 2001; Pederzoli 1993a; Rokke 2007; Sainio 1995; Xue 2009); the remaining trials did not state clearly whether they included any participants with acute necrotising pancreatitis. All the trials that included acute necrotising pancreatitis either stated explicitly or implied that they excluded participants with infected necrotising pancreatitis.

Two trials included only participants with mild acute pancreatitis (Chen 2002a; Yang 2012). Twenty-six trials included only severe acute pancreatitis (Balldin 1983; Berling 1994; Birk 1994; Chen 2000; Chen 2002b; Chooklin 2007; Delcenserie 1996; Dellinger 2007; Garcia-Barrasa 2009; Grupo Español 1996; Guo 2015; Hejtmankova 2003; Luiten 1995; Martinez 1984; Olah 2007; Pettila 2010; Plaudis 2010; Rokke 2007; Spicak 2002; Spicak 2003; Wang 2011; Wang 2013a; Wang 2016; Xia 2014; Xue 2009; Zhu 2014). Two trials reported data separately for mild and severe acute pancreatitis (Abraham 2013; Wang 2013c). These trials presented the data separately for mild pancreatitis and acute severe pancreatitis. The remaining trials either included mild and severe acute pancreatitis or did not state the severity of pancreatitis in the participants. It should be noted that none of the trials used the current definition of severe acute pancreatitis (i.e. organ failure persisting for 48 hours or more).

The potential effect modifiers, arranged by comparisons, are shown in Table 2. As shown in the table, important potential effect modifiers were missing. In addition, it appeared that most trials in the comparison on antibiotics versus no active intervention included participants with necrotising pancreatitis. Because of this, there were serious concerns about the inclusion of similar participants in the different comparisons.

Source of funding: seven trials were not funded or they were funded by agencies without vested interest in results (Bansal 2011; Garcia-Barrasa 2009; Wang 2013a; Wang 2013c; Wang 2016; Xue 2009; Yang 2012). Pharmaceutical companies partially or fully funded

21 trials (Balldin 1983; Berling 1994; Besselink 2008; Dellinger 2007; Ebbehøj 1985; Hansky 1969; Imrie 1978; Isenmann 2004; Johnson 2001; Kingsnorth 1995; McKay 1997b; Moreau 1986; MRC Multicentre Trial 1977; Pettila 2010; Rokke 2007; Sharma 2011; Siriwardena 2007; Trapnell 1974; Tykka 1985; Uhl 1999; Valderrama 1992). The source of funding was not available from the remaining trials.

Excluded studies

None of the excluded studies were eligible for this review. The reasons for exclusion are listed in 'Characteristics of excluded studies'.

Risk of bias in included studies

We summarised the overall risk of bias in Figure 2 and Figure 3. Only Wang 2016 was at low risk of bias in all the domains and can be considered a trial at overall low risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

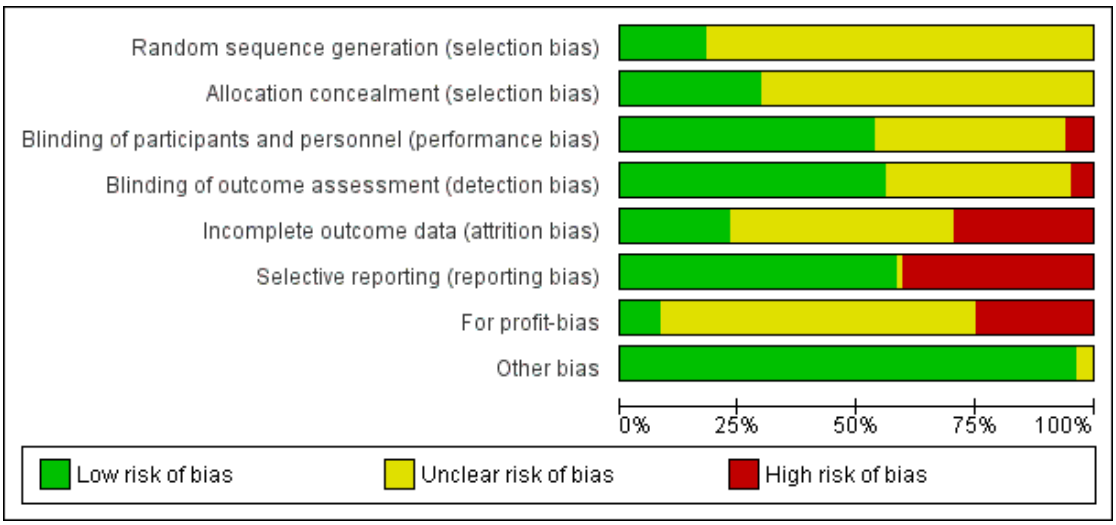
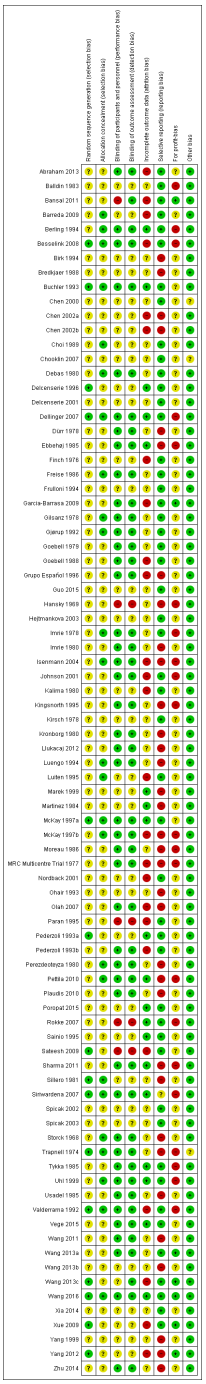


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Fifteen trials were at low risk of bias for random sequence generation (Besselink 2008; Buchler 1993; Delcenserie 1996; Dellinger 2007; McKay 1997a; Pederzoli 1993a; Sateesh 2009; Sillero 1981; Siriwardena 2007; Trapnell 1974; Valderrama 1992; Wang 2013c; Wang 2016; Xue 2009; Yang 2012). Twenty-six trials were at low risk of bias for allocation concealment (Barreda 2009; Berling 1994; Besselink 2008; Buchler 1993; Choi 1989; Debas 1980; Dellinger 2007; Freise 1986; Gilsanz 1978; Gjørup 1992; Imrie 1978; Isenmann 2004; Luengo 1994; Luiten 1995; McKay 1997a; McKay 1997b; Perezdeoteyza 1980; Pettila 2010; Sharma 2011; Sillero 1981; Siriwardena 2007; Storck 1968; Trapnell 1974; Uhl 1999; Valderrama 1992; Wang 2016). Eight trials were at low risk of selection bias (Besselink 2008; Buchler 1993; Dellinger 2007; McKay 1997a; Siriwardena 2007; Trapnell 1974; Valderrama 1992; Wang 2016). The remaining trials were at unclear risk of selection bias since they did not describe random sequence generation or allocation concealment.

Blinding

Forty-five trials were at low risk of bias for blinding of participants, healthcare providers, and outcomes assessors (Abraham 2013; Berling 1994; Besselink 2008; Buchler 1993; Debas 1980; Dellinger 2007; Dürr 1978; Ebbehøj 1985; Freise 1986; Garcia-Barrasa 2009; Gilsanz 1978; Gjørup 1992; Goebell 1979; Goebell 1988; Grupo Español 1996; Imrie 1978; Imrie 1980; Isenmann 2004; Johnson 2001; Kingsnorth 1995; Kronborg 1980; Llukacaj 2012; Luengo 1994; McKay 1997a; McKay 1997b; Moreau 1986; MRC Multicentre Trial 1977; Olah 2007; Pederzoli 1993b; Perezdeoteyza 1980; Pettila 2010; Plaudis 2010; Sharma 2011; Siriwardena 2007; Storck 1968; Trapnell 1974; Tykka 1985; Uhl 1999; Usadel 1985; Valderrama 1992; Vege 2015; Wang 2011; Wang 2013a; Wang 2016; Zhu 2014). While Bansal 2011 and Wang 2013c were also at low risk of bias for the blinding of outcome assessors, Bansal 2011 was at high risk and Wang 2013c at unclear risk for the blinding of participants and healthcare providers. Overall, five trials were at high risk of bias due to lack of blinding (Bansal 2011; Hansky 1969; Paran 1995; Rokke 2007; Sateesh 2009). The remaining trials were at unclear risk of bias for blinding.

Incomplete outcome data

Nineteen trials were at low risk of attrition bias due to missing outcome data (Berling 1994; Buchler 1993; Delcenserie 1996; Dellinger 2007; Ebbehøj 1985; Marek 1999; Martinez 1984; McKay 1997a; Pederzoli 1993a; Pettila 2010; Poropat 2015; Rokke 2007; Sainio 1995; Sharma 2011; Siriwardena 2007; Tykka 1985; Uhl 1999; Vege 2015; Wang 2016). Twenty-five trials were at high risk of attrition bias (Abraham 2013; Bansal 2011; Barreda 2009; Besselink 2008; Chen 2002a; Chen 2002b; Finch 1976; Garcia-Barrasa 2009; Goebell 1988; Grupo Español 1996; Isenmann 2004; Johnson 2001; Kalima 1980; Luiten 1995; McKay 1997b; MRC Multicentre Trial 1977; Nordback 2001; Olah 2007; Paran 1995; Pederzoli 1993b; Sateesh 2009; Valderrama 1992; Wang 2013c; Xue 2009; Yang 2012). The remaining trials were at unclear risk of attrition bias.

Selective reporting

Forty-nine trials were at low risk of selective reporting bias (Abraham 2013; Balldin 1983; Bansal 2011; Barreda 2009; Berling 1994; Besselink 2008; Buchler 1993; Chen 2000; Choi 1989; Debas 1980; Delcenserie 1996; Delcenserie 2001; Dellinger 2007; Finch 1976; Freise 1986; Frulloni 1994; Garcia-Barrasa 2009; Gilsanz 1978; Gjørup 1992; Goebell 1979; Goebell 1988; Guo 2015; Hejtmankova 2003; Imrie 1978; Johnson 2001; Kalima 1980; Kirsch 1978; Luiten 1995; McKay 1997a; Nordback 2001; Paran 1995; Pederzoli 1993a; Pederzoli 1993b; Poropat 2015; Rokke 2007; Sainio 1995; Sateesh 2009; Siriwardena 2007; Spicak 2002; Spicak 2003; Tykka 1985; Uhl 1999; Valderrama 1992; Vege 2015; Wang 2013a; Wang 2013c; Wang 2016; Xia 2014; Xue 2009). The remaining trials were at high or unclear risk of reporting bias.

Other potential sources of bias

Source of funding bias: seven trials were at low risk of due to source of funding (Bansal 2011; Garcia-Barrasa 2009; Wang 2013a; Wang 2013c; Wang 2016; Xue 2009; Yang 2012). Twenty-one trials were at high risk of bias due to source of funding (Balldin 1983; Berling 1994; Besselink 2008; Dellinger 2007; Ebbehøj 1985; Hansky 1969; Imrie 1978; Isenmann 2004; Johnson 2001; Kingsnorth 1995; McKay 1997b; Moreau 1986; MRC Multicentre Trial 1977; Pettila 2010; Rokke 2007; Sharma 2011; Siriwardena 2007; Trapnell 1974; Tykka 1985; Uhl 1999; Valderrama 1992). The remaining trials were at unclear risk of bias due to the source of funding.

No other bias was noted in any of the trials.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings (mortality); **Summary of findings 2** Summary of findings (other primary outcomes)

Primary outcomes

Mortality

Short-term mortality

A total of 67 studies (N = 6638) reported short-term mortality (Abraham 2013; Balldin 1983; Bansal 2011; Barreda 2009; Berling 1994; Besselink 2008; Buchler 1993; Chen 2000; Choi 1989; Debas 1980; Delcenserie 1996; Delcenserie 2001; Dellinger 2007; Dürr 1978; Finch 1976; Freise 1986; Frulloni 1994; Garcia-Barrasa 2009; Gjørup 1992; Goebell 1979; Goebell 1988; Grupo Español 1996; Guo 2015; Hansky 1969; Hejtmankova 2003; Imrie 1978; Imrie 1980; Johnson 2001; Kalima 1980; Kingsnorth 1995; Kirsch 1978; Kronborg 1980; Llukacaj 2012; Luengo 1994; Luiten 1995; Martinez 1984; McKay 1997a; McKay 1997b; MRC Multicentre Trial 1977; Nordback 2001; Olah 2007; Paran 1995; Pederzoli 1993a; Pederzoli 1993b; Perezdeoteyza 1980; Pettila 2010; Poropat 2015; Rokke 2007; Sainio 1995; Sateesh 2009; Siriwardena 2007; Spicak 2002; Spicak 2003; Storck 1968; Trapnell 1974; Tykka 1985; Uhl 1999; Usadel 1985; Valderrama 1992; Vege 2015; Wang 2011; Wang 2013a; Wang 2013c; Wang 2016; Xia 2014; Xue 2009; Yang 2012). There was no evidence of difference in any of the comparisons (Analysis 1.1).

Long-term mortality (maximum follow-up)

Only one study (N = 62) reported mortality beyond six months (Gilsanz 1978). There was no evidence of difference in the only comparison possible.

Serious adverse events

A total of 17 studies (N = 1139) reported serious adverse events as a proportion or participants who experienced at least one serious adverse event (i.e. each person with a serious adverse event will be counted only once regardless of the number of serious adverse events that the person develops) (Bansal 2011; Chen 2002a; Debas 1980; Delcenserie 1996; Dellinger 2007; Freise 1986; Frulloni 1994; Garcia-Barrasa 2009; Gjørup 1992; Goebell 1988; Kalima 1980; Llukacaj 2012; McKay 1997a; Sainio 1995; Siriwardena 2007; Tykka 1985; Yang 1999). There was no evidence of difference in any of the comparisons (Analysis 1.2).

A total of 37 studies (N = 3804) reported the number of serious adverse events observed in all participants (i.e. if a person develops more than one serious adverse event, the number of serious adverse events that the person develops is included) (Balldin 1983; Bansal 2011; Barreda 2009; Berling 1994; Besselink 2008; Buchler 1993; Chen 2000; Choi 1989; Debas 1980; Delcenserie 1996; Delcenserie 2001; Garcia-Barrasa 2009; Gjørup 1992; Guo 2015; Imrie 1978; Isenmann 2004; Johnson 2001; Kirsch 1978; McKay 1997a; Nordback 2001; Olah 2007; Paran 1995; Pederzoli 1993a; Poropat 2015; Sainio 1995; Sillero 1981; Spicak 2002; Spicak 2003; Tykka 1985; Uhl 1999; Valderrama 1992; Vege 2015; Wang 2013a; Wang 2013c; Xia 2014; Xue 2009; Zhu 2014). There were fewer serious adverse events in participants receiving lexipafant (rate ratio 0.67, 95% CI 0.46 to 0.96; participants = 290; studies = 1), octreotide (rate ratio 0.74, 95% CI 0.60 to 0.89; participants = 770; studies = 5), somatostatin plus omeprazole (rate ratio 0.36, 95% CI 0.19 to 0.70; participants = 140; studies = 1), and somatostatin plus ulinastatin (rate ratio 0.30, 95% CI 0.15 to 0.60; participants = 122; studies = 1) than control. There were also fewer serious adverse events in participants taking octreotide plus ulinastatin compared to octreotide (rate ratio 0.30, 95% CI 0.17 to 0.51; participants = 120; studies = 1) and in participants taking somatostatin plus ulinastatin versus somatostatin (rate ratio 0.28, 95% CI 0.15 to 0.56; participants = 123; studies = 1). There was no evidence of difference in the remaining comparisons (Analysis 1.3).

Organ failure

A total of 18 studies (N = 2220) reported organ failure (Abraham 2013; Bansal 2011; Besselink 2008; Delcenserie 1996; Freise 1986; Garcia-Barrasa 2009; Johnson 2001; McKay 1997a; McKay 1997b; Olah 2007; Pederzoli 1993a; Poropat 2015; Rokke 2007; Sateesh 2009; Siriwardena 2007; Vege 2015; Wang 2013c; Wang 2016). The proportion of people with organ failure was lower in the octreotide group than in control (OR 0.51, 95% CI 0.27 to 0.97; participants = 430; studies = 3). There was no evidence of difference in any of the remaining comparisons (Analysis 1.4).

Infected pancreatic necrosis

A total of 15 studies (N = 1173) reported infected pancreatic necrosis (Barreda 2009; Besselink 2008; Delcenserie 1996; Dellinger 2007; Garcia-Barrasa 2009; Isenmann 2004; Llukacaj 2012; McKay 1997a; Olah 2007; Pederzoli 1993a; Poropat 2015; Rokke 2007; Spicak 2002; Spicak 2003; Zhu 2014). As shown in Analysis 1.5, there was no evidence of difference in any of the comparisons.

Sepsis

A total of 11 studies (N = 1350) reported sepsis (Balldin 1983; Berling 1994; Buchler 1993; Freise 1986; Frulloni 1994; Johnson 2001; Olah 2007; Paran 1995; Sainio 1995; Uhl 1999; Valderrama 1992). The proportion of people with sepsis was lower in those receiving lexipafant compared to control (OR 0.26, 95% CI 0.08 to 0.83; participants = 290; studies = 1). There was no evidence of difference in any of the remaining comparisons (Analysis 1.6).

Health-related quality of life

None of the trials reported health-related quality of life at any time point.

Secondary outcomes

Adverse events

A total of 27 studies (N = 2807) reported adverse events as a proportion or participants who experienced at least one adverse event (i.e. each person with an adverse event will be counted only once regardless of the number of adverse events that the person develops) (Bansal 2011; Buchler 1993; Chen 2002a; Chen 2002b; Debas 1980; Dellinger 2007; Finch 1976; Freise 1986; Frulloni 1994; Gjørup 1992; Goebell 1979; Kalima 1980; Kingsnorth 1995; Llukacaj 2012; McKay 1997a; Nordback 2001; Olah 2007; Paran 1995; Pederzoli 1993b; Rokke 2007; Sainio 1995; Tykka 1985; Uhl 1999; Valderrama 1992; Wang 2016; Xia 2014; Yang 1999). This proportion was lower in those receiving antibiotics (OR 0.51, 95% CI 0.32 to 0.80; participants = 429; studies = 6) and somatostatin plus omeprazole (OR 0.00, 95% CI 0.00 to 0.04; participants = 140; studies = 1) compared to control. There was no evidence of difference in the remaining comparisons (Analysis 1.7).

A total of 40 studies (N = 3894) reported the number of adverse events observed in all participants (i.e. if a person develops more than one adverse event, the number of adverse events that the person develops is included) (Abraham 2013; Balldin 1983; Bansal 2011; Barreda 2009; Berling 1994; Besselink 2008; Buchler 1993; Chen 2000; Choi 1989; Debas 1980; Garcia-Barrasa 2009; Gilsanz 1978; Gjørup 1992; Goebell 1979; Guo 2015; Hejtmankova 2003; Imrie 1978; Isenmann 2004; Johnson 2001; Kirsch 1978; Kronborg 1980; Luiten 1995; McKay 1997a; Nordback 2001; Olah 2007; Paran 1995; Pederzoli 1993a; Pederzoli 1993b; Poropat 2015; Sainio 1995; Sateesh 2009; Sillero 1981; Spicak 2002; Spicak 2003; Tykka 1985; Uhl 1999; Valderrama 1992; Wang 2013c; Xue 2009; Zhu 2014). Compared to control, there were fewer adverse events in participants receiving antibiotics (rate ratio 0.75, 95% CI 0.58 to 0.95; participants = 755; studies = 12), gabexate (rate ratio 0.76, 95% CI 0.61 to 0.95; participants = 375; studies = 3), and lexipafant (rate ratio 0.61, 95% CI 0.44 to 0.85; participants = 290; studies = 1). There were also fewer adverse events for the octreotide plus ulinastatin group versus ulinastatin alone (rate ratio 0.29, 95% CI 0.17 to 0.48; participants = 120; studies = 1). There was no evidence of difference in any of the remaining comparisons (Analysis 1.8).

Measures of decreased complication or earlier recovery

Length of hospital stay

Forty-four trials (N = 4405) reported the length of hospital stay (Abraham 2013; Balldin 1983; Bansal 2011; Barreda 2009; Berling 1994; Besselink 2008; Bredkjaer 1988; Buchler 1993; Debas 1980; Delcenserie 1996; Dürr 1978; Ebbehøj 1985; Finch 1976; Garcia-Barrasa 2009; Gjørup 1992; Goebell 1979; Guo 2015; Hansky 1969; Hejtmankova 2003; Isenmann 2004; Johnson 2001; Luengo 1994; Luiten 1995; Martinez 1984; McKay 1997a; McKay 1997b; Ohair 1993; Olah 2007; Paran 1995; Pettila 2010; Rokke 2007; Sainio 1995; Sateesh 2009; Sharma 2011; Siriwardena 2007; Spicak 2002; Spicak 2003; Uhl 1999; Vege 2015; Wang 2011; Wang 2013c; Wang 2016; Xue 2009; Yang 2012). Since most trials did not report the mean and standard deviation, we reported this outcome in Table 3. As seen in the table, none of the interventions consistently decreased length of hospital stay.

Length of intensive care unit stay

Thirteen trials (N = 1188) reported the length of intensive care unit (ICU) stay (Berling 1994; Besselink 2008; Garcia-Barrasa 2009; Isenmann 2004; Johnson 2001; Nordback 2001; Rokke 2007; Sainio 1995; Sharma 2011; Siriwardena 2007; Spicak 2002; Vege 2015; Wang 2011). Since most trials did not report the mean and standard deviation, we reported the ICU stay in Table 4. As seen in the table, none of the interventions consistently decreased length of ICU stay.

Requirement for additional invasive intervention

A total of 32 studies (N = 3495) reported requirement for additional invasive intervention (Barreda 2009; Berling 1994; Besselink 2008; Buchler 1993; Chen 2000; Delcenserie 1996; Dürr 1978; Garcia-Barrasa 2009; Gilsanz 1978; Goebell 1979; Goebell 1988; Hejtmankova 2003; Isenmann 2004; Llukacaj 2012; Luengo 1994; Luiten 1995; Martinez 1984; MRC Multicentre Trial 1977; Nordback 2001; Ohair 1993; Olah 2007; Pederzoli 1993a; Pederzoli 1993b; Rokke 2007; Sainio 1995; Sillero 1981; Spicak 2002; Spicak 2003; Tykka 1985; Uhl 1999; Wang 2013c; Xue 2009). The proportion of people who needed an additional invasive intervention was lower in the gabexate group compared to control (OR 0.58, 95% CI 0.37 to 0.90; participants = 426; studies = 3). There was no evidence of difference in any of the remaining comparisons (Analysis 1.9).

Endoscopic or radiological drainage of collections

Three studies (N = 436) reported endoscopic or radiological drainage of collections (Delcenserie 1996; Wang 2013c; Zhu 2014). As shown in Analysis 1.10, there was no evidence of difference in any of the comparisons.

Time to return to normal activity

None of the trials reported this outcome.

Time to work

None of the trials reported this outcome.

Costs

None of the trials reported this outcome.

Subgroup analysis

Because of the paucity of data, we could only analyse a subgroup of acute necrotising pancreatitis and severe acute pancreatitis participants.

Acute necrotising pancreatitis

There was no evidence of difference in any of the outcomes (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6).

Severe acute pancreatitis

Short-term mortality was lower in the gabexate group versus control (OR 0.19, 95% CI 0.04 to 0.99; participants = 52; studies = 1) (Analysis 3.1)

There was no evidence of difference in the proportion of participants experiencing serious adverse events in any of the comparisons (Analysis 3.2). The number of serious adverse events was lower in the somatostatin plus omeprazole group (rate ratio 0.36, 95% CI 0.19 to 0.70; participants = 140; studies = 1) and the somatostatin plus ulinastatin group (rate ratio 0.30, 95% CI 0.15 to 0.60; participants = 122; studies = 1) compared to control. There were also fewer serious adverse events in the somatostatin plus ulinastatin group versus somatostatin alone (rate ratio 0.28, 95% CI 0.15 to 0.56; participants = 123; studies = 1). There was no evidence of differences in other comparisons (Analysis 3.3). Organ failure was lower in the ulinastatin group than in control (OR 0.05, 95% CI 0.01 to 0.21; participants = 67; studies = 1). There was no evidence of differences between other comparisons (Analysis 3.4). There was no evidence of differences in infected pancreatic necrosis or sepsis in any of the comparisons (Analysis 3.5; Analysis 3.6).

Readers should keep in mind that all the comparisons in which there was evidence of difference are based on single trials at high risk of bias and with small sample size (i.e. random errors).

Sensitivity analysis

All the trials except one were at unclear or high risk of bias in one or more domains (Wang 2016). Since most trials reported median rather than mean for length of hospital stay and length of ICU stay, we did not perform a meta-analysis by imputing mean and standard deviation. So, we did not perform a sensitivity analysis excluding trials in which either the mean or the standard deviation or both were imputed. We did not perform a sensitivity analysis imputing missing data based on different scenarios since the details of the postrandomisation dropouts were not available from the different trials in which there were postrandomisation dropouts.

Quality of evidence

Most of the comparisons in all the outcomes had low or very low quality evidence because of the risk of bias in the trials (downgraded by one level), imprecision (small sample size (downgraded by one level), and/or overlap of confidence intervals with clinically insignificant effect or no effect (downgraded by one level). There was evidence of heterogeneity in some of the outcomes, which resulted in further downgrading by one level for some comparisons.

Reporting bias

We evaluated the reporting bias for short-term mortality, serious adverse events (number), infected pancreatic necrosis, adverse events (number), and the requirement for additional intervention for antibiotics versus control, the only comparisons with at least 10 trials. There was no evidence of reporting bias either on visual inspection or by Egger's test for the short-term mortality, infected pancreatic necrosis, and requirement for additional intervention (Figure 4, P = 0.88; Figure 5, P = 0.74; and Figure 6, P = 0.98, respectively). There was evidence of reporting bias both on visual inspection and by Egger's test for number of serious adverse events (Figure 7; P = 0.021). There was evidence of reporting bias on visual inspection but not by Egger's test for number of adverse events (Figure 8; P = 0.079).

Figure 4. Funnel plot of short-term mortality indicating no evidence of reporting bias.

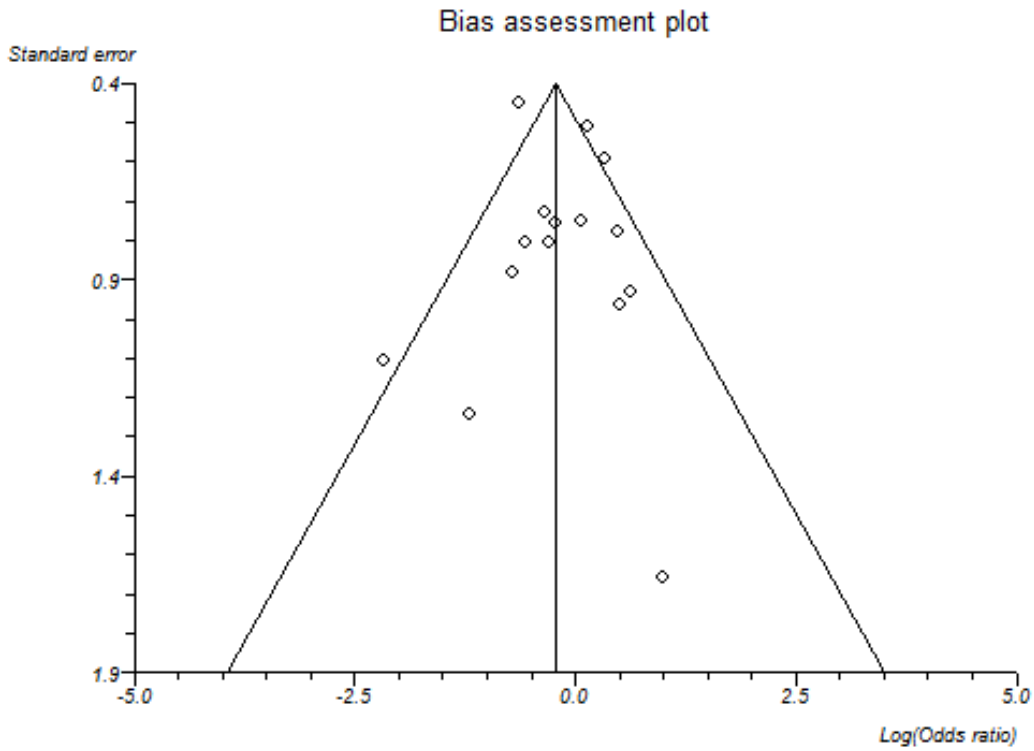


Figure 5. Funnel plot of infected pancreatic necrosis indicating no evidence of reporting bias.

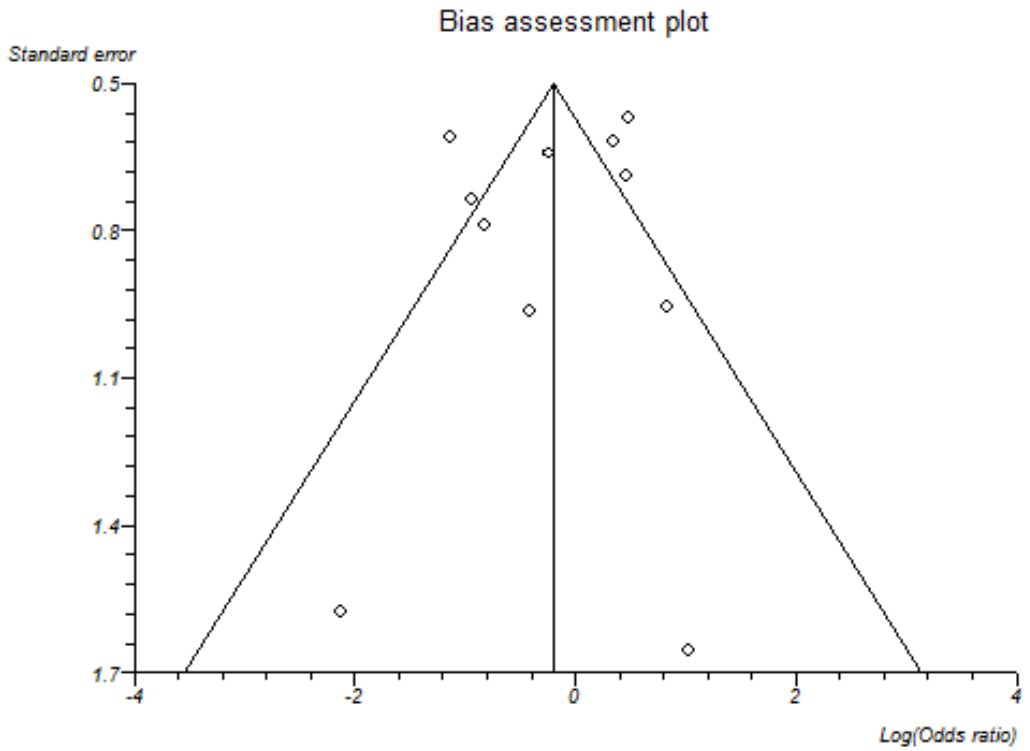


Figure 6. Funnel plot of requirement for additional invasive intervention indicating no evidence of reporting bias.

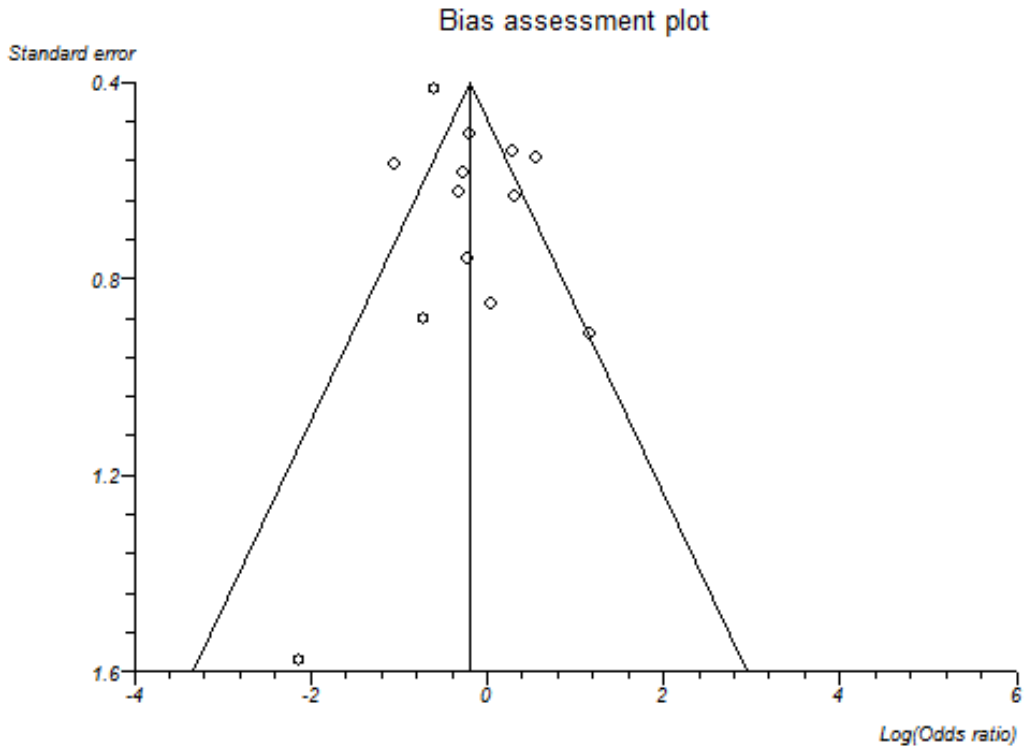


Figure 7. Funnel plot of serious adverse events (number) indicating that trials with lower precision favoured antibiotics without matching trials with lower precision which showed no effect or favouring control.

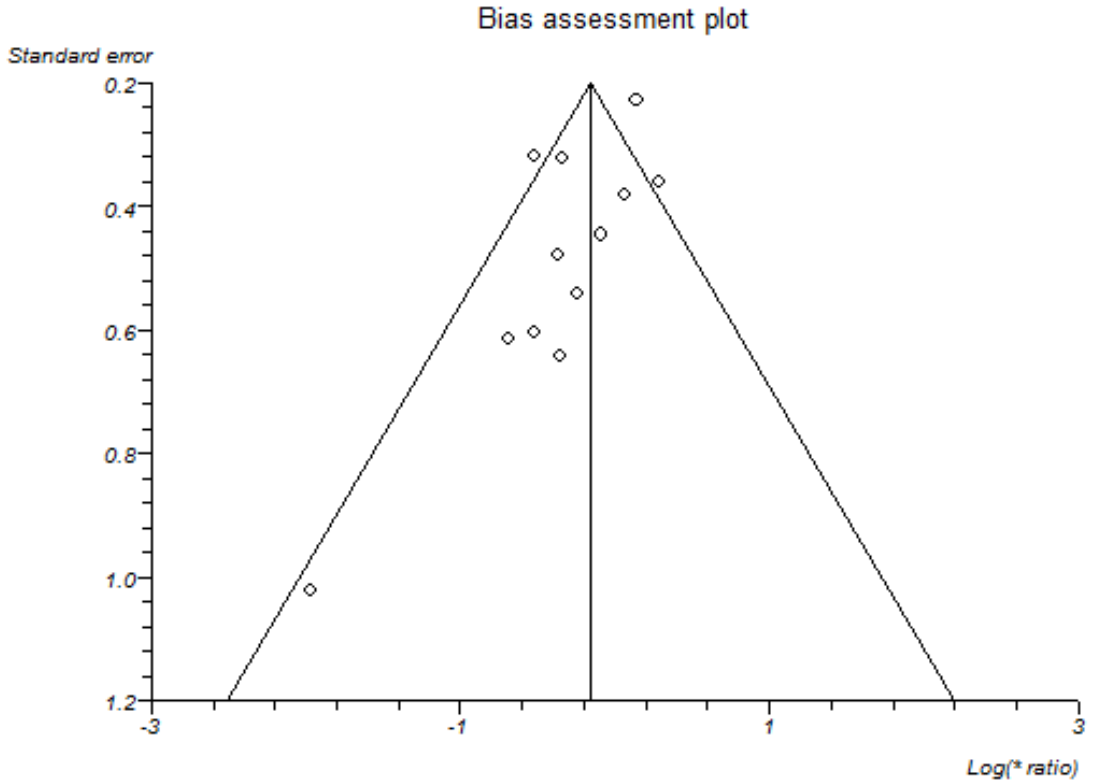
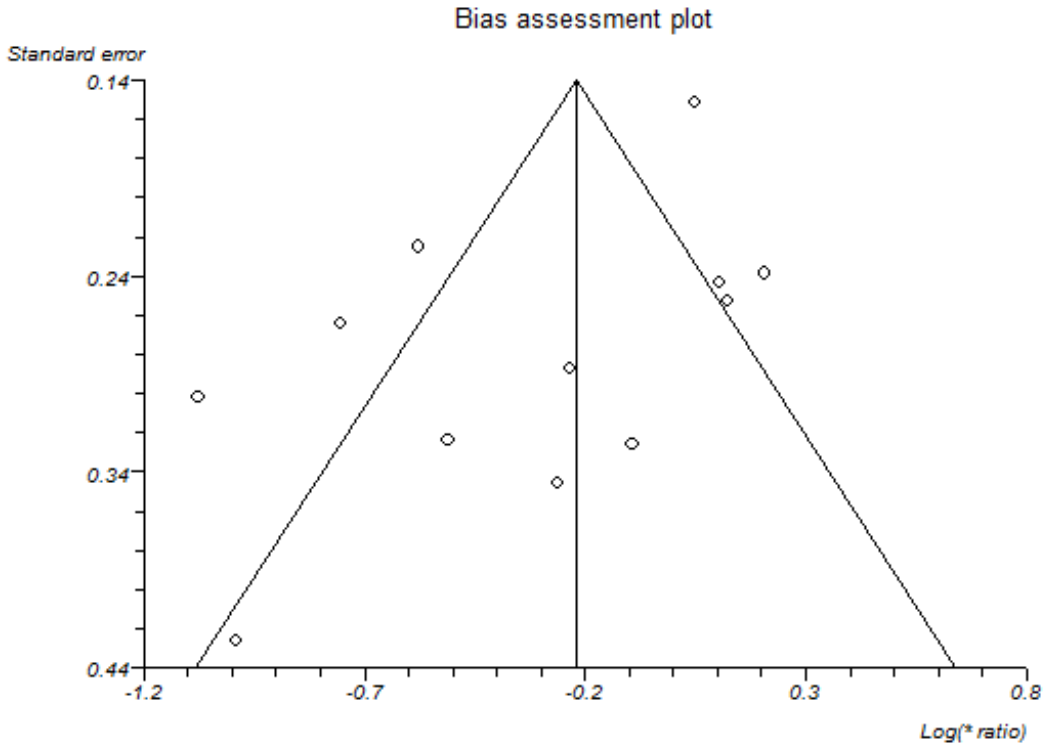


Figure 8. Funnel plot of adverse events (number) indicating that trials with lower precision favoured antibiotics while trials with greater precision favoured control.



ADDITIONAL SUMMARY OF FINDINGS [*Explanation*]

Pharmacological interventions for treatment of acute severe pancreatitis (other outcomes)

Patient or population: people with acute pancreatitis
Settings: secondary or tertiary setting
Intervention: various treatments
Control: inactive control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Inactive control	Various treatments			
Serious adverse events (proportion) Follow-up: up to 3 months	**Antibiotics**		**OR 0.65** (0.37 to 1.15)	304 (5 studies)	⊕◯◯◯ **Very low**[a,b,c]
	147 per 1000	**101 per 1000** (60 to 166)			
	Antioxidants		**OR 1.98** (0.48 to 8.13)	82 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]
	147 per 1000	**255 per 1000** (77 to 584)			
	EDTA		**OR 0.52** (0.11 to 2.39)	64 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	147 per 1000	**83 per 1000** (19 to 292)			
	Gabexate		**OR 1.31** (0.31 to 5.60)	201 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]
	147 per 1000	**185 per 1000** (51 to 492)			
	Glucagon		**OR 0.29** (0.01 to 7.46)	127 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]

	147 per 1000	**48 per 1000** (2 to 563)			
	Octreotide		**OR 1.73** (0.61 to 4.93)	58 (1 study)	⊕◯◯◯ **Very low**[a,b,c,d]
	147 per 1000	**230 per 1000** (95 to 460)			
	Somatostatin		**OR 1.07** (0.35 to 3.27)	111 (2 studies)	⊕◯◯◯ **Very low**[a,b,c,d]
	147 per 1000	**156 per 1000** (57 to 361)			
Serious adverse events (number) Follow-up: up to 3 months	**Antibiotics**		Rate ratio**0.86** (0.68 to 1.07)	716 (12 studies)	⊕◯◯◯ **Very low**[a,b,c]
	437 per 1000	**374 per 1000** (298 to 469)			
	Antioxidants		Rate ratio**0.22** (0.02 to 2.21)	71 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]
	437 per 1000	**94 per 1000** (9 to 967)			
	Aprotinin		Rate ratio**0.79** (0.49 to 1.29)	264 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]
	437 per 1000	**345 per 1000** (212 to 562)			
	Cimetidine		Rate ratio**1.00** (0.20 to 4.95)	60 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	437 per 1000	**437 per 1000** (88 to 2165)			
	EDTA		Rate ratio**0.94** (0.19 to 4.65)	64 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	437 per 1000	**411 per 1000** (83 to 2034)			

Gabexate		Rate ratio**0.86** (0.64 to 1.15)	375 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]
437 per 1000	**375 per 1000** (279 to 503)			
Glucagon		Rate ratio**1.00** (0.02 to 50.40)	68 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
437 per 1000	**437 per 1000** (9 to 22027)			
Lexipafant		rate ratio**0.67** (0.46 to 0.96)	290 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
437 per 1000	**292 per 1000** (203 to 420)			
Octreotide		Rate ratio**0.74** (0.60 to 0.89)	770 (5 studies)	⊕◯◯◯ **Very low**[a,b,c]
437 per 1000	**321 per 1000** (264 to 391)			
Probiotics		Rate ratio**0.94** (0.65 to 1.36)	397 (3 studies)	⊕◯◯◯ **Very low**[a,b,c,d]
437 per 1000	**412 per 1000** (286 to 595)			
Somatostatin		Rate ratio**1.03** (0.66 to 1.59)	257 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]
437 per 1000	**449 per 1000** (290 to 695)			
Somatostatin plus omeprazole		Rate ratio**0.36** (0.19 to 0.70)	140 (1 study)	⊕⊕◯◯ **Low**[a,b]
437 per 1000	**159 per 1000** (82 to 308)			
Somatostatin plus ulinastatin		Rate ratio**0.30** (0.15 to 0.60)	122 (1 study)	⊕⊕◯◯ **Low**[a,b]

	437 per 1000	**133 per 1000** (68 to 262)			
Organ failure Follow-up: up to 3 months	**Antibiotics**		**OR 0.78** (0.44 to 1.38)	258 (5 studies)	⊕◯◯◯ **Very low**[a,b,c]
	289 per 1000	**241 per 1000** (152 to 360)			
	Antioxidants		**OR 0.92** (0.39 to 2.12)	163 (4 studies)	⊕◯◯◯ **Very low**[a,b,c]
	289 per 1000	**271 per 1000** (138 to 463)			
	Gabexate		**OR 0.32** (0.01 to 8.25)	50 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	289 per 1000	**115 per 1000** (5 to 770)			
	Lexipafant		**OR 0.68** (0.36 to 1.27)	340 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]
	289 per 1000	**216 per 1000** (128 to 341)			
	Octreotide		**OR 0.51** (0.27 to 0.97)	430 (3 studies)	⊕◯◯◯ **Very low**[a,b,c,d]
	289 per 1000	**173 per 1000** (99 to 284)			
	Probiotics		**OR 0.80** (0.26 to 2.47)	358 (2 studies)	⊕◯◯◯ **Very low**[a,b,c,d]
	289 per 1000	**246 per 1000** (95 to 501)			
	Ulinastatin		**OR 0.27** (0.01 to 6.67)	129 (2 studies)	⊕◯◯◯ **Very low**[a,b,c,d]
	289 per 1000	**100 per 1000** (5 to 731)			

Infected pancreatic necrosis Follow-up: up to 3 months	**Antibiotics**		**OR 0.82** (0.53 to 1.25)	714 (11 studies)	⊕◯◯◯ **Very low**[a,b,c]
	140 per 1000	**118 per 1000** (80 to 169)			
	Octreotide		**OR 0.52** (0.04 to 6.06)	58 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	140 per 1000	**78 per 1000** (7 to 497)			
	Probiotics		**OR 1.10** (0.62 to 1.96)	397 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]
	140 per 1000	**152 per 1000** (92 to 243)			
Sepsis Follow-up: up to 3 months	**Antibiotics**		**OR 0.42** (0.11 to 1.60)	60 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	122 per 1000	**56 per 1000** (15 to 182)			
	Aprotinin		**OR 1.84** (0.49 to 6.96)	103 (2 studies)	⊕◯◯◯ **Very low**[a,b,c]
	122 per 1000	**204 per 1000** (63 to 492)			
	Gabexate		**OR 1.10** (0.55 to 2.19)	373 (3 studies)	⊕◯◯◯ **Very low**[a,b,c]
	122 per 1000	**133 per 1000** (71 to 233)			
	Lexipafant		**OR 0.26** (0.08 to 0.83)	290 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	122 per 1000	**35 per 1000** (12 to 103)			
	Octreotide		**OR 0.40** (0.05 to 3.53)	340 (2 studies)	⊕◯◯◯ **Very low**[a,b,c,d]

	122 per 1000	**53 per 1000** (6 to 329)			
	Probiotics		**OR 0.36** (0.10 to 1.36)	62 (1 study)	⊕◯◯◯ **Very low**[a,b,c]
	122 per 1000	**48 per 1000** (13 to 159)			
Health-related quality of life	None of the trials reported this outcome.				

*The basis for the **assumed risk** is the average control group proportion across all comparisons. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence intervals; OR = odds ratio; EDTA = ethylenediaminetetraacetic acid

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Risk of bias: downgraded by one level.
[b]Imprecision: downgraded one level for wide confidence intervals.
[c]Imprecision: downgraded one level for small sample size.
[d]Heterogeneity: downgraded one level for lack of overlap of confidence intervals and high I^2.

DISCUSSION

Summary of main results

A total of 7366 participants in 78 trials contributed to one or more outcomes for this review. The treatments assessed in these 78 trials included antibiotics, antioxidants, aprotinin, atropine, calcitonin, cimetidine, EDTA, gabexate, glucagon, iniprol, lexipafant, NSAID, octreotide, oxyphenonium, probiotics, activated protein C, somatostatin, somatostatin plus omeprazole, somatostatin plus ulinastatin, thymosin, ulinastatin, and inactive control.

Despite the number of trials included, network meta-analysis was not performed because of major concerns about the transitivity assumption, that is, whether all participants in the network were sufficiently similar and therefore had an equal chance of receiving any of the treatments in the network . In particular, we highlight the fact that a total of 18 trials were included in the comparison under antibiotics versus inactive control (Delcenserie 1996; Delcenserie 2001; Dellinger 2007; Finch 1976; Garcia-Barrasa 2009; Hejtmankova 2003; Isenmann 2004; Llukacaj 2012; Luiten 1995; Nordback 2001; Pederzoli 1993a; Poropat 2015; Rokke 2007; Sainio 1995; Spicak 2002; Spicak 2003; Xue 2009). Ten of these trials included only participants with acute necrotising pancreatitis (Barreda 2009; Delcenserie 2001; Dellinger 2007; Garcia-Barrasa 2009; Llukacaj 2012 Nordback 2001; Pederzoli 1993a; Rokke 2007; Sainio 1995; Xue 2009). Just two other trials that included only participants with acute necrotising pancreatitis were featured in all the other comparisons put together (Chen 2002b; Frulloni 1994). Thus, there is some clinical heterogeneity in the type of participants that were included in the different comparisons. As a result, we performed direct comparison only.

There was no evidence of difference in short-term mortality between the groups in any of the comparisons. However, the confidence intervals were wide and consistent with significant benefits or harms of interventions. Because of the number of outcomes reported in the different trials, it is reasonable to expect that the beneficial effect is consistent across clinical outcomes. Interventions with at least two clinical benefits were: lexipafant, which was associated with fewer adverse events (and severe adverse events) and a lower proportion of people with sepsis; octreotide, which was associated with fewer serious adverse events and a lower proportion of people with organ failure; and gabexate, which was associated with fewer adverse events and a lower proportion of people requiring an additional invasive intervention compared to inactive intervention. However, because of the number of analyses performed ('Potential biases in the review process'), concerns about the availability of the drug ('Overall completeness and applicability of evidence'), and the quality of evidence ('Quality of the evidence'), further trials are required before recommending any of the interventions routinely.

Only one trial reported mortality beyond six months (Gilsanz 1978). The follow-up in the remaining trials was three months in six trials (Besselink 2008; Buchler 1993; Chen 2000; Frulloni 1994; Goebell 1988; Pederzoli 1993b), while in the rest it was less than six weeks. A three-month follow-up would identify all the complications related to acute pancreatitis and most deaths related to these complications. However, a period less than three months is likely to miss a considerable proportion. None of the trials reported health-related quality of life, costs, or other important socioeconomic measures such as return to work. Health-related quality of life continues to improve between three months and one year after necrotising pancreatitis, although some impairment in quality of life may remain beyond then (Wright 2009). The quality of life after acute severe pancreatitis also appears to be impaired even several years after the acute pancreatitis episode (Hochman 2006; Pendharkar 2014). Future trials on acute pancreatitis should assess the health-related quality of life for at least 3 months to 12 months and report socioeconomic measures so that it is possible to understand whether the treatments are cost-effective.

We can only speculate on why no intervention showed any consistent benefit. One possible reason is that the trials were not powered to measure differences in short-term mortality. The short-term mortality in the inactive control group was 12% overall and 17.4% (102/586) in the subgroup of acute severe pancreatitis. To measure a 20% relative risk reduction in short-term mortality using an alpha error of 5% and a beta error of 20%, 3422 participants are required. Clearly, the trials included only a small proportion of the required sample size, so the lack of evidence of difference may be due to random error. The complications related to mild pancreatitis are very infrequent, which means that an even greater sample size than 3422 is required to demonstrate a difference in clinical benefits. On the other hand, if the interventions are targeted against patients with severe pancreatitis, then it can take several hours or even days for the full picture of severe acute pancreatitis to develop. By this time, the damage may be too much for any treatment (other than supportive treatment including organ support) to make a difference. Several prognostic indexes exist for predicting whether the pancreatitis is mild or severe before the clinical picture fully emerges. However, these indexes have a modest sensitivity and specificity in predicting severe acute pancreatitis (Gao 2015a), so it may be reasonable to administer the treatment in all patients with acute pancreatitis and accept that only a proportion will benefit. The proportion of patients with severe pancreatitis in trials that included both mild and severe acute pancreatitis in this review ranged between 17% and 87% (median 35%). The sample size of the trial may have to be estimated on the basis that only the subgroup of severe acute pancreatitis will benefit. It is unlikely that trials powered to measure differences in mortality can be conducted in patients with acute pancreatitis. Using outcomes such as health-related quality of life or clinically significant complications may allow clinically meaningful trials to be conducted in this population.

Overall completeness and applicability of

evidence

This review included all pharmacological interventions without restriction by the year of publication of the trials or whether the drugs are currently licensed. The European Agency for the Evaluation of Medicinal Products (EMEA) had refused marketing authorisation for lexipafant in 1998 after reviewing the data submitted by the company (WHO 2001). Some of the reasons for this refusal included concerns about not having a functional independent data monitoring committee to monitor the results and allegations of financial misconduct by the company that manufactured lexipafant (Hampton 2000; Masood 1998).

Apart from the trials comparing antibiotics versus control, most of the remaining trials did not clearly state whether they included participants with necrotising pancreatitis. So, it is not clear whether this evidence is applicable to patients with acute necrotising pancreatitis. Most trials included a totality or at least a significant proportion of participants with severe acute pancreatitis, so the results of the review are applicable to patients with severe acute pancreatitis in addition to those with mild acute pancreatitis.

This review is only about pharmacological interventions for acute pancreatitis. We have not included any nutritional interventions or interventions on fluid management in this review. We are unable to comment on whether any of the above are effective in the treatment of acute pancreatitis based on the results of this review. We have only reviewed treatment of acute pancreatitis and not prophylaxis. Thus, our review is applicable only in people with acute pancreatitis.

Quality of the evidence

We assessed the quality of the evidence formally only for short-term mortality, probably the most important outcome for patients with acute pancreatitis. This was low for most of the comparisons. The reason for this is that the risk of bias was unclear or high and because the results were imprecise. Overall, there was not much heterogeneity within each comparison or across comparisons as demonstrated by the I^2 and Chi^2 values within comparisons. There was no evidence of publication bias in the one comparison we could assess for short-term mortality (antibiotics versus control). However, there was evidence of publication bias in serious adverse events (number).There was no indirectness in the short-term mortality because of the nature of the outcome.

Although we did not undertake a formal assessment of the quality of evidence for the remaining outcomes, the quality of evidence is similarly low because of the issues discussed above, or possibly even lower (i.e. very low) because of having a smaller overall sample size. In addition, there appeared to be reporting bias for the number of both serious adverse events and all adverse events for the comparison antibiotics versus control, although Egger's test was statistically significant only for the number of serious adverse events.

Potential biases in the review process

We followed the *Cochrane Handbook for Systematic Reviews of Interventions* for the conduct of the direct comparison of the review. Two review authors selected studies and extracted data, reducing the errors in data collection. We used formal search strategies to identify the trials. While the likelihood of missing trials from the identified references was low, the review included the time frame before the mandatory trial registration era, and it was possible that some trials were not reported in journals because of their results. However, one has to be pragmatic and accept that this is the best level of evidence that is currently available.

Network meta-analysis has its advantages in combining direct and indirect evidence (resulting in more precise evidence); however, when providing effect estimates in the absence of direct comparison and calculating the probability that an intervention is the best treatment, one has to be wary about the transitivity assumption (i.e. whether similar participants were included in the trials across all the comparisons and thus had an equal chance of being randomised to each treatment). As mentioned above, there is some clinical heterogeneity in the type of participants who were included in 'antibiotics versus control' (a high proportion of trials included only participants with acute necrotising pancreatitis) compared to other comparisons (only a very low proportion of trials included only participants with acute necrotising pancreatitis). In the presence of such heterogeneity, it is not appropriate to conduct a network meta-analysis. In addition to the differences in the presence or absence of necrotising pancreatitis, the type of participants included in the trials were also different in terms of the severity of pancreatitis. We are not able to assess this fully since the definitions used in the trials were not the current definition of severe acute pancreatitis. So, there is likely to be heterogeneity in the type of participants included in the trials. In addition to the clinical heterogeneity in the type of participants included, there were variations in the treatments used in the trials; the definitions used for the different outcomes were not clear or were different in different trials. We did not find any systematic differences in the definitions used for specific comparisons; nevertheless, the lack of uniform definitions used in the trials along with other heterogeneity mentioned above is another potential bias in this review.

We included a number of outcomes to assess effectiveness. Although the outcomes are clinically significant, the outcomes reported in different trials were different. While we found evidence of reporting bias only in a few outcomes where it was possible to formally assess the reporting bias by funnel plots, there is a significant possibility that the outcomes reported in the trials were based on the results of the outcome. Examining a lot of outcomes can also lead to false positives because of multiplicity issues. However, we have decreased the impact of this by focusing on the most important outcome in acute pancreatitis, that is, mortality.

We were not able to obtain full texts for two references (Hansen 1966; Perez 1980). From the title, it appears that Perez 1980 was an abstract of an included trial (Perezdeoteyza 1980). The second

reference was published 50 years ago and may or may not be a randomised controlled trial (Hansen 1966), but even if it were, it is unlikely to alter our conclusions.

Agreements and disagreements with other studies or reviews

This is the first attempted network meta-analysis on this topic. We agree with Villatoro 2010 and Jiang 2012 in that there is no evidence that antibiotics decrease mortality or infected pancreatic necrosis in patients with acute pancreatitis.

Of the systematic reviews on other interventions, we agree with Xu 2013 that octreotide does not appear to be beneficial in major clinical outcomes related to acute pancreatitis and with Messori 1995 that gabexate might decrease the complications without affecting mortality. We disagree with Andriulli 1998 that somatostatin and octreotide decrease mortality. The differences in conclusions between Andriulli 1998 and this review may be due to the inclusion of non-randomised studies and the publication of new trials subsequent to the conduct of the systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

Very low-quality evidence suggests that no pharmacological treatment leads to a decrease in short-term mortality in people with acute pancreatitis. However, the confidence intervals were wide and consistent with an increase or decrease in short-term mortality. We did not find consistent clinical benefits with any intervention.

Implications for research

Because of the limitations in the prognostic scoring systems and because damage to organs may occur in acute pancreatitis before they are clinically manifest, future trials should consider including pancreatitis of all severity but power the study to measure the differences in the subgroup of people with severe acute pancreatitis. It may be difficult to power the studies based on mortality. Future trials in patients with acute pancreatitis should consider other outcomes such as complications or health-related quality of life as primary outcomes. Such trials should include health-related quality of life, costs, and return to work as outcomes and should follow patients for at least three months (preferably for at least one year).

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REFERENCES

References to studies included in this review

Abraham 2013 *{published data only}*
Abraham P, Rodriques J, Moulick N, Dharap S, Chafekar N, Verma PK, et al. Efficacy and safety of intravenous ulinastatin versus placebo along with standard supportive care in subjects with mild or severe acute pancreatitis. *Journal of the Association of Physicians of India* 2013;**61**(8): 535–8.

Balldin 1983 *{published data only}*
Balldin G, Borgström A, Genell S, Ohlsson K. The effect of peritoneal lavage and aprotinin in the treatment of severe acute pancreatitis. *Research in Experimental Medicine. Zeitschrift für die Gesamte Experimentelle Medizin Einschliesslich Experimenteller Chirurgie* 1983;**183**(3): 203–13.

Bansal 2011 *{published data only}*
Bansal D, Bhalla A, Bhasin DK, Pandhi P, Sharma N, Rana S, et al. Safety and efficacy of vitamin-based antioxidant therapy in patients with severe acute pancreatitis: a randomized controlled trial. *Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association* 2011;**17**(3):174–9.

Barreda 2009 *{published data only}*
Barreda L, Targarona Modena J, Milian W, Portugal J, Sequeiros J, Pando E, et al. Is the prophylactic antibiotic therapy with imipenem effective for patients with pancreatic necrosis? [Es la antibioticoterapia profilactica con Imipenem efectiva en los pacientes con necrosis pancreatica?]. *Acta Gastroenterologica Latinoamericana* 2009;**39**(1):24–9.

Berling 1994 *{published data only}*
Berling R, Borgstrom A, Ohlsson K. Peritoneal lavage with aprotinin in patients with severe acute pancreatitis: effects on plasma and peritoneal levels of trypsin and leukocyte proteases and their major inhibitors. *International Journal of Pancreatology* 1998;**24**(1):9–17.
* Berling R, Genell IS, Ohlsson K. High-dose intraperitoneal aprotinin treatment of acute severe pancreatitis: a

double-blind randomized multi-center trial. *Journal of Gastroenterology* 1994;**29**(4):479–85.
Berling R, Ohlsson K. Effects of high-dose intraperitoneal aprotinin treatment on complement activation and acute phase response in acute severe pancreatitis. *Journal of Gastroenterology* 1996;**31**(5):702–9.

Besselink 2008 *{published data only}*
Besselink MG, van Santvoort HC, Boermeester MA, Fischer K, Renooij W, de Smet MB, et al. Intestinal barrier dysfunction in a randomised placebo-controlled trial of probiotic prophylaxis in acute pancreatitis. *European Journal of Gastroenterology & Hepatology* 2009;**21**(3):A2–A.
Besselink MG, van Santvoort HC, Buskens E, Akkermans LM, Gooszen HG, Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis - reply. *Lancet* 2008;**372**(9633):114.
* Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, Goor H, Timmerman HM, et al. Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Erratum in: Lancet 2008; 371(9620):1246. *Lancet* 2008;**371**(9613):651–9.
Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in patients with predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial [Probioticaprofylaxe bij voorspeld ernstige acute pancreatitis: een gerandomiseerde, dubbelblinde, placebogecontroleerde trial.]. *Nederlands Tijdschrift voor Geneeskunde* 2008;**152**(12):685–96.
Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *European Journal of Gastroenterology & Hepatology* 2009;**21**(3):A8–9.
Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**371**(9613):651–9.
Besselink MG, van Santvoort HC, Renooij W, Smet MB, Boermeester MA, Fischer K, et al. Intestinal barrier dysfunction in a randomized trial of a specific probiotic composition in acute pancreatitis. *Annals of Surgery* 2009;**250**(5):712–9.
Besselink MGH, Timmerman HM, Buskens E, Nieuwenhuijs VB, Akkermans LMA, Gooszen HG. Probiotic prophylaxis in patients with predicted severe acute pancreatitis (propatria): design and rationale of a double-blind, placebo controlled randomised multicenter trial [ISCRTN 38327949]. *BMC Surgery* 2004;**4**:12.
Besselink MGH, van Santvoort HC, Buskens E, Boermeester MA, Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**371**(9620):1246.
The Editors of The Lancet. Expression of concern-probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010;**375**(9718):875–6.

Birk 1994 *{published data only}*
Birk D, Schoenberg MH, Adler G, Beger HG. Oxidative stress in acute-pancreatitis - results of a prospective randomized clinical pilot-study. *Gastroenterology* 1994;**106**(4):A286–A.

Bredkjaer 1988 *{published data only}*
Bredkjaer HE, Bülow S, Ebbehøj N, Friis J, Lindewald H, Rasmussen SG, et al. Treatment of acute pancreatitis with indomethacin. A controlled study of the formation of pseudocysts and their subsequent course [Indometacinbehandling ved pancreatitis acuta. En kontrolleret undersogelse af forekomst og forlob af pseudocystedannelse]. *Ugeskrift for Laeger* 1988;**150**(47):2902–3.

Buchler 1993 *{published data only}*
* Buchler M, Malfertheiner P, Uhl W, Scholmerich J, Stockmann F, Adler G, et al. Gabexate mesilate in human acute pancreatitis. German pancreatitis study group. *Gastroenterology* 1993;**104**(4):1165–70.
Buchler M, Malfertheiner P, Uhl W, Scholmerich J, Stockmann F, Adler G, et al. Gabexate-mesilate in human acute pancreatitis: results from the German multicenter trial with 4 g/day [abstract]. *Digestion* 1990;**46**(3):130.

Chen 2000 *{published data only}*
Chen HM, Chen JC, Hwang TL, Jan YY, Chen MF. Prospective and randomized study of gabexate mesilate for the treatment of severe acute pancreatitis with organ dysfunction. *Hepato-Gastroenterology* 2000;**47**(34):1147–50.

Chen 2002a *{published data only}*
Chen SY, Wang JY. Ulinastatin in the treatment of acute pancreatitis: a multicenter clinical trial. *Chinese Journal of Digestive Diseases* 2002;**3**(2):70–4.

Chen 2002b *{published data only}*
Chen SY, Wang JY. Ulinastatin in the treatment of acute pancreatitis: a multicenter clinical trial. *Chinese Journal of Digestive Diseases* 2002;**3**(2):70–4.

Choi 1989 *{published data only}*
Choi TK, Mok F, Zhan WH, Fan ST, Lai EC, Wong J. Somatostatin in the treatment of acute pancreatitis: a prospective randomised controlled trial. *Gut* 1989;**30**(2):223–7.

Chooklin 2007 *{published data only}*
Chooklin S, Vatseba R. N-acetylcysteine and dexamethasone in the prevention of respiratory complications in acute pancreatitis [abstract]. *European Respiratory Journal* 2007;**30**(Suppl 51):51s [E470].

Debas 1980 *{published data only}*
Debas HT, Hancock RJ, Soon-Shiong P. Glucagon therapy in acute pancreatitis: prospective randomized double-blind study. *Canadian Journal of Surgery* 1980;**23**(6):578–80.

Delcenserie 1996 *{published data only}*

Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. *Pancreas* 1996;**13**(2):198–201.

Delcenserie 2001 *{published data only}*

Delcenserie R, Dellion-Lozinguez MP, Pagenault M, Hastier P, Yzet T, Dupas JL, et al. Prophylactic ciprofloxacin treatment in acute necrotizing pancreatitis: a prospective randomized multicenter clinical trial. *Gastroenterology* 2001;**120**(5):A25–A.

Dellinger 2007 *{published data only}*

* Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. *Annals of Surgery* 2007;**245**(5): 674–83.

Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Re: Early antibiotic treatment for severe acute necrotizing pancreatitis - reply. *Annals of Surgery* 2008;**247**(2):394–5.

Dürr 1978 *{published data only}*

Dürr HK, Kunz R, Zelder O. The treatment of acute pancreatitis with glucagon: a double blind study. *Archives Francaises des Maladies de l'Appareil Digestif* 1975;**64**(7 Suppl 4):349.

* Dürr HK, Maroske D, Zelder O, Bode Ch J. Glucagon therapy in acute pancreatitis. Report of a double-blind trial. *Gut* 1978;**19**(3):175–9.

Dürr HK, Zelder O, Maroske D, Bode JC. Treatment of acute pancreatitis with glucagon. Report on a double blind study [Zur behandlung der akuten pankreatitis mit glucagon. Bericht über eine doppelblindstudie]. *Verhandlungen der Deutschen Gesellschaft für Innere Medizin* 1976;**82 Pt 1**:970–3.

Ebbehøj 1985 *{published data only}*

Ebbehøj N, Bülow S, Friis J, Madsen P, Svendsen LB. Indomethacin treatment of acute pancreatitis. *Scandinavian Journal of Gastroenterology Supplement* 1984;**19**(Suppl 98): 36.

* Ebbehøj N, Friis J, Svendsen B. Indomethacin treatment of acute pancreatitis. A controlled double-blind trial. *Scandinavian Journal of Gastroenterology* 1985;**20**(7): 798–800.

Finch 1976 *{published data only}*

Finch WT, Sawyers JL, Schenker S. A prospective study to determine the efficacy of antibiotics in acute pancreatitis. *Annals of Surgery* 1976;**183**(6):667–71.

Freise 1986 *{published data only}*

Freise J, Melzer P. Foy in the treatment of acute-pancreatitis - results of the Hannover multicentric double-blind-study with 50 patients. *Zeitschrift Für Gastroenterologie* 1985;**23** (9):429.

* Freise J, Melzer P, Schmidt FW, Horbach L. Gabexate mesilate in the treatment of acute pancreatitis - results of the Hannover multicenter double-blind trial with 50 patients [Gabexat mesilat in der behandlung der akuten pankreatitis. Ergebnisse der hannoverschen multizentrischen doppelblindstudie mit 50 patienten]. *Zeitschrift Fur Gastroenterologie* 1986;**24**(4):200–11.

Frulloni 1994 *{published data only}*

Frulloni L, Bassi C, Bovo P, Falconi M, Di Francesco V, Pederzoli P, et al. Gabexate mesilate vs aprotinin in the treatment of acute necrotizing pancreatitis. *Argomenti di Gastroenterologia Clinica* 1994;**7**(1):31–6.

Garcia-Barrasa 2009 *{published data only}*

Garcia-Barrasa A, Borobia FG, Pallares R, Jorba R, Poves I, Busquets J, et al. A double-blind, placebo-controlled trial of ciprofloxacin prophylaxis in patients with acute necrotizing pancreatitis. *Journal of Gastrointestinal Surgery* 2009;**13**(4): 768–74.

Gilsanz 1978 *{published data only}*

Gilsanz V, Oteyza CP, Rebollar JL. Glucagon vs anticholinergics in the treatment of acute pancreatitis. A double-blind controlled trial. *Archives of Internal Medicine* 1978;**138**(4):535–8.

Gjørup 1992 *{published data only}*

* Gjørup I, Roikjaer O, Andersen B, Burcharth F, Hovendal C, Pedersen SA, et al. A double-blinded multicenter trial of somatostatin in the treatment of acute pancreatitis. *Surgery, Gynecology & Obstetrics* 1992;**175**(5):397–400.

Gjørup I, Roikjær O, Andersen B, Burcharth F, Hovendal C, Pedersen SA, et al. Somatostatin in the treatment of acute pancreatitis a double-blind multicenter trial [abstract]. *Digestion* 1990;**46**(3):140.

Goebell 1979 *{published data only}*

Goebell H, Ammann R, Akovbiantz A. Calcitonin in the treatment of acute pancreatitis. A multi centre double blind study. *Irish Journal of Medical Science* 1977;**146**(Suppl 1): 105.

* Goebell H, Ammann R, Herfarth C. A double-blind trial of synthetic salmon calcitonin in the treatment of acute pancreatitis. *Scandinavian Journal of Gastroenterology* 1979; **14**(7):881–9.

Goebell 1988 *{published data only}*

Goebell H. Multicenter double-blind trial of low-dose intravenous proteinase-inhibitor (foy-r) in patients with acute-pancreatitis. *Zeitschrift Für Gastroenterologie* 1988;**26** (9):447.

Goebell H. Multicenter double-blind-study of gabexate-mesilate (foy), given intravenously in low-dose in acute-pancreatitis. *Digestion* 1988;**40**(2):83–.

Grupo Español 1996 *{published data only}*

Grupo Español Cooperativo para el Estudio de la Somatostatina en el Tratamiento de la Pancreatitis Aguda Grave. [Somatostatina en el tratamiento de la pancreatitis aguda grave: ensayo clínico multicentrico, controlado, con asignación aleatoria y doble ciego. Presentación de resultados en el análisis secuencial]. *Revista Española de Enfermedades Digestivas* 1996;**88**(10):717–8.

Guo 2015 *{published data only}*

Guo H, Chen J, Suo D. Clinical efficacy and safety of ulinastatin plus octreotide for patients with severe acute

pancreatitis. *Zhonghua Yixue Zazhi [Chinese Medical Journal]* 2015;**95**(19):1471–4. PUBMED: 26178495]

Hansky 1969 *{published data only}*

Hansky J. The use of a peptidase inhibitor in the treatment of acute pancreatitis. *Medical Journal of Australia* 1969;**1** (25):1284–5.

Hejtmankova 2003 *{published data only}*

Hejtmankova S, Cech P, Hoskovec D, Kostka R, Leffler J, Kasalicky M, et al. Antibiotic prophylaxis in severe acute pancreatitis: randomized multicenter prospective study with meropenem. *Gastroenterology* 2003;**124**(4):A85–A.

Imrie 1978 *{published data only}*

Imrie CW, Benjamin IS, Ferguson JC. A single centre double blind trial of trasylol therapy in primary acute pancreatitis. *Irish Journal of Medical Science* 1977;**146** (suppl.1):no.103.

* Imrie CW, Benjamin IS, Ferguson JC. A single-centre double-blind trial of trasylol therapy in primary acute pancreatitis. *British Journal of Surgery* 1978;**65**(5):337–41.

Imrie CW, Benjamin IS, Ferguson JC. Single centre double-blind trial of trasylol therapy in primary acute pancreatitis. *Gut* 1977;**18**(11):A957–A8.

Imrie CW, Benjamin IS, Ferguson JC, McKay AJ, Mackenzie I, Oneill J, et al. Single center double-blind trial of trasylol therapy in primary acute-pancreatitis. *Gastroenterologie Clinique et Biologique* 1978;**2**(11):954.

Imrie CW, Benjamin IS, Ferguson JC, Thomson WO, McKay AJ, Blumgart LH. Single-center double-blind trial of aprotinin (trasylol) therapy in primary acute-pancreatitis. *Annals of the Royal College of Surgeons of England* 1978;**60** (2):142.

Imrie 1980 *{published data only}*

Imrie CW, McKay AJ, Neill JO, Campbell FC, Gordon DA, Lang JA. Short duration megadosage iv trasylol in primary acute pancreatitis - a double-blind trial [abstract]. *Gut* 1980;**21**(Suppl 21):A457.

Isenmann 2004 *{published data only}*

Beger HG, Isenmann R. Discussion on prophylactic antibiotic treatment in patients with predicted severe pancreatitis: a placebo-controlled, double-blind trial - reply. *Gastroenterology* 2004;**127**(3):1016–7.

Isenmann R, Ruenzi M, Kron M, Goebell H, Beger HG. Prophylactic antibiotics in severe acute pancreatitis. Results of a double-blind, placebo-controlled multicenter trial. *Gastroenterology* 2003;**124**(4):A32–A.

* Isenmann R, Runzi M, Kron M, Kahl S, Kraus D, Jung N. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology* 2004;**126**(4):997-1004. [see comment].

Johnson 2001 *{published data only}*

* Johnson CD, Kingsnorth AN, Imrie CW, McMahon MJ, Neoptolemos JP, McKay C, et al. Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. *Gut* 2001;**48**(1):62–9.

Kingsnorth AN. Early treatment with lexipafant, a platelet activating factor antagonist reduces mortality in acute pancreatitis: a double blind, randomized, placebo controlled study. *Gastroenterology* 1997;**112**(4):A453–A.

Toh SKC. Lexipafant, a platelet activation factor (paf) antagonist, reduces mortality in a randomised placebo-controlled study in patients with severe acute pancreatitis [abstract]. *Gut* 1997;**40**(Suppl 1):A12.

Kalima 1980 *{published data only}*

Kalima TV, Lempinen M. The effect of zinc-protamine-glucagon in acute pancreatitis. *Annales Chirurgiae et Gynaecologiae* 1980;**69**(6):293–5.

Kingsnorth 1995 *{published data only}*

Galloway SW, Formela L, Kingsnorth AN. A double blind placebo controlled study of bb-882 (a potent paf antogonist) in human acute pancreatitis. *Gut* 1994;**35**(Suppl 5):T139.

Galloway SW, Formela L, Kingsnorth AN. A double-blind placebo controlled study of lexipafant (a potent paf antagonist) in acute pancreatitis. *Gut* 1995;**36**(3):A478.

* Kingsnorth AN, Galloway SW, Formela LJ. Randomized, double-blind phase ii trial of lexipafant, a platelet-activating factor antagonist, in human acute pancreatitis. *British Journal of Surgery* 1995;**82**(10):1414–20.

Kirsch 1978 *{published data only}*

Kirsch A, Werner U, Heinze D. Proteinase inhibiting agents and glucagon in acute pancreatitis (author's transl). *Zentralblatt für Chirurgie* 1978;**103**(5):291–303.

Kronborg 1980 *{published data only}*

* Kronborg O, Bulow S, Joergensen PM, Svendsen LB. A randomized double-blind trial of glucagon in treatment of first attack of severe acute pancreatitis without associated biliary disease. *American Journal of Gastroenterology* 1980; **73**(5):423–5.

Kronborg O, Jorgensen PM, Bulow S. Controlled randomized trial of glucagon in treatment of 1st attack of severe acute-pancreatitis without associated biliary disease, interim-report. *Scandinavian Journal of Gastroenterology* 1976;**11**:13.

Llukacaj 2012 *{published data only}*

Llukacaj A, Naco M, Mandi A, Rakipi B, Kodra N. Prophylactic antibiotic treatment for severe acute necrotizing pancreatitis. *European Journal of Anaesthesiology* 2012;**29** (Suppl 50):28.

Luengo 1994 *{published data only}*

Luengo L, Gómez R, Castellote M, Ros S, Feliu F, Vadillo J. Influence of somatostatin in the evolution of acute pancreatitis. *Cirugía Española* 1994;**56**(Suppl 1):11–2.

* Luengo L, Vicente V, Gris F, Coronas JM, Escuder J, Gomez JR, et al. Influence of somatostatin in the evolution of acute pancreatitis: a prospective randomized study. *International Journal of Pancreatology* 1994;**15**(2):139–44.

Luiten 1995 *{published data only}*

Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment

of severe acute pancreatitis. *Annals of Surgery* 1995;**222**(1): 57–65.

Marek 1999 ***{published data only}***

Marek TA, Dziurkowska-Marek A, Nowak A, Kacperek-Hartleb T, Sierka E, Nowakowska-Dulawa E. Prospective, randomized, placebo-controlled trial of ascorbic acid in human acute pancreatitis. *Gut* 1999;**45**(Suppl. V):A315.

Martinez 1984 ***{published data only}***

Martinez E, Navarrete F. A controlled trial of synthetic salmon calcitonin in the treatment of severe acute pancreatitis. *World Journal of Surgery* 1984;**8**(3):354–9.

McKay 1997a ***{published data only}***

* McKay C, Baxter J, Imrie C. A randomized, controlled trial of octreotide in the management of patients with acute pancreatitis. *International Journal of Pancreatology* 1997;**21** (1):13–9.

McKay C, Baxter JN, Imrie CW. Octreotide in acute-pancreatitis - a randomized controlled trial. *British Journal of Surgery* 1994;**81**(12):1814–.

McKay 1997b ***{published data only}***

Curran FJM, Sharples CE, Young CA, Curtis L, McKay CJ, Baxter JN, et al. Controlled trial of lexipafant in severe acute pancreatitis. *Pancreas* 1995;**11**(4):424.

* McKay CJ, Curran F, Sharples C, Baxter JN, Imrie CW. Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis. *British Journal of Surgery* 1997;**84**(9):1239–43.

McKay CJ, Imrie CW. Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis - reply. *British Journal of Surgery* 1998;**85**(2): 280.

Moreau 1986 ***{published data only}***

Moreau J, Bommelaer G, Buscail L, Benque A, Jacob C, Galleyrand J, et al. Preliminary-results of a multicentric double-blind trial of somatostatin (s) vs placebo (p) in acute-pancreatitis (ap). *Digestive Diseases and Sciences* 1986; **31**(10):S24–S.

MRC Multicentre Trial 1977 ***{published data only}***

Death from acute pancreatitis. M.R.C. Multicentre trial of glucagon and aprotinin. *Lancet* 1977;**2**(8039):632–5.

Nordback 2001 ***{published data only}***

Nordback I, Sand J, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis--a single-center randomized study. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 2001;**5**(2):113–8.

Ohair 1993 ***{published data only}***

Ohair DP, Hoffman RG, Schroeder H, Wilson SD. Octreotide in the treatment of acute-pancreatitis - a prospective, randomized trial. *Gastroenterology* 1993;**104** (4):A326–A.

Olah 2007 ***{published data only}***

Olah A, Belagyi T, Poto L, Romics Jr L, Bengmark S. Synbiotic control of inflammation and infection in severe acute pancreatitis: a prospective, randomized, double blind study. *Hepato-Gastroenterology* 2007;**54**(74):590–4.

Paran 1995 ***{published data only}***

Paran H, Neufeld D, Mayo A, Shwartz I, Singer P, Kaplan O, et al. Preliminary report of a prospective randomized study of octreotide in the treatment of severe acute pancreatitis. *Journal of the American College of Surgeons* 1995;**181**(2):121–4.

Pederzoli 1993a ***{published data only}***

Bassi C, Cavallini G, Bovo P, Bonora A, Vesentini S, Pederzoli P. Gabexate mesilate in acute pancreatitis (ap). The Italian multicentric trial. *International Journal of Pancreatology* 1992;**12**(1):76.

Bassi C, Vesentini S, Campedelli A, Nifosi F, Girelli R, Falconi M, et al. Imipenem prophylaxis in necrotizing pancreatitis: results of a multicenter study. *International Journal of Pancreatology* 1992;**12**(1):77.

* Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surgery, Gynecology & Obstetrics* 1993;**176**(5):480–3.

Pederzoli 1993b ***{published data only}***

Bassi C, Cavallini G, Bovo P, Bonora A, Vesentini S, Pederzoli P. Gabexate mesilate in acute pancreatitis (ap). The Italian multicentric trial. *International Journal of Pancreatology* 1992;**12**(1):76.

Bassi C, DiCarlo V, Zerbi A, Galloro V, Uomo G, Fontana G, et al. Role of imipenem (i) in preventing infected necrosis (in) during acute pancreatitis (np) results of the Italian multicenter study [abstract]. *Digestion* 1992;**52**(2): 68.

* Pederzoli P, Cavallini G, Falconi M, Bassi C. Gabexate mesilate vs aprotinin in human acute pancreatitis (ga.Me.P.A.): A prospective, randomized, double-blind multicenter study. *International Journal of Pancreatology* 1993;**14**(2):117–24.

Perezdeoteyza 1980 ***{published data only}***

Perezdeoteyza C, Rebollar JL, Ballarin M, Chantres MT, Alonso A, Marin J, et al. Controlled treatment of acute-pancreatitis - double-blind-study with cimetidine [Tratamiento controlado de la pancreatitis aguda. Ensayo doble ciego con cimetidina]. *Revista Clinica Española* 1980; **158**(6):263–6.

Pettila 2010 ***{published data only}***

Kyhala L, Lindstrom O, Kylanpaa L, Mustonen H, Puolakkainen P, Kemppainen E, et al. Activated protein C retards recovery from coagulopathy in severe acute pancreatitis. *Scandinavian Journal of Clinical and Laboratory Investigation* 2016;**76**(1):10–6.

* Pettila V, Kyhala L, Kylanpaa ML, Leppaniemi A, Tallgren M, Markkola A, et al. APCAP - activated protein C in acute pancreatitis: a double-blind randomized human pilot trial. *Critical Care* 2010;**14**(4):R139.

Plaudis 2010 ***{published data only}***

Plaudis H, Boka V, Pupelis G. Early low volume oral synbiotic/prebiotic supplemented enteral stimulation of the gut in patients with sap: randomized double blind prospective study. *HPB* 2010;**12**(Suppl 1):49.

Poropat 2015 *{published data only}*

Poropat G, Giljaca V, Licul V, Hauser G, Milic S, Stimac D. Imipenem prophylaxis for predicted severe acute pancreatitis-preliminary results of a randomized clinical trial. *United European Gastroenterology Journal* 2015;**3**(5 Suppl):A172.

Rokke 2007 *{published data only}*

Rokke O, Harbitz TB, Liljedal J, Pettersen T, Fetvedt T, Heen LO, et al. Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. *Scandinavian Journal of Gastroenterology* 2007;**42**(6):771–6.

Sainio 1995 *{published data only}*

* Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, et al. Early antibiotic treatment in acute necrotising pancreatitis. *Lancet* 1995;**346**(8976): 663–7.

Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, et al. Early antibiotic-treatment in acute necrotizing pancreatitis - a prospective randomized study. *Gastroenterology* 1994;**106**(4):A319–A.

Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, et al. Prophylactic antibiotic-treatment in acute necrotizing pancreatitis - a prospective randomized study. *Gastroenterology* 1993;**104**(4):A332–A.

Sateesh 2009 *{published data only}*

Sateesh J, Bhardwaj P, Singh N, Saraya A. Effect of antioxidant therapy on hospital stay and complications in patients with early acute pancreatitis: a randomised controlled trial. *Tropical Gastroenterology* 2009;**30**(4): 201–6.

Sharma 2011 *{published data only}*

Sharma B, Srivastava S, Singh N, Sachdev V, Kapur S, Saraya A. Role of probiotics on gut permeability and endotoxemia in patients with acute pancreatitis: a double-blind randomized controlled trial. *Journal of Clinical Gastroenterology* 2011;**45**(5):442–8.

Sillero 1981 *{published data only}*

Sillero C, Perez-Mateo M, Vazquez N, Martin A. Controlled trial of cimetidine in acute pancreatitis. *European Journal of Clinical Pharmacology* 1981;**21**(1):17–21.

Siriwardena 2007 *{published data only}*

Sinwardena AK, Mason JM, Balachandra S, Bagul A, Galloway S, Formela L, et al. Randomized, double-blind, placebo-controlled, trial of high-dose intravenous anti-oxidant therapy in severe acute pancreatitis. *Gastroenterology* 2006;**130**(4):A83–A.

* Siriwardena AK, Mason JM, Balachandra S, Bagul A, Galloway S, Formela L, et al. Randomised, double blind, placebo controlled trial of intravenous antioxidant (n-acetylcysteine, selenium, vitamin c) therapy in severe acute pancreatitis. *Gut* 2007;**56**(10):1439–44.

Spicak 2002 *{published data only}*

Hubaczova M, Spicak J, Antos F, Bartova I, Cech P, Kasalicky P, et al. The role of antibiotic treatment in severe form of acute pancreatitis: a randomized prospective study. *Gastroenterology* 2001;**120**(5):A645–A.

Hubaczová M, Spicák J, Antós F, Bártová I, Cech P, Kasalický M, et al. The role of antibiotic treatment in severe form of acute pancreatitis: a randomized prospective study [abstract]. *Gut* 2000;**47**(Suppl III):A142.

* Spicak J, Hubaczova M, Antos F, Bartova J, Cech P, Kasalicky M, et al. Antibiotics in the treatment of acute pancreatitis - findings from a randomized multi-centre prospective study [Antibiotika v léč bě akutní pankreatitidy – pouč ení z randomizonvané multicentrické prospektivni studie]. *Ceska a Slovenska Gastroenterologie a Hepatologie* 2002;**56**(5):183–9.

Spicak 2003 *{published data only}*

Spicak J, Hejtmankova S, Hubaczova M, Antos F, Bartova J, Cech P, et al. Antibiotic prophylaxis of infectious complications of acute pancreatitis - the results of randomised study by meropenem [Antibiotiká profylaxe infekč ních komplikací u akutní pankreatitidy – výsledky randomizonvané studie s meropenemem]. *Ceska a Slovenska Gastroenterologie a Hepatologie* 2003;**57**(6):222–7.

Storck 1968 *{published data only}*

Storck G, Persson B. Trasylol treatment of acute pancreatitis. A double-blind study [Trasylol vid akut pankreatit. En dubbel–blindstudie]. *Nordisk Medicin* 1968;**79**(20):651–3.

Trapnell 1974 *{published data only}*

Trapnell JE. Controlled study of aprotinin in the treatment of acute pancreatitis [Etude controlee de l'aprotinine dans le traitement de la pancreatie aigue]. *Annales de Chirurgie* 1976;**30**(3):201.

* Trapnell JE, Rigby CC, Talbot CH, Duncan EH. A controlled trial of trasylol in the treatment of acute pancreatitis. *British Journal of Surgery* 1974;**61**(3):177–82.

Trapnell JE, Rigby CC, Talbot CH, Duncan EH. Controlled study on trasylol in the treatment of acute pancreatitis [Eine kontrollierte prufung von trasylol bie der behandlung der akuten pankreatitis]. *Die Medizinische Welt* 1974;**25**(50): 2106–11.

Trapnell JE, Talbot CH, Capper WM. Trasylol in acute pancreatitis. *The American Journal of Digestive Diseases* 1967;**12**(4):409–12.

Tykka 1985 *{published data only}*

Tykka HT, Vaittinen EJ, Mahlberg KL. A randomized double-blind study using cana2edta, a phospholipase a2 inhibitor, in the management of human acute pancreatitis. *Scandinavian Journal of Gastroenterology* 1985;**20**(1):5–12.

Uhl 1999 *{published data only}*

* Uhl W, Buchler MW, Malfertheiner P, Beger HG, Adler G, Gaus W. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 1999;**45**(1):97–104.

Uhl W, Malfertheiner P, Adler G, Bruch HP, Lankisch PG, Lorenz D, et al. A randomized controlled multicentric

trial on the role of octreotide in human acute pancreatitis. *Gastroenterology* 1997;**112**(4):A488–A.

Usadel 1985 ***{published data only}***
Usadel KH, Uberla KK, Leuschner U. Treatment of acute-pancreatitis with somatostatin - results of the multicenter double-blind trial (apts-study). *Digestive Diseases and Sciences* 1985;**30**(10):992.

Valderrama 1992 ***{published data only}***
Valderrama R, Pérez-Mateo M, Navarro S, Vázquez N, Sanjosé L, Adrián MJ, et al. Multicenter double-blind trial of gabexate mesylate (foy) in unselected patients with acute pancreatitis. *Digestion* 1992;**51**(2):65–70.

Vege 2015 ***{published data only}***
* Vege SS, Atwal T, Bi Y, Chari ST, Clemens MA, Enders FT. Pentoxifylline treatment in severe acute pancreatitis: a pilot, double-blind, placebo-controlled, randomized trial. *Gastroenterology* 2015;**149**(2):318–20.e3.
Vege SS, Atwal T, Chari ST, Pearson RK, Loftus CG, Enders F, et al. Pentoxifylline treatment in predicted severe acute pancreatitis: a randomized double-blind placebo-controlled trial. *Gastroenterology* 2013;**144**(Suppl 1):S111–2.

Wang 2011 ***{published data only}***
Wang X, Li W, Niu C, Pan L, Li N, Li J. Thymosin alpha 1 is associated with improved cellular immunity and reduced infection rate in severe acute pancreatitis patients in a double-blind randomized control study. *Inflammation* 2011;**34**(3):198–202.

Wang 2013a ***{published data only}***
Wang G, Wen J, Wilbur RR, Wen P, Zhou SF, Xiao X. The effect of somatostatin, ulinastatin and salvia miltiorrhiza on severe acute pancreatitis treatment. *American Journal of the Medical Sciences* 2013;**346**(5):371–6.

Wang 2013b ***{published data only}***
Wang R, Yang F, Guo Z, Yi Z, Huang L, Hu B, et al. Alleviation of acute pancreatitis with octreotide and celecoxib-a randomized controlled trial. *Journal of Gastroenterology and Hepatology* 2013;**28**(Suppl):16–7.
Wang R, Yang F, Guo Z, Yi Z, Huang L, Tang C. Alleviation of acute pancreatitis with octreotide and celecoxib: a prospective randomized controlled trial. *Gastroenterology* 2013;**144**(Suppl 1):S139.
Wang R, Yang F, Guo ZZ, Yi ZH, Huang LB, Hu B, et al. Alleviation of acute pancreatitis with octreotide and celecoxib: a prospective randomized controlled trial. *Journal of Digestive Diseases* 2014;**15**(Suppl 1):8.

Wang 2013c ***{published data only}***
Wang R, Yang F, Wu H, Wang Y, Huang Z, Hu B, et al. High-dose versus low-dose octreotide in the treatment of acute pancreatitis: a randomized controlled trial. *Peptides* 2013;**40**:57–64. [DOI: 10.1016/j.peptides.2012.12.018]
Wang R, Yang F, Wu H, Wang YF, Hu B, Zhang MG, et al. Octreotide at high dose in the treatment of acute pancreatitis: a prospective randomized controlled trial. *Gastroenterology* 2012;**142**(5):S62.

Wang 2016 ***{published data only}***
Wang G, Liu Y, Zhou SF, Qiu P, Xu L, Wen P, et al. Effect of somatostatin, ulinastatin and gabexate on the treatment of severe acute pancreatitis. *American Journal of the Medical Sciences* 2016;**351**(5):506–12.

Xia 2014 ***{published data only}***
Xia YX, Liu XZ, Zhang XD, Shang PJ, Guo J. Efficacy and safety of omeprazole combined with somatostatin in treatment of severe acute pancreatitis. *Shijie Huaren Xiaohua Zazhi [World Chinese Journal of Digestology]* 2014; **22**(8):1179–83.

Xue 2009 ***{published data only}***
Xue P, Deng LH, Zhang ZD, Yang XN, Wan MH, Song B, et al. Effect of antibiotic prophylaxis on acute necrotizing pancreatitis: Results of a randomized controlled trial. *Journal of Gastroenterology and Hepatology (Australia)* 2009; **24**(5):736–42.

Yang 1999 ***{published data only}***
Yang JQ, Wang P, Zhong J, Liu YK, Liu ZJ. A controlled study of somatostatin in the treatment of acute pancreatitis. *Journal of Jinan University* 1999;**20**(2):50–2.

Yang 2012 ***{published data only}***
Yang F, Wu H, Li Y, Li Z, Wang C, Yang J, et al. Prevention of severe acute pancreatitis with octreotide in obese patients: a prospective multi-center randomized controlled trial. *Pancreas* 2012;**41**(8):1206–12.

Zhu 2014 ***{published data only}***
Zhu YM, Lin S, Dang XW, Wang M, Li L, Sun RQ, et al. Effects of probiotics in treatment of severe acute pancreatitis. *Shijie Huaren Xiaohua Zazhi [World Chinese Journal of Digestology]* 2014;**22**(32):5013–7.

References to studies excluded from this review

Akzhigitov 1968 ***{published data only}***
Akzhigitov GN. Use of monoaminoxidase inhibitor vetrazine in the treatment of acute pancreatitis [Primenenie ingibitora monoaminoksidazy vetrazina pri lechenii ostrogo pankreatita]. *Terapevticheskii Arkhiv* 1968;**40**(10):82–4.

Akzhigitov 1969 ***{published data only}***
Akzhigitov GN, Grach Z, Rubtsova LK, Koroleva VG, Pozdniakova VP. Use of glycocycline in the treatment of patients with acute pancreatitis and cholepancreatitis. *Antibiotiki* 1969;**14**(2):174–8.

Al-Leswas 2013a ***{published data only}***
Al-Leswas D, Arshad A, Eltweri A, Chung WY, Al-Taan O, Pollard C, et al. An omega-3 rich lipid emulsion is associated with improved clinical outcome in patients with severe acute pancreatitis: a randomised double-blind controlled trial. *British Journal of Surgery* 2013;**100**(Suppl 4):2.

Al-Leswas 2013b ***{published data only}***
Al-Leswas D, Chung WY, Eltweri A, Arshad A, Al-Taan O, Pollard C, et al. Evaluation of the acute inflammatory response to omega-3 fatty acids in patients with severe acute pancreatitis: a randomised controlled trial. *Pancreatology* 2013;**13**(1):e6.

Al-Leswas 2013c *{published data only}*
Al-Leswas D, Chung WY, Eltweri A, Stephenson J, Arshad A, Pollard C, et al. Evaluation of the cytokines response to omega-3 fatty acids in patients with severe acute pancreatitis: a randomised controlled trial. *Clinical Nutrition* 2013;**32** (Suppl 1):S2.

Al-Leswas 2013d *{published data only}*
Al-Leswas D, Eltweri A, Arshad A, Chung WY, Al-Taan O, Pollard C, et al. Progression of the early warning scores (ews) in severe acute pancreatitis patients treated with omega-3 fish oil: a randomised control trial. *Clinical Nutrition* 2013;**32**(Suppl 1):S47–S8.

Al-Leswas 2013e *{published data only}*
Al-Leswas D, Eltweri A, Arshad A, Chung WY, Stephenson J, Pollard C, et al. An omega-3 rich lipid emulsion is associated with fewer new organ failures, less systemic inflammatory response syndrome and improves the outcome in patients with severe acute pancreatitis: a randomised double-blind, phase ii control trial. *Pancreatology* 2013;**13** (1):e2.

Al-Leswas 2013f *{published data only}*
Al-Leswas D, Eltweri A, Chung WY, Al-Taan O, Arshad A, Pollard C, et al. An omega-3 rich lipid emulsion is associated with fewer new organ failures, less systemic inflammatory response syndrome and improves the outcome in patients with severe acute pancreatitis: A randomised double-blind, phase ii control trial. *Clinical Nutrition* 2013;**32**(Suppl 1): S2–3.

Al-Leswas 2013g *{published data only}*
Al-Leswas D, Eltweri A, Hall T, Stephenson J, Pollard C, Garcea G, et al. Safety and tolerability of two parenteral lipid emulsions in patients with severe acute pancreatitis as measured by serum triglyceride and cholesterol levels: a randomised controlled trial. *Clinical Nutrition* 2013;**32** (Suppl 1):S49–50.

Amundsen 1972 *{published data only}*
Amundsen E. The use of protease inhibitors during acute haemorrhagic pancreatitis. Experimental findings and clinical implications. *Annales Chirurgiae et Gynaecologiae Fenniae* 1972;**61**(5):284–7.

Andersson 2008 *{published data only}*
Andersson RG. Probiotics in acute pancreatitis. *British Journal of Surgery* 2008;**95**(8):941–2.

Baden 1967 *{published data only}*
Baden H, Jordal K, Lund F, Zachariae F. A double-blind controlled clinical trial of trasylol. Preliminary results in acute pancreatitis and in prophylaxis against postoperative pancreatitis. *Acta Chirurgica Scandinavica* 1967;**378** (Suppl):97–102.

Baden 1969 *{published data only}*
Baden H, Jordal K, Lund F, Zachariae F. Prophylactic and curative action of trasylol in pancreatitis; a double blind trial. *Scandinavian Journal of Gastroenterology* 1969;**4**(3): 291–5.

Bai 2013 *{published data only}*
Bai YT, Guo XZ, Li HY, Shao XD, Cui ZM, Wang D, et al. Therapeutic effect of ulinastatin vs gabexate mesilate in management of acute pancreatitis. *Shijie Huaren Xiaohua Zazhi [World Chinese Journal of Digestology]* 2013;**21**(14): 1339–42.

Bassi 1998 *{published data only}*
Bassi C, Falconi M, Talamini G, Uomo G, Papaccio G, Dervenis C, et al. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. *Gastroenterology* 1998;**115**(6):1513–7.

Beechey-Newman 1991 *{published data only}*
Beechey-Newman N, Lee W, Wilkinson M, Grogono J, McPherson GAD. Treatment with high dose octreotide improves the clinical course of acute pancreatitis [abstract]. *Gut* 1991;**32**(Suppl.5):A558.

Beechey-Newman 1993 *{published data only}*
Beechey-Newman N. Controlled trial of high-dose octreotide in treatment of acute pancreatitis. Evidence of improvement in disease severity. *Digestive Diseases and Sciences* 1993;**38**(4):644–7.

Beger 2001 *{published data only}*
Beger HG. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis - a single-center randomized study - commentary. *Journal of Gastrointestinal Surgery* 2001;**5**(2):119–20.

Bender 1992 *{published data only}*
Bender HJ, Albrecht MD, Quintel M, Ackern K. Use of octreotidacetate (sandostatin) in the treatment of necrotising haemorrhagic pancreatitis. *Der Anaesthesist* 1992;**41**(Suppl 2):S130.

Binder 1993 *{published data only}*
Binder M, Buchler M, Uhl W, Friess H, Dennler HJ, Beger HG. Octreotide in the treatment of acute pancreatitis: results of an unicentric prospective trial with three different octreotide dosages [Octreotide bei akuter pankreatitis: Ergebnisse einer unizentrischen prospektiven studie mit drei verschiedenen octreotide–dosierungen]. *Langenbecks Archiv fur Chirurgie* 1993;**Suppl 1 Forumband**:233–8.

Binder 1994 *{published data only}*
Binder M, Uhl W, Friess H, Malfertheiner P, Buchler MW. Octreotide in the treatment of acute pancreatitis: results of a unicenter prospective trial with three different octreotide dosages. *Digestion* 1994;**55**(Suppl 1):20–3.

Brown 2004 *{published data only}*
Brown A. Prophylactic antibiotic use in severe acute pancreatitis: Hemlock, help, or hype?. *Gastroenterology* 2004;**126**(4):1195–8.

Buchler 1988 *{published data only}*
Buchler M, Malfertheiner P, Uhl W, Wolf HR, Schwab G, Beger HG. Gabexate mesilate in the therapy of acute pancreatitis. Multicenter study of tolerance of a high intravenous dose (4 g/day) [Gabexat–mesilat in der therapie der akuten pankreatitis. Multicenterstudie zur vertraglichkeit einer hohen intravenosen dosis (4 g/Tag)]. *Medizinische Klinik* 1988;**83**(10):320-4, 52.

Cameron 1979 *{published data only}*
Cameron JL, Mehigan D, Zuidema GD. Evaluation of atropine in acute pancreatitis. *Surgery Gynecology and Obstetrics* 1979;**148**(2):206–8.

Cheng 2008 *{published data only}*
Cheng YX, Wang M, Cheng X. Effect of dachaihu decoction in treating acute mild pancreatitis of gan-qi stagnant type. *Zhongguo Zhongxiyi Jiehe Zqzhi [Chinese Journal of Integrated Traditional and Western Medicine]* 2008;**28**(9):793–6.

Cullimore 2008 *{published data only}*
Cullimore J, Cotter L, Gonzalez A. Antibiotics in acute necrotising pancreatitis [author reply]. *Lancet* 2008;**371** (9618):1072.

Curtis 1997 *{published data only}*
Curtis LD. Lexipafant(bb-882), a potent PAF antagonist in acute pancreatitis. *Advances in Experimental Medicine and Biology* 1997;**416**:361–3.

D'Amico 1990 *{published data only}*
D'Amico D, Favia G, Biasiato R, Casaccia M, Falcone F, Fersini M, et al. The use of somatostatin in acute pancreatitis--results of a multicenter trial. *Hepato-Gastroenterology* 1990;**37**(1):92–8.

Da Silvereira 2002 *{published data only}*
Da Silveira EBV, Barkin JS. Antibiotic prophylaxis in acute necrotizing pancreatitis. *American Journal of Gastroenterology* 2002;**97**(6):1557–9.

De Vries 2007 *{published data only}*
De Vries AC, Besselink MG, Buskens E, Ridwan BU, Schipper M, van Erpecum KJ, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. *Pancreatology* 2007;**7**(5-6):531–8.

Dikkenberg 2008 *{published data only}*
Dikkenberg GM. Probiotic prophylaxis in patients with predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial and informed consent procedure [author reply - 4] [Probioticaprofylaxe bij voorspeld ernstige acute pancreatitis; gerandomiseerde, dubbelblinde, placebogecontroleerde trial en informed–consentprocedure]. *Nederlands Tijdschrift voor Geneeskunde* 2008;**152**(28):1592.

Dreiling 1977 *{published data only}*
Dreiling DA, Nacchiero M, Kaplan. I. Is there a place for steroids in the treatment of pancreatic inflammation?. *American Journal of Gastroenterology* 1977;**67**(1):21–8.

Du 2002 *{published data only}*
Du W, Shen D, Huang C, Zhou Y. Effect of high-dose vitamin C on cellular immunity of patients with acute pancreatitis. *Wei Chang Bing Xue [Chinese Journal of Gastroenterology]* 2002;**7**(4):213–5.

Du 2003 *{published data only}*
Du WD, Yuan ZR, Sun J, Tang JX, Cheng AQ, Shen DM, et al. Therapeutic efficacy of high-dose vitamin c on acute pancreatitis and its potential mechanisms. *World Journal of Gastroenterology* 2003;**9**(11):2565–9.

Dürr 1985 *{published data only}*
Dürr GH, Schaefers A, Maroske D, Bode JC. A controlled study on the use of intravenous fat in patients suffering from acute attacks of pancreatitis. *Infusionstherapie und Klinische Ernahrung* 1985;**12**(3):128–33.

Freise 1985 *{published data only}*
Freise J, Schmidt FW, Maferstedt P, Schmid K. Gabexate mesilate and camostate: New inhibitors of phospholipase a2 and their influence on the alpha-amylase activity in serum of patients with acute pancreatitis. *Clinical Biochemistry* 1985;**18**(4):224–9.

Friess 1994 *{published data only}*
Friess H, Hofbauer B, Buchler MW. The role of somatostatin and octreotide in pancreatic surgery and in acute and chronic pancreatitis. *Digestive Surgery* 1994;**11**(3-6):445–50.

Gabryelewicz 1968 *{published data only}*
Gabryelewicz A, Niewiarowski S. Activation of blood clotting and inhibition of fibrinolysis in acute pancreatitis. *Thrombosis et Diathesis Haemorrhagica* 1968;**20**(3):409–14.

Gabryelewicz 1976 *{published data only}*
Gabryelewicz A, Olszewski S, Szalaj W, Puchalski Z, Stasiewicz J. Heparin and glucagon treatment of acute pancreatitis--results (author's transl) [Wyniki leczenia ostrego zapalenia trzustki za pomoca heparyny lub glukagonu]. *Przeglad Lekarski* 1976;**33**(2):323–8.

Gao 2015b *{published data only}*
Gao Q, Liang N. Integrated traditional Chinese medicine improves acute pancreatitis via the downregulation of prss1 and spink1. *Experimental and Therapeutic Medicine* 2015;**9** (3):947–54.

Garcia 2005 *{published data only}*
Garcia DA, Gonzalez JA, Rodriguez N, Britton CS, Hinojo E, Quintanilla C, et al. Utility of synbiotic therapy in acute pancreatitis. A double blind randomized clinical trial. *Gastroenterology* 2005;**128**(4 Suppl 2):A173–A.

Gostishchev 1977 *{published data only}*
Gostishchev VK, Lutsevich EV, Tolstykh PI, Vladimirov VG, Sergienko VI. [effectiveness of proteolysis inhibitors in treatment of acute pancreatitis]. *Khirurgiia* 1977, (7): 87–92.

Guo 2013 *{published data only}*
Guo Z, Wang R, Tang C. Effect of octreotide on plasma levels of somatostatin, interleukin-6, and tumor necrosis factor-alpha in patients with acute pancreatitis: A prospective single-center randomized controlled trial. *Gastroenterology* 2013;**144**(5 Suppl):S566.

Hajdu 2012 *{published data only}*
Hajdu N, Belagyi T, Issekutz A, Bartek P, Gartner B, Olah A. Intravenous glutamine and early nasojejunal nutrition in severe acute pancreatitis -- a prospective randomized clinical study [Intravenas glutamin es korai nasojejunalis taplalas egyuttes alkalmazasa sulyos acut pancreatitisben —- prospektiv randomizalt kettos vak kontrollalt klinikai vizsgalat]. *Magyar sebeszet* 2012;**65**(2):44–51.

Harinath 2002 *{published data only}*

Harinath G, O'Riordan B. Prospective randomized double-blind placebo-controlled trial of glyceryl trinitrate in endoscopic retrograde cholangiopacreatography-induced pancreatitis (Br J Surg 2001;88:1178-82). *The British Journal of Surgery* 2002;**89**(5):628-9; discussion 9.

Hart 2008 *{published data only}*

Hart PA, Bechtold ML, Marshall JB, Choudhary A, Puli SR, Roy PK. Prophylactic antibiotics in necrotizing pancreatitis: a meta-analysis. *Southern Medical Journal* 2008;**101**(11): 1126–31.

He 2004 *{published data only}*

He XL, Ma QJ, Lu JG, Chu YK, Du XL. Effect of total parenteral nutrition (tpn) with and without glutamine dipeptide supplementation on outcome in severe acute pancreatitis (sap). *Clinical Nutrition, Supplement* 2004;**1**(1): 43–7.

Helton 2001 *{published data only}*

Helton S, Nordback I, Rattner DW, Gloor B, Kumar A, Sarr MG, et al. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis - a single-center randomized study - discussion. *Journal of Gastrointestinal Surgery* 2001;**5**(2):118–9.

Hoekstra 2008 *{published data only}*

Hoekstra JH. Probiotic prophylaxis in patients with predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial and informed consent procedure [Probioticaprofylaxe bij voorspeld ernstige acute pancreatitis; gerandomiseerde, dubbelblinde, placebogecontroleerde trial en informed–consentprocedure]. *Nederlands Tijdschrift voor Geneeskunde* 2008;**152**(28): 1591-2; author reply 3-4.

Holub 1974 *{published data only}*

Holub K, Om P. Treatment of acute pancreatitis using glucagon [Glukagonbehandlung der akuten pankreatitis]. *Zentralblatt fur Chirurgie* 1974;**99**(24):748–50.

Howard 2007 *{published data only}*

Howard TJ. As good as it gets: the study of prophylactic antibiotics in severe acute pancreatitis. *Annals of Surgery* 2007;**245**(5):684–5.

Howes 1975 *{published data only}*

Howes R, Zuidema GD, Cameron JL. Evaluation of prophylactic antibiotics in acute pancreatitis. *Journal of Surgical Research* 1975;**18**(2):197–200.

Huang 2008 *{published data only}*

Huang XX, Wang XP, Ma JJ, Jing DD, Wang PW, Wu K. Effects of enteral nutrition supplemented with glutamine and arginine on gut barrier in patients with severe acute pancreatitis: a prospective randomized controlled trial. *National Medical Journal of China* 2008;**88**(34):2407–9.

Issekutz 2002 *{published data only}*

Issekutz A, Olah A, Bengmark S. Early enteral supply of lactobacilli + fibre vs. Placebo + fibre in severe acute pancreatitis - a prospective, randomized, controlled trial. *Zeitschrift fur Gastroenterologie* 2002;**40**(5):338.

Ivanov 2002 *{published data only}*

Ivanov Iu V, Chudnykh SM, Mozgalin AG. Effectiveness of mexidol in acute pancreatitis [Effektivnost' meksidola pri ostrom pankreatite]. *Klinicheskaia Meditsina* 2002;**80**(9): 44–6.

Jiang 1988 *{published data only}*

Jiang LS, Fang PS, Xu ZH. Controlled trial of calcium channel blocker, rou gui qing, and -receptor blocker for treatment of 80 patients with acute pancreatitis. *Linchuang Gandanbing Zazhi [Chinese Journal of Clinical Hepatology]* 1988;**4**(4):48.

Karakan 2007 *{published data only}*

Karakan T, Ergun M, Dogan I, Cindoruk M, Unal S. Comparison of early enteral nutrition in severe acute pancreatitis with prebiotic fiber supplementation versus standard enteral solution: a prospective randomized double-blind study. *World Journal of Gastroenterology* 2007;**13**(19): 2733–7.

Karakoyunlar 1999 *{published data only}*

Karakoyunlar O, Sivrel E, Tanir N, Denecli AG. High dose octreotide in the management of acute pancreatitis. *Hepato-Gastroenterology* 1999;**46**(27):1968–72.

Karavanov 1966 *{published data only}*

Karavanov AG, Osingolts SL. The use of epsilon-aminocaproic acid in the treatment of acute pancreatits [Primenenie epsilon–aminokapronovoi kisloty (E–AKK) v lechenii ostrykh pankreatitov]. *Klinicheskaia Meditsina* 1966;**44**(5):13–5.

Lasztity 2005a *{published data only}*

Lasztity N, Hamvas J, Biró L, Németh E, Marosvölgyi T, Decsi T, et al. Effect of enterally administered n-3 polyunsaturated fatty acids in acute pancreatitis--a prospective randomized clinical trial. *Clinical Nutrition* 2005;**24**(2):198–205.

Lasztity 2005b *{published data only}*

Lasztity N, Pap A, Hamvas J, Biro L, Nemeth E, Marosvolgyi T, et al. Effect of enterally administered n-3 polyunsaturated fatty acids in acute pancreatitis - a prospective randomized clinical trial. *Gastroenterology* 2005; **128**(4):A174–A.

Lasztity 2006 *{published data only}*

Lasztity N, Hamvas J, Biro L, Nemeth E, Marosvolgyi T, Decsi T, et al. Enteral administration of n-3 polyunsaturated fatty acids in acute pancreatitis [Az n–3 többszörösen telítetlen zsírsavak enteralis adása akut pancreatitisben – elő zetes eredmények]. *Lege Artis Medicinae* 2006;**16**(10): 848–54.

Lata 1998 *{published data only}*

Lata J, Dít P, Julínková K, Precechtě lová M, Prásek J. Effect of octreotide on the clinical course of acute pancreatitis and levels of free oxygen radicals and antioxidants [Vliv octreotidu na klinicky prubeh akutni pankreatitidy a hladinu volnych kyslikovych radikala a antioxidacnich latek]. *Vnitrní lékarství* 1998;**44**(9):524–7.

Lata 2010 *{published data only}*

Lata J, Juránková J, Stibu rek O, Príbramská V, Senkyrík M, Vanásek T. Probiotics in acute pancreatitis--a randomised, placebo-controlled, double-blind study [Probiotika u akutni pankreatitidy—-randomizovana, placebem kontrolovana, dvojite slepa studie]. *Vnitrní lékarstvíí* 2010;**56**(2):111–4.

Lim 2015 *{published data only}*

Lim CL, Lee W, Liew YX, Tang SS, Chlebicki MP, Kwa AL. Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. *Journal of Gastrointestinal Surgery* 2015;**19** (3):480–91.

Lu 2006 *{published data only}*

Lu J, Liu CW, Zheng YK, Hu W, Zhu KY, Hu WH. Effects of glutamine in hemodynamics and oxygen metabolism in patients with severe acute pancreatitis. *Zhongguo Linchuang Yingyang Zazhi [Chinese Journal of Clinical Nutrition]* 2006; **14**(4):227–30.

Lu 2008 *{published data only}*

Lu HG, Shi YB, Zhao LM, Bai C, Wang X. Role of enteral ebselen and ethylhydroxyethyl cellulose in pancreatitis-associated multiple-organ dysfunction in humans. *Journal of Organ Dysfunction* 2008;**4**(1):43–50.

Manes 2003 *{published data only}*

Manes G, Rabitti PG, Menchise A, Riccio E, Balzano A, Uomo G. Prophylaxis with meropenem of septic complications in acute pancreatitis: a randomized, controlled trial versus imipenem. *Pancreas* 2003;**27**(4): e79–83.

Manes 2006 *{published data only}*

Manes G, Uomo I, Menchise A, Rabitti PG, Ferrara EC, Uomo G. Timing of antibiotic prophylaxis in acute pancreatitis: a controlled randomized study with meropenem. *American Journal of Gastroenterology* 2006;**101** (6):1348–53.

McClave 2009 *{published data only}*

McClave SA, Heyland DK, Wischmeyer PE. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomized, double-blind, placebo-controlled trial. *Journal of Parenteral and Enteral Nutrition* 2009;**33**(4):444–6.

Mercadier 1973 *{published data only}*

Mercadier M, Chigot JP, Clot JP. Has glucagon a value in the treatment of acute pancreatitis? [Le glucagon a–t–il un intert dans le traitement des pancreatites aigues]. *Nouvelle Presse Medicale* 1973;**2**(40):2692.

Niu 2014 *{published data only}*

Niu G, Zhao R, Gao F, Zheng D, Liu X, Wu H, et al. Effect of omega-3 polyunsaturated fatty acids on intestinal mucosal barrier of patients with severe acute pancreatitis. *Zhongguo Linchuang Yingyang Zazhi [Chinese Journal of Clinical Nutrition]* 2014;**22**(6):329–33.

Pearce 2006 *{published data only}*

Pearce CB, Sadek SA, Walters AM, Goggin PM, Somers SS, Toh SK, et al. A double-blind, randomised, controlled trial to study the effects of an enteral feed supplemented with glutamine, arginine, and omega-3 fatty acid in predicted acute severe pancreatitis. *Journal of the Pancreas* 2006;**7**(4): 361–71.

Pederzoli 1995 *{published data only}*

Pederzoli P, Bassi C, Falconi M, De Santis L, Uomo G, Rabitti PG, et al. Gabexate mesilate in the treatment of acute pancreatitis. *Annali Italiani di Chirurgia* 1995;**66**(2): 191–5.

Pezzilli 1997 *{published data only}*

Pezzilli R, Dragonetti C, Innocenti P, Miglioli M. A multicenter, open label, copmarative, randomized study of two schedules of gabexate mesilate (1500 mg/day vs. 900 mg/day) for the treatment of severe acute pancreatitis. An interim report [abstract]. *Italian Journal of Gastroenterology and Hepatology* 1997;**29**(Suppl 1):A7. Abstract 17.

Pezzilli 1999 *{published data only}*

Pezzilli R, Dragonetti C, Innocenti P, Miglioli M. Amulticenter, open label, comparative, randomized study of two schedules of gabexate mesilate for the treatment of severe acute pancreatitis.[abstract]. *Gut* 1999;**45**(Suppl V): A315.

Pezzilli 2001 *{published data only}*

Pezzilli R, Miglioli M. Multicentre comparative study of two schedules of gabexate mesilate in the treatment of acute pancreatitis. *Digestive and Liver Disease* 2001;**33**(1):49–57.

Piascik 2010 *{published data only}*

Piascik M, Rydzewska G, Milewski J, Olszewski S, Furmanek M, Walecki J, et al. The results of severe acute pancreatitis treatment with continuous regional arterial infusion of protease inhibitor and antibiotic: a randomized controlled study. *Pancreas* 2010;**39**(6):863–7.

Plaudis 2012 *{published data only}*

Plaudis H, Pupelis G, Zeiza K, Boka V. Early low volume oral synbiotic/prebiotic supplemented enteral stimulation of the gut in patients with severe acute pancreatitis: a prospective feasibility study. *Acta Chirurgica Belgica* 2012; **112**(2):131–8.

Rahman 2003 *{published data only}*

Rahman SH, Catton JA, McMahon MJ. Letter 2: Randomized clinical trial of specific lactobacillus and fibre supplement to early enteral nutrition in patients with acute pancreatitis (Br J Surg 2002; 89: 1103-1107) [comment]. *British Journal of Surgery* 2003;**90**(1):123.

Ranson 1976 *{published data only}*

Ranson JH, Rifkind KM, Turner JW. Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. *Surgery, Gynecology & Obstetrics* 1976;**143**(2):209–19.

Reddy 2008 *{published data only}*

Reddy BS, MacFie J. Probiotic prophylaxis in predicted severe acute pancreatitis. *Lancet* 2008;**372**(9633):113–.

Santen 2008 *{published data only}*

Santen GW, Benus RF, van der Werf TS. Probiotic prophylaxis in patients with predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial and informed consent procedure [Probioticaprofylaxe bij voorspeld ernstige acute pancreatitis;

gerandomiseerde, dubbelblinde, placebogecontroleerde trial en informed–consentprocedure]. *Nederlands Tijdschrift voor Geneeskunde* 2008;**152**(28):1591; author reply 3-4.

Singer 1966 ***{published data only}***
Singer A, Tornya P, Skyring A. Double-blind study of trasylol in treatment of acute pancreatitis. *Gut* 1966;**7**(3): 304–&.

Skyring 1965 ***{published data only}***
Skyring A, Singer A, Tornya P. Treatment of acute pancreatitis with trasylol: report of a controlled therapeutic trial. *British Medical Journal* 1965;**2**(5462):627–9.

Tanaka 1979 ***{published data only}***
Tanaka N, Tsuchiya R, Ishii K. Comparative clinical study of foy and trasylol in acute pancreatitis. *Advances in Experimental Medicine and Biology* 1979;**120 B**:367–78.

Tang 2005 ***{published data only}***
Tang WF, Wan MH, Zhu L, Chen GY, Xia Q, Huang X. Immuno-modulatory effect of somatostatin combined with traditional Chinese medicine on severe acute pancreatitis at early stage: a randomized control trial. *Zhongxiyi Jiehe Xuebao [Journal of Chinese Integrative Medicine]* 2005;**3**(2): 103–7.

Tang 2007 ***{published data only}***
Tang WF, Wang YG, Zhu L, Wan MH, Chen GY, Xia Q, et al. Effect of somatostatin on immune inflammatory response in patients with severe acute pancreatitis. *Multiphase Pumping and Technologies Conference and Exhibition 2007* 2007;**8**(2):96–102.

Ukai 2015 ***{published data only}***
Ukai T, Shikata S, Inoue M, Noguchi Y, Igarashi H, Isaji S, et al. Early prophylactic antibiotics administration for acute necrotizing pancreatitis: A meta-analysis of randomized controlled trials. *Journal of Hepato-biliary-pancreatic Sciences* 2015;**22**(4):316–21.

Usadel 1980 ***{published data only}***
Usadel KH, Leuschner U, Uberla KK. Treatment of acute pancreatitis with somatostatin: a multicenter double blind study. *New England Journal of Medicine* 1980;**303**(17): 999–1000.

Venkatesan 2008 ***{published data only}***
Venkatesan T. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Nutrition in Clinical Practice* 2008;**23**(6): 662–3.

Villatoro 2010 ***{published data only}***
Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD002941.pub3]

Wang 2008 ***{published data only}***
Wang X, Li W, Li N, Li J. Omega-3 fatty acids - supplemented parenteral nutrition decreases hyperinflammatory response and attenuates systemic disease sequelae in severe acute pancreatitis: a randomized and controlled study. *Journal of Parenteral and Enteral Nutrition* 2008;**32**(3):236–41.

Wang 2009 ***{published data only}***
Wang X, Li W, Zhang F, Pan L, Li N, Li J. Fish oil-supplemented parenteral nutrition in severe acute pancreatitis patients and effects on immune function and infectious risk: a randomized controlled trial. *Inflammation* 2009;**32**(5):304–9.

Weismann 2010 ***{published data only}***
Weismann D, Maier SKG. Activated protein C in acute pancreatitis - a double-blind, randomized, placebo-controlled study [Aktiviertes protein C bei akuter pankreatitis - eine doppelblinde, randomisierte, placebo–kontrollierte studie]. *Medizinische Klinik* 2010; **105**(10):747.

Wyncoll 1998 ***{published data only}***
Wyncoll DL, Beale RJ. Prospective placebo-controlled randomized trial of lexipafant in predicted severe acute pancreatitis. *The British Journal of Surgery* 1998;**85**(2): 279–80.

Xiong 2009 ***{published data only}***
Xiong J, Zhu S, Zhou Y, Wu H, Wang C. Regulation of omega-3 fish oil emulsion on the sirs during the initial stage of severe acute pancreatitis. *Journal of Huazhong University of Science and Technology - Medical Science* 2009;**29**(1):35–8.

Xu 2012 ***{published data only}***
Xu QH, Cai GL, Lu XC, Hu CB, Chen J, Yan J. The effects of omega-3 fish oil lipid emulsion on inflammation-immune response and organ function in patients with severe acute pancreatitis. *Zhonghua Neike Zazhi [Chinese Journal of Internal Medicine]* 2012;**51**(12):962–5.

Yang 2008a ***{published data only}***
Yang JS, Hou Y, Zuo Y. Effect of combined therapy with sandostatin and yiyan mixture in treating severe acute pancreatitis. *Zhongguo Zhongxiyi Jiehe Zqzhi [Chinese Journal of Integrated Traditional and Western Medicine]* 2008;**28**(8):708–10.

Yang 2008b ***{published data only}***
Yang SQ, Xu JG. Effect of glutamine on serum interleukin-8 and tumor necrosis factor-alpha levels in patients with severe pancreatitis. *Nanfang Yeie Daxue Xuebao [Journal of Southern Medical University]* 2008;**28**(1):129–31.

Yang 2009 ***{published data only}***
Yang XN, Deng LH, Xue P, Zhao L, Jin T, Wan MH, et al. Non-preventive use of antibiotics in patients with severe acute pancreatitis treated with integrated traditional Chinese and western medicine therapy: a randomized controlled trial. *Zhongxiyi Jiehe Xuebao [Journal of Chinese Integrative Medicine]* 2009;**7**(4):330–3.

Zapater 2000 ***{published data only}***
Zapater P, Abad-Santos F, Alcalde-Rubio M, Moreno-Otero R. Do muscarinic receptors play a role in acute pancreatitis? A randomised comparison of pirenzepine and nasogastric suction. *Clinical Drug Investigation* 2000;**20**(6):401–8.

References to studies awaiting assessment

Hansen 1966 *{published data only}*
Hansen HT, Drube HC, Brüning W, Borm D. Therapy of acute pancreatitis with and without proteinase inhibitor. Comparative clinical studies with trasylol [Behandlung der akuten pankreatitis mit und ohne proteinaseninhibitor. Vergleichende klinische untersuchungen mit trasylol]. *Medizinische Klinik* 1966;**61**(32):1254–7.

Perez 1980 *{published data only}*
Perez Oteyza C, Rebollar J, Ballarin M. Treatment of acute pancreatitis with cimetidine. Double-blind controlled trial. *Hepato-Gastroenterology* 1980;**27**(Suppl):F8.2.

References to ongoing studies

ChiCTR-IPR-16008301 *{published data only}*
ChiCTR-IPR-16008301. The effect of proton pump inhibitors on acute pancreatitis--a randomly prospective control study [The effect of proton pump inhibitors on acute pancreatitis—-a randomly prospective control study]. www.chictr.org.cn/showproj.aspx?proj=14089 (first received 18 April 2016).

EUCTR2014-004844-37-ES *{published data only}*
EUCTR2014-004844-37-ES. Trial of indomethacin in pancreatitis [A randomized controlled pilot trial of indomethacin in acute pancreatitis]. www.clinicaltrialsregister.eu/ctr-search/trial/2014-004844-37/ES (first received 8 May 2015).

NCT01132521 *{published data only}*
NCT01132521. Ulinastatin in severe acute pancreatitis [Multicenter, double–bind, randomised, placebo controlled study of ulinastatin in severe acute pancreatitis]. clinicaltrials.gov/show/NCT01132521 (first received 26 May 2010).

NCT02025049 *{published data only}*
NCT02025049. DP-b99 in the treatment of acute high-risk pancreatitis [Pilot trial of intravenous DP–b99 in the treatment of first–ever episode of non–obstructive acute high–risk pancreatitis]. clinicaltrials.gov/show/NCT02025049 (first received 25 December 2013).

NCT02212392 *{published data only}*
NCT02212392. Comparing the outcome in patients of acute pancreatitis, with and without prophylactic antibiotics [Comparing the outcome in patients of acute pancreatitis, with and without prophylactic antibiotics]. clinicaltrials.gov/show/NCT02212392 (first received 5 August 2014).

NCT02692391 *{published data only}*
NCT02692391. A randomized controlled pilot trial of indomethacin in acute pancreatitis [A randomized controlled pilot trial of indomethacin in acute pancreatitis]. clinicaltrials.gov/show/NCT02692391 (first received 15 February 2016).

NCT02885441 *{published data only}*
NCT02885441. Treatment of acute pancreatitis with ketorolac [Treatment of acute pancreatitis with ketorolac]. clinicaltrials.gov/show/NCT02885441 (first received 23 August 2016).

Additional references

Andriulli 1998
Andriulli A, Leandro G, Clemente R, Festa V, Caruso N, Annese V, et al. Meta-analysis of somatostatin, octreotide and gabexate mesilate in the therapy of acute pancreatitis. *Alimentary Pharmacology & Therapeutics* 1998;**12**(3): 237–45.

Ayub 2010
Ayub K, Slavin J, Imada R. Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD003630.pub3]

Bang 2008
Bang UC, Semb S, Nojgaard C, Bendtsen F. Pharmacological approach to acute pancreatitis. *World Journal of Gastroenterology* 2008;**14**(19):2968–76.

Banks 2013
Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;**62**(1):102–11.

Bone 1992
Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;**101**(6):1644–55.

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

Dias 2012a
Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 1: Introduction to evidence synthesis for decision making, 2012. www.nicedsu.org.uk/TSD1%20Introduction.final.08.05.12.pdf (accessed 27 March 2014).

Dias 2012b
Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials, 2012. www.nicedsu.org.uk/TSD4%20Inconsistency.final.08.05.12.pdf (accessed 27 March 2014).

Dias 2012c
Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment, 2012. www.nicedsu.org.uk/TSD3%20Heterogeneity.final%20report.08.05.12.pdf (accessed 27 March 2014).

Dias 2013
Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials, 2013. www.nicedsu.org.uk/TSD2%20General%20meta%20analysis%20corrected%20Mar2013.pdf (accessed 27 March 2014).

Egger 1997
Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 1997;**315**(7109):629–34.

Elmunzer 2012
Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *New England Journal of Medicine* 2012;**366**(15):1414–22.

FDA 2006
Center for Biologics Evaluation and Research, U.S. Food, Drug Administration. Guidance for industry adverse reactions section of labeling for human prescription drug and biological products - Content and format. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf 2006 (accessed 4th July 2014).

Gao 2015a
Gao W, Yang HX, Ma CE. The value of BISAP score for predicting mortality and severity in acute pancreatitis: a systematic review and meta-analysis. *PLOS ONE* 2015;**10**(6):e0130412.

Hampton 2000
Hampton JR. Clinical trial safety committees: the devil's spoon. *BMJ (Clinical research ed.)* 2000;**320**(7229):244–5.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

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.

Hochman 2006
Hochman D, Louie B, Bailey R. Determination of patient quality of life following severe acute pancreatitis. *Canadian Journal of Surgery* 2006;**49**(2):101–6.

ICH-GCP 1997
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Code of Federal Regulation & ICH Guidelines*. Pennsylvania: Barnett International/PAREXEL, 1997.

Jiang 2012
Jiang K, Huang W, Yang XN, Xia Q. Present and future of prophylactic antibiotics for severe acute pancreatitis. *World Journal of Gastroenterology* 2012;**18**(3):279–84.

Lu 2004
Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 2004;**23**(20):3105–24.

Lu 2007
Lu G, Ades AE, Sutton AJ, Cooper NJ, Briggs AH, Caldwell DM. Meta-analysis of mixed treatment comparisons at multiple follow-up times. *Statistics in Medicine* 2007;**26**(20):3681–99.

Masood 1998
Masood E. Chief to leave troubled British biotech. Nature 1998; Vol. 393, issue 6683:299.

Messori 1995
Messori A, Rampazzo R, Scroccaro G, Olivato R, Bassi C, Falconi M, et al. Effectiveness of gabexate mesilate in acute pancreatitis. A metaanalysis. *Digestive Diseases and Sciences* 1995;**40**(4):734–8.

MHRA 2013
Medicines and Healthcare products Regulatory Agency (MHRA). Clinical trials for medicines: Safety reporting - SUSARs and DSURs. 2013. www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARsandASRs/ (accessed 4 July 2014).

Mills 2012
Mills EJ, Ioannidis JP, Thorlund K, Schunemann HJ, Puhan MA, Guyatt GH. How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA* 2012;**308**(12):1246–53.

NCBI 2014
NCBI. MeSH. NLM Controlled Vocabulary. Pancreas. www.ncbi.nlm.nih.gov/mesh/68010179 (accessed 4 July 2014).

Neumann 2011
Neumann I, Grassi B, Bdair F, Rada G. Antiproteases for acute pancreatitis. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/14651858.CD009426]

Newell 1992
Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *International Journal of Epidemiology* 1992;**21**(5):837–41.

Peery 2012
Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012;**143**(5):1179–87.

Pendharkar 2014
Pendharkar SA, Salt K, Plank LD, Windsor JA, Petrov MS. Quality of life after acute pancreatitis: a systematic review and meta-analysis. *Pancreas* 2014;**43**(8):1194–200.

Puhan 2014
Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment

effect estimates from network meta-analysis. *BMJ (Clinical Research Ed.)* 2014;**349**:g5630.

Rada 2011
Rada G, Neumann I, Roa M, Rojas L. Antioxidants for acute pancreatitis. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD009049]

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roberts 2013
Roberts SE, Akbari A, Thorne K, Atkinson M, Evans PA. The incidence of acute pancreatitis: impact of social deprivation, alcohol consumption, seasonal and demographic factors. *Alimentary Pharmacology and Therapeutics* 2013;**38**(5):539–48.

Sah 2013
Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. *Current Opinion in Gastroenterology* 2013;**29**(5):523–30.

Salanti 2011
Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163–71.

Schmid 1999
Schmid SW, Uhl W, Friess H, Malfertheiner P, Buchler MW. The role of infection in acute pancreatitis. *Gut* 1999; **45**(2):311–6.

Tenner 2013
Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. *American Journal of Gastroenterology* 2013;**108**(9):1400–15.

WHO 2001
World Health Organization. Essential drugs and medicines - quality assurance and safety of medicines health technology and pharmaceuticals. Pharmaceuticals: restrictions in use and availability. 2001. apps.who.int/medicinedocs/pdf/s2203e/s2203e.pdf (accessed on 5 October 2016).

WinBUGS 1.4 [Computer program]
Imperial College and MRC. WinBUGS with DoodleBUGS. Version 1.4.3. London, UK: Imperial College and MRC, 2007.

Wright 2009
Wright SE, Lochan R, Imrie K, Baker C, Nesbitt ID, Kilner AJ, et al. Quality of life and functional outcome at 3, 6 and 12 months after acute necrotising pancreatitis. *Intensive Care Medicine* 2009;**35**(11):1974–8.

Xu 2013
Xu W, Zhou YF, Xia SH. Octreotide for primary moderate to severe acute pancreatitis: a meta-analysis. *Hepato-gastroenterology* 2013;**60**(126):1504–8.

Yadav 2006
Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006;**33**(4):323–30.

Yang 2008
Yang AL, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Archives of Internal Medicine* 2008;**168**(6):649–56.

Yang 2011
Yang X, Zeng X, Wu T. Lexipafant for acute pancreatitis. *Cochrane Database of Systematic Reviews* 2011, Issue 9. [DOI: 10.1002/14651858.CD009309]

Zhang 2009
Zhang Y, Chen QB, Gao ZY, Xie WF. Meta-analysis: octreotide prevents post-ERCP pancreatitis, but only at sufficient doses. *Alimentary Pharmacology & Therapeutics* 2009;**29**(11):1155–64.

References to other published versions of this review

Gurusamy 2014
Gurusamy KS. Pharmacological interventions for acute pancreatitis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD011384]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abraham 2013

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 135 Postrandomisation dropouts: 6 (4.4%) Revised sample size: 129 Average age: 39 years Women: 13 (10.1%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 62 (48.1%) Moderate pancreatitis: not stated Severe pancreatitis: 67 (51.9%) Persistent organ failure: not stated Infected pancreatitis: 0 Inclusion criteria 1. Adults (18-70 years) 2. Acute pancreatitis (mild or severe) 3. Elevated C-reactive protein
Interventions	Group 1: ulinastatin (n = 30), 200,000 IU twice daily for 5 days Group 2: placebo (n = 32)
Outcomes	Mortality, adverse events, organ failure, hospital stay Follow-up: until discharge or maximum of 22 days
Notes	Reasons for postrandomisation dropouts: withdrew consent, screening error, died

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India"

Abraham 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Balldin 1983

Methods	Randomised clinical trial
Participants	Country: Sweden Number randomised: 55 Postrandomisation dropouts: not stated Revised sample size: 55 Average age: not stated Women: 15 (27.3%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 55 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: acute pancreatitis undergoing peritoneal lavage
Interventions	Group 1: aprotinin (n = 26), 500,000 KIU in lavage fluid every 2 h for an average of 2.7 days Group 2: no intervention (n = 29)
Outcomes	Mortality, serious adverse events, adverse events, sepsis, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Balldin 1983 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Comment: supported by grants from the ….Bayer AG….
Other bias	Low risk	Comment: no other risk of bias

Bansal 2011

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 44 Postrandomisation dropouts: 5 (11.4%) Revised sample size: 39 Average age: 39 years Women: 9 (23.1%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis within 96 h of onset of symptoms Exclusion criteria 1. Age <18 or >75 years 2. Pregnancy 3. Acute pancreatitis secondary to surgery, trauma, or malignancy 4. Psychosis (except alcoholic delirium) 5. Need for urgent therapeutic intervention (endoscopic papillotomy, cholecystectomy, and/or choledochotomy) 6. Those enrolled in any other trial 7. People with serious diseases of the heart, brain, liver, or kidney 8. Peptic ulcer 9. Autoimmune disease

Bansal 2011 (*Continued*)

Interventions	Group 1: antioxidants (n = 19): vitamin A, C, E - initially parenterally and then orally when the participant could consume orally for a total of 14 days Group 2: no intervention (n = 20)
Outcomes	Mortality, serious adverse events, adverse events, organ failure, hospital stay Follow-up: until discharge
Notes	Reasons for postrandomisation dropouts: lost to follow-up, withdrew consent

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "[t]his was a single-center, prospective randomized, open-label with blinded endpoint assessment study of antioxidant therapy"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[t]his was a single-center, prospective randomized, open-label with blinded endpoint assessment study of antioxidant therapy"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Low risk	Quote: "[s]ource of support: Nil".
Other bias	Low risk	Comment: no other risk of bias.

Barreda 2009

Methods	Randomised clinical trial
Participants	Country: Peru Number randomised: 80 Postrandomisation dropouts: 22 (27.5%) Revised sample size: 58 Average age: 50 years Women: 24 (41.4%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 58 (100%) Mild pancreatitis: not stated

Barreda 2009 (*Continued*)

	Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with necrotising pancreatitis Exclusion criteria 1. Treated in other institutions for more than 4 days 2. Received other prophylactic antibiotics
Interventions	Group 1: antibiotics (n = 24): imipenem 500 mg 4 times daily for 14 days Group 2: no intervention (n = 34)
Outcomes	Mortality, serious adverse events, adverse events, infected pancreatic necrosis, requirement for additional intervention, length of hospital stay Follow-up: 2 months
Notes	Reasons for postrandomisation dropouts: protocol violations

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Berling 1994

Methods	Randomised clinical trial
Participants	Country: multicentric, international Number randomised: 48 Postrandomisation dropouts: not stated Revised sample size: 48 Average age: 56 years Women: 17 (35.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 48 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: participants with acute severe pancreatitis with circulatory insufficiency or peritonitis Exclusion criteria 1. People who had several surgeries before 2. Renal failure 3. Previous allergy to aprotinin or history of severe allergies 4. Age < 15 years 5. Pregnant women
Interventions	Group 1: aprotinin (n = 22), 20 million KIU in 7 lavages over 30 h Group 2: no intervention (n = 26)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay, ICU stay Follow-up: 1 month
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[t]he Bayer . . . and was also responsible for coding the bottles."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "prospective double-blind randomized multicenter trial"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "prospective double-blind randomized multicenter trial"

Berling 1994 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[t]his study was supported by grants from Bayer AG".
Other bias	Low risk	Comment: no other risk of bias

Besselink 2008

Methods	Randomised clinical trial
Participants	Country: Netherlands Number randomised: 298 Postrandomisation dropouts: 2 (0.7%) Revised sample size: 296 Average age: 60 years Women: 122 (41.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with predicted severe acute pancreatitis
Interventions	Group 1: probiotics (n = 152): ecologic 641 (maximum of 28 days or until development of pancreatic necrosis or fluid collection) Group 2: placebo (n = 144)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, organ failure, infected pancreatic necrosis, hospital stay, ICU stay Follow-up: 3 months
Notes	Reasons for postrandomisation dropouts: did not receive drug, wrong diagnosis of acute pancreatitis

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "[r]andomisation was done with a computer-generated permuted-block sequence."

Besselink 2008 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "[b]oth the probiotic and placebo preparations were packaged in identical, numbered sachets that were stored in identical, numbered containers."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[a]ll doctors, nurses, research staff , and patients involved remained unaware of the actual product administered during the entire study period."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[a]ll doctors, nurses, research staff , and patients involved remained unaware of the actual product administered during the entire study period."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "HMT is an employee of Winclove Bio Industries, Amsterdam"
Other bias	Low risk	Comment: no other risk of bias

Birk 1994

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 20 Postrandomisation dropouts: not stated Revised sample size: 20 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 20 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis
Interventions	Group 1: antioxidants (n = 10): sodium selenite 600 μg/day for 8 days Group 2: no intervention (n = 10)
Outcomes	None of the outcomes of interest were reported. Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Birk 1994 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias.

Bredkjaer 1988

Methods	Randomised clinical trial
Participants	Country: Denmark Number randomised: 66 Postrandomisation dropouts: 9 (13.6%) Revised sample size: 57 Average age: not stated Women: 26 (45.6%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria: 1. Chronic pancreatitis 2. Previous pseudocyst

Bredkjaer 1988 (*Continued*)

	3. Malignancy 4. Gastroduodenal ulcer 5. Coagulation disease
Interventions	Group 1: NSAID (n = 27): indomethacin 100 mg rectal for 7 days Group 2: placebo (n = 30)
Outcomes	The outcomes reported were: hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: chronic pancreatitis, wrong diagnosis, death

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Buchler 1993

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 223 Postrandomisation dropouts: not stated Revised sample size: 223 Average age: 50 years

Buchler 1993 (*Continued*)

	Women: 87 (39%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with moderate or severe acute pancreatitis Exclusion criteria 1. Pre-existing renal insufficiency 2. Age < 18 years 3. Pregnancy 4. Psychosis 5. Previous treatment with aprotinin, glucagon, calcitonin, or somatostatin 6. Previous participation in the study
Interventions	Group 1: gabexate mesilate (n = 115), 53 mg/kg/day for 7 days Group 2: placebo (n = 108)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay Follow-up: 3 months
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "[a] randomization list was applied to get a random sequence of GM and placebos for increasing package numbers."
Allocation concealment (selection bias)	Low risk	Quote: "[t]he drug packages for each hospital were numbered sequentially and the package number was used as patient number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "randomized, double-blind trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "randomized, double-blind trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.

Buchler 1993 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Chen 2000

Methods	Randomised clinical trial
Participants	Country: Taiwan Number randomised: 52 Postrandomisation dropouts: not stated Revised sample size: 52 Average age: 44 years Women: 15 (28.8%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 0 (0%) Persistent organ failure: 52 (100%) Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis with organ failure
Interventions	Group 1: gabexate mesilate (n = 26), 100 mg/h for 7 days Group 2: placebo (n = 26)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery Follow-up: 3 months
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.

Chen 2000 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Unclear risk	Comment: this information was not available.

Chen 2002a

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 68 Postrandomisation dropouts: 6 (8.8%) Revised sample size: 62 Average age: 53 years Women: 33 (53.2%) Acute interstitial oedematous pancreatitis: 62 (100%) Necrotising pancreatitis: 0 (0%) Mild pancreatitis: 62 (100%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 0 (0%) Persistent organ failure: 0 (0%) Infected pancreatitis: not stated Inclusion criteria: people with mild pancreatitis
Interventions	Group 1: ulinastatin (n = 48), 50,000 IU twice daily for 3 days followed by once daily for 5 days Group 2: gabexate mesilate (n = 14), 100 mg twice daily for 3 days followed by once daily for 5 days
Outcomes	Serious adverse events, adverse events Follow-up: not stated (probably 2 weeks)
Notes	Reasons for postrandomisation dropouts: recent or current treatment with other drugs

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.

Chen 2002a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Chen 2002b

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 26 Postrandomisation dropouts: 1 (3.8%) Revised sample size: 25 Average age: 59 years Women: 12 (48%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 15 (60%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 25 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe necrotising pancreatitis
Interventions	Group 1: ulinastatin (n = 14), 100,000 IU twice daily for 3 days followed by 50,000 IU once daily for 5-10 days Group 2: octreotide (n = 11), 0.3 mg twice daily for 3 days followed by 0.1 mg once daily for 5 days
Outcomes	Adverse events Follow-up: not stated (probably 2 weeks)
Notes	Reasons for postrandomisation dropouts: death after starting treatment

Chen 2002b (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Choi 1989

Methods	Randomised clinical trial
Participants	Country: Hong Kong, China Number randomised: 71 Postrandomisation dropouts: not stated Revised sample size: 71 Average age: 61 years Women: 39 (54.9%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 15 (21.1%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria: people with acute pancreatitis caused by trauma, iatrogenic, or malignancy

Choi 1989 (*Continued*)

Interventions	Group 1: somatostatin (n = 35), 250 μg bolus followed by 100 μg/h for 48 h Group 2: no intervention (n = 36)
Outcomes	Mortality, serious adverse events, adverse events Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[r]andomisation was done by drawing sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Chooklin 2007

Methods	Randomised clinical trial
Participants	Country: Ukraine Number randomised: 34 Postrandomisation dropouts: not stated Revised sample size: 34 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated

Chooklin 2007 (*Continued*)

	Moderate pancreatitis: not stated Severe pancreatitis: 34 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: antioxidants (N-acetyl cysteine, unspecified dose and duration) plus corticosteroids (dexamethasone, unspecified dose and duration) (n = 16) Group 2: no intervention (n = 18)
Outcomes	None of the outcomes of interest were reported. Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Unclear risk	Comment: no other risk of bias

Debas 1980

Methods	Randomised clinical trial
Participants	Country: Canada Number randomised: 66 Postrandomisation dropouts: not stated Revised sample size: 66 Average age: 53 years Women: 25 (37.9%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: glucagon (n = 33), 1 mg every 3 h (duration not stated) Group 2: placebo (n = 33)
Outcomes	Mortality, serious adverse events, adverse events, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[o]nce we decided to enter a patient into the study, the hospital pharmacy randomly assigned…"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[p]rospective randomized double-blind study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[p]rospective randomized double-blind study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.

Debas 1980 (*Continued*)

Other bias	Low risk	Comment: no other risk of bias

Delcenserie 1996

Methods	Randomised clinical trial
Participants	Country: France Number randomised: 23 Postrandomisation dropouts: 0 (0%) Revised sample size: 23 Average age: 43 years Women: 2 (8.7%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: 23 (100%) Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with severe acute pancreatitis (alcoholic) 2. No previous pancreatic disease 3. No previous antibiotic treatment 4. Admission within 48 h of onset Exclusion criteria 1. Age <18 years 2. Antibiotic allergy 3. Need to carry out ERCP
Interventions	Group 1: antibiotics (n = 11), ceftazidime 2 g IV 3 times daily; amikacin 7.5 mg/kg IV BD; and metronidazole 0.5 g IV 3 times daily for 10 days Group 2: no intervention (n = 12)
Outcomes	Mortality, serious adverse events, requirement for surgery, requirement for endoscopic or radiological drainage, organ failure, infected pancreatic necrosis, hospital stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random-number table"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Delcenserie 1996 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Delcenserie 2001

Methods	Randomised clinical trial
Participants	Country: France Number randomised: 81 Postrandomisation dropouts: not stated Revised sample size: 81 Average age: 47 years Women: 14 (17.3%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 81 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with acute necrotising pancreatitis 2. Within 48 h of onset of symptoms 3. No previous antibiotic treatment
Interventions	Group 1: antibiotics (n = 53): ciprofloxacin for 7 days or 21 days (random choice); dose not stated Group 2: no intervention (n = 28)
Outcomes	Mortality, serious adverse events Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Delcenserie 2001 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Dellinger 2007

Methods	Randomised clinical trial
Participants	Country: multicentric, international Number randomised: 100 Postrandomisation dropouts: 0 (0%) Revised sample size: 100 Average age: 50 years Women: 30 (30%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 100 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 100 (100%) Persistent organ failure: not stated Infected pancreatitis: 0 Inclusion criteria 1. People with necrotising pancreatitis 2. Within 5 days of onset of symptoms Exclusion criteria 1. People with concurrent pancreatic or peripancreatic infection

Dellinger 2007 (*Continued*)

	2. Received meropenem within previous 30 days 3. Antimicrobial therapy in previous 48 h 4. Allergy to beta-lactam antibiotics 5. Received or likely to receive probenecid 6. Pregnancy or lactation 7. Neutropenia 8. Decompensated cirrhosis
Interventions	Group 1: antibiotics (n = 50): meropenem 1 g IV 3 times daily for 7-21 days (recommended duration: 14 days) Group 2: placebo (n = 50)
Outcomes	Mortality, serious adverse events, adverse events, infected pancreatic necrosis Follow-up: 1.5 months
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "[t]he treatment given to each patient was determined by a random scheme prepared by the Biostatistics group at AstraZeneca (Wilmington, DE), using computer software that incorporates a standard procedure for generating random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "[t]he treatment given to each patient was determined by a random scheme prepared by the Biostatistics group at AstraZeneca (Wilmington, DE), using computer software that incorporates a standard procedure for generating random numbers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[s]upported by a grant from AstraZeneca Pharmaceuticals"

Dellinger 2007 (*Continued*)

Other bias	Low risk	Comment: no other risk of bias

Dürr 1978

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 69 Postrandomisation dropouts: not stated Revised sample size: 69 Average age: 49 years Women: 27 (39.1%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: glucagon (n = 33), 10 mg daily until surgery or at least 5 days in those who did not undergo surgery Group 2: placebo (n = 36)
Outcomes	Mortality, requirement for surgery, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"

Dürr 1978 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Ebbehøj 1985

Methods	Randomised clinical trial
Participants	Country: Denmark Number randomised: 30 Postrandomisation dropouts: 0 (0%) Revised sample size: 30 Average age: 55 years Women: 10 (33.3%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: NSAID (n = 14), indomethacin 50 mg PR twice daily for 7 days Group 2: placebo (n = 16)
Outcomes	Hospital stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Ebbehøj 1985 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[c]ontrolled double-blind trial".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[c]ontrolled double-blind trial".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "[i]ndomethacin (Confortid) and placebo were generously supplied by Dumex Ltd, Denmark"
Other bias	Low risk	Comment: no other risk of bias

Finch 1976

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 62 Postrandomisation dropouts: 4 (6.5%) Revised sample size: 58 Average age: 36 years Women: 24 (41.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. History of blunt trauma 2. Previous history compatible with gallstones 3. Medications: steroids, thorazine, thiaziole diuretics 4. Parathyroid disease 5. Duodenal peptic ulcer disease 6. A source of fever, independent of the pancreatitis 7. Ancillary antibiotic coverage
Interventions	Group 1: antibiotics (n = 31): ampicillin 500 mg to 1 g 4 times daily for 7 days (keflin 1 g 4 times daily for 7 days in people allergic to penicillin)

Finch 1976 (*Continued*)

	Group 2: no intervention (n = 27)
Outcomes	Mortality, adverse events, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: required surgery, developed pneumonia, went home against medical advice, malignancy

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "[o]n a randomized pre-selected basis a card was drawn to determine in which group (antibiotic treatment or non-antibiotic treatment) the patient was to be included." Comment: further details on whether the card was an open or held by a researcher not involved in recruitment are not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Freise 1986

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 50 Postrandomisation dropouts: not stated Revised sample size: 50 Average age: not stated Women: 17 (34%)

Freise 1986 (*Continued*)

	Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Duration of symptoms more than 48 h 2. < 18 years 3. Pregnancy 4. Chronic renal insufficiency
Interventions	Group 1: gabexate mesilate (n = 25), 150 mg IV 3 times daily for 7 days Group 2: placebo (n = 25)
Outcomes	Mortality, serious adverse events, adverse events, organ failure, sepsis Follow-up: not stated
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Comment: the drug code was concealed by third party.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Frulloni 1994

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 116 Postrandomisation dropouts: not stated Revised sample size: 116 Average age: 57 years Women: 49 (42.2%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 116 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with acute necrotising pancreatitis 2. Within 72 h of onset of symptoms 3. No skin sensitivity to aprotinin
Interventions	Group 1: gabexate mesilate (n = 65), 3 g/day for 7 days Group 2: aprotinin (n = 51), 1.5 million KIU/day for 7 days
Outcomes	Mortality, serious adverse events, adverse events, sepsis Follow-up: 3 months
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.

Frulloni 1994 (*Continued*)

For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Garcia-Barrasa 2009

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 46 Postrandomisation dropouts: 5 (10.9%) Revised sample size: 41 Average age: 63 years Women: 12 (29.3%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 41 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 41 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute necrotising pancreatitis
Interventions	Group 1: antibiotics (n = 22): ciprofloxacin 300 mg twice daily for 10 days Group 2: placebo (n = 19)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, organ failure, infected pancreatic necrosis, hospital stay, ICU stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: 3 - no confirmed necrosis; 2 fulminant pancreatitis

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[p]rospective, randomized, placebo-controlled, double-blind study"

Garcia-Barrasa 2009 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[p]rospective, randomized, placebo-controlled, double-blind study"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Low risk	Quote: "[t]his study was promoted by the "Bellvitge Hospital" and has not received any grant or payment from the pharmaceutical industry"
Other bias	Low risk	Comment: no other risk of bias

Gilsanz 1978

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 62. Postrandomisation dropouts: not stated Revised sample size: 62 Average age: 52 years Women: 44 (71%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: 48 (77.4%) Severe pancreatitis: 14 (22.6%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Post-traumatic pancreatitis 2. Postsurgical pancreatitis 3. Previous pancreatitic bouts
Interventions	Group 1: glucagon (n = 31), 1 mg IV every 4 h (duration - not stated) Group 2: oxyphenonium gromomethylate (n = 31), 1 mg IV every 4 h (duration - not stated)
Outcomes	Mortality, adverse events, requirement for surgery Follow-up: 24 months
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias		***Risk of bias***

Gilsanz 1978 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Gjørup 1992

Methods	Randomised clinical trial
Participants	Country: Denmark Number randomised: 63 Postrandomisation dropouts: not stated Revised sample size: 63 Average age: 49 years Women: 22 (34.9%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with first attack of acute pancreatitis 2. Within 24 h of onset of symptoms
Interventions	Group 1: somatostatin (n = 33), 250 μg/h for 3 days Group 2: placebo (n = 30)

Gjørup 1992 (*Continued*)

Outcomes	Mortality, serious adverse events, adverse events, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "by selecting sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blinded trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blinded trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Goebell 1979

Methods	Randomised clinical trial
Participants	Country: multicentric, international Number randomised: 94 Postrandomisation dropouts: not stated Revised sample size: 94 Average age: 55 years Women: 37 (39.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 29 (30.9%) Moderate pancreatitis: 49 (52.1%) Severe pancreatitis: 16 (17%) Persistent organ failure: not stated Infected pancreatitis: not stated

Goebell 1979 (*Continued*)

	Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Serum creatinine levels above 5 mg/100 ml 2. Post-operative acute pancreatitis
Interventions	Group 1: calcitonin (n = 50), synthetic salmon calcitonin 20 μg 3 times daily for 6 days Group 2: placebo (n = 44)
Outcomes	Mortality, adverse events, requirement for surgery, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Goebell 1988

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 162 Postrandomisation dropouts: 11 (6.8%) Revised sample size: 151 Average age: not stated

Goebell 1988 (*Continued*)

	Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with moderate or severe pancreatitis
Interventions	Group 1: gabexate mesilate (n = 76), 150 mg every 2 h followed by 0.5 mg/kg/h for 7 days Group 2: placebo (n = 75)
Outcomes	Mortality, serious adverse events, requirement for surgery Follow-up: 3 months
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Grupo Español 1996

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 70 Postrandomisation dropouts: 9 (12.9%) Revised sample size: 61 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 61 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis
Interventions	Group 1: somatostatin (n = 30), 250 μg/h for 5 days Group 2: placebo (n = 31)
Outcomes	Mortality Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: did not complete the study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.

Grupo Español 1996 (*Continued*)

Other bias	Low risk	Comment: no other risk of bias

Guo 2015

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 120 Postrandomisation dropouts: not stated Revised sample size: 120 Average age: 46 years Women: 58 (48.3%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 120 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis
Interventions	Group 1: octerotide plus ulinastatin (n = 60), 0.1 mg SC 3 times daily for 7-14 days Group 2: octreotide (n = 60), 10 million units IV continuous for 7-14 days
Outcomes	Mortality, serious adverse events, adverse events, length of hospital stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.

Guo 2015 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Hansky 1969

Methods	Randomised clinical trial
Participants	Country: Australia Number randomised: 24 Postrandomisation dropouts: not stated Revised sample size: 24 Average age: not stated Women: 7 (29.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 3 (12.5%) Moderate pancreatitis: 15 (62.5%) Severe pancreatitis: 6 (25%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: iniprol (n = 15), single IV dose of 1 million units, followed by 500,000 units IV 4 times daily for 4-8 days depending upon clinical course Group 2: no intervention (n = 9)
Outcomes	Mortality, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "[t]he drug was not evaluated in a double-blind manner"

Hansky 1969 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "[t]he drug was not evaluated in a double-blind manner"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "I am grateful to Difrex (Australia) laboratories for supplying . . ."
Other bias	Low risk	Comment: no other risk of bias

Hejtmankova 2003

Methods	Randomised clinical trial
Participants	Country: not stated Number randomised: 41 Postrandomisation dropouts: not stated Revised sample size: 41 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 41 (100%). Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis
Interventions	Group 1: antibiotics (n = 20): meropenem 500 mg 3 times daily for 10 days Group 2: no intervention (n = 21)
Outcomes	Mortality, adverse events, requirement for surgery, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.

Hejtmankova 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Imrie 1978

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 161 Postrandomisation dropouts: not stated Revised sample size: 161 Average age: 51 years Women: 92 (57.1%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 60 (37.3%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Post-traumatic pancreatitis 2. Postsurgical pancreatitis 3. Previous pancreatitic bouts
Interventions	Group 1: aprotinin (n = 80), 500 000 KIU bolus followed by 200 000 KIU 4 times daily for 5 days Group 2: placebo (n = 81)
Outcomes	Mortality, serious adverse events, adverse events Follow-up: not stated (probably until discharge)

Imrie 1978 (*Continued*)

Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelope".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind trial".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind trial".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[i]n addition to providing both Trasylol and placebo, Bayer Pharmaceuticals contributed the financial support of a research assistant"
Other bias	Low risk	Comment: no other risk of bias

Imrie 1980

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 50 Postrandomisation dropouts: not stated Revised sample size: 50 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 29 (58%) Moderate pancreatitis: not stated Severe pancreatitis: 21 (42%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis

Imrie 1980 (*Continued*)

Interventions	Group 1: aprotinin (n = 25), 2 million units KIU bolus followed by 400,000 KIU 4 h later Group 2: placebo (n = 25)
Outcomes	Mortality Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind trial"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Isenmann 2004

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 119 Postrandomisation dropouts: 5 (4.2%) Revised sample size: 114 Average age: 47 years Women: 27 (23.7%) Acute interstitial oedematous pancreatitis: 38 (33.3%) Necrotising pancreatitis: 76 (66.7%)

Isenmann 2004 (*Continued*)

	Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with predicted severe pancreatitis
Interventions	Group 1: antibiotics (n = 58): metronidazole 500 mg twice daily and ciprofloxacin 400 mg twice daily (duration not reported) Group 2: placebo (n = 56)
Outcomes	Serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis, hospital stay, ICU stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: lost to follow-up, withdrawn from study prior to medication

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[s]tudy medication for each patient (verum or placebo) was packed in identical vials and labelled with consecutive patient numbers according to the randomization sequence"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind trial"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "[s]upported by study medication provided from Bayer Vital and Ratiopharm as well as a financial grant from Bayer Vital"
Other bias	Low risk	Comment: no other risk of bias

Johnson 2001

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 291 Postrandomisation dropouts: 1 (0.3%) Revised sample size: 290 Average age: 63 years Women: 124 (42.8%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with predicted severe acute pancreatitis 2. Premenopausal women in whom pregnancy could not be excluded 3. Pancreatitis secondary to trauma, surgery, malignancy, or ERCP 4. Person unsuitable for ventilation 5. Other investigational agents in the last 3 years 6. People receiving oral anti-coagulant therapy 7. People who had received lexipafant previously Exclusion criteria: age < 18 or > 80 years
Interventions	Group 1: lexipafant (n = 151), 100 mg daily for 7 days Group 2: placebo (n = 139)
Outcomes	Mortality, serious adverse events, adverse events, organ failure, sepsis, hospital stay, ICU stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: withdrew from the study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind, placebo controlled, randomised, parallel group"

Johnson 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind, placebo controlled, randomised, parallel group"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[t]his study was funded by British Biotech Pharmaceuticals Ltd, Oxford, UK"
Other bias	Low risk	Comment: no other risk of bias

Kalima 1980

Methods	Randomised clinical trial
Participants	Country: Finland Number randomised: 80 Postrandomisation dropouts: 9 (11.3%) Revised sample size: 71 Average age: 46 years Women: 28 (39.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: glucagon (n = 32), 7.5 mg twice daily for 4-5 days Group 2: placebo (n = 29)
Outcomes	Mortality, serious adverse events, adverse events Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: underwent surgery, wrong diagnosis

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.

Kalima 1980 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although placebo was used, there was no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported
For profit-bias	Unclear risk	Comment: this information was not available
Other bias	Low risk	Comment: no other risk of bias

Kingsnorth 1995

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 83 Postrandomisation dropouts: not stated Revised sample size: 83 Average age: 59 years Women: 41 (49.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 54 (65.1%) Moderate pancreatitis: not stated Severe pancreatitis: 29 (34.9%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis within 48 h of onset of symptoms Exclusion criteria 1. Age < 18 years 2. Unsterilised premenopausal women 3. Concomitant anticoagulant therapy
Interventions	Group 1: lexipafant (n = 42), 15 mg 4 times daily for 3 days Group 2: placebo (n = 41)
Outcomes	Mortality, adverse events Follow-up: 1 week

Kingsnorth 1995 (*Continued*)

Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "S.W.G. was supported by British Biotech, Oxford, UK"
Other bias	Low risk	Comment: no other risk of bias

Kirsch 1978

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 150 Postrandomisation dropouts: not stated Revised sample size: 150 Average age: 53 years Women: 78 (52%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 35 (23.3%) Moderate pancreatitis: 61 (40.7%) Severe pancreatitis: 54 (36%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis

Kirsch 1978 (*Continued*)

Interventions	Group 1: glucagon (n = 75), 10 mg/day for 4 days Group 2: atropine (n = 75), 4 days (dose not stated)
Outcomes	Mortality, serious adverse events, adverse events Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Kronborg 1980

Methods	Randomised clinical trial
Participants	Country: Denmark Number randomised: 22 Postrandomisation dropouts: not stated Revised sample size: 22 Average age: not stated Women: 4 (18.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: 11 (50%) Mild pancreatitis: not stated Moderate pancreatitis: not stated

Kronborg 1980 (*Continued*)

	Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with acute pancreatitis (first attack only) 2. Deteriorating clinical condition or in shock 3. No suspected biliary disease
Interventions	Group 1: glucagon (n = 10), 1 mg IV followed by 6 mg/day for 3 days Group 2: placebo (n = 12)
Outcomes	Mortality, adverse events Follow-up: until discharge
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: although authors stated they did not exclude any participants for wrong diagnosis, it was not clear whether they excluded participants for other reasons
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Llukacaj 2012

Methods	Randomised clinical trial
Participants	Country: Albania Number randomised: 80 Postrandomisation dropouts: not stated Revised sample size: 80 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 80 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: 0 Inclusion criteria: people with non-infected necrotising pancreatitis
Interventions	Group 1: antibiotics (n = 40): imipenem 750 mg IV twice daily for 7 days Group 2: placebo (n = 40)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis Follow-up: 1 month
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: although authors stated they did not exclude any participants for wrong diagnosis, it was not clear whether they excluded participants for other reasons
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported

Llukacaj 2012 (*Continued*)

For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Luengo 1994

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 100 Postrandomisation dropouts: not stated Revised sample size: 100 Average age: 55 years Women: 39 (39%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 78 (78%) Moderate pancreatitis: not stated Severe pancreatitis: 22 (22%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Pancreatitis following trauma, surgery, endoscopy, malignancy, drugs, or pregnancy 2. Allergy to one of the antibiotics 3. < 18 years of age 4. Postoperative pancreatitis 5. Infected pancreatic necrosis
Interventions	Group 1: somatostatin (n = 50), 250 μg/h for 48 h following a 250 μg bolus Group 2: no intervention (n = 50)
Outcomes	Mortality, requirement for surgery, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[p]atients were randomly divided by means of the sealed-envelope method and grouped according to therapy"

Luengo 1994 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: although authors stated they did not exclude any participants for wrong diagnosis, it was not clear whether they excluded participants for other reasons
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Luiten 1995

Methods	Randomised clinical trial
Participants	Country: the Netherlands Number randomised: 109 Postrandomisation dropouts: 7 (6.4%) Revised sample size: 102 Average age: 55 years Women: 42 (41.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 102 (100%) Persistent organ failure: not stated Infected pancreatitis: 0 Inclusion criteria: people with severe pancreatitis
Interventions	Group 1: antibiotics (n = 50): selective digestive decontamination using colistin 200 mg, amphotericin 500 mg, and norfloxacin 50 mg 4 times daily orally and as rectal enema along with short course of cefotaxime 500 mg IV 3 times daily until gram-negative bacteria were eliminated from oral cavity and rectum. Total duration of treatment: until patient was extubated and taking oral feeds Group 2: no intervention (n = 52)
Outcomes	Mortality, adverse events, requirement for surgery, hospital stay Follow-up: until discharge

Luiten 1995 (*Continued*)

Notes	Reasons for postrandomisation dropouts: perioperatively proven infected pancreatic necrosis or wrong clinical diagnosis

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[a] 24-hour randomization service was available to randomize patients with stratification per center"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Marek 1999

Methods	Randomised clinical trial
Participants	Country: Poland Number randomised: 73 Postrandomisation dropouts: 0 (0%) Revised sample size: 73 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 56 (76.7%) Moderate pancreatitis: not stated Severe pancreatitis: 17 (23.3%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis

Marek 1999 (*Continued*)

Interventions	Group 1: antioxidants (n = 35): vitamin C 500 mg IV 3 times daily for 5 days Group 2: placebo (n = 38)
Outcomes	None of the outcomes of interest were reported. Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Martinez 1984

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 31 Postrandomisation dropouts: 0 (0%) Revised sample size: 31 Average age: 48 years Women: 6 (19.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%)

Martinez 1984 (*Continued*)

	Moderate pancreatitis: 0 (0%) Severe pancreatitis: 31 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis
Interventions	Group 1: calcitonin (n = 14), synthetic salmon calcitonin 100 MRC units (equivalent to 100 IU) IV 3 times daily for 5 days or more Group 2: placebo (n = 17)
Outcomes	Mortality, requirement for surgery, hospital stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although some participants were excluded from hospital stay, they were included for mortality and requirement of surgical intervention
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

McKay 1997a

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 58 Postrandomisation dropouts: 0 (0%) Revised sample size: 58 Average age: 69 years Women: 32 (55.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with moderate or severe pancreatitis Exclusion criteria 1. < 18 years of age 2. Women in whom pregnancy could not be excluded 3. People with acute pancreatitis following pregnancy
Interventions	Group 1: octreotide (n = 28), 1 mg/day IV for 5 days Group 2: placebo (n = 30)
Outcomes	Mortality, serious adverse events, adverse events, organ failure, infected pancreatic necrosis, hospital stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "[r]andomization was by the use of sequentially numbered treatment packs containing either octreotide or placebo as determined by a computer-generated random code."
Allocation concealment (selection bias)	Low risk	Quote: "[r]andomization was by the use of sequentially numbered treatment packs containing either octreotide or placebo as determined by a computer-generated random code."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[p]atients, investigators, and medical staff were blinded regarding the nature of the trial infusion"

McKay 1997a (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[p]atients, investigators, and medical staff were blinded regarding the nature of the trial infusion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

McKay 1997b

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 51 Postrandomisation dropouts: 1 (2%) Revised sample size: 50 Average age: 65 years Women: 21 (42%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with predicted severe pancreatitis Exclusion criteria 1. Pregnancy 2. ERCP induced pancreatitis 3. Oral anticoagulant use 4. Other trial drugs within 3 months of study 5. Previous use of lexipafant
Interventions	Group 1: lexipafant (n = 26), 4 mg bolus IV followed by 4 mg/h by continuous infusion for 5-7 days Group 2: placebo (n = 24)
Outcomes	Mortality, organ failure, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: incorrect diagnosis

Risk of bias		***Risk of bias***

McKay 1997b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[p]acks were numbered sequentially and prepared in advance by British Biotech (Oxford, UK)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[i]nvestigators and patients were unaware of the nature of the trial infusion."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[i]nvestigators and patients were unaware of the nature of the trial infusion."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "[t]his study was supported by a grant from British Biotech"
Other bias	Low risk	Comment: no other risk of bias

Moreau 1986

Methods	Randomised clinical trial
Participants	Country: France Number randomised: 87 Postrandomisation dropouts: 3 (3.4%) Revised sample size: 84 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Acute pancreatitis following surgery or ERCP 2. Duration of symptoms for more than 48 h

Moreau 1986 (*Continued*)

Interventions	Group 1: somatostatin (n = 44), 400 μg for first 3 days, tapered and stopped on 4th day Group 2: placebo (n = 41)
Outcomes	None of the outcomes of interest were reported. Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "Sonafi, kindly donated"
Other bias	Low risk	Comment: no other risk of bias

MRC Multicentre Trial 1977

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 264 Postrandomisation dropouts: 7 (2.7%) Revised sample size: 257 Average age: not stated Women: 153 (59.5%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated

MRC Multicentre Trial 1977 (*Continued*)

	Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: aprotinin (n = 66), 500,000 IU IV followed by 300,000 units every 6 h for 5 days Group 2: glucagon (n = 68), 2 mg IV followed by 2 mg every 6 h for 5 days Group 3: placebo (n = 123)
Outcomes	Mortality, requirement for surgery Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: initial amylase was too low

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Comment: the drugs and placebo were supplied by the pharmaceutical company
Other bias	Low risk	Comment: no other risk of bias

Nordback 2001

Methods	Randomised clinical trial
Participants	Country: Finland Number randomised: 90 Postrandomisation dropouts: 32 (35.6%) Revised sample size: 58 Average age: 46 years Women: 7 (12.1%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 58 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: 0 (0%) Infected pancreatitis: not stated Inclusion criteria: people with acute necrotising pancreatitis Exclusion criteria 1. People who had already been started on antibiotics 2. Those admitted to intensive care unit with multiorgan failure 3. Suspected to have a reaction to study drugs
Interventions	Group 1: antibiotics (n = 25): imipenem 1 g plus cilastatin IV 3 times daily; duration not stated Group 2: placebo (n = 33)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, ICU stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: older than 70 years of age, did not begin antibiotic as scheduled, criteria for pancreatic necrosis not fulfilled

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed

Nordback 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Ohair 1993

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 180 Postrandomisation dropouts: not stated Revised sample size: 180 Average age: 37 years Women: 41 (22.8%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: octreotide (n = 90), 100 μg 3 times daily SC for duration of hospital stay Group 2: placebo (n = 90)
Outcomes	Requirement for surgery, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed

Ohair 1993 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Olah 2007

Methods	Randomised clinical trial
Participants	Country: Hungary Number randomised: 83 Postrandomisation dropouts: 21 (25.3%) Revised sample size: 62 Average age: 47 years Women: 10 (16.1%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 62 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis Exclusion criteria: people with acute exacerbation of chronic pancreatitis
Interventions	Group 1: probiotics (n = 33): Synbiotic 2000 once daily for at least 1 week Group 2: no intervention (n = 29) Both groups received prebiotics (an intervention not of interest for this review)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, organ failure, sepsis, infected pancreatic necrosis, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: because they were not severe acute pancreatitis after 48 h, did not tolerate jejunal feeding, participant removed the feeding tube

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Olah 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Paran 1995

Methods	Randomised clinical trial
Participants	Country: Israel Number randomised: 51 Postrandomisation dropouts: 13 (25.5%) Revised sample size: 38 Average age: 61 years Women: 18 (47.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: octreotide (n = 19), 01. mg SC 3 times daily for 14 days Group 2: no intervention (n = 19)
Outcomes	Mortality, serious adverse events, adverse events, sepsis, hospital stay Follow-up: not stated (probably until discharge)

Paran 1995 (*Continued*)

Notes	Reasons for postrandomisation dropouts: failure to meet inclusion criteria, incomplete data, incorrect diagnosis

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "[a]s placebo vials were not available to us, the study was double blinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "[a]s placebo vials were not available to us, the study was double blinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Pederzoli 1993a

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 74 Postrandomisation dropouts: not stated Revised sample size: 74 Average age: 52 years Women: 30 (40.5%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 74 (100%) Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis

Pederzoli 1993a (*Continued*)

Interventions	Group 1: antibiotics (n = 41): imipenem 0.5 g every 8 h for 2 weeks Group 2: no intervention (n = 33)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, organ failure, infected pancreatic necrosis Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "casual numbers table".
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Pederzoli 1993b

Methods	Randomised clinical trial
Participants	Country: Italy Number randomised: 199 Postrandomisation dropouts: 17 (8.5%) Revised sample size: 182 Average age: 58 years Women: 78 (42.9%) Acute interstitial oedematous pancreatitis: 66 (36.3%) Necrotising pancreatitis: 116 (63.7%) Mild pancreatitis: 0 (0%)

Pederzoli 1993b (*Continued*)

	Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: gabexate mesilate (n = 91), 3 g/day for 7 days Group 2: aprotinin (n = 91), 1,500,000 KIU/day for 7 days
Outcomes	Mortality, adverse events, requirement for surgery Follow-up: 3 months for mortality; all other complications - 2 weeks
Notes	Reasons for postrandomisation dropouts: major protocol violations

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Perezdeoteyza 1980

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 40 Postrandomisation dropouts: not stated Revised sample size: 40

Perezdeoteyza 1980 (*Continued*)

	Average age: 56 years Women: 24 (60%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Post-traumatic pancreatitis 2. Postsurgical pancreatitis 3. Previous pancreatitic bouts
Interventions	Group 1: cimetidine (n = 20), 1200 mg IV for 4-5 days followed by 1000 mg oral for 10 days Group 2: placebo (n = 20)
Outcomes	Mortality Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[r]andomisation code was held by pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.

Perezdeoteyza 1980 (*Continued*)

Other bias	Low risk	Comment: no other risk of bias

Pettila 2010

Methods	Randomised clinical trial
Participants	Country: Finland Number randomised: 32 Postrandomisation dropouts: 0 (0%) Revised sample size: 32 Average age: 45 years Women: 3 (9.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 32 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with acute severe pancreatitis 2. Admitted to hospital < 4 days of onset of pain 3. At least one organ dysfunction 4. < 48 h from the first organ dysfunction
Interventions	Group 1: activated protein C (n = 16): drotrecogin alpha activated 24 μg/kg/h for 96 h Group 2: placebo (n = 16)
Outcomes	Mortality, hospital stay Follow-up: not stated (probably 2 weeks)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[t]he code for study medication was concealed using sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"

Pettila 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "Eli Lilly in part provided the study drug for this investigator-initiated study"
Other bias	Low risk	Comment: no other risk of bias

Plaudis 2010

Methods	Randomised clinical trial
Participants	Country: Latvia Number randomised: 90 Postrandomisation dropouts: not stated Revised sample size: 58 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 58 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute severe pancreatitis
Interventions	Group 1: probiotics (n = 30): 4 bioactive lactic acid bacteria Group 2: no intervention (n = 28) Both groups received prebiotics (an intervention not of interest for this review)
Outcomes	None of the outcomes of interest were reported. Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Plaudis 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Poropat 2015

Methods	Randomised clinical trial
Participants	Country: Croatia Number randomised: 43 Postrandomisation dropouts: 0 (0%) Revised sample size: 43 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with acute pancreatitis 2. APACHE II score $\geq$ 8
Interventions	Group 1: antibiotics (n = 23): imipenem 500 mg IV 3 times daily for 10 days Group 2: no intervention (n = 24)

Poropat 2015 (*Continued*)

Outcomes	Mortality, serious adverse events, adverse events, infected pancreatic necrosis, and organ failure Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Rokke 2007

Methods	Randomised clinical trial
Participants	Country: Norway Number randomised: 73 Postrandomisation dropouts: 0 (0%) Revised sample size: 73 Average age: 58 years Women: 24 (32.9%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 73 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 73 (100%) Persistent organ failure: not stated

Rokke 2007 (*Continued*)

	Infected pancreatitis: not stated Inclusion criteria 1. People with acute necrotising pancreatitis 2. Duration of symptoms < 72 h Exclusion criteria 1. Age < 18 years 2. Ongoing antibiotic treatment 3. Previous episodes of acute pancreatitis 4. Post-ERCP pancreatitis 5. Concomitant bacterial infection 6. Allergy to imipenem 7. Pregnancy
Interventions	Group 1: antibiotics (n = 36): imipenem 0.5 g every 8 h for 5-7 days Group 2: no intervention (n = 37)
Outcomes	Mortality, adverse events, requirement for surgery, organ failure, infected pancreatic necrosis, hospital stay, ICU stay Follow-up: not stated (probably 2 weeks)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "[t]he study was unblinded to all attending physicians"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "[t]he study was unblinded to all attending physicians"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[w]e are grateful to the pharmaceutical company MSD for economic support in organizing meetings for the Steering Committee"
Other bias	Low risk	Comment: no other risk of bias

Sainio 1995

Methods	Randomised clinical trial
Participants	Country: Finland Number randomised: 60 Postrandomisation dropouts: 0 (0%) Revised sample size: 60 Average age: 41 years Women: 7 (11.7%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 60 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with alcohol-induced necrotising pancreatitis Exclusion criteria 1. Treatment elsewhere for more than 48 h of onset of symptoms 2. Continuing antimicrobial treatment 3. Previous severe episode of pancreatitis 4. Aetiology other than alcohol and no history of alcohol intake prior to admission
Interventions	Group 1: antibiotics (n = 30): cefuroxime 1.5 g IV 3 times daily continued until clinical recovery and fall to normal level of C-reactive protein, after which oral administration of 250 mg twice daily until 14 days Group 2: no intervention (n = 30)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay, ICU stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.

Sainio 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Sateesh 2009

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 56 Postrandomisation dropouts: 3 (5.4%) Revised sample size: 53 Average age: 39 years Women: 33 (62.3%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 10 (18.9%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with acute pancreatitis 2. < 72 h of onset of symptoms Exclusion criteria 1. Acute exacerbation of chronic pancreatitis 2. Prior antioxidant therapy 3. Delayed presentation to the ward 4. Severe comorbidity 5. Pregnancy
Interventions	Group 1: antioxidants (n = 23): vitamin C 500 mg once daily, N-acteyl cysteine 200 mg 3 times daily, Antoxyl Forte 1 capsule 3 times daily); duration not stated Group 2: no intervention (n = 30)
Outcomes	Mortality, adverse events, organ failure, hospital stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: did not receive allocated treatment, discontinued medication

Risk of bias ***Risk of bias***

Sateesh 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "according to a computer generated random number table"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "[t]he study was unblinded".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "[t]he study was unblinded".
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Sharma 2011

Methods	Randomised clinical trial
Participants	Country: India Number randomised: 50 Postrandomisation dropouts: 0 (0%) Revised sample size: 50 Average age: 41 years Women: 27 (54%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 28 (56%) Moderate pancreatitis: not stated Severe pancreatitis: 22 (44%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with acute pancreatitis 2. < 72 h of onset of symptoms or had not been taking anything orally for up to 5 days Exclusion criteria 1. Malignancy 2. Infection or sepsis related to source other than pancreatic bed

Sharma 2011 (*Continued*)

	3. Intra-oeprative diagnosis of acute pancreatitis 4. Immunodeficiency 5. Earlier use of probiotics or prebiotics 6. Pregnant women
Interventions	Group 1: probiotics (n = 24): 2.5 billion bacteria per sachet and 25 mg of fructo-oligosaccharide every day for 7 days Group 2: placebo (n = 26)
Outcomes	Hospital stay, ICU stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Quote: "[t]he method of allocation concealment was sequentially numbered sealed opaque envelopes technique"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "[t]he authors disclose that Alkem provided the probiotics and placebo on complimentary basis."
Other bias	Low risk	Comment: no other risk of bias

Sillero 1981

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 60 Postrandomisation dropouts: not stated Revised sample size: 60 Average age: 52 years Women: 36 (60%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: cimetidine (n = 30): 1200 mg IV for 4 days followed by 1000 mg oral for 10 days Group 2: placebo (n = 30)
Outcomes	Serious adverse events, adverse events, requirement for surgery Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: although a placebo was used, it was not clear blinding was performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported

Sillero 1981 (*Continued*)

For profit-bias	Unclear risk	Comment: this information was not available
Other bias	Low risk	Comment: no other risk of bias

Siriwardena 2007

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 43 Postrandomisation dropouts: 0 (0%) Revised sample size: 43 Average age: 67 years Women: 28 (65.1%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with predicted severe pancreatitis 2. Within 72 h of admission to hospital 3. 16 years of older 4. Not enrolled in other trials 5. No history of allergy to intravenous antioxidant therapy 6. Enrolled in the trial with a previous episode of pancreatitis
Interventions	Group 1: antioxidants (n = 22) selenium started with 1000 mg and then tapered to 200 mg/day for a total duration of 7 days; vitamin C started with 2000 mg and then tapered to 1000 mg/day for a total duration of 7 days; N-acetyl cysteine started with 300 mg and then tapered to 75 mg/day for a total duration of 7 days Group 2: placebo (n = 21)
Outcomes	Mortality, serious adverse events, organ failure, hospital stay, ICU stay Follow-up: until discharge
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random number generation" Comment: probably computer-generated

Siriwardena 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "[t]he pharmacy administered the randomisation and storage of therapeutics for all participating centres"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Unclear risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "the costs of antioxidants and placebo were met by Pharmanord UK"
Other bias	Low risk	Comment: no other risk of bias

Spicak 2002

Methods	Randomised clinical trial
Participants	Country: Czech Republic Number randomised: 63 Postrandomisation dropouts: not stated Revised sample size: 63 Average age: 55 years Women: 25 (39.7%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 63 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with severe acute pancreatitis 2. Within 4 days of onset of symptoms Exclusion criteria 1. < 18 years of age 2. More than 48 h from onset of symptoms 3. Iatrogenic pancreatitis 4. Infectious complications 5. Already receiving antibiotics for previous 2 weeks

Spicak 2002 (*Continued*)

Interventions	Group 1: antibiotics (n = 33): metronidazole 500 mg 3 times daily and ciprofloxacin 200 mg twice daily for 2 weeks Group 2: no intervention (n = 30)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis, hospital stay, ICU stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Spicak 2003

Methods	Randomised clinical trial
Participants	Country: Czech Republic Number randomised: 41 Postrandomisation dropouts: not stated Revised sample size: 41 Average age: 58 years Women: 10 (24.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated

Spicak 2003 (*Continued*)

	Mild pancreatitis: 0 (0%). Moderate pancreatitis: 0 (0%) Severe pancreatitis: 41 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. < 18 years of age 2. More than 48 h from onset of symptoms 3. Pancreatitis following surgery or ERCP 4. Infectious complications 5. Already receiving antibiotics for previous 2 weeks
Interventions	Group 1: antibiotics (n = 20): meropenem 0.5 mg 3 times daily for 10 days Group 2: no intervention (n = 21)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis, hospital stay Follow-up: not stated
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This information was not available.
Allocation concealment (selection bias)	Unclear risk	This information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	This information was not available.
Other bias	Low risk	Comment: no other risk of bias

Storck 1968

Methods	Randomised clinical trial
Participants	Country: Sweden Number randomised: 43 Postrandomisation dropouts: not stated Revised sample size: 43 Average age: 59 years Women: 28 (65.1%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: aprotinin (n = 21), first half of the trial - 50,000 to 100,000 units per day and then dose doubled for an average of 12 days Group 2: placebo (n = 22)
Outcomes	Mortality Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[s]ealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported

Storck 1968 (*Continued*)

For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Trapnell 1974

Methods	Randomised clinical trial
Participants	Country: UK Number randomised: 105 Postrandomisation dropouts: not stated Revised sample size: 105 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with first attack of acute pancreatitis 2. Aetiology: gallstones or idiopathic pancreatitis
Interventions	Group 1: aprotinin (n = 53), 200,000 units IV stat followed by 200,000 units IV 4 times daily for 5 days Group 2: placebo (n = 52)
Outcomes	Mortality Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "[t]he envelopes of allotment were placed in a recognized position in each hospital together with the packs of Trasylol"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"

Trapnell 1974 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	High risk	Quote: "[w]e are particularly indebted to Dr Brian Allen of Bayer Pharmaceuticals for the supplies of Trasylol and the preparation of the A and B ampoules"
Other bias	Unclear risk	Comment: no other risk of bias

Tykka 1985

Methods	Randomised clinical trial
Participants	Country: Finland Number randomised: 64 Postrandomisation dropouts: 0 (0%) Revised sample size: 64 Average age: 51 years Women: 23 (35.9%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis Exclusion criteria 1. Post-traumatic pancreatitis 2. Postsurgical pancreatitis
Interventions	Group 1: EDTA (n = 33), dose and duration not reported Group 2: placebo (n = 31) Follow-up: not stated (probably until discharge)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery
Notes	-

Risk of bias ***Risk of bias***

Tykka 1985 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[w]e are also grateful for the drugs and support from Sinclair Pharmaceutical Limited, England." Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Uhl 1999

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 302 Postrandomisation dropouts: 0 (0%) Revised sample size: 302 Average age: 50 years Women: 104 (34.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: 108 (35.8%) Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with moderate to severe acute pancreatitis 2. Duration of symptoms < 4 days Exclusion criteria 1. Known chronic renal failure

Uhl 1999 (*Continued*)

	2. < 18 years of age 3. Pregnancy 4. Psychosis (except alcoholic delirium) 5. Previous treatment with aprotinin, glucagon, calcitonin, pirenzepine, atropine, or native somatostatin 6. Previous included in the study (i.e. relapse after previous inclusion in the study)
Interventions	Group 1: octreotide (n = 199), 100 μg or 200 μg (randomised) SC 3 times daily for 7 days Group 2: placebo (n = 103)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Low risk	Quote: "[t]he packages were used sequentially as the patients were enrolled in the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[t]he preparation, randomisation, and delivery of the study medication, as well as the monitoring of the study centres by checking the information in the CRFs, were carried out by Novartis (formerly Sandoz), Nuremberg (Germany)"
Other bias	Low risk	Comment: no other risk of bias

Usadel 1985

Methods	Randomised clinical trial
Participants	Country: Germany Number randomised: 77 Postrandomisation dropouts: not stated Revised sample size: 77 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: somatostain (n = 36), 250 ng/h for 7 days Group 2: placebo (n = 41)
Outcomes	Mortality Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.

Usadel 1985 (*Continued*)

Other bias	Low risk	Comment: no other risk of bias

Valderrama 1992

Methods	Randomised clinical trial
Participants	Country: Spain Number randomised: 105 Postrandomisation dropouts: 5 (4.8%) Revised sample size: 100 Average age: 57 years Women: 53 (53%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis
Interventions	Group 1: gabexate mesilate (n = 51), 12 mg/kg/day continuous IV for 4-12 days based on disappearance of abdominal pain or requirement for surgery Group 2: placebo (n = 49)
Outcomes	Mortality, serious adverse events, adverse events, sepsis Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: protocol violations

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer generated"
Allocation concealment (selection bias)	Low risk	Quote: "consecutively numbered boxes containing FOY or placebo"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"

Valderrama 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	High risk	Quote: "[t]he authors thank Laboratorio Dr Esteve SA for supplies of gabexate mesylate (FOY)"
Other bias	Low risk	Comment: no other risk of bias

Vege 2015

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 28 Postrandomisation dropouts: not stated Revised sample size: 28 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with predicted severe acute pancreatitis 2. < 72 h of onset of symptoms
Interventions	Group 1: antioxidant (n = 14): pentoxifylline 400 mg oral 3 times daily for 3 days Group 2: placebo (n = 14)
Outcomes	Mortality, serious adverse events, organ failure, hospital stay, ICU stay Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Vege 2015 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Wang 2011

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 24 Postrandomisation dropouts: not stated Revised sample size: 24 Average age: 46 years Women: 15 (62.5%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 24 (100%). Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis.
Interventions	Group 1: thymosin alpha (n = 12), 3.2 mg twice daily for 7 days Group 2: placebo (n = 12)
Outcomes	Mortality, hospital stay, ICU stay Follow-up: 1 month
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Wang 2011 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Wang 2013a

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 183 Postrandomisation dropouts: not stated Revised sample size: 183 Average age: 42 years Women: 89 (48.6%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 159 (86.9%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with severe acute pancreatitis 2. Age: 18 to 45 years 3. < 2 days from onset of symptoms 4. Presence of gastrointestinal ileus or distension Exclusion criteria 1. History of renal dysfunction 2. Pregnant or lactating

Wang 2013a (*Continued*)

	3. Expected to receive extracorporeal removal 4. Inflammatory bowel disease 5. Infections at the time of hospital admission 6. Received recent NSAID
Interventions	Group 1: somatostatin plus ulinastatin (n = 62) Group 2: somatostatin (n = 61) Group 3: no intervention (n = 60) Somatostatin: 250 μg/h IV for 10 days. Ulinastatin: 10,000 units IV twice daily for 10 days
Outcomes	Mortality, serious adverse events Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Low risk	Quote: "[t]he authors have no direct relationship with any of the companies mentioned in this article, either by employment or by receiving research grants"
Other bias	Low risk	Comment: no other risk of bias

Wang 2013b

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 354 Postrandomisation dropouts: not stated Revised sample size: 354 Average age: not stated Women: not stated Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with predicted severe acute pancreatitis
Interventions	Group 1: octreotide plus NSAID (n = not reported) Group 2: octreotide (n = not reported) Octreotide: 50 μg/h for first 3 days followed by 25 μg/h for next 4 days NSAID: celecoxib 200 mg twice daily for 7 days
Outcomes	None of the outcomes of interest were reported. Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported

Wang 2013b (*Continued*)

For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Wang 2013c

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 372 Postrandomisation dropouts: not stated Revised sample size: 372 Average age: 45 years Women: 174 (46.8%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 0 (0%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with predicted severe acute pancreatitis or acute pancreatitis 2. Age 18 to 70 years 3. Admission in < 48 h of onset of symptoms 4. No other severe diseases such as cirrhosis, chronic obstructive airway disease, chronic renal insufficiency, malignant tumours Exclusion criteria: people with alcohol dependence
Interventions	Group 1: octreotide (n = 157), 50 μg/h for first 3 days followed by 25 μg/h for next 4 days or 25 μg/h for 7 days (randomised) Group 2: no intervention (n = 79)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, requirement for endoscopic or radiological drainage, organ failure, hospital stay Follow-up: some outcomes were measured on 8th day and others at 1 month
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.

Wang 2013c (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "[t]he physicians and nurses who managed the patients were blinded so that they did not know the patient has been allocated to and what treatment they had received". Comment: there is no mention of participant blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[t]he physicians and nurses who managed the patients were blinded so that they did not know the patient has been allocated to and what treatment they had received"
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Low risk	Quote: "[t]his study was supported by a Key Grant # 30330270 from the Natural Science Fund of China and the National Ministry of Health Fund for the Public Welfare 2-13"
Other bias	Low risk	Comment: no other risk of bias

Wang 2016

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 492 Postrandomisation dropouts: not stated Revised sample size: 492 Average age: 41 years Women: 238 (48.4%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 492 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with severe acute pancreatitis Exclusion criteria 1. Evidence or a known history of renal dysfunction 2. Pregnancy 3. Malignancy 4. Immunodeficiency 5. Pre-existing chronic kidney diseases requiring regular hemodialysis

Wang 2016 (*Continued*)

Interventions	Group 1: somatostatin plus ulinastatin plus gabexate (n = 116) Group 2: somatostatin plus ulinastatin (n = 124) Group 3: somatostatin plus gabexate (n = 130) Group 4: somatostatin (n = 122) Somatostatin: 3 mg IV for 10 days Ulinastatin: 10,000 units IV twice daily for 10 days Gabexate: 0.1 g IV 3 times daily for 10 days
Outcomes	Mortality, adverse events, organ failure, length of hospital stay Follow-up: not stated (probably until discharge)
Notes	-

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "[a]ccording to a computerized random number generation . . ."
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "[t]his was a prospective and double-blind study" Comment: a placebo was used to achieve blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "[t]his was a prospective and double-blind study" Comment: a placebo was used to achieve blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there were no postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Low risk	Quote: "[t]his work was supported by National Natural Science Foundation of China, China (81360080, 81071594) and the Science Foundation of Science and Technology Hall of Jiangxi Province, China (20091391308000)."
Other bias	Low risk	Comment: no other risk of bias

Xia 2014

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 140 Postrandomisation dropouts: not stated Revised sample size: 140 Average age: 43 years Women: 48 (34.3%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: 140 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with severe acute pancreatitis 2. No associated severe liver disease or biliary diseases 3. Pancreatitis not resulting from trauma, malignancy 4. No contraindications or allergies to somatostatin 5. No treatment with other drugs which could affect the results of this study
Interventions	Group 1: somatostatin (3 mg IV twice daily for 7 days) plus omeprazole (40 mg IV twice daily for 7 days) (n = 70) Group 2: no intervention (n = 70)
Outcomes	Mortality, serious adverse events, adverse events Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.

Xia 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Xue 2009

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 59 Postrandomisation dropouts: 3 (5.1%) Revised sample size: 56 Average age: 48 years Women: 28 (50%) Acute interstitial oedematous pancreatitis: 0 (0%) Necrotising pancreatitis: 56 (100%) Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 56 (100%) Persistent organ failure: not stated Infected pancreatitis: 0 Inclusion criteria 1. People with acute necrotising pancreatitis and identified as severe acute pancreatitis 2. Within 3 days of onset of symptoms 3. Age at least 18 years Exclusion criteria 1. Concurrent sepsis or peripancreatic infection 2. Direct transfer to ICU for multiorgan failure 3. Pancreatitis secondary to trauma, ERCP, or operation 4. Recurrent pancreatitis 5. Pregnancy, malignancy, or immunodeficiency 6. History of antibiotic administration within 48 h prior to enrolment 7. Possible death within 48 h after enrolment
Interventions	Group 1: antibiotics (n = 29): imipenem-cilastatin 0.5 g every 8 h for 7-14 days Group 2: no intervention (n = 27)
Outcomes	Mortality, serious adverse events, adverse events, requirement for surgery, hospital stay Follow-up: 1 month
Notes	Reasons for postrandomisation dropouts: death after starting treatment, transferred to operation

Xue 2009 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-derived random number sequence"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	Low risk	Comment: mortality and adverse events were reported.
For profit-bias	Low risk	Quote: "[w]e thank Sichuan Province Science and Technology Tackling Key Project (no. 05SG011-021-1) for providing financial support for the trial and the publication of the paper"
Other bias	Low risk	Comment: no other risk of bias

Yang 1999

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 48 Postrandomisation dropouts: not stated Revised sample size: 48 Average age: 45 years Women: 26 (54.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: not stated Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria: people with acute pancreatitis

Yang 1999 (*Continued*)

Interventions	Group 1: somatostatin (n = 25), 250 μg/h for 3-4 days Group 2: no intervention (n = 23)
Outcomes	Serious adverse events, adverse events Follow-up: not stated (probably until discharge)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

Yang 2012

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 163 Postrandomisation dropouts: 6 (3.7%) Revised sample size: 157 Average age: 46 years Women: 71 (45.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 157 (100%)

Yang 2012 (*Continued*)

	Moderate pancreatitis: not stated Severe pancreatitis: not stated Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with mild pancreatitis 2. Aged between 18 and 70 years 3. < 48 h of symptoms 4. People with a BMI > 25 kg/m² Exclusion criteria 1. People with alcohol dependence 2. Pregnancy 3. Drug abuse 4. Psychosis 5. Cirrhosis 6. Chronic obstructive pulmonary disease 7. Chronic renal insufficiency 8. Malignancy
Interventions	Group 1: octreotide (n = 80), 50 μg/h for 3 days Group 2: no intervention (n = 77)
Outcomes	Mortality, hospital stay Follow-up: 1 month
Notes	Reasons for postrandomisation dropouts: loss to follow-up; lack of data

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this information was not available.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: this information was not available.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: there were postrandomisation dropouts.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported

Yang 2012 (*Continued*)

For profit-bias	Low risk	Quote: "[t]his study was supported by Key Grant # 30330270 of the Natural Science Fund of China and the National Ministry of Health Fund for Public Welfare 2-13. "
Other bias	Low risk	Comment: no other risk of bias

Zhu 2014

Methods	Randomised clinical trial
Participants	Country: China Number randomised: 39 Postrandomisation dropouts: not stated Revised sample size: 39 Average age: 43 years Women: 18 (46.2%) Acute interstitial oedematous pancreatitis: not stated Necrotising pancreatitis: not stated Mild pancreatitis: 0 (0%) Moderate pancreatitis: 0 (0%) Severe pancreatitis: 39 (100%) Persistent organ failure: not stated Infected pancreatitis: not stated Inclusion criteria 1. People with severe acute pancreatitis 2. < 48 h from onset of symptoms 3. < 65 years of age Exclusion criteria 1. Chronic pancreatitis 2. Associated with primary infection, tumours, low immunity
Interventions	Group 1: probiotics (n = 20), 2 tablets twice daily for 14 days (Japanese preparation) Group 2: placebo (n = 19)
Outcomes	Serious adverse events, adverse events, requirement for endoscopic or radiological drainage, infected pancreatic necrosis Follow-up: not stated (probably 2 weeks)
Notes	Reasons for postrandomisation dropouts: not stated

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: this information was not available.

Zhu 2014 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: this information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: this information was not available.
Selective reporting (reporting bias)	High risk	Comment: either mortality or adverse events were not reported
For profit-bias	Unclear risk	Comment: this information was not available.
Other bias	Low risk	Comment: no other risk of bias

ERCP: endoscopic retrograde cholangiopancreatography; **ICU**: intensive care unit; **IU**: international unit; **IV**: intravenous; **KIU**: kallikrein inhibitor units; **MRC**: Medical Research Council (1 MRC = 1 IU); **PR**: per rectum; **SC**: subcutaneous.

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

Study	Reason for exclusion
Akzhigitov 1968	Not an RCT
Akzhigitov 1969	Not an RCT
Al-Leswas 2013a	Comparison of 2 different antioxidants
Al-Leswas 2013b	Comparison of 2 different antioxidants
Al-Leswas 2013c	Comparison of 2 different antioxidants
Al-Leswas 2013d	Comparison of 2 different antioxidants
Al-Leswas 2013e	Comparison of 2 different antioxidants
Al-Leswas 2013f	Comparison of 2 different antioxidants
Al-Leswas 2013g	Comparison of 2 different antioxidants

(*Continued*)

Amundsen 1972	Not conducted in humans
Andersson 2008	Not a primary research study (commentary)
Baden 1967	Quasi-RCT (allocation based on birth date) comparing 2 different preparations of aprotinin
Baden 1969	Quasi-RCT (allocation based on birth date) comparing 2 different preparations of aprotinin
Bai 2013	Not an RCT
Bassi 1998	Comparison of 2 different antibiotic regimens
Beechey-Newman 1991	Not an RCT
Beechey-Newman 1993	Not an RCT
Beger 2001	Not a primary research study (commentary)
Bender 1992	Not an RCT
Binder 1993	Comparison of different doses of octreotide
Binder 1994	Comparison of different doses of octreotide
Brown 2004	Not a primary research study (editorial)
Buchler 1988	Not an RCT
Cameron 1979	Quasi-randomised study (allocation by patient number)
Cheng 2008	There was no control group for pharmacological intervention
Cullimore 2008	Not a primary research study (letter to editor)
Curtis 1997	Not a primary research study (review)
D'Amico 1990	Not an RCT
Da Silvereira 2002	Not a primary research study (commentary)
De Vries 2007	Not a primary research study (systematic review)
Dikkenberg 2008	Not a primary research study (commentary)
Dreiling 1977	Not an RCT
Du 2002	Comparison of 2 doses of vitamin C

(*Continued*)

Du 2003	Comparison of 2 doses of vitamin C
Dürr 1985	Quasi-RCT (allocation by alternation)
Freise 1985	Not an RCT
Friess 1994	Not a primary research study (review)
Gabryelewicz 1968	Not in humans
Gabryelewicz 1976	Not an RCT
Gao 2015b	Not a pharmacological intervention
Garcia 2005	Comparison of 2 variations of probiotics
Gostishchev 1977	Not a primary research study (review)
Guo 2013	Comparison of different doses of octreotide
Hajdu 2012	Variations in nutritional supplementation
Harinath 2002	Prophylactic intervention (not in people with acute pancreatitis)
Hart 2008	Not a primary research study (review)
He 2004	Not a pharmacological intervention
Helton 2001	Not a primary research study (comment)
Hoekstra 2008	Not a primary research study (letter to editor)
Holub 1974	Not a primary research study (letter to editor)
Howard 2007	Not a primary research study (editorial)
Howes 1975	Quasi-RCT (allocation by hospital number)
Huang 2008	Variations in different types of nutritional supplementation
Issekutz 2002	No suitable control (3 groups were: probiotics + fibre versus inactivated lactobacilli + fibre versus standard nutrition; it is not possible to obtain the effect estimate of probiotics alone from this comparison)
Ivanov 2002	Not an RCT
Jiang 1988	Not an RCT

(*Continued*)

Karakan 2007	Not a pharmacological intervention (fibre supplementation only)
Karakoyunlar 1999	Not an RCT
Karavanov 1966	Not an RCT
Lasztity 2005a	Variations in fatty acids used in enteral nutrition
Lasztity 2005b	Variations in fatty acids used in enteral nutrition
Lasztity 2006	Variations in fatty acids used in enteral nutrition
Lata 1998	Not an RCT
Lata 2010	This started as a RCT but was converted to a cohort study after publication of negative results
Lim 2015	Not a primary research study (review)
Lu 2006	Not a pharmacological intervention (variations in parenteral nutrition)
Lu 2008	Intervention includes a non-pharmacological treatment in addition to antioxidant
Manes 2003	Comparison of 2 different antibiotics
Manes 2006	Comparison of 2 different antibiotic regimens
McClave 2009	Not a primary research study (editorial)
Mercadier 1973	Not an RCT
Niu 2014	Comparison of 2 different fats
Pearce 2006	Variations in composition of enteral feeds
Pederzoli 1995	Not primary research (review)
Pezzilli 1997	Comparison of two doses of gabexate mesilate
Pezzilli 1999	Comparison of 2 doses of gabexate mesilate
Pezzilli 2001	Comparison of 2 doses of gabexate mesilate
Piascik 2010	In addition to the difference in the groups in terms of whether the patients received protease inhibitor, the antibiotic regimen differed between the groups
Plaudis 2012	Not an RCT

(*Continued*)

Rahman 2003	Not a primary research study (letter to editor)
Ranson 1976	Not an RCT
Reddy 2008	Not a primary research study (letter to editor)
Santen 2008	Not primary research (letter to editor)
Singer 1966	No mention about randomisation
Skyring 1965	No mention about randomisation
Tanaka 1979	There were 2 trials reported in this publication. Of these, 1 was a quasi-RCT (alternate allocation) and it was not clear whether the second trial was an RCT
Tang 2005	Only the control group received Chinese medicines
Tang 2007	Not an RCT
Ukai 2015	Not a primary research study (review)
Usadel 1980	Not a primary research study (letter to editor)
Venkatesan 2008	Not a primary research study (commentary)
Villatoro 2010	Not primary research (review)
Wang 2008	Variations in composition of parenteral nutrition
Wang 2009	Variations in composition of parenteral nutrition
Weismann 2010	Not a primary research study (commentary)
Wyncoll 1998	Not a primary research study (letter to editor)
Xiong 2009	Variations in parenteral nutrition
Xu 2012	Variations in parenteral nutrition
Yang 2008a	Not an RCT
Yang 2008b	Variations in total parenteral nutrition
Yang 2009	Chinese medicines were given to the control group but not the intervention group

(*Continued*)

Zapater 2000	The co-interventions in the groups varied apart from the drug being evaluated (nasogastric suction was used only in the control group)

RCT = randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Hansen 1966

Methods	Awaiting full text
Participants	-
Interventions	-
Outcomes	-
Notes	-

Perez 1980

Methods	Awaiting full text
Participants	-
Interventions	-
Outcomes	-
Notes	-

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR-IPR-16008301

Trial name or title	The effect of proton pump inhibitors on acute pancreatitis--a randomly prospective control study
Methods	Randomised controlled trial
Participants	Adults with acute pancreatitis
Interventions	Proton pump inhibitor (omeprazole) versus placebo
Outcomes	Duration of hospital stay, gastrointestinal bleeding, and hospital costs

ChiCTR-IPR-16008301 (*Continued*)

Starting date	September 2016
Contact information	Xiao Ma (mxiao_9101@163.com)
Notes	-

EUCTR2014-004844-37-ES

Trial name or title	Trial of indomethacin in pancreatitis
Methods	Randomised controlled trial
Participants	Adults with acute pancreatitis
Interventions	Non-steroidal anti-inflammatory drugs (indomethacin) versus placebo
Outcomes	Mortality and organ failure
Starting date	May 2015
Contact information	Enrique de Madaria Pascual (madaria@hotmail.com)
Notes	ChiCTR-IPR-16008301, NCT02692391

NCT01132521

Trial name or title	Ulinastatin in severe acute pancreatitis
Methods	Randomised controlled trial
Participants	Adults with severe acute pancreatitis
Interventions	Ulinastatin versus placebo
Outcomes	mortality, organ failure, requirement for additional invasive intervention, hospital stay, intensive care unit stay
Starting date	June 2010
Contact information	Chunyou Wang (Wuhan Union Hospital, China)
Notes	The study is currently suspended.

NCT02025049

Trial name or title	DP-b99 in the treatment of acute high-risk pancreatitis
Methods	Randomised controlled trial
Participants	Adults with predicted severe acute pancreatitis
Interventions	DP-b99 versus placebo
Outcomes	Complications
Starting date	December 2013
Contact information	Gilad Rosenberg (Wuhan Union Hospital, China)
Notes	The University Hospital Brno, Gastroenterology Clinic, Brno, Czech Republic, 62500

NCT02212392

Trial name or title	Comparing the outcome in patients of acute pancreatitis, with and without prophylactic antibiotics
Methods	Randomised controlled trial
Participants	Adults with acute pancreatitis
Interventions	Antibiotics (meropenem) versus no intervention
Outcomes	Infections and hospital stay
Starting date	Jan 2013
Contact information	Fazal H Shah (Benazir Bhutto Hospital, Rawalpindi, Punjab, Pakistan, 46000)
Notes	-

NCT02692391

Trial name or title	A randomized controlled pilot trial of indomethacin in acute pancreatitis
Methods	Randomised controlled trial
Participants	Adults with acute pancreatitis
Interventions	Non-steroidal anti-inflammatory drugs (indomethacin) versus placebo
Outcomes	Mortality and organ failure
Starting date	April 2014

NCT02692391 (*Continued*)

Contact information	Georgios I Papachristou (papachri@pitt.edu)
Notes	-

NCT02885441

Trial name or title	Treatment of acute pancreatitis with ketorolac
Methods	Randomised controlled trial
Participants	Adults with predicted severe acute pancreatitis
Interventions	Non-steroidal anti-inflammatory drugs (ketorolac) versus placebo
Outcomes	New onset organ failure, pancreatic necrosis, and duration of hospital stay
Starting date	September 2016
Contact information	Shaahin Shahbazi (mdkabe@gmail.com)
Notes	-

DATA AND ANALYSES

Comparison 1. Acute pancreatitis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term mortality	67		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Antibiotics versus control	17	1058	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.57, 1.15]
1.2 Antioxidants versus control	4	163	Odds Ratio (M-H, Fixed, 95% CI)	2.01 [0.53, 7.56]
1.3 Aprotinin versus control	7	651	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.14]
1.4 Calcitonin versus control	2	125	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.15, 2.00]
1.5 Cimetidine versus control	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 17.18]
1.6 EDTA versus control	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.12, 7.08]
1.7 Gabexate versus control	5	576	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.30]
1.8 Glucagon versus control	5	409	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.51, 1.87]
1.9 Iniprol versus control	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 1.67]
1.10 Lexipafant versus control	3	423	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.30, 1.01]
1.11 Octreotide versus control	5	927	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.47, 1.23]
1.12 Probiotics versus control	2	358	Odds Ratio (M-H, Fixed, 95% CI)	1.70 [0.87, 3.30]
1.13 Activated protein C versus control	1	32	Odds Ratio (M-H, Fixed, 95% CI)	8.56 [0.41, 180.52]
1.14 Somatostatin versus control	6	493	Odds Ratio (M-H, Fixed, 95% CI)	0.57 [0.29, 1.10]
1.15 Somatostatin plus omeprazole versus control	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 1.11]
1.16 Somatostatin plus ulinastatin versus control	1	122	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.23]
1.17 Thymosin versus control	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.18 Ulinastatin versus control	1	132	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.12, 1.72]
1.19 Gabexate versus aprotinin	2	298	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.32, 1.20]
1.20 Glucagon versus aprotinin	1	134	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.44, 4.08]
1.21 Glucagon versus atropine	1	150	Odds Ratio (M-H, Fixed, 95% CI)	4.17 [0.45, 38.21]
1.22 Octreotide plus ulinastatin versus octreotide	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.06, 1.60]
1.23 Somatostatin plus gabexate versus somatostatin	1	252	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.37, 2.33]
1.24 Somatostatin plus ulinastatin versus somatostatin	2	369	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.34, 1.56]
1.25 Somatostatin plus ulinastatin plus gabexate versus somatostatin	1	238	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.21, 1.74]
1.26 Somatostatin plus ulinastatin versus somatostatin plus gabexate	1	254	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.26, 1.95]

1.27 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate	1	246	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.23, 1.86]
1.28 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin	1	240	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.30, 2.80]
2 Serious adverse events (proportion)	17		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Antibiotics versus control	5	304	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.37, 1.15]
2.2 Antioxidants versus control	2	82	Odds Ratio (M-H, Fixed, 95% CI)	1.98 [0.48, 8.13]
2.3 EDTA versus control	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.11, 2.39]
2.4 Gabexate versus control	2	201	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.31, 5.60]
2.5 Glucagon versus control	2	127	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 7.46]
2.6 Octreotide versus control	1	58	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.61, 4.93]
2.7 Somatostatin versus control	2	111	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.35, 3.27]
2.8 Gabexate versus aprotinin	1	116	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.22, 4.91]
2.9 Ulinastatin versus gabexate	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Serious adverse events (number)	37		Rate Ratio (Fixed, 95% CI)	Subtotals only
3.1 Antibiotics versus control	12	716	Rate Ratio (Fixed, 95% CI)	0.86 [0.68, 1.07]
3.2 Antioxidants versus control	2	71	Rate Ratio (Fixed, 95% CI)	0.22 [0.02, 2.21]
3.3 Aprotinin versus control	3	264	Rate Ratio (Fixed, 95% CI)	0.79 [0.49, 1.29]
3.4 Cimetidine versus control	1	60	Rate Ratio (Fixed, 95% CI)	1.0 [0.20, 4.95]
3.5 EDTA versus control	1	64	Rate Ratio (Fixed, 95% CI)	0.94 [0.19, 4.65]
3.6 Gabexate versus control	3	375	Rate Ratio (Fixed, 95% CI)	0.86 [0.64, 1.15]
3.7 Glucagon versus control	1	68	Rate Ratio (Fixed, 95% CI)	1.0 [0.02, 50.40]
3.8 Lexipafant versus control	1	290	Rate Ratio (Fixed, 95% CI)	0.67 [0.46, 0.96]
3.9 Octreotide versus control	4	770	Rate Ratio (Fixed, 95% CI)	0.74 [0.60, 0.89]
3.10 Probiotics versus control	3	397	Rate Ratio (Fixed, 95% CI)	0.94 [0.65, 1.36]
3.11 Somatostatin versus control	3	257	Rate Ratio (Fixed, 95% CI)	1.03 [0.66, 1.59]
3.12 Somatostatin plus omeprazole versus control	1	140	Rate Ratio (Fixed, 95% CI)	0.36 [0.19, 0.70]
3.13 Somatostatin plus ulinastatin versus control	1	122	Rate Ratio (Fixed, 95% CI)	0.30 [0.15, 0.60]
3.14 Glucagon versus atropine	1	150	Rate Ratio (Fixed, 95% CI)	0.33 [0.03, 3.20]
3.15 Octreotide plus ulinastatin versus octreotide	1	120	Rate Ratio (Fixed, 95% CI)	0.30 [0.17, 0.51]
3.16 Somatostatin plus ulinastatin versus somatostatin	1	123	Rate Ratio (Fixed, 95% CI)	0.28 [0.15, 0.56]
4 Organ failure	18		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Antibiotics versus control	5	258	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.44, 1.38]
4.2 Antioxidants versus control	4	163	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.39, 2.12]
4.3 Gabexate versus control	1	50	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.25]
4.4 Lexipafant versus control	2	340	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.36, 1.27]
4.5 Octreotide versus control	2	430	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.27, 0.97]
4.6 Probiotics versus control	2	358	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.26, 2.47]
4.7 Ulinastatin versus control	1	129	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.01, 6.67]

4.8 Somatostatin plus gabexate versus somatostatin	1	252	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.33, 1.80]
4.9 Somatostatin plus ulinastatin versus somatostatin	1	246	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.23, 1.45]
4.10 Somatostatin plus ulinastatin plus gabexate versus somatostatin	1	238	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.17, 1.25]
4.11 Somatostatin plus ulinastatin versus somatostatin plus gabexate	1	254	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.29, 1.92]
4.12 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate	1	246	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.21, 1.65]
4.13 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin	1	240	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.27, 2.35]
5 Infected pancreatic necrosis	15		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Antibiotics versus control	11	714	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.53, 1.25]
5.2 Octreotide versus control	1	58	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.04, 6.06]
5.3 Probiotics versus control	3	397	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.62, 1.96]
6 Sepsis	11		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Antibiotics versus control	1	60	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.11, 1.60]
6.2 Aprotinin versus control	2	103	Odds Ratio (M-H, Random, 95% CI)	1.84 [0.49, 6.96]
6.3 Gabexate versus control	3	373	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.55, 2.19]
6.4 Lexipafant versus control	1	290	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.08, 0.83]
6.5 Octreotide versus control	2	340	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.05, 3.53]
6.6 Probiotics versus control	1	62	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.10, 1.36]
6.7 Gabexate versus aprotinin	1	116	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.22, 4.91]
7 Adverse events (proportion)	27		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Antibiotics versus control	6	429	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.32, 0.80]
7.2 Antioxidants versus control	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Calcitonin versus control	1	94	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.12, 6.49]
7.4 EDTA versus control	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.27, 2.31]
7.5 Gabexate versus control	3	373	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.54, 1.27]
7.6 Glucagon versus control	2	127	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.00, 1.69]
7.7 Lexipafant versus control	1	83	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.16, 1.12]
7.8 Octreotide versus control	3	398	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.65, 1.55]
7.9 Probiotics versus control	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.12, 1.01]
7.10 Somatostatin versus control	2	111	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.19, 1.02]
7.11 Somatostatin plus omeprazole versus control	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.00 [0.00, 0.04]
7.12 Gabexate versus aprotinin	2	298	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.23, 0.70]
7.13 Ulinastatin versus gabexate	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.14 Ulinastatin versus octreotide	1	25	Odds Ratio (M-H, Fixed, 95% CI)	2.33 [0.46, 11.81]
7.15 Somatostatin plus gabexate versus somatostatin	1	252	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.44, 1.95]

7.16 Somatostatin plus ulinastatin versus somatostatin	1	246	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.25, 1.34]
7.17 Somatostatin plus ulinastatin plus gabexate versus somatostatin	1	238	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.20, 1.20]
7.18 Somatostatin plus ulinastatin versus somatostatin plus gabexate	1	254	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.27, 1.44]
7.19 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate	1	246	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.22, 1.28]
7.20 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin	1	240	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.32, 2.22]
8 Adverse events (number)	40		Rate Ratio (Random, 95% CI)	Subtotals only
8.1 Antibiotics versus control	12	755	Rate Ratio (Random, 95% CI)	0.75 [0.58, 0.95]
8.2 Antioxidants versus control	2	94	Rate Ratio (Random, 95% CI)	0.82 [0.38, 1.79]
8.3 Aprotinin versus control	3	264	Rate Ratio (Random, 95% CI)	0.98 [0.69, 1.39]
8.4 Calcitonin versus control	1	94	Rate Ratio (Random, 95% CI)	0.88 [0.12, 6.25]
8.5 Cimetidine versus control	1	60	Rate Ratio (Random, 95% CI)	1.14 [0.64, 2.02]
8.6 EDTA versus control	1	64	Rate Ratio (Random, 95% CI)	0.63 [0.28, 1.39]
8.7 Gabexate versus control	3	375	Rate Ratio (Random, 95% CI)	0.76 [0.61, 0.95]
8.8 Glucagon versus control	2	90	Rate Ratio (Random, 95% CI)	1.19 [0.51, 2.80]
8.9 Lexipafant versus control	1	290	Rate Ratio (Random, 95% CI)	0.61 [0.44, 0.85]
8.10 Octreotide versus control	4	634	Rate Ratio (Random, 95% CI)	0.78 [0.58, 1.05]
8.11 Probiotics versus control	3	397	Rate Ratio (Random, 95% CI)	0.84 [0.52, 1.36]
8.12 Somatostatin versus control	2	134	Rate Ratio (Random, 95% CI)	0.75 [0.26, 2.18]
8.13 Ulinastatin versus control	1	129	Rate Ratio (Random, 95% CI)	0.69 [0.32, 1.46]
8.14 Gabexate versus aprotinin	1	182	Rate Ratio (Random, 95% CI)	0.66 [0.38, 1.14]
8.15 Glucagon versus atropine	1	150	Rate Ratio (Random, 95% CI)	0.79 [0.36, 1.73]
8.16 Oxyphenonium versus glucagon	1	62	Rate Ratio (Random, 95% CI)	0.93 [0.65, 1.34]
8.17 Octreotide plus ulinastatin versus octreotide	1	120	Rate Ratio (Random, 95% CI)	0.29 [0.17, 0.48]
9 Requirement for additional invasive intervention	32		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Antibiotics versus control	14	884	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.59, 1.13]
9.2 Aprotinin versus control	2	237	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.23, 1.47]
9.3 Calcitonin versus control	2	125	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.08, 1.16]
9.4 Cimetidine versus control	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.61]
9.5 EDTA versus control	1	64	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.14, 3.29]
9.6 Gabexate versus control	3	426	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.37, 0.90]
9.7 Glucagon versus control	2	260	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.58, 2.77]
9.8 Octreotide versus control	3	854	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.48, 1.21]
9.9 Probiotics versus control	2	358	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [0.83, 2.71]
9.10 Somatostatin versus control	1	100	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.11, 1.38]

9.11 Gabexate versus aprotinin	1	182	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.19, 1.32]
9.12 Glucagon versus aprotinin	1	134	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.44, 4.08]
9.13 Oxyphenonium versus glucagon	1	62	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.13, 7.59]
10 Endoscopic or radiological drainage of collections	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Antibiotics versus control	1	23	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 9.07]
10.2 Octreotide versus control	1	372	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.40, 1.96]
10.3 Probiotics versus control	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.20, 4.44]

Comparison 2. Acute necrotising pancreatitis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term mortality	11		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Antibiotics versus control	10	683	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.30]
1.2 Gabexate versus aprotinin	1	116	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.20, 1.36]
2 Serious adverse events (proportion)	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Antibiotics versus control	4	281	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.46, 1.54]
2.2 Gabexate versus aprotinin	1	116	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.22, 4.91]
3 Serious adverse events (number)	7		Rate Ratio (Fixed, 95% CI)	Subtotals only
3.1 Antibiotics versus control	7		Rate Ratio (Fixed, 95% CI)	0.79 [0.59, 1.06]
4 Organ failure	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Antibiotics versus control	4	211	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.42, 1.45]
5 Infected pancreatic necrosis	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Antibiotics versus control	6	426	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.51, 1.42]
6 Sepsis	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Antibiotics versus control	1	60	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.11, 1.60]
6.2 Gabexate versus aprotinin	1	116	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.22, 4.91]

Comparison 3. Severe acute pancreatitis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Short-term mortality	22		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Antibiotics versus control	9	542	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.53, 1.27]
1.2 Aprotinin versus control	2	103	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.19, 2.30]
1.3 Calcitonin versus control	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.11, 5.46]
1.4 Gabexate versus control	1	52	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.99]
1.5 Probiotics versus control	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.05, 1.34]
1.6 Activated protein C versus control	1	32	Odds Ratio (M-H, Fixed, 95% CI)	8.56 [0.41, 180.52]

1.7 Somatostatin versus control	2	182	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.21, 1.23]
1.8 Somatostatin plus omeprazole versus control	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 1.11]
1.9 Somatostatin plus ulinastatin versus control	1	122	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.15, 1.23]
1.10 Thymosin versus control	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.11 Ulinastatin versus control	1	70	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.04, 1.29]
1.12 Octreotide plus ulinastatin versus octreotide	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.06, 1.60]
1.13 Somatostatin plus gabexate versus somatostatin	1	252	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.37, 2.33]
1.14 Somatostatin plus ulinastatin versus somatostatin	2	369	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.34, 1.56]
1.15 Somatostatin plus ulinastatin plus gabexate versus somatostatin	1	238	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.21, 1.74]
1.16 Somatostatin plus ulinastatin versus somatostatin plus gabexate	1	254	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.26, 1.95]
1.17 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate	1	246	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.23, 1.86]
1.18 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin	1	240	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.30, 2.80]
2 Serious adverse events (proportion)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Antibiotics versus control	3	164	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.27, 1.18]
3 Serious adverse events (number)	13		Rate Ratio (Random, 95% CI)	Subtotals only
3.1 Antibiotics versus control	5		Rate Ratio (Random, 95% CI)	0.81 [0.52, 1.25]
3.2 Aprotinin versus control	2		Rate Ratio (Random, 95% CI)	0.65 [0.25, 1.71]
3.3 Gabexate versus control	1		Rate Ratio (Random, 95% CI)	0.64 [0.37, 1.10]
3.4 Probiotics versus control	2		Rate Ratio (Random, 95% CI)	0.62 [0.24, 1.59]
3.5 Somatostatin versus control	1		Rate Ratio (Random, 95% CI)	1.07 [0.67, 1.69]
3.6 Somatostatin plus omeprazole versus control	1		Rate Ratio (Random, 95% CI)	0.36 [0.19, 0.70]
3.7 Somatostatin plus ulinastatin versus control	1		Rate Ratio (Random, 95% CI)	0.30 [0.15, 0.60]
3.8 Octreotide plus ulinastatin versus octreotide	1		Rate Ratio (Random, 95% CI)	0.30 [0.17, 0.51]
3.9 Somatostatin plus ulinastatin versus somatostatin	1		Rate Ratio (Random, 95% CI)	0.28 [0.15, 0.56]
4 Organ failure	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Antibiotics versus control	3	137	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.40, 1.99]
4.2 Lexipafant versus control	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Probiotics versus control	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.12, 1.36]
4.4 Ulinastatin versus control	1	67	Odds Ratio (M-H, Fixed, 95% CI)	0.05 [0.01, 0.21]

4.5 Somatostatin plus gabexate versus somatostatin	1	252	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.33, 1.80]
4.6 Somatostatin plus ulinastatin versus somatostatin	1	246	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.23, 1.45]
4.7 Somatostatin plus ulinastatin plus gabexate versus somatostatin	1	238	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.17, 1.25]
4.8 Somatostatin plus ulinastatin versus somatostatin plus gabexate	1	254	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.29, 1.92]
4.9 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate	1	246	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.21, 1.65]
4.10 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin	1	240	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.27, 2.35]
5 Infected pancreatic necrosis	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Antibiotics versus control	6	341	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.41, 1.33]
5.2 Probiotics versus control	2	101	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.22, 1.68]
6 Sepsis	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Aprotinin versus control	2	103	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [0.50, 6.98]
6.2 Probiotics versus control	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.10, 1.36]

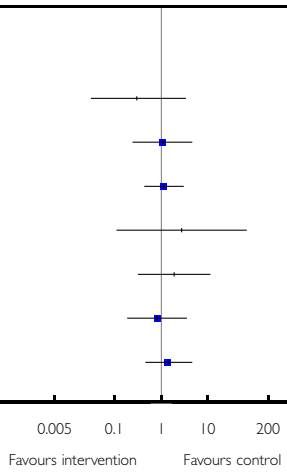
Analysis 1.1. Comparison 1 Acute pancreatitis, Outcome 1 Short-term mortality.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 1 Short-term mortality

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Antibiotics versus control					
Barreda 2009	0/24	0/34			Not estimable
Delcenserie 1996	1/11	3/12		3.8 %	0.30 [0.03, 3.43]
Delcenserie 2001	6/53	3/28		5.0 %	1.06 [0.24, 4.62]
Dellinger 2007	10/50	9/50		10.4 %	1.14 [0.42, 3.10]
Finch 1976	1/31	0/27		0.7 %	2.70 [0.11, 69.19]
Garcia-Barrasa 2009	4/22	2/19		2.5 %	1.89 [0.31, 11.68]
Hejtmankova 2003	4/20	5/21		5.6 %	0.80 [0.18, 3.54]
Llukacaj 2012	8/40	6/40		6.9 %	1.42 [0.44, 4.53]



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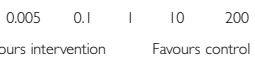
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Luiten 1995	11/50	18/52		19.9 %	0.53 [0.22, 1.28]
Nordback 2001	2/25	5/33		5.7 %	0.49 [0.09, 2.75]
Pederzoli 1993a	3/41	4/33		5.9 %	0.57 [0.12, 2.76]
Poropat 2015	3/23	2/24		2.5 %	1.65 [0.25, 10.91]
Rokke 2007	3/36	4/37		5.2 %	0.75 [0.16, 3.62]
Sainio 1995	1/30	7/30		9.8 %	0.11 [0.01, 0.99]
Spicak 2002	5/33	3/30		3.9 %	1.61 [0.35, 7.39]
Spicak 2003	4/20	5/21		5.6 %	0.80 [0.18, 3.54]
Xue 2009	4/30	5/28		6.5 %	0.71 [0.17, 2.96]
Subtotal (95% CI)	**539**	**519**		**100.0 %**	**0.81 [0.57, 1.15]**
Total events: 70 (Intervention), 81 (Control)					
Heterogeneity: Chi^2 = 9.40, df = 15 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
2 Antioxidants versus control					
Bansal 2011	0/19	2/20		74.4 %	0.19 [0.01, 4.22]
Sateesh 2009	1/23	0/30		12.8 %	4.07 [0.16, 104.53]
Siriwardena 2007	4/22	0/21		12.9 %	10.46 [0.53, 207.40]
Vege 2015	0/14	0/14			Not estimable
Subtotal (95% CI)	**78**	**85**		**100.0 %**	**2.01 [0.53, 7.56]**
Total events: 5 (Intervention), 2 (Control)					
Heterogeneity: Chi^2 = 3.58, df = 2 (P = 0.17); I^2 =44%					
Test for overall effect: Z = 1.03 (P = 0.30)					
3 Aprotinin versus control					
Balldin 1983	0/26	3/29		9.2 %	0.14 [0.01, 2.90]
Berling 1994	4/22	4/26		8.5 %	1.22 [0.27, 5.59]
Imrie 1978	7/80	7/81		18.0 %	1.01 [0.34, 3.03]
Imrie 1980	1/25	0/25		1.3 %	3.12 [0.12, 80.39]
MRC Multicentre Trial 1977	6/66	13/123		23.4 %	0.85 [0.31, 2.34]
Storck 1968	2/21	2/22		5.0 %	1.05 [0.13, 8.24]
Trapnell 1974	4/53	13/52		34.4 %	0.24 [0.07, 0.81]
Subtotal (95% CI)	**293**	**358**		**100.0 %**	**0.68 [0.40, 1.14]**
Total events: 24 (Intervention), 42 (Control)					
Heterogeneity: Chi^2 = 6.11, df = 6 (P = 0.41); I^2 =2%					
Test for overall effect: Z = 1.47 (P = 0.14)					
4 Calcitonin versus control					
Goebell 1979	2/50	4/44		63.8 %	0.42 [0.07, 2.39]



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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Martinez 1984	2/14	3/17		36.2 %	0.78 [0.11, 5.46]
Subtotal (95% CI)	**64**	**61**		**100.0 %**	**0.55 [0.15, 2.00]**
Total events: 4 (Intervention), 7 (Control)					
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² =0.0%					
Test for overall effect: Z = 0.91 (P = 0.36)					
5 Cimetidine versus control					
Perezdeoteyza 1980	1/20	1/20		100.0 %	1.00 [0.06, 17.18]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**1.00 [0.06, 17.18]**
Total events: 1 (Intervention), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
6 EDTA versus control					
Tykka 1985	2/33	2/31		100.0 %	0.94 [0.12, 7.08]
Subtotal (95% CI)	**33**	**31**		**100.0 %**	**0.94 [0.12, 7.08]**
Total events: 2 (Intervention), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
7 Gabexate versus control					
Buchler 1993	18/115	16/108		39.4 %	1.07 [0.51, 2.22]
Chen 2000	2/26	8/26		20.9 %	0.19 [0.04, 0.99]
Freise 1986	5/25	2/25		4.5 %	2.88 [0.50, 16.48]
Goebell 1988	8/76	11/75		28.0 %	0.68 [0.26, 1.81]
Valderrama 1992	0/51	2/49		7.1 %	0.18 [0.01, 3.94]
Subtotal (95% CI)	**293**	**283**		**100.0 %**	**0.79 [0.48, 1.30]**
Total events: 33 (Intervention), 39 (Control)					
Heterogeneity: Chi² = 6.56, df = 4 (P = 0.16); I² =39%					
Test for overall effect: Z = 0.91 (P = 0.36)					
8 Glucagon versus control					
Debas 1980	3/33	1/33		4.9 %	3.20 [0.32, 32.48]
Dürr 1978	4/33	5/36		22.8 %	0.86 [0.21, 3.50]
Kalima 1980	0/32	1/29		8.4 %	0.29 [0.01, 7.46]
Kronborg 1980	5/10	8/12		19.7 %	0.50 [0.09, 2.81]
MRC Multicentre Trial 1977	8/68	13/123		44.2 %	1.13 [0.44, 2.87]
Subtotal (95% CI)	**176**	**233**		**100.0 %**	**0.97 [0.51, 1.87]**
Total events: 20 (Intervention), 28 (Control)					
Heterogeneity: Chi² = 2.24, df = 4 (P = 0.69); I² =0.0%					
Test for overall effect: Z = 0.08 (P = 0.94)					
9 Iniprol versus control					
Hansky 1969	1/15	3/9		100.0 %	0.14 [0.01, 1.67]

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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**15**	**9**		**100.0 %**	**0.14 [0.01, 1.67]**
Total events: 1 (Intervention), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
10 Lexipafant versus control					
Johnson 2001	15/151	23/139		74.3 %	0.56 [0.28, 1.12]
Kingsnorth 1995	2/42	2/41		6.6 %	0.98 [0.13, 7.27]
McKay 1997b	3/26	6/24		19.0 %	0.39 [0.09, 1.78]
Subtotal (95% CI)	**219**	**204**		**100.0 %**	**0.55 [0.30, 1.01]**
Total events: 20 (Intervention), 31 (Control)					
Heterogeneity: Chi^2 = 0.51, df = 2 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.93 (P = 0.053)					
11 Octreotide versus control					
McKay 1997a	5/28	6/30		12.7 %	0.87 [0.23, 3.25]
Paran 1995	2/19	6/19		14.4 %	0.25 [0.04, 1.48]
Uhl 1999	27/199	16/103		48.7 %	0.85 [0.44, 1.67]
Wang 2013c	7/91	4/45		13.2 %	0.85 [0.24, 3.08]
Wang 2013c	4/157	2/79		6.9 %	1.01 [0.18, 5.62]
Yang 2012	0/80	1/77		4.1 %	0.32 [0.01, 7.90]
Subtotal (95% CI)	**574**	**353**		**100.0 %**	**0.76 [0.47, 1.23]**
Total events: 45 (Intervention), 35 (Control)					
Heterogeneity: Chi^2 = 2.06, df = 5 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 1.13 (P = 0.26)					
12 Probiotics versus control					
Besselink 2008	24/152	9/144		56.5 %	2.81 [1.26, 6.28]
Olah 2007	2/33	6/29		43.5 %	0.25 [0.05, 1.34]
Subtotal (95% CI)	**185**	**173**		**100.0 %**	**1.70 [0.87, 3.30]**
Total events: 26 (Intervention), 15 (Control)					
Heterogeneity: Chi^2 = 6.52, df = 1 (P = 0.01); I^2 =85%					
Test for overall effect: Z = 1.56 (P = 0.12)					
13 Activated protein C versus control					
Pettila 2010	3/16	0/16		100.0 %	8.56 [0.41, 180.52]
Subtotal (95% CI)	**16**	**16**		**100.0 %**	**8.56 [0.41, 180.52]**
Total events: 3 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
14 Somatostatin versus control					
Choi 1989	1/35	2/36		7.9 %	0.50 [0.04, 5.78]

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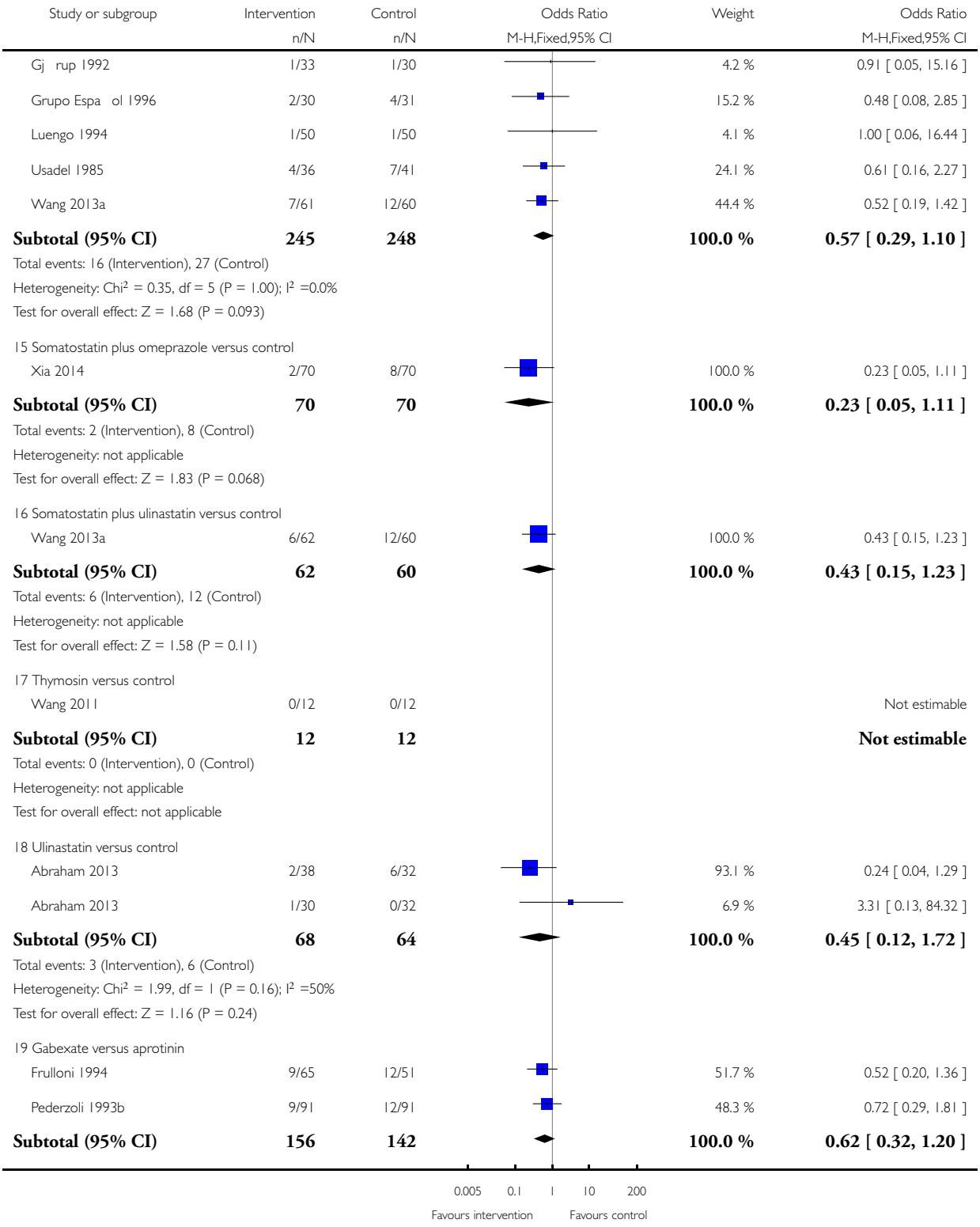

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gj rup 1992	1/33	1/30		4.2 %	0.91 [0.05, 15.16]
Grupo Espa ol 1996	2/30	4/31		15.2 %	0.48 [0.08, 2.85]
Luengo 1994	1/50	1/50		4.1 %	1.00 [0.06, 16.44]
Usadel 1985	4/36	7/41		24.1 %	0.61 [0.16, 2.27]
Wang 2013a	7/61	12/60		44.4 %	0.52 [0.19, 1.42]
Subtotal (95% CI)	**245**	**248**		**100.0 %**	**0.57 [0.29, 1.10]**
Total events: 16 (Intervention), 27 (Control)					
Heterogeneity: Chi² = 0.35, df = 5 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 1.68 (P = 0.093)					
15 Somatostatin plus omeprazole versus control					
Xia 2014	2/70	8/70		100.0 %	0.23 [0.05, 1.11]
Subtotal (95% CI)	**70**	**70**		**100.0 %**	**0.23 [0.05, 1.11]**
Total events: 2 (Intervention), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.83 (P = 0.068)					
16 Somatostatin plus ulinastatin versus control					
Wang 2013a	6/62	12/60		100.0 %	0.43 [0.15, 1.23]
Subtotal (95% CI)	**62**	**60**		**100.0 %**	**0.43 [0.15, 1.23]**
Total events: 6 (Intervention), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.58 (P = 0.11)					
17 Thymosin versus control					
Wang 2011	0/12	0/12			Not estimable
Subtotal (95% CI)	**12**	**12**			**Not estimable**
Total events: 0 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
18 Ulinastatin versus control					
Abraham 2013	2/38	6/32		93.1 %	0.24 [0.04, 1.29]
Abraham 2013	1/30	0/32		6.9 %	3.31 [0.13, 84.32]
Subtotal (95% CI)	**68**	**64**		**100.0 %**	**0.45 [0.12, 1.72]**
Total events: 3 (Intervention), 6 (Control)					
Heterogeneity: Chi² = 1.99, df = 1 (P = 0.16); I² =50%					
Test for overall effect: Z = 1.16 (P = 0.24)					
19 Gabexate versus aprotinin					
Frulloni 1994	9/65	12/51		51.7 %	0.52 [0.20, 1.36]
Pederzoli 1993b	9/91	12/91		48.3 %	0.72 [0.29, 1.81]
Subtotal (95% CI)	**156**	**142**		**100.0 %**	**0.62 [0.32, 1.20]**

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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 18 (Intervention), 24 (Control)					
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² =0.0%					
Test for overall effect: Z = 1.42 (P = 0.16)					
20 Glucagon versus aprotinin					
MRC Multicentre Trial 1977	8/68	6/66		100.0 %	1.33 [0.44, 4.08]
Subtotal (95% CI)	**68**	**66**		**100.0 %**	**1.33 [0.44, 4.08]**
Total events: 8 (Intervention), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.61)					
21 Glucagon versus atropine					
Kirsch 1978	4/75	1/75		100.0 %	4.17 [0.45, 38.21]
Subtotal (95% CI)	**75**	**75**		**100.0 %**	**4.17 [0.45, 38.21]**
Total events: 4 (Intervention), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					
22 Octreotide plus ulinastatin versus octreotide					
Guo 2015	2/60	6/60		100.0 %	0.31 [0.06, 1.60]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**0.31 [0.06, 1.60]**
Total events: 2 (Intervention), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
23 Somatostatin plus gabexate versus somatostatin					
Wang 2016	10/130	10/122		100.0 %	0.93 [0.37, 2.33]
Subtotal (95% CI)	**130**	**122**		**100.0 %**	**0.93 [0.37, 2.33]**
Total events: 10 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					
24 Somatostatin plus ulinastatin versus somatostatin					
Wang 2013a	6/62	7/61		40.1 %	0.83 [0.26, 2.62]
Wang 2016	7/124	10/122		59.9 %	0.67 [0.25, 1.82]
Subtotal (95% CI)	**186**	**183**		**100.0 %**	**0.73 [0.34, 1.56]**
Total events: 13 (Intervention), 17 (Control)					
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
25 Somatostatin plus ulinastatin plus gabexate versus somatostatin					
Wang 2016	6/116	10/122		100.0 %	0.61 [0.21, 1.74]
Subtotal (95% CI)	**116**	**122**		**100.0 %**	**0.61 [0.21, 1.74]**
Total events: 6 (Intervention), 10 (Control)					
Heterogeneity: not applicable					

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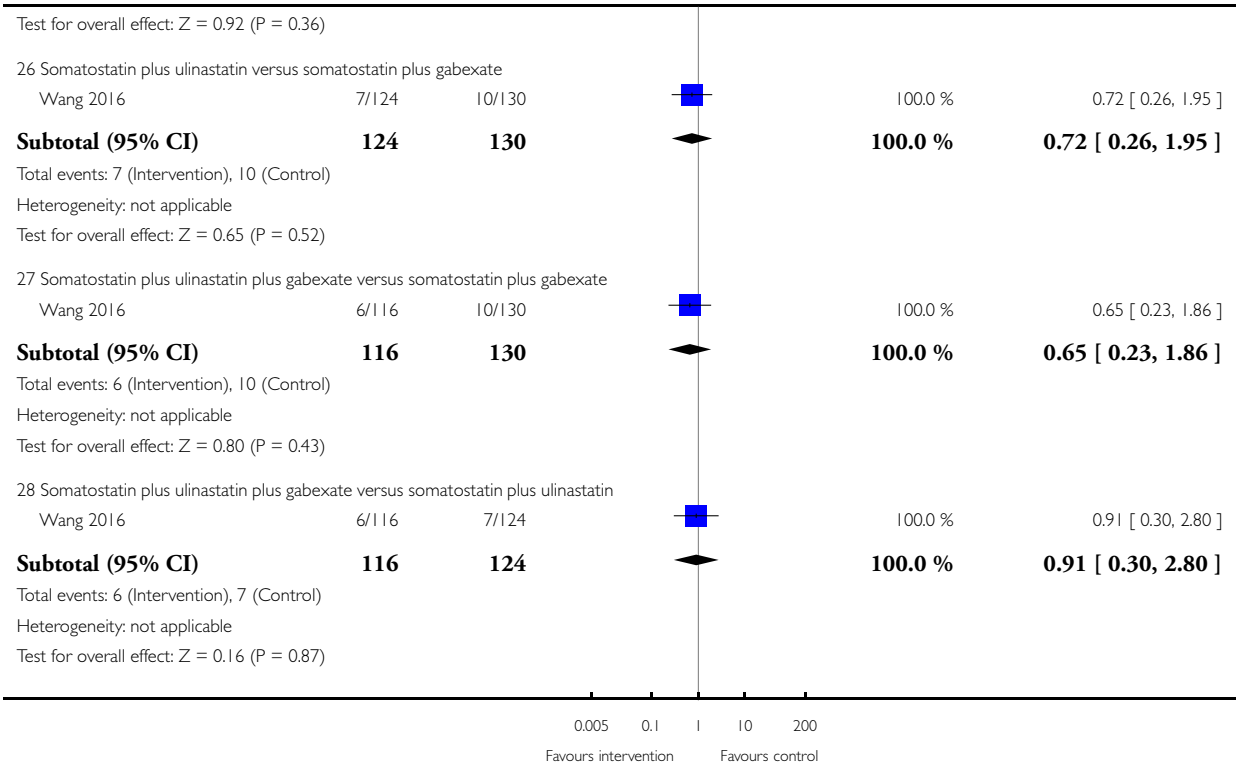
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.92 (P = 0.36)					
26 Somatostatin plus ulinastatin versus somatostatin plus gabexate					
Wang 2016	7/124	10/130		100.0 %	0.72 [0.26, 1.95]
Subtotal (95% CI)	**124**	**130**		**100.0 %**	**0.72 [0.26, 1.95]**
Total events: 7 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
27 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate					
Wang 2016	6/116	10/130		100.0 %	0.65 [0.23, 1.86]
Subtotal (95% CI)	**116**	**130**		**100.0 %**	**0.65 [0.23, 1.86]**
Total events: 6 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.43)					
28 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin					
Wang 2016	6/116	7/124		100.0 %	0.91 [0.30, 2.80]
Subtotal (95% CI)	**116**	**124**		**100.0 %**	**0.91 [0.30, 2.80]**
Total events: 6 (Intervention), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.16 (P = 0.87)					

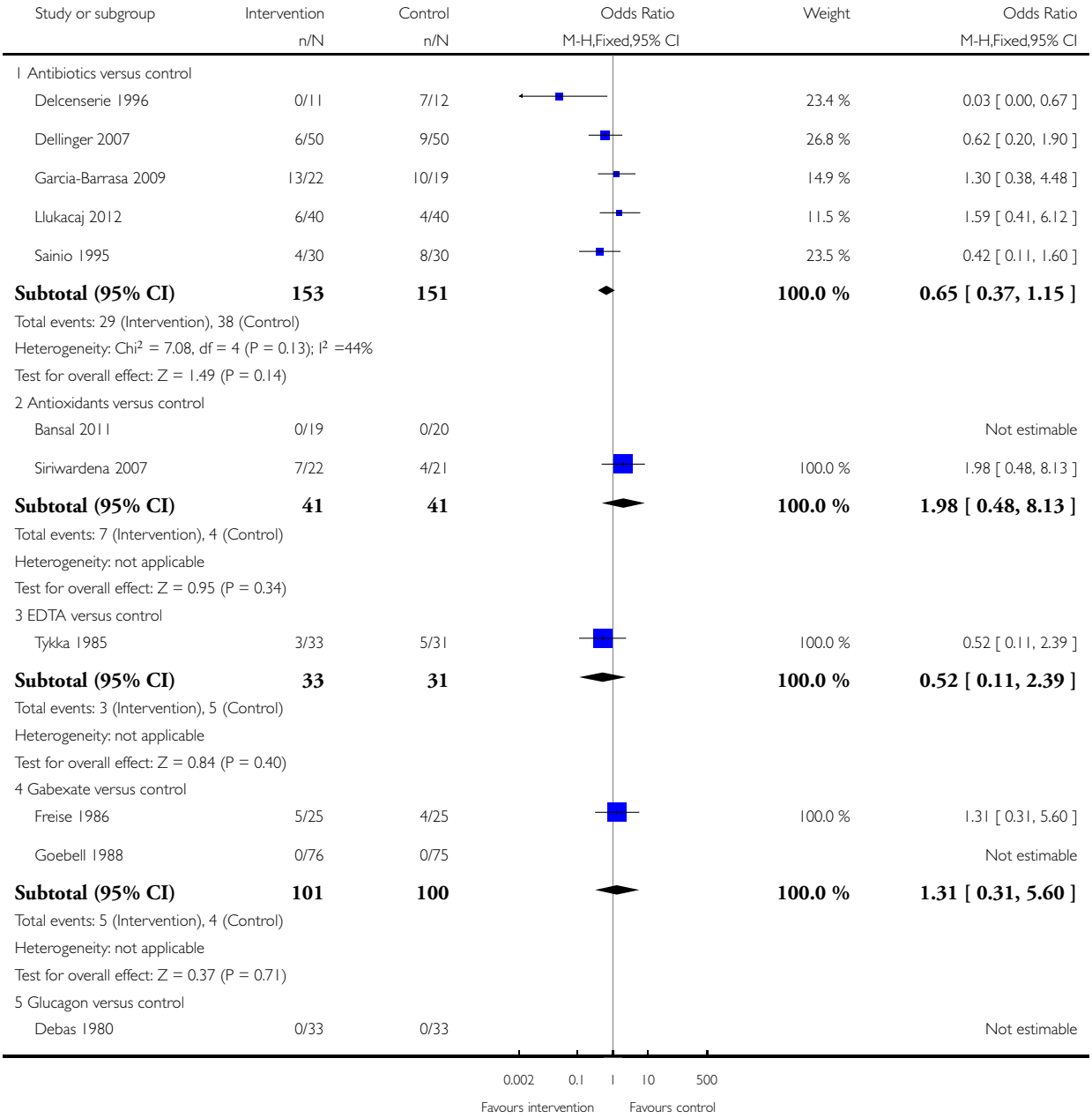


Analysis 1.2. Comparison 1 Acute pancreatitis, Outcome 2 Serious adverse events (proportion).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 2 Serious adverse events (proportion)



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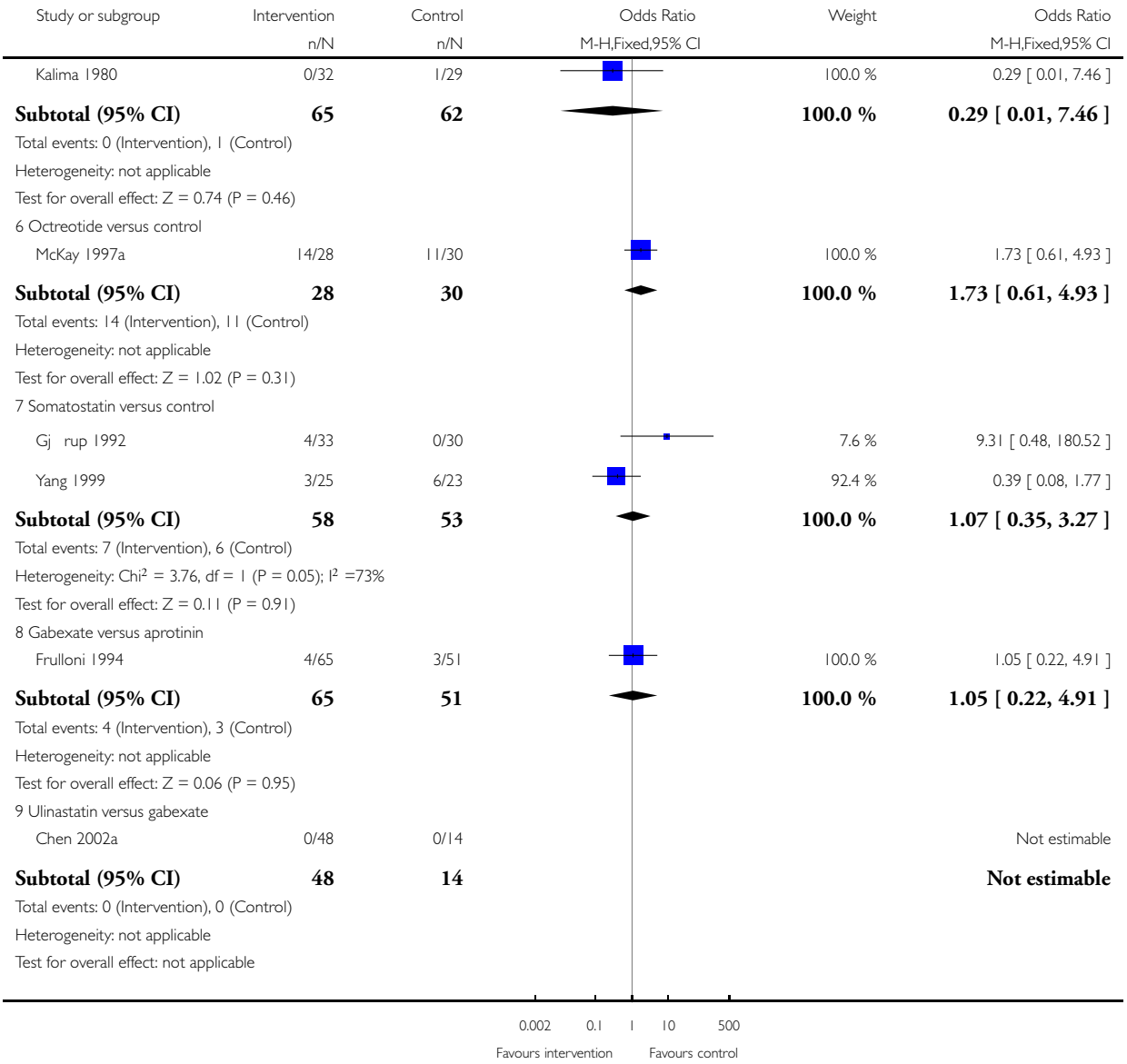
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kalima 1980	0/32	1/29		100.0 %	0.29 [0.01, 7.46]
Subtotal (95% CI)	**65**	**62**		**100.0 %**	**0.29 [0.01, 7.46]**
Total events: 0 (Intervention), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					
6 Octreotide versus control					
McKay 1997a	14/28	11/30		100.0 %	1.73 [0.61, 4.93]
Subtotal (95% CI)	**28**	**30**		**100.0 %**	**1.73 [0.61, 4.93]**
Total events: 14 (Intervention), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					
7 Somatostatin versus control					
Gj rup 1992	4/33	0/30		7.6 %	9.31 [0.48, 180.52]
Yang 1999	3/25	6/23		92.4 %	0.39 [0.08, 1.77]
Subtotal (95% CI)	**58**	**53**		**100.0 %**	**1.07 [0.35, 3.27]**
Total events: 7 (Intervention), 6 (Control)					
Heterogeneity: Chi^2 = 3.76, df = 1 (P = 0.05); I^2 =73%					
Test for overall effect: Z = 0.11 (P = 0.91)					
8 Gabexate versus aprotinin					
Frulloni 1994	4/65	3/51		100.0 %	1.05 [0.22, 4.91]
Subtotal (95% CI)	**65**	**51**		**100.0 %**	**1.05 [0.22, 4.91]**
Total events: 4 (Intervention), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
9 Ulinastatin versus gabexate					
Chen 2002a	0/48	0/14			Not estimable
Subtotal (95% CI)	**48**	**14**			**Not estimable**
Total events: 0 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

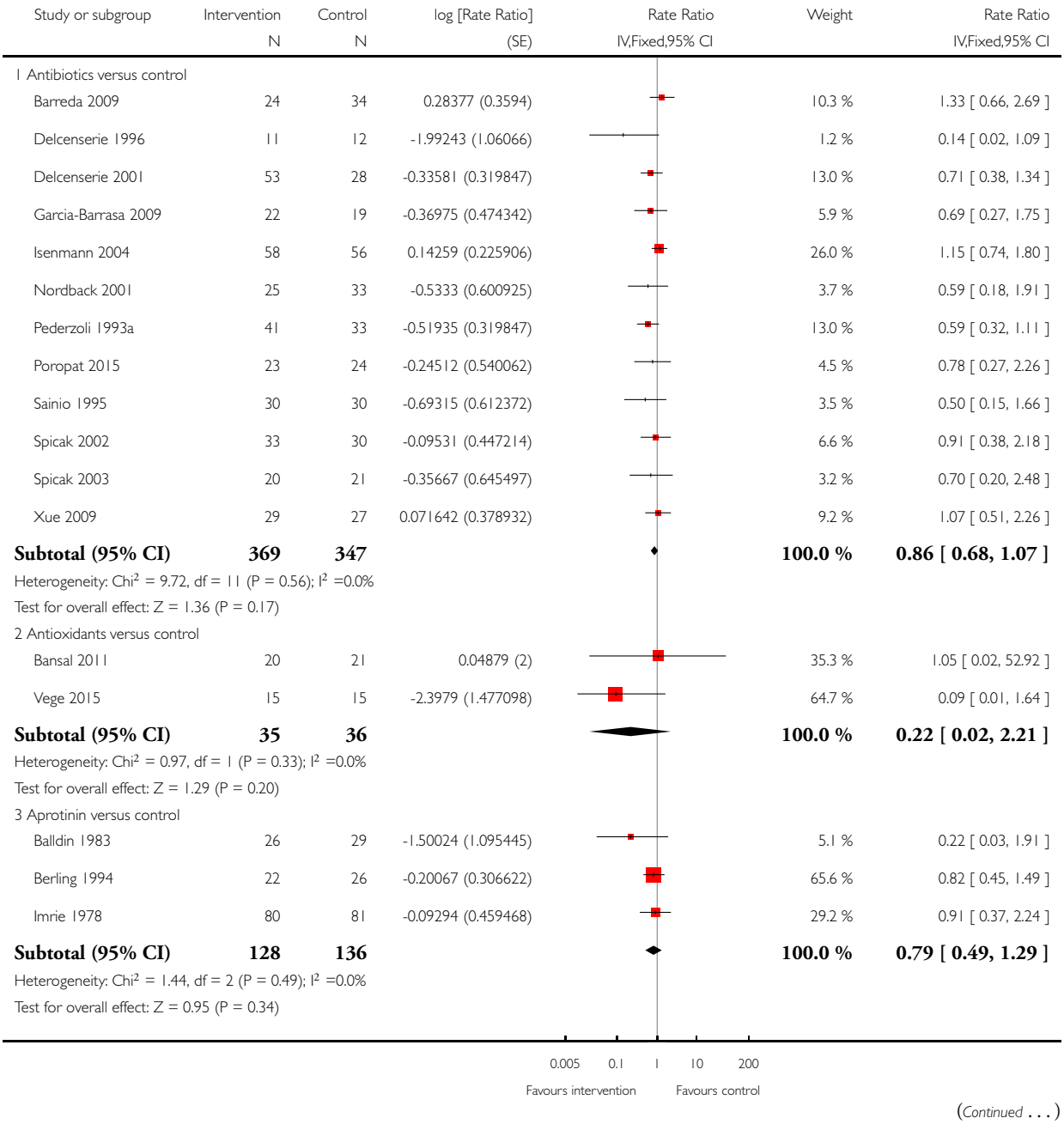


Analysis 1.3. Comparison 1 Acute pancreatitis, Outcome 3 Serious adverse events (number).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 3 Serious adverse events (number)



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Study or subgroup	Intervention N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
4 Cimetidine versus control						
Sillero 1981	30	30	0 (0.816497)		100.0 %	1.00 [0.20, 4.95]
Subtotal (95% CI)	**30**	**30**			**100.0 %**	**1.00 [0.20, 4.95]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						
5 EDTA versus control						
Tykka 1985	33	31	-0.06252 (0.816497)		100.0 %	0.94 [0.19, 4.65]
Subtotal (95% CI)	**33**	**31**			**100.0 %**	**0.94 [0.19, 4.65]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
6 Gabexate versus control						
Buchler 1993	115	108	-0.0628 (0.182574)		67.9 %	0.94 [0.66, 1.34]
Chen 2000	26	26	-0.45199 (0.279145)		29.1 %	0.64 [0.37, 1.10]
Valderrama 1992	51	49	0.653142 (0.866025)		3.0 %	1.92 [0.35, 10.49]
Subtotal (95% CI)	**192**	**183**			**100.0 %**	**0.86 [0.64, 1.15]**
Heterogeneity: Chi^2 = 2.26, df = 2 (P = 0.32); I^2 =11%						
Test for overall effect: Z = 1.03 (P = 0.31)						
7 Glucagon versus control						
Debas 1980	34	34	0 (2)		100.0 %	1.00 [0.02, 50.40]
Subtotal (95% CI)	**34**	**34**			**100.0 %**	**1.00 [0.02, 50.40]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P = 1.0)						
8 Lexipafant versus control						
Johnson 2001	151	139	-0.40489 (0.185722)		100.0 %	0.67 [0.46, 0.96]
Subtotal (95% CI)	**151**	**139**			**100.0 %**	**0.67 [0.46, 0.96]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.18 (P = 0.029)						
9 Octreotide versus control						
McKay 1997a	28	30	0.212094 (0.378932)		6.9 %	1.24 [0.59, 2.60]
Paran 1995	19	19	-0.72824 (0.32544)		9.4 %	0.48 [0.26, 0.91]
Uhl 1999	199	103	-0.09579 (0.186763)		28.6 %	0.91 [0.63, 1.31]
Wang 2013c	157	79	-0.47916 (0.186697)		28.6 %	0.62 [0.43, 0.89]
Wang 2013c	91	45	-0.33647 (0.193925)		26.5 %	0.71 [0.49, 1.04]
Subtotal (95% CI)	**494**	**276**			**100.0 %**	**0.74 [0.60, 0.89]**
Heterogeneity: Chi^2 = 5.70, df = 4 (P = 0.22); I^2 =30%						
Test for overall effect: Z = 3.08 (P = 0.0021)						
10 Probiotics versus control						
Besselink 2008	152	144	0.241397 (0.233465)		64.3 %	1.27 [0.81, 2.01]
Olah 2007	33	29	-0.86681 (0.366589)		26.1 %	0.42 [0.20, 0.86]

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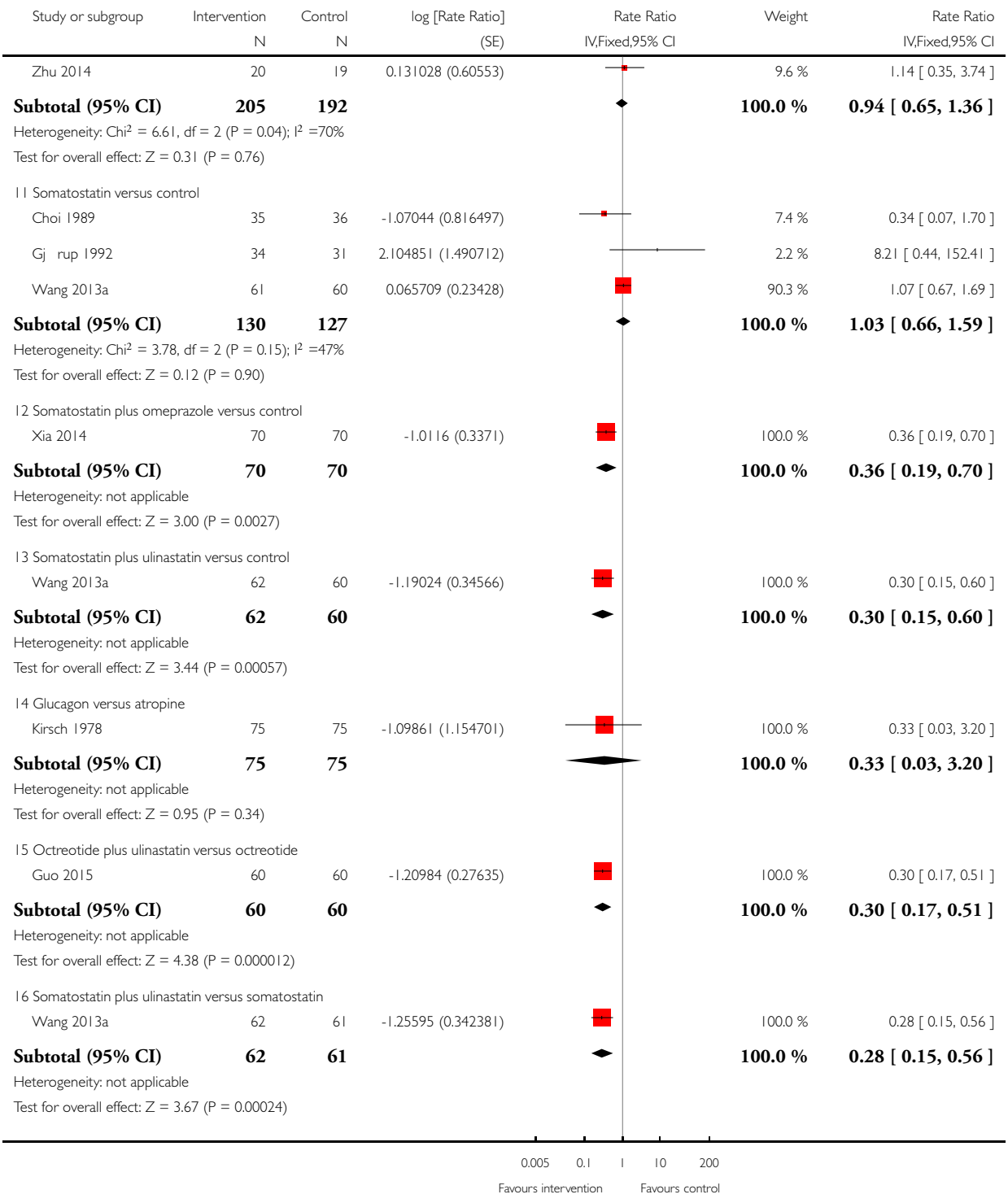
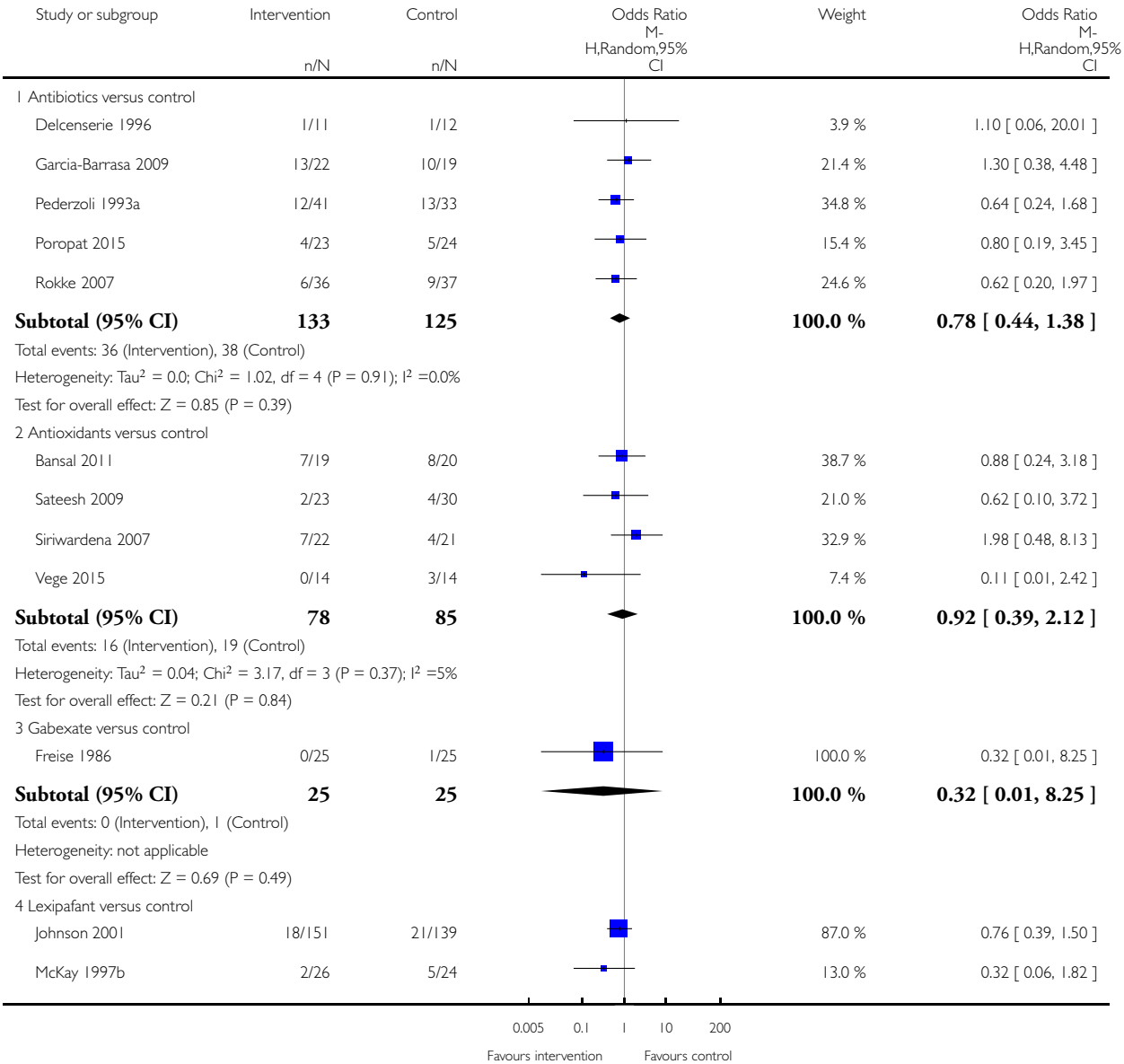


Analysis 1.4. Comparison 1 Acute pancreatitis, Outcome 4 Organ failure.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 4 Organ failure



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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**177**	**163**		**100.0 %**	**0.68 [0.36, 1.27]**
Total events: 20 (Intervention), 26 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.84, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 1.21 (P = 0.23)					
5 Octreotide versus control					
McKay 1997a	12/28	11/30		23.3 %	1.30 [0.45, 3.72]
Wang 2013c	53/157	45/79		42.8 %	0.39 [0.22, 0.67]
Wang 2013c	40/91	30/45		34.0 %	0.39 [0.19, 0.83]
Subtotal (95% CI)	**276**	**154**		**100.0 %**	**0.51 [0.27, 0.97]**
Total events: 105 (Intervention), 86 (Control)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 4.27, df = 2 (P = 0.12); I^2 =53%					
Test for overall effect: Z = 2.04 (P = 0.041)					
6 Probiotics versus control					
Besselink 2008	21/152	16/144		59.9 %	1.28 [0.64, 2.57]
Olah 2007	5/33	9/29		40.1 %	0.40 [0.12, 1.36]
Subtotal (95% CI)	**185**	**173**		**100.0 %**	**0.80 [0.26, 2.47]**
Total events: 26 (Intervention), 25 (Control)					
Heterogeneity: Tau^2 = 0.43; Chi^2 = 2.63, df = 1 (P = 0.10); I^2 =62%					
Test for overall effect: Z = 0.39 (P = 0.70)					
7 Ulinastatin versus control					
Abraham 2013	12/35	29/32		50.1 %	0.05 [0.01, 0.21]
Abraham 2013	5/30	4/32		49.9 %	1.40 [0.34, 5.80]
Subtotal (95% CI)	**65**	**64**		**100.0 %**	**0.27 [0.01, 6.67]**
Total events: 17 (Intervention), 33 (Control)					
Heterogeneity: Tau^2 = 4.80; Chi^2 = 10.41, df = 1 (P = 0.001); I^2 =90%					
Test for overall effect: Z = 0.80 (P = 0.43)					
8 Somatostatin plus gabexate versus somatostatin					
Wang 2016	11/130	13/122		100.0 %	0.78 [0.33, 1.80]
Subtotal (95% CI)	**130**	**122**		**100.0 %**	**0.78 [0.33, 1.80]**
Total events: 11 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.55)					
9 Somatostatin plus ulinastatin versus somatostatin					
Wang 2016	8/124	13/122		100.0 %	0.58 [0.23, 1.45]
Subtotal (95% CI)	**124**	**122**		**100.0 %**	**0.58 [0.23, 1.45]**
Total events: 8 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.17 (P = 0.24)					
10 Somatostatin plus ulinastatin plus gabexate versus somatostatin					
Wang 2016	6/116	13/122		100.0 %	0.46 [0.17, 1.25]

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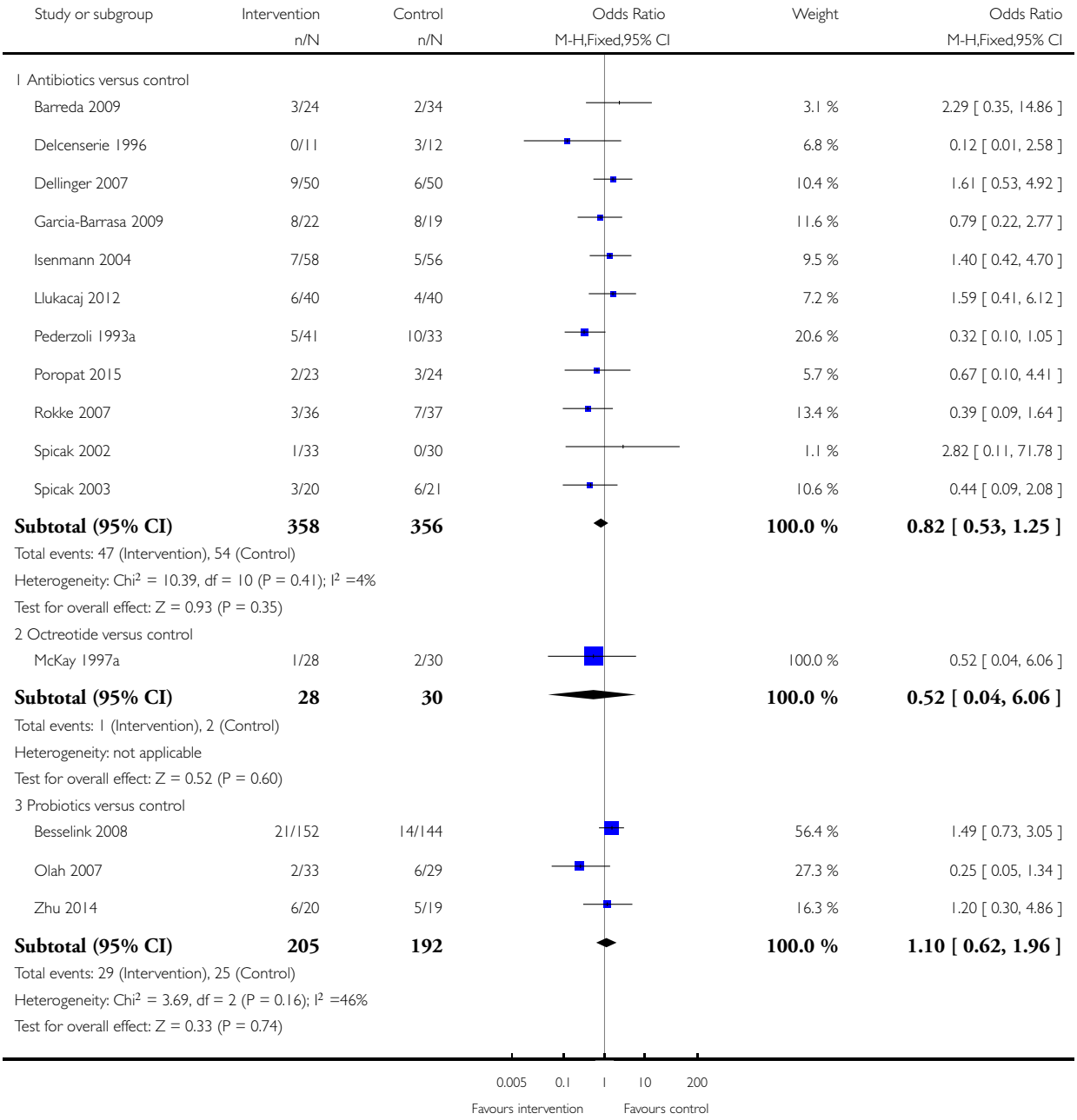
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**116**	**122**		**100.0 %**	**0.46 [0.17, 1.25]**
Total events: 6 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
11 Somatostatin plus ulinastatin versus somatostatin plus gabexate					
Wang 2016	8/124	11/130		100.0 %	0.75 [0.29, 1.92]
Subtotal (95% CI)	**124**	**130**		**100.0 %**	**0.75 [0.29, 1.92]**
Total events: 8 (Intervention), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
12 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate					
Wang 2016	6/116	11/130		100.0 %	0.59 [0.21, 1.65]
Subtotal (95% CI)	**116**	**130**		**100.0 %**	**0.59 [0.21, 1.65]**
Total events: 6 (Intervention), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
13 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin					
Wang 2016	6/116	8/124		100.0 %	0.79 [0.27, 2.35]
Subtotal (95% CI)	**116**	**124**		**100.0 %**	**0.79 [0.27, 2.35]**
Total events: 6 (Intervention), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					

Analysis 1.5. Comparison 1 Acute pancreatitis, Outcome 5 Infected pancreatic necrosis.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 5 Infected pancreatic necrosis

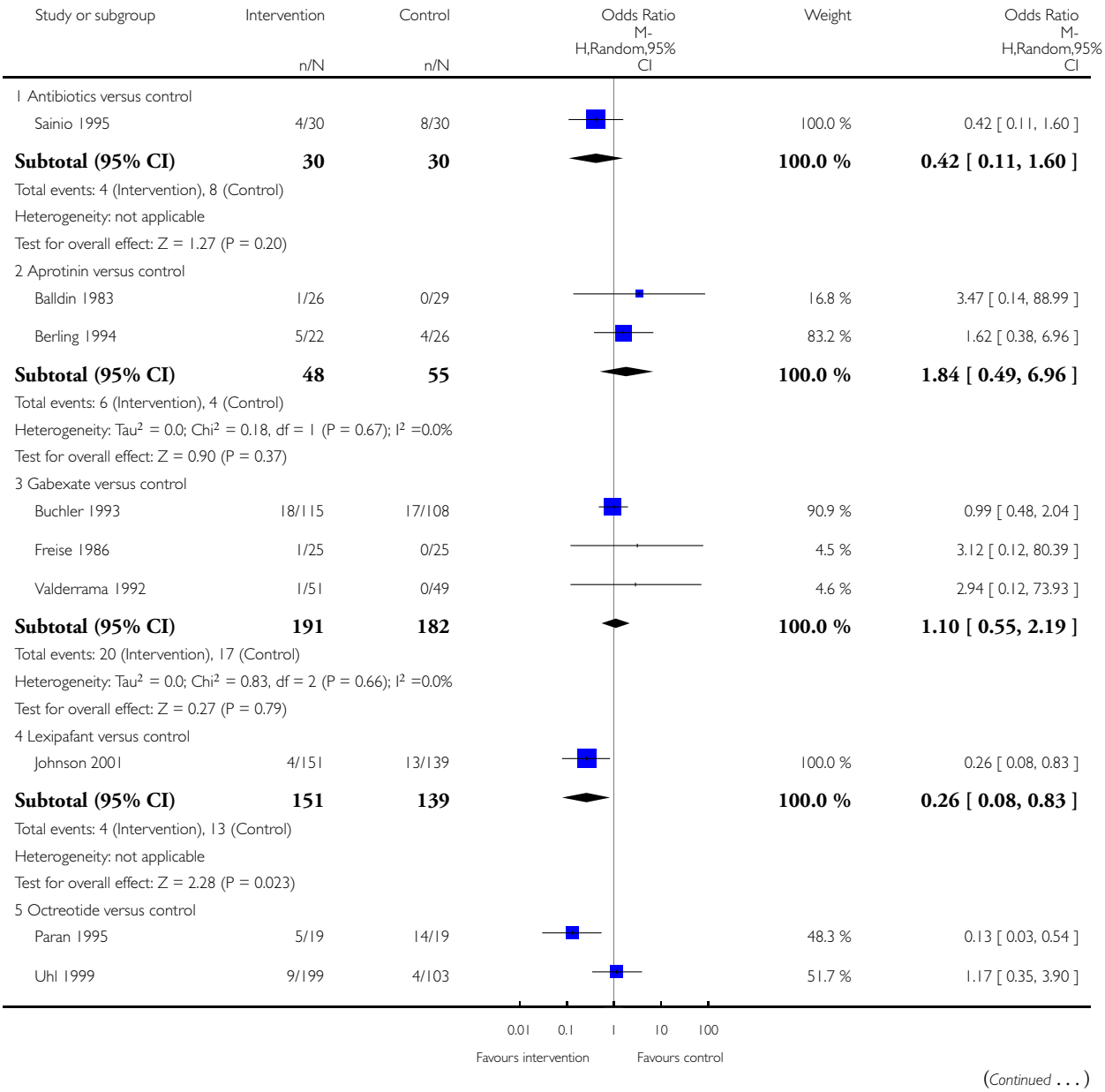


Analysis 1.6. Comparison 1 Acute pancreatitis, Outcome 6 Sepsis.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 6 Sepsis



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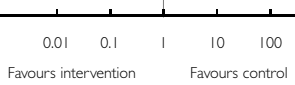
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Subtotal (95% CI)	**218**	**122**		**100.0 %**	**0.40 [0.05, 3.53]**
Total events: 14 (Intervention), 18 (Control)					
Heterogeneity: Tau^2 = 2.00; Chi^2 = 5.35, df = 1 (P = 0.02); I^2 =81%					
Test for overall effect: Z = 0.82 (P = 0.41)					
6 Probiotics versus control					
Olah 2007	4/33	8/29		100.0 %	0.36 [0.10, 1.36]
Subtotal (95% CI)	**33**	**29**		**100.0 %**	**0.36 [0.10, 1.36]**
Total events: 4 (Intervention), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.50 (P = 0.13)					
7 Gabexate versus aprotinin					
Frulloni 1994	4/65	3/51		100.0 %	1.05 [0.22, 4.91]
Subtotal (95% CI)	**65**	**51**		**100.0 %**	**1.05 [0.22, 4.91]**
Total events: 4 (Intervention), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					

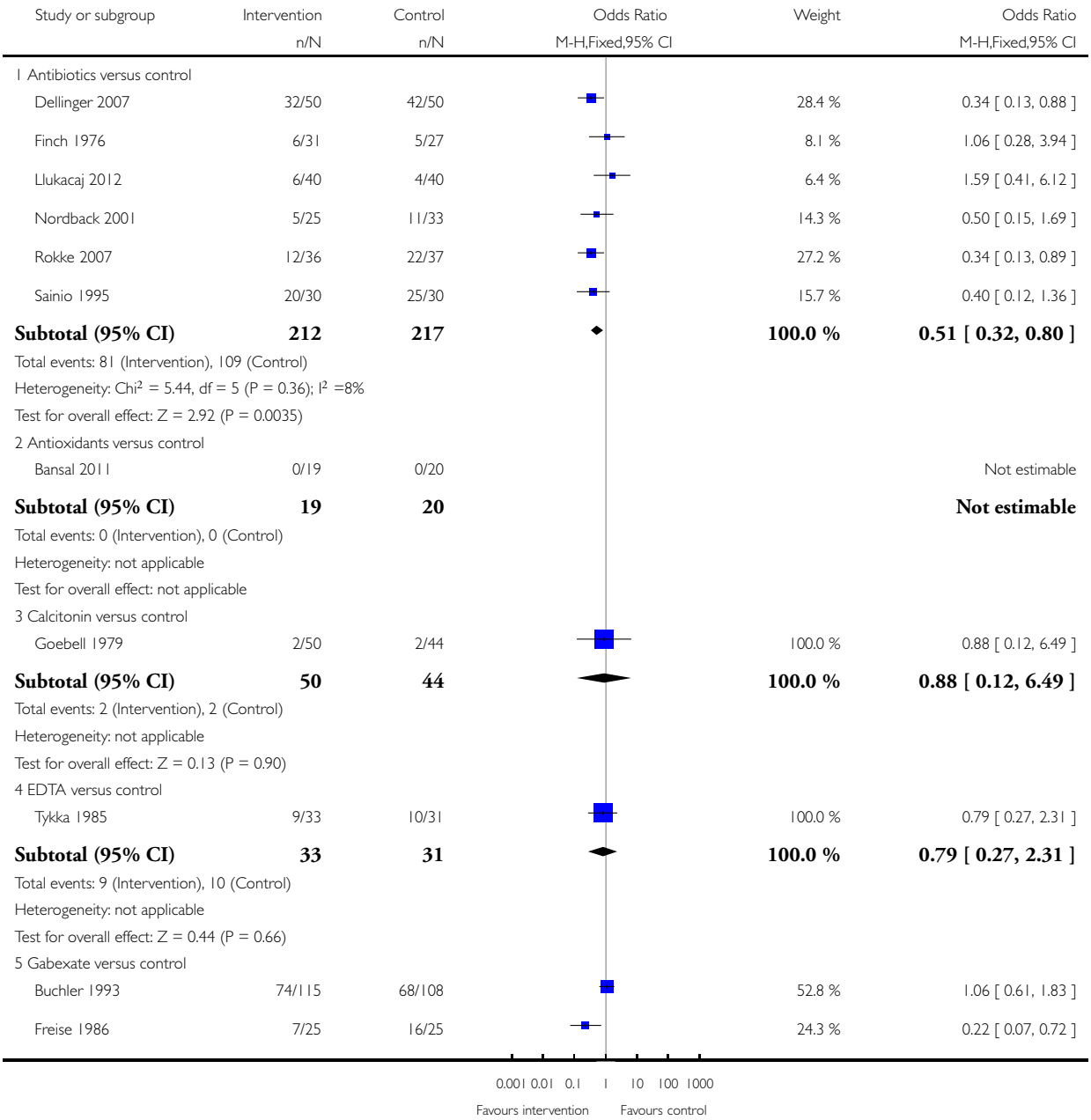


Analysis 1.7. Comparison 1 Acute pancreatitis, Outcome 7 Adverse events (proportion).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 7 Adverse events (proportion)



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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Valderrama 1992	15/51	15/49		22.8 %	0.94 [0.40, 2.22]
Subtotal (95% CI)	**191**	**182**		**100.0 %**	**0.83 [0.54, 1.27]**
Total events: 96 (Intervention), 99 (Control)					
Heterogeneity: Chi^2 = 5.65, df = 2 (P = 0.06); I^2 =65%					
Test for overall effect: Z = 0.87 (P = 0.39)					
6 Glucagon versus control					
Debas 1980	0/33	0/33			Not estimable
Kalima 1980	0/32	4/29		100.0 %	0.09 [0.00, 1.69]
Subtotal (95% CI)	**65**	**62**		**100.0 %**	**0.09 [0.00, 1.69]**
Total events: 0 (Intervention), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
7 Lexipafant versus control					
Kingsnorth 1995	9/42	16/41		100.0 %	0.43 [0.16, 1.12]
Subtotal (95% CI)	**42**	**41**		**100.0 %**	**0.43 [0.16, 1.12]**
Total events: 9 (Intervention), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.73 (P = 0.084)					
8 Octreotide versus control					
McKay 1997a	15/28	11/30		12.2 %	1.99 [0.70, 5.70]
Paran 1995	5/19	14/19		25.5 %	0.13 [0.03, 0.54]
Uhl 1999	147/199	73/103		62.2 %	1.16 [0.68, 1.97]
Subtotal (95% CI)	**246**	**152**		**100.0 %**	**1.00 [0.65, 1.55]**
Total events: 167 (Intervention), 98 (Control)					
Heterogeneity: Chi^2 = 9.78, df = 2 (P = 0.01); I^2 =80%					
Test for overall effect: Z = 0.00 (P = 1.0)					
9 Probiotics versus control					
Olah 2007	9/33	15/29		100.0 %	0.35 [0.12, 1.01]
Subtotal (95% CI)	**33**	**29**		**100.0 %**	**0.35 [0.12, 1.01]**
Total events: 9 (Intervention), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.95 (P = 0.052)					
10 Somatostatin versus control					
Gj rup 1992	19/33	21/30		56.0 %	0.58 [0.21, 1.65]
Yang 1999	3/25	8/23		44.0 %	0.26 [0.06, 1.12]
Subtotal (95% CI)	**58**	**53**		**100.0 %**	**0.44 [0.19, 1.02]**
Total events: 22 (Intervention), 29 (Control)					
Heterogeneity: Chi^2 = 0.79, df = 1 (P = 0.37); I^2 =0.0%					
Test for overall effect: Z = 1.92 (P = 0.055)					

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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
11 Somatostatin plus omeprazole versus control					
Xia 2014	18/70	70/70		100.0 %	0.00 [0.00, 0.04]
Subtotal (95% CI)	**70**	**70**		**100.0 %**	**0.00 [0.00, 0.04]**
Total events: 18 (Intervention), 70 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.15 (P = 0.000034)					
12 Gabexate versus aprotinin					
Frulloni 1994	13/65	23/51		50.4 %	0.30 [0.13, 0.69]
Pederzoli 1993b	14/91	24/91		49.6 %	0.51 [0.24, 1.06]
Subtotal (95% CI)	**156**	**142**		**100.0 %**	**0.41 [0.23, 0.70]**
Total events: 27 (Intervention), 47 (Control)					
Heterogeneity: Chi^2 = 0.83, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 3.24 (P = 0.0012)					
13 Ulinastatin versus gabexate					
Chen 2002a	0/48	0/14			Not estimable
Subtotal (95% CI)	**48**	**14**			**Not estimable**
Total events: 0 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 Ulinastatin versus octreotide					
Chen 2002b	8/14	4/11		100.0 %	2.33 [0.46, 11.81]
Subtotal (95% CI)	**14**	**11**		**100.0 %**	**2.33 [0.46, 11.81]**
Total events: 8 (Intervention), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					
15 Somatostatin plus gabexate versus somatostatin					
Wang 2016	16/130	16/122		100.0 %	0.93 [0.44, 1.95]
Subtotal (95% CI)	**130**	**122**		**100.0 %**	**0.93 [0.44, 1.95]**
Total events: 16 (Intervention), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					
16 Somatostatin plus ulinastatin versus somatostatin					
Wang 2016	10/124	16/122		100.0 %	0.58 [0.25, 1.34]
Subtotal (95% CI)	**124**	**122**		**100.0 %**	**0.58 [0.25, 1.34]**
Total events: 10 (Intervention), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
17 Somatostatin plus ulinastatin plus gabexate versus somatostatin					
Wang 2016	8/116	16/122		100.0 %	0.49 [0.20, 1.20]

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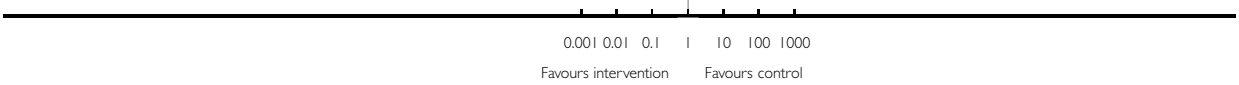
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**116**	**122**		**100.0 %**	**0.49 [0.20, 1.20]**
Total events: 8 (Intervention), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.57 (P = 0.12)					
18 Somatostatin plus ulinastatin versus somatostatin plus gabexate					
Wang 2016	10/124	16/130		100.0 %	0.63 [0.27, 1.44]
Subtotal (95% CI)	**124**	**130**		**100.0 %**	**0.63 [0.27, 1.44]**
Total events: 10 (Intervention), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
19 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate					
Wang 2016	8/116	16/130		100.0 %	0.53 [0.22, 1.28]
Subtotal (95% CI)	**116**	**130**		**100.0 %**	**0.53 [0.22, 1.28]**
Total events: 8 (Intervention), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
20 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin					
Wang 2016	8/116	10/124		100.0 %	0.84 [0.32, 2.22]
Subtotal (95% CI)	**116**	**124**		**100.0 %**	**0.84 [0.32, 2.22]**
Total events: 8 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					



Analysis 1.8. Comparison 1 Acute pancreatitis, Outcome 8 Adverse events (number).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 8 Adverse events (number)

Study or subgroup	Intervention N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
1 Antibiotics versus control						
Barreda 2009	24	34	0.20723 (0.23795)		9.4 %	1.23 [0.77, 1.96]
Garcia-Barrasa 2009	22	19	-0.26439 (0.343592)		6.8 %	0.77 [0.39, 1.51]
Hejtmankova 2003	20	21	-0.23889 (0.288675)		8.1 %	0.79 [0.45, 1.39]
Isenmann 2004	58	56	0.046826 (0.153072)		11.7 %	1.05 [0.78, 1.41]
Luiten 1995	50	52	-1.08292 (0.307708)		7.6 %	0.34 [0.19, 0.62]
Nordback 2001	25	33	-0.99533 (0.427618)		5.3 %	0.37 [0.16, 0.85]
Pederzoli 1993a	41	33	-0.74513 (0.262905)		8.7 %	0.47 [0.28, 0.79]
Poropat 2015	23	24	-0.50749 (0.324235)		7.3 %	0.60 [0.32, 1.14]
Sainio 1995	30	30	-0.58779 (0.22771)		9.7 %	0.56 [0.36, 0.87]
Spicak 2002	33	30	-0.09531 (0.324443)		7.2 %	0.91 [0.48, 1.72]
Spicak 2003	20	21	0.107631 (0.242641)		9.2 %	1.11 [0.69, 1.79]
Xue 2009	29	27	0.122697 (0.255198)		8.9 %	1.13 [0.69, 1.86]
Subtotal (95% CI)	**375**	**380**			**100.0 %**	**0.75 [0.58, 0.95]**
Heterogeneity: Tau^2 = 0.11; Chi^2 = 28.59, df = 11 (P = 0.003); I^2 =62%						
Test for overall effect: Z = 2.35 (P = 0.019)						
2 Antioxidants versus control						
Bansal 2011	20	21	0.04879 (2)		3.9 %	1.05 [0.02, 52.92]
Sateesh 2009	23	30	-0.2043 (0.403113)		96.1 %	0.82 [0.37, 1.80]
Subtotal (95% CI)	**43**	**51**			**100.0 %**	**0.82 [0.38, 1.79]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
3 Aprotinin versus control						
Balldin 1983	26	29	0.2523 (0.378932)		22.5 %	1.29 [0.61, 2.70]
Berling 1994	22	26	-0.09531 (0.242846)		54.9 %	0.91 [0.56, 1.46]
Imrie 1978	80	81	-0.13068 (0.378932)		22.5 %	0.88 [0.42, 1.84]
Subtotal (95% CI)	**128**	**136**			**100.0 %**	**0.98 [0.69, 1.39]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.70, df = 2 (P = 0.71); I^2 =0.0%						
Test for overall effect: Z = 0.14 (P = 0.89)						

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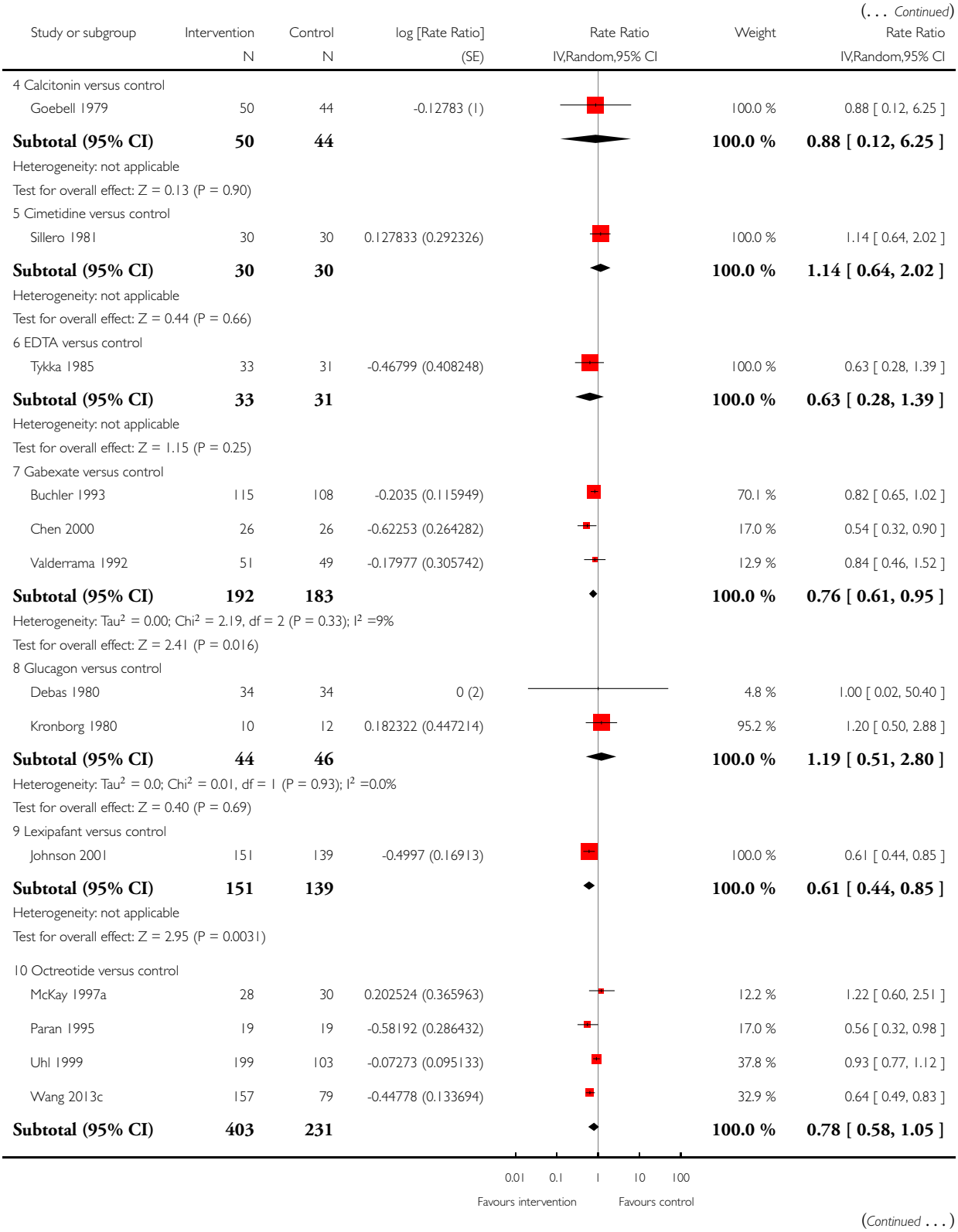

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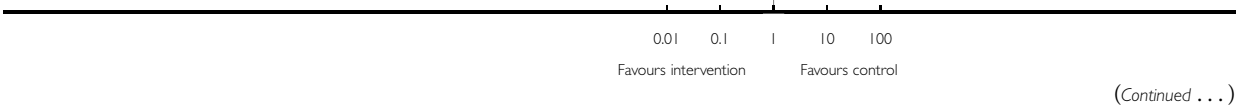
Study or subgroup	Intervention N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Heterogeneity: Tau² = 0.05; Chi² = 8.20, df = 3 (P = 0.04); I² =63%						
Test for overall effect: Z = 1.66 (P = 0.097)						
11 Probiotics versus control						
Besselink 2008	152	144	0.113925 (0.106076)		45.0 %	1.12 [0.91, 1.38]
Olah 2007	33	29	-0.78314 (0.34194)		25.3 %	0.46 [0.23, 0.89]
Zhu 2014	20	19	-0.09212 (0.285774)		29.7 %	0.91 [0.52, 1.60]
Subtotal (95% CI)	**205**	**192**			**100.0 %**	**0.84 [0.52, 1.36]**
Heterogeneity: Tau² = 0.13; Chi² = 6.45, df = 2 (P = 0.04); I² =69%						
Test for overall effect: Z = 0.70 (P = 0.48)						
12 Somatostatin versus control						
Choi 1989	35	36	-0.92734 (0.526235)		41.4 %	0.40 [0.14, 1.11]
Gj rup 1992	33	30	0.172954 (0.260525)		58.6 %	1.19 [0.71, 1.98]
Subtotal (95% CI)	**68**	**66**			**100.0 %**	**0.75 [0.26, 2.18]**
Heterogeneity: Tau² = 0.43; Chi² = 3.51, df = 1 (P = 0.06); I² =72%						
Test for overall effect: Z = 0.52 (P = 0.60)						
13 Ulinastatin versus control						
Abraham 2013	30	32	0.005698 (0.242641)		50.6 %	1.01 [0.63, 1.62]
Abraham 2013	35	32	-0.76078 (0.256321)		49.4 %	0.47 [0.28, 0.77]
Subtotal (95% CI)	**65**	**64**			**100.0 %**	**0.69 [0.32, 1.46]**
Heterogeneity: Tau² = 0.23; Chi² = 4.72, df = 1 (P = 0.03); I² =79%						
Test for overall effect: Z = 0.97 (P = 0.33)						
14 Gabexate versus aprotinin						
Pederzoli 1993b	91	91	-0.42121 (0.280836)		100.0 %	0.66 [0.38, 1.14]
Subtotal (95% CI)	**91**	**91**			**100.0 %**	**0.66 [0.38, 1.14]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
15 Glucagon versus atropine						
Kirsch 1978	75	75	-0.24116 (0.402911)		100.0 %	0.79 [0.36, 1.73]
Subtotal (95% CI)	**75**	**75**			**100.0 %**	**0.79 [0.36, 1.73]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
16 Oxyphenonium versus glucagon						
Gilsanz 1978	31	31	-0.06899 (0.185806)		100.0 %	0.93 [0.65, 1.34]
Subtotal (95% CI)	**31**	**31**			**100.0 %**	**0.93 [0.65, 1.34]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
17 Octreotide plus ulinastatin versus octreotide						



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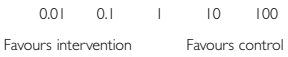
Study or subgroup	Intervention N	Control N	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
Guo 2015	60	60	-1.25276 (0.26726)		100.0 %	0.29 [0.17, 0.48]
Subtotal (95% CI)	**60**	**60**			**100.0 %**	**0.29 [0.17, 0.48]**
Heterogeneity: not applicable						
Test for overall effect: Z = 4.69 (P < 0.00001)						



Analysis 1.9. Comparison 1 Acute pancreatitis, Outcome 9 Requirement for additional invasive intervention.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 9 Requirement for additional invasive intervention

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Antibiotics versus control					
Barreda 2009	4/24	2/34		1.7 %	3.20 [0.54, 19.11]
Delcenserie 1996	0/11	3/12		3.9 %	0.12 [0.01, 2.58]
Garcia-Barrasa 2009	11/22	8/19		5.2 %	1.38 [0.40, 4.73]
Hejtmankova 2003	4/20	5/21		4.7 %	0.80 [0.18, 3.54]
Isenmann 2004	10/58	6/56		6.1 %	1.74 [0.59, 5.15]
Llukacaj 2012	10/40	8/40		7.3 %	1.33 [0.46, 3.83]
Luiten 1995	16/50	24/52		19.4 %	0.55 [0.25, 1.23]
Nordback 2001	2/25	5/33		4.8 %	0.49 [0.09, 2.75]
Pederzoli 1993a	12/41	11/33		10.4 %	0.83 [0.31, 2.22]
Rokke 2007	3/36	3/37		3.3 %	1.03 [0.19, 5.48]
Sainio 1995	7/30	14/30		13.0 %	0.35 [0.11, 1.05]
Spicak 2002	6/33	7/30		7.3 %	0.73 [0.21, 2.48]

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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Spicak 2003	4/20	5/21		4.7 %	0.80 [0.18, 3.54]
Xue 2009	8/29	9/27		8.2 %	0.76 [0.24, 2.39]
Subtotal (95% CI)	**439**	**445**		**100.0 %**	**0.82 [0.59, 1.13]**
Total events: 97 (Intervention), 110 (Control)					
Heterogeneity: Chi^2 = 10.79, df = 13 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 1.22 (P = 0.22)					
2 Aprotinin versus control					
Berling 1994	0/22	6/26		45.6 %	0.07 [0.00, 1.32]
MRC Multicentre Trial 1977	6/66	11/123		54.4 %	1.02 [0.36, 2.89]
Subtotal (95% CI)	**88**	**149**		**100.0 %**	**0.59 [0.23, 1.47]**
Total events: 6 (Intervention), 17 (Control)					
Heterogeneity: Chi^2 = 3.08, df = 1 (P = 0.08); I^2 =68%					
Test for overall effect: Z = 1.14 (P = 0.25)					
3 Calcitonin versus control					
Goebell 1979	2/50	5/44		60.4 %	0.33 [0.06, 1.77]
Martinez 1984	1/14	4/17		39.6 %	0.25 [0.02, 2.55]
Subtotal (95% CI)	**64**	**61**		**100.0 %**	**0.30 [0.08, 1.16]**
Total events: 3 (Intervention), 9 (Control)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 1.75 (P = 0.080)					
4 Cimetidine versus control					
Sillero 1981	0/30	3/30		100.0 %	0.13 [0.01, 2.61]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**0.13 [0.01, 2.61]**
Total events: 0 (Intervention), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					
5 EDTA versus control					
Tykka 1985	3/33	4/31		100.0 %	0.68 [0.14, 3.29]
Subtotal (95% CI)	**33**	**31**		**100.0 %**	**0.68 [0.14, 3.29]**
Total events: 3 (Intervention), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.49 (P = 0.63)					
6 Gabexate versus control					
Buchler 1993	23/115	25/108		40.1 %	0.83 [0.44, 1.57]
Chen 2000	7/26	13/26		18.5 %	0.37 [0.12, 1.17]
Goebell 1988	14/76	26/75		41.5 %	0.43 [0.20, 0.90]
Subtotal (95% CI)	**217**	**209**		**100.0 %**	**0.58 [0.37, 0.90]**
Total events: 44 (Intervention), 64 (Control)					
Heterogeneity: Chi^2 = 2.45, df = 2 (P = 0.29); I^2 =18%					
Test for overall effect: Z = 2.43 (P = 0.015)					

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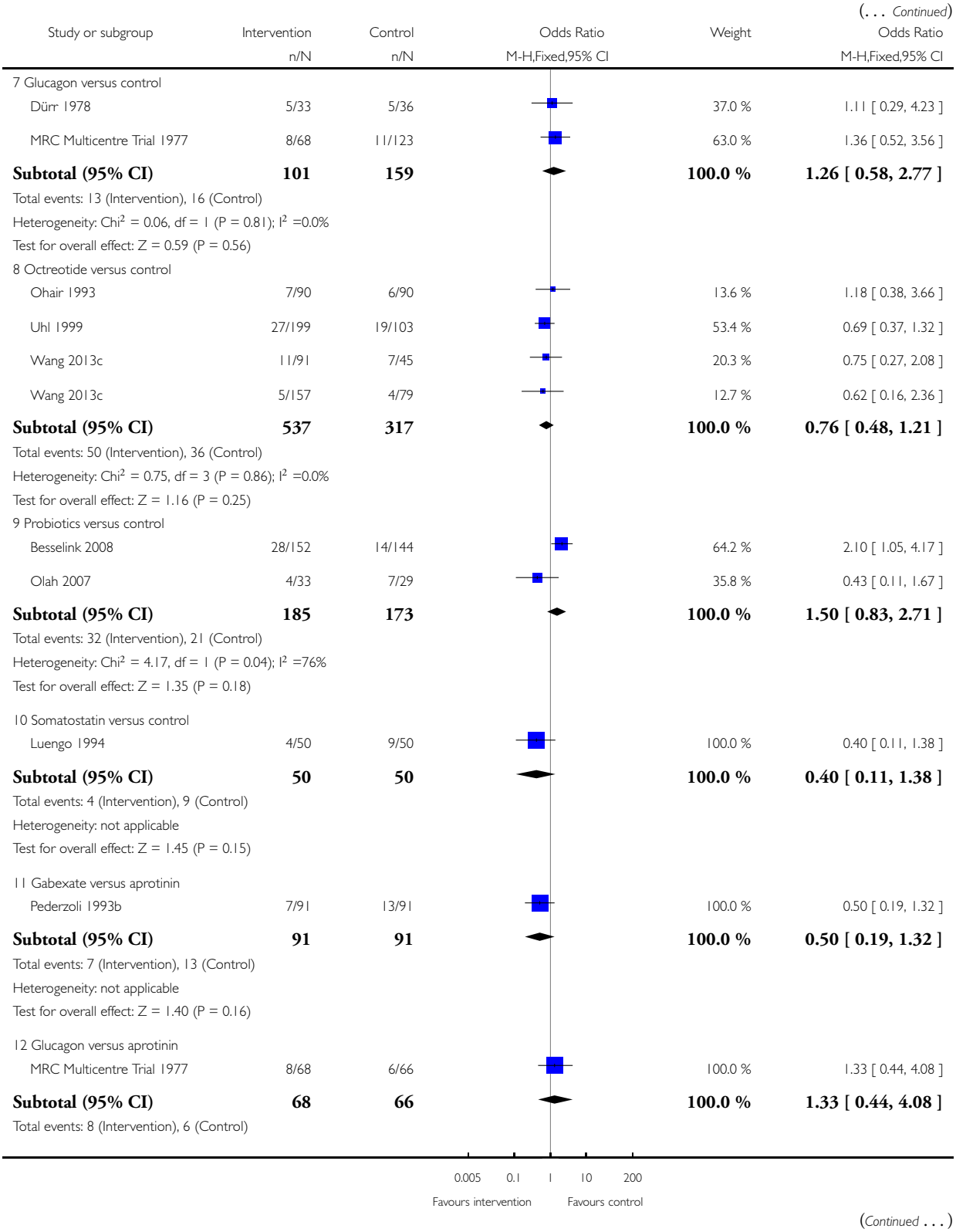

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
7 Glucagon versus control					
Dürr 1978	5/33	5/36		37.0 %	1.11 [0.29, 4.23]
MRC Multicentre Trial 1977	8/68	11/123		63.0 %	1.36 [0.52, 3.56]
Subtotal (95% CI)	**101**	**159**		**100.0 %**	**1.26 [0.58, 2.77]**
Total events: 13 (Intervention), 16 (Control)					
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 0.59 (P = 0.56)					
8 Octreotide versus control					
Ohair 1993	7/90	6/90		13.6 %	1.18 [0.38, 3.66]
Uhl 1999	27/199	19/103		53.4 %	0.69 [0.37, 1.32]
Wang 2013c	11/91	7/45		20.3 %	0.75 [0.27, 2.08]
Wang 2013c	5/157	4/79		12.7 %	0.62 [0.16, 2.36]
Subtotal (95% CI)	**537**	**317**		**100.0 %**	**0.76 [0.48, 1.21]**
Total events: 50 (Intervention), 36 (Control)					
Heterogeneity: Chi^2 = 0.75, df = 3 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 1.16 (P = 0.25)					
9 Probiotics versus control					
Besselink 2008	28/152	14/144		64.2 %	2.10 [1.05, 4.17]
Olah 2007	4/33	7/29		35.8 %	0.43 [0.11, 1.67]
Subtotal (95% CI)	**185**	**173**		**100.0 %**	**1.50 [0.83, 2.71]**
Total events: 32 (Intervention), 21 (Control)					
Heterogeneity: Chi^2 = 4.17, df = 1 (P = 0.04); I^2 =76%					
Test for overall effect: Z = 1.35 (P = 0.18)					
10 Somatostatin versus control					
Luengo 1994	4/50	9/50		100.0 %	0.40 [0.11, 1.38]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**0.40 [0.11, 1.38]**
Total events: 4 (Intervention), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
11 Gabexate versus aprotinin					
Pederzoli 1993b	7/91	13/91		100.0 %	0.50 [0.19, 1.32]
Subtotal (95% CI)	**91**	**91**		**100.0 %**	**0.50 [0.19, 1.32]**
Total events: 7 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
12 Glucagon versus aprotinin					
MRC Multicentre Trial 1977	8/68	6/66		100.0 %	1.33 [0.44, 4.08]
Subtotal (95% CI)	**68**	**66**		**100.0 %**	**1.33 [0.44, 4.08]**
Total events: 8 (Intervention), 6 (Control)					

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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.50 (P = 0.61)					
13 Oxyphenonium versus glucagon					
Gilsanz 1978	2/31	2/31		100.0 %	1.00 [0.13, 7.59]
Subtotal (95% CI)	**31**	**31**		**100.0 %**	**1.00 [0.13, 7.59]**
Total events: 2 (Intervention), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					

Analysis 1.10. Comparison 1 Acute pancreatitis, Outcome 10 Endoscopic or radiological drainage of collections.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 1 Acute pancreatitis

Outcome: 10 Endoscopic or radiological drainage of collections

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Antibiotics versus control					
Delcenserie 1996	0/11	1/12		100.0 %	0.33 [0.01, 9.07]
Subtotal (95% CI)	**11**	**12**		**100.0 %**	**0.33 [0.01, 9.07]**
Total events: 0 (Intervention), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.51)					
2 Octreotide versus control					
Wang 2013c	6/157	3/79		29.8 %	1.01 [0.25, 4.14]
Wang 2013c	14/91	8/45		70.2 %	0.84 [0.32, 2.18]
Subtotal (95% CI)	**248**	**124**		**100.0 %**	**0.89 [0.40, 1.96]**
Total events: 20 (Intervention), 11 (Control)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					

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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.29 (P = 0.77)					
3 Probiotics versus control					
Zhu 2014	4/20	4/19		100.0 %	0.94 [0.20, 4.44]
Subtotal (95% CI)	**20**	**19**		**100.0 %**	**0.94 [0.20, 4.44]**
Total events: 4 (Intervention), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					

Analysis 2.1. Comparison 2 Acute necrotising pancreatitis, Outcome 1 Short-term mortality.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 2 Acute necrotising pancreatitis

Outcome: 1 Short-term mortality

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Antibiotics versus control					
Barreda 2009	0/24	0/34			Not estimable
Delcenserie 2001	6/53	3/28		8.7 %	1.06 [0.24, 4.62]
Dellinger 2007	10/50	9/50		17.9 %	1.14 [0.42, 3.10]
Garcia-Barrasa 2009	4/22	2/19		4.4 %	1.89 [0.31, 11.68]
Llukacaj 2012	8/40	6/40		11.9 %	1.42 [0.44, 4.53]
Nordback 2001	2/25	5/33		9.9 %	0.49 [0.09, 2.75]
Pederzoli 1993a	3/41	4/33		10.2 %	0.57 [0.12, 2.76]
Rokke 2007	3/36	4/37		9.0 %	0.75 [0.16, 3.62]
Sainio 1995	1/30	7/30		16.8 %	0.11 [0.01, 0.99]
Xue 2009	4/30	5/28		11.2 %	0.71 [0.17, 2.96]

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Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**351**	**332**		**100.0 %**	**0.82 [0.52, 1.30]**
Total events: 41 (Intervention), 45 (Control)					
Heterogeneity: Chi^2 = 6.00, df = 8 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 0.85 (P = 0.40)					
2 Gabexate versus aprotinin					
Frulloni 1994	9/65	12/51		100.0 %	0.52 [0.20, 1.36]
Subtotal (95% CI)	**65**	**51**		**100.0 %**	**0.52 [0.20, 1.36]**
Total events: 9 (Intervention), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					

Analysis 2.2. Comparison 2 Acute necrotising pancreatitis, Outcome 2 Serious adverse events (proportion).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 2 Acute necrotising pancreatitis

Outcome: 2 Serious adverse events (proportion)

Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Antibiotics versus control					
Dellinger 2007	6/50	9/50		35.0 %	0.62 [0.20, 1.90]
Garcia-Barrasa 2009	13/22	10/19		19.4 %	1.30 [0.38, 4.48]
Llukacaj 2012	6/40	4/40		15.0 %	1.59 [0.41, 6.12]
Sainio 1995	4/30	8/30		30.6 %	0.42 [0.11, 1.60]
Subtotal (95% CI)	**142**	**139**		**100.0 %**	**0.84 [0.46, 1.54]**
Total events: 29 (Intervention), 31 (Control)					
Heterogeneity: Chi^2 = 2.64, df = 3 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 Gabexate versus aprotinin					
Frulloni 1994	4/65	3/51		100.0 %	1.05 [0.22, 4.91]

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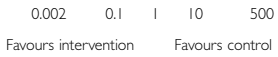
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**65**	**51**		**100.0 %**	**1.05 [0.22, 4.91]**
Total events: 4 (Intervention), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					



Analysis 2.3. Comparison 2 Acute necrotising pancreatitis, Outcome 3 Serious adverse events (number).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 2 Acute necrotising pancreatitis

Outcome: 3 Serious adverse events (number)

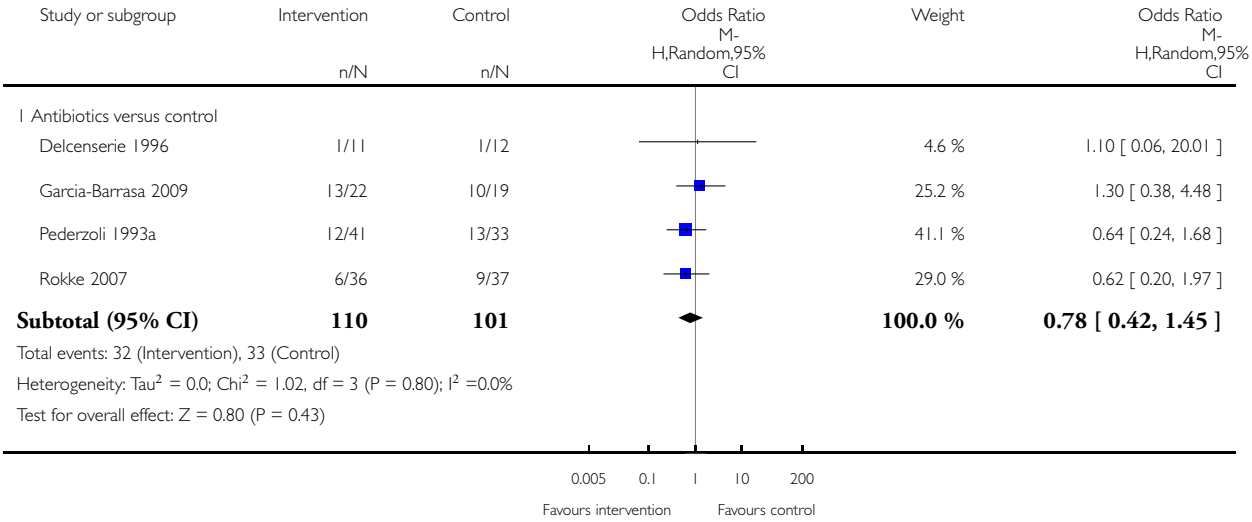
Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Antibiotics versus control				
Barreda 2009	0.28377 (0.3594)		17.5 %	1.33 [0.66, 2.69]
Delcenserie 2001	-0.33581 (0.319847)		22.1 %	0.71 [0.38, 1.34]
Garcia-Barrasa 2009	-0.36975 (0.474342)		10.1 %	0.69 [0.27, 1.75]
Nordback 2001	-0.5333 (0.600925)		6.3 %	0.59 [0.18, 1.91]
Pederzoli 1993a	-0.51935 (0.319847)		22.1 %	0.59 [0.32, 1.11]
Sainio 1995	-0.69315 (0.612372)		6.0 %	0.50 [0.15, 1.66]
Xue 2009	0.071642 (0.378932)		15.8 %	1.07 [0.51, 2.26]
Subtotal (95% CI)			**100.0 %**	**0.79 [0.59, 1.06]**
Heterogeneity: Chi^2 = 4.51, df = 6 (P = 0.61); I^2 =0.0%				
Test for overall effect: Z = 1.60 (P = 0.11)				

Analysis 2.4. Comparison 2 Acute necrotising pancreatitis, Outcome 4 Organ failure.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 2 Acute necrotising pancreatitis

Outcome: 4 Organ failure

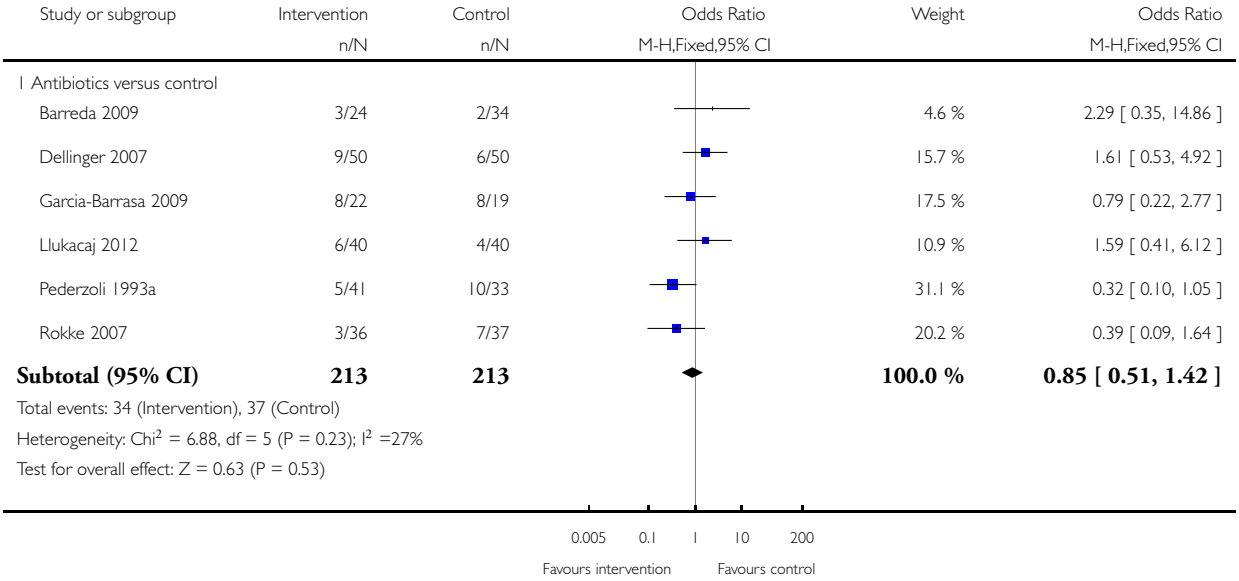


Analysis 2.5. Comparison 2 Acute necrotising pancreatitis, Outcome 5 Infected pancreatic necrosis.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 2 Acute necrotising pancreatitis

Outcome: 5 Infected pancreatic necrosis

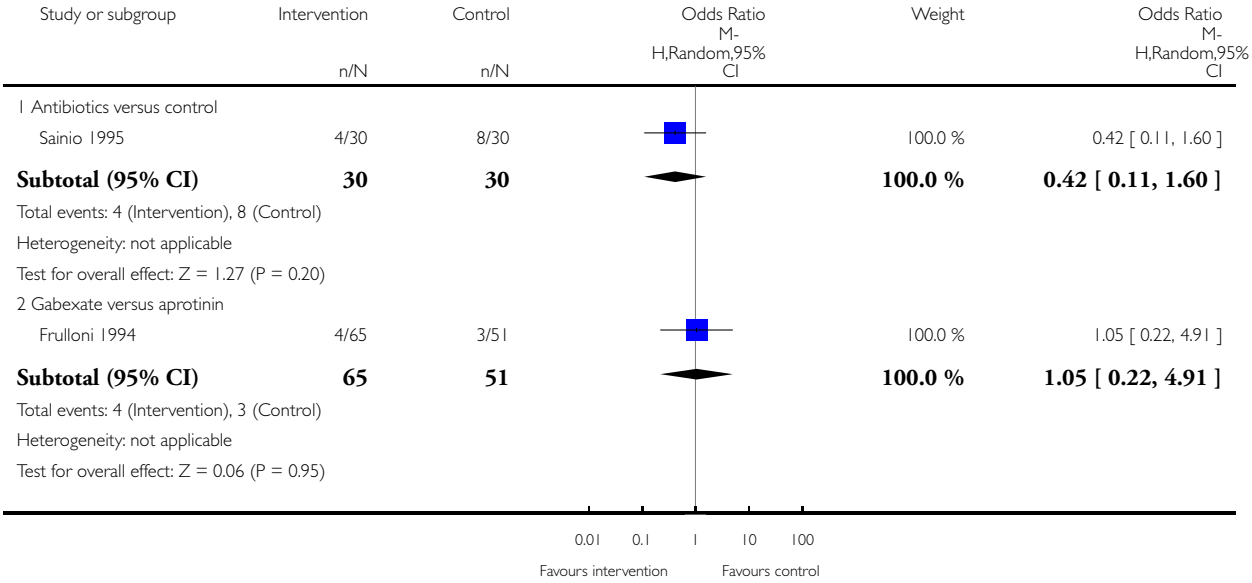


Analysis 2.6. Comparison 2 Acute necrotising pancreatitis, Outcome 6 Sepsis.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 2 Acute necrotising pancreatitis

Outcome: 6 Sepsis

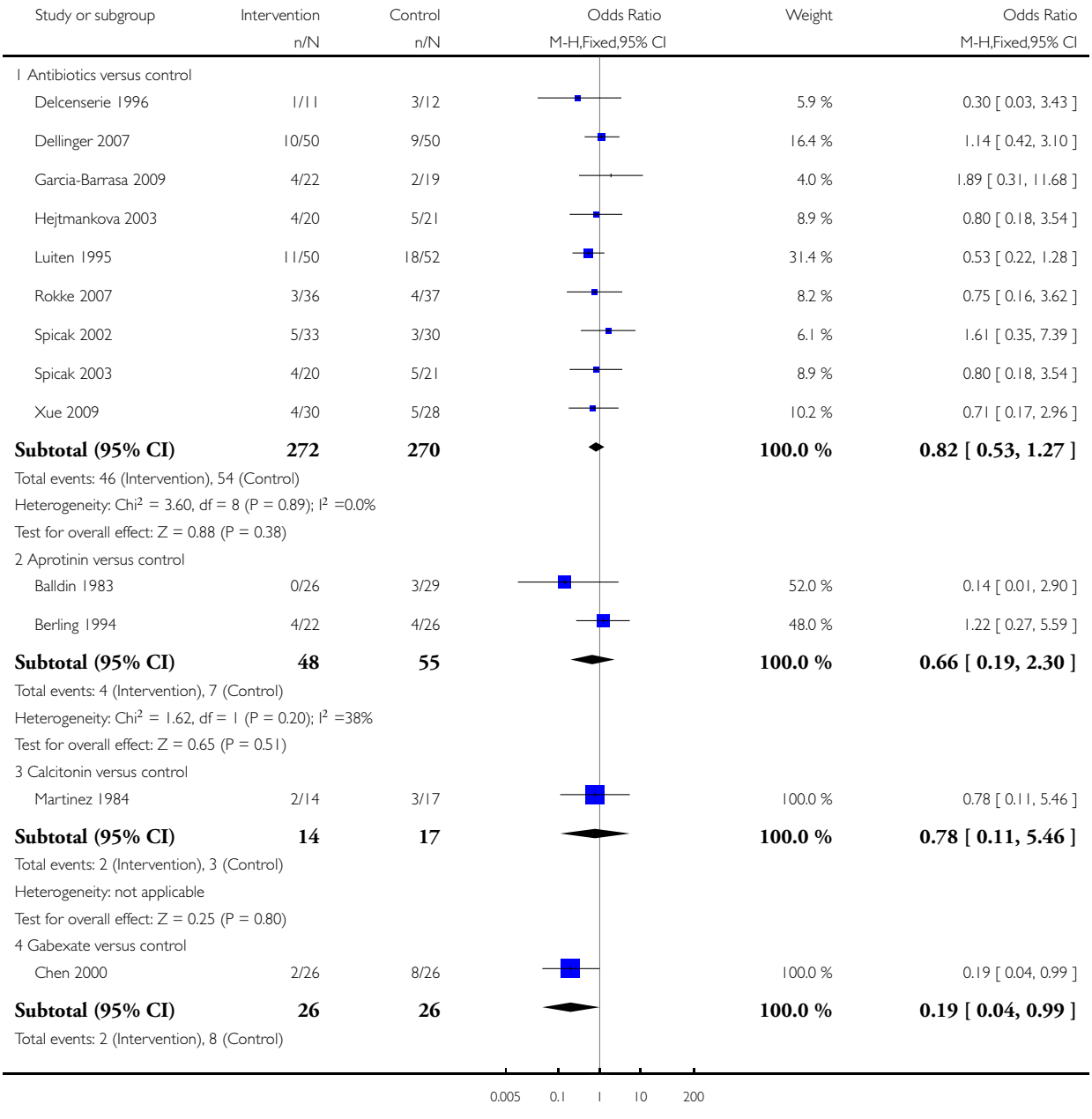


Analysis 3.1. Comparison 3 Severe acute pancreatitis, Outcome 1 Short-term mortality.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 3 Severe acute pancreatitis

Outcome: 1 Short-term mortality



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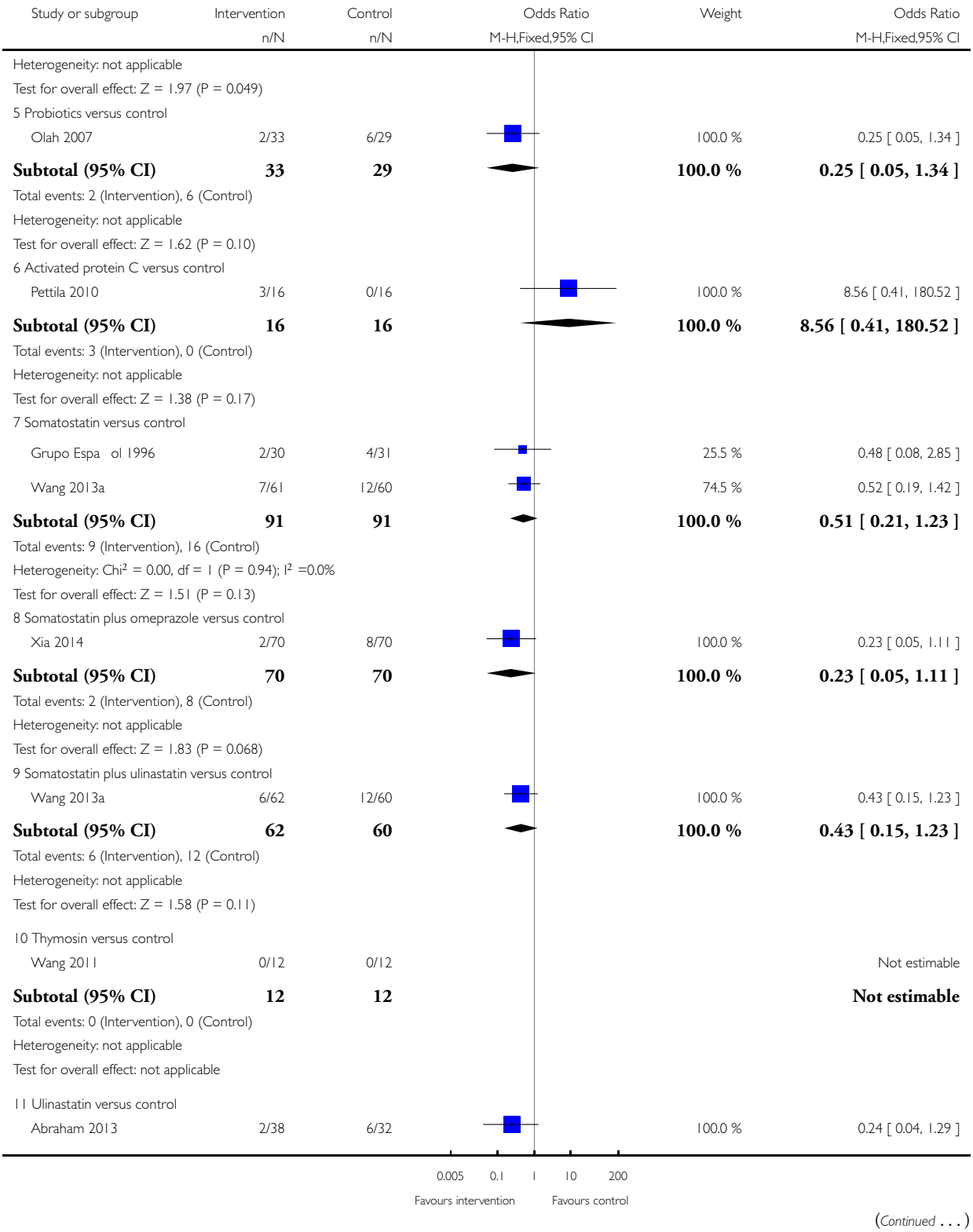

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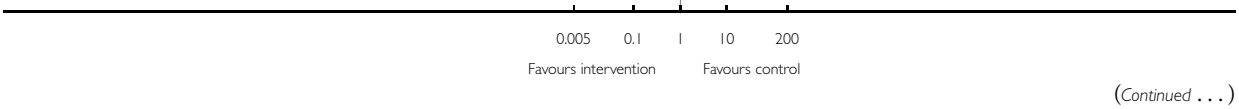
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**38**	**32**		**100.0 %**	**0.24 [0.04, 1.29]**
Total events: 2 (Intervention), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.66 (P = 0.096)					
12 Octreotide plus ulinastatin versus octreotide					
Guo 2015	2/60	6/60		100.0 %	0.31 [0.06, 1.60]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**0.31 [0.06, 1.60]**
Total events: 2 (Intervention), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
13 Somatostatin plus gabexate versus somatostatin					
Wang 2016	10/130	10/122		100.0 %	0.93 [0.37, 2.33]
Subtotal (95% CI)	**130**	**122**		**100.0 %**	**0.93 [0.37, 2.33]**
Total events: 10 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					
14 Somatostatin plus ulinastatin versus somatostatin					
Wang 2013a	6/62	7/61		40.1 %	0.83 [0.26, 2.62]
Wang 2016	7/124	10/122		59.9 %	0.67 [0.25, 1.82]
Subtotal (95% CI)	**186**	**183**		**100.0 %**	**0.73 [0.34, 1.56]**
Total events: 13 (Intervention), 17 (Control)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
15 Somatostatin plus ulinastatin plus gabexate versus somatostatin					
Wang 2016	6/116	10/122		100.0 %	0.61 [0.21, 1.74]
Subtotal (95% CI)	**116**	**122**		**100.0 %**	**0.61 [0.21, 1.74]**
Total events: 6 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
16 Somatostatin plus ulinastatin versus somatostatin plus gabexate					
Wang 2016	7/124	10/130		100.0 %	0.72 [0.26, 1.95]
Subtotal (95% CI)	**124**	**130**		**100.0 %**	**0.72 [0.26, 1.95]**
Total events: 7 (Intervention), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.52)					
17 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate					
Wang 2016	6/116	10/130		100.0 %	0.65 [0.23, 1.86]
Subtotal (95% CI)	**116**	**130**		**100.0 %**	**0.65 [0.23, 1.86]**
Total events: 6 (Intervention), 10 (Control)					



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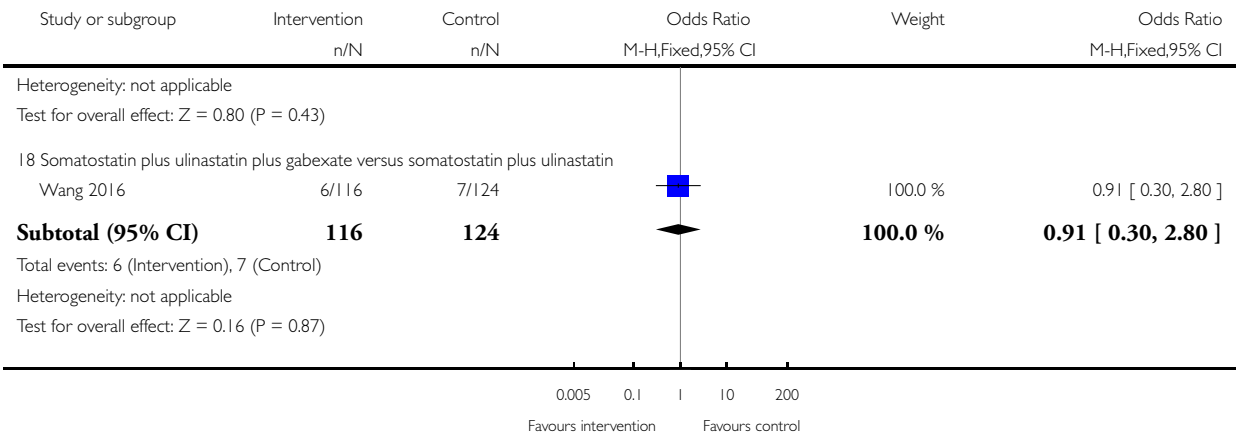
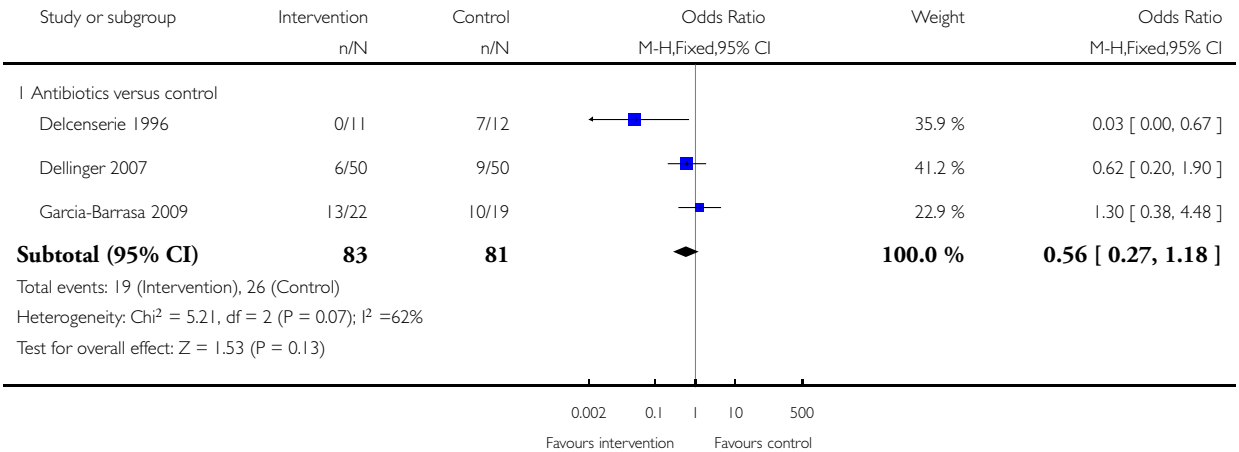


Analysis 3.2. Comparison 3 Severe acute pancreatitis, Outcome 2 Serious adverse events (proportion).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 3 Severe acute pancreatitis

Outcome: 2 Serious adverse events (proportion)

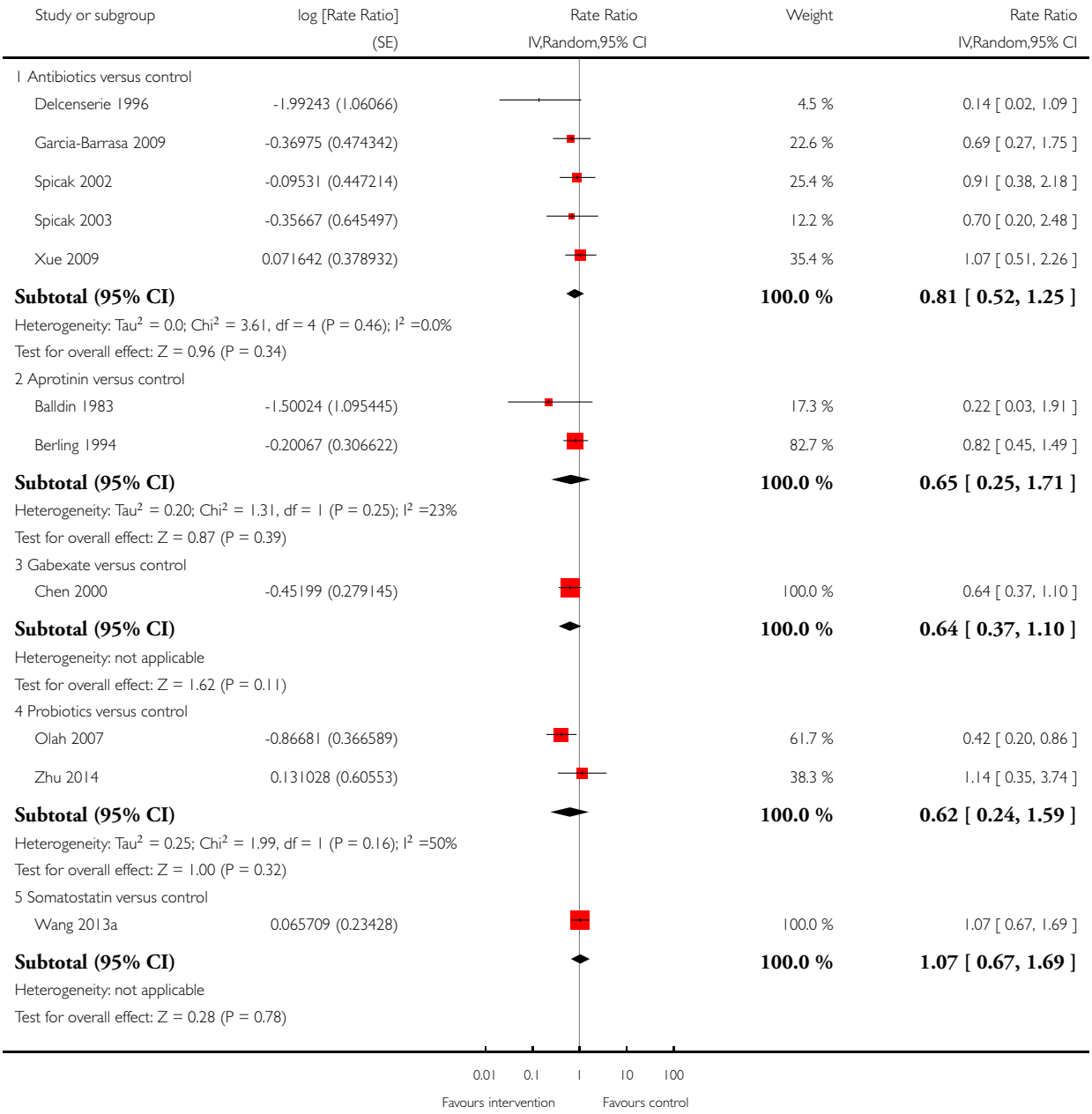


Analysis 3.3. Comparison 3 Severe acute pancreatitis, Outcome 3 Serious adverse events (number).

Review: Pharmacological interventions for acute pancreatitis

Comparison: 3 Severe acute pancreatitis

Outcome: 3 Serious adverse events (number)



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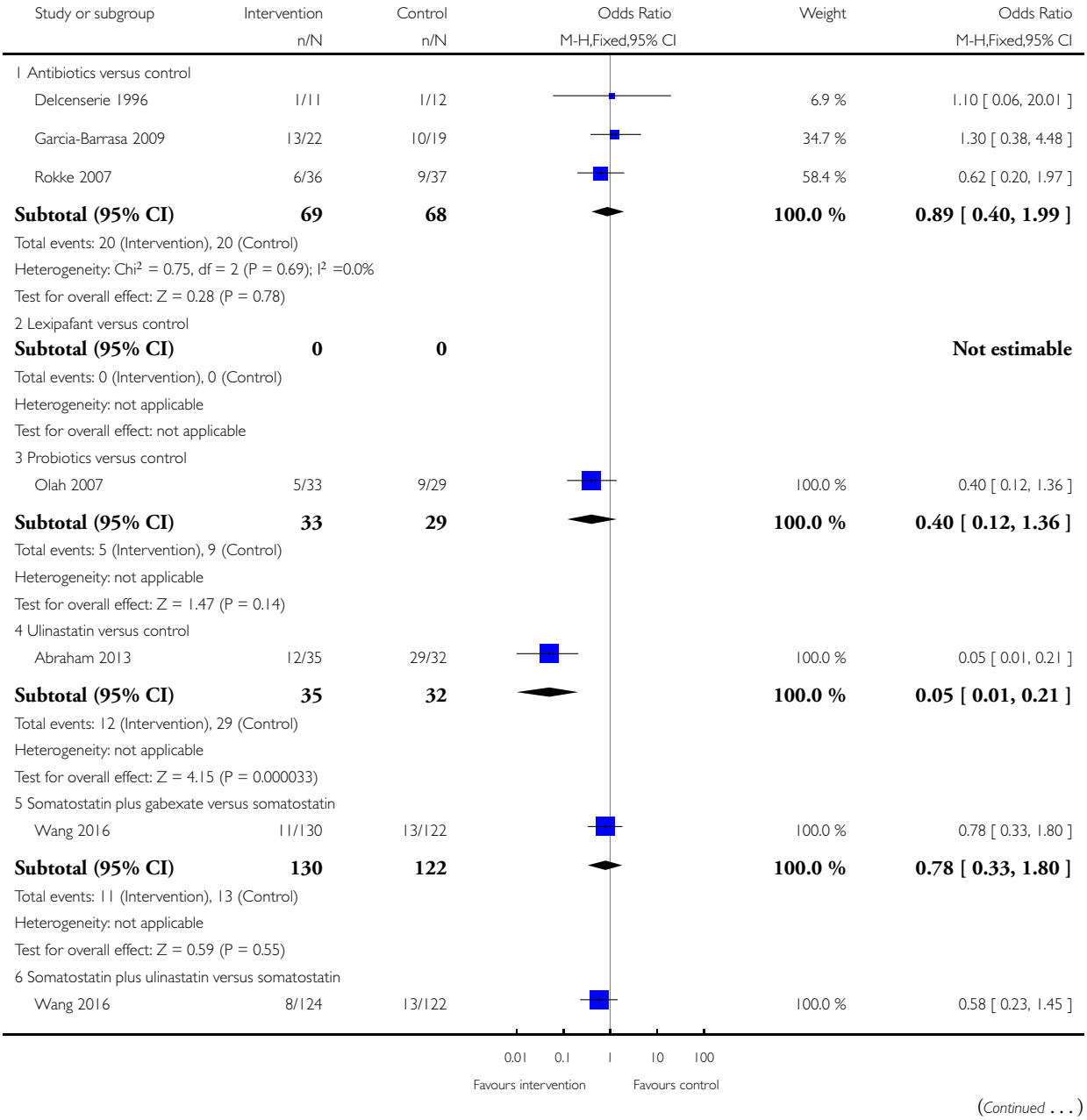
Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Random,95% CI	Weight	Rate Ratio IV,Random,95% CI
6 Somatostatin plus omeprazole versus control				
Xia 2014	-1.0116 (0.3371)		100.0 %	0.36 [0.19, 0.70]
Subtotal (95% CI)			**100.0 %**	**0.36 [0.19, 0.70]**
Heterogeneity: not applicable				
Test for overall effect: Z = 3.00 (P = 0.0027)				
7 Somatostatin plus ulinastatin versus control				
Wang 2013a	-1.19024 (0.34566)		100.0 %	0.30 [0.15, 0.60]
Subtotal (95% CI)			**100.0 %**	**0.30 [0.15, 0.60]**
Heterogeneity: not applicable				
Test for overall effect: Z = 3.44 (P = 0.00057)				
8 Octreotide plus ulinastatin versus octreotide				
Guo 2015	-1.20984 (0.27635)		100.0 %	0.30 [0.17, 0.51]
Subtotal (95% CI)			**100.0 %**	**0.30 [0.17, 0.51]**
Heterogeneity: not applicable				
Test for overall effect: Z = 4.38 (P = 0.000012)				
9 Somatostatin plus ulinastatin versus somatostatin				
Wang 2013a	-1.25595 (0.342381)		100.0 %	0.28 [0.15, 0.56]
Subtotal (95% CI)			**100.0 %**	**0.28 [0.15, 0.56]**
Heterogeneity: not applicable				
Test for overall effect: Z = 3.67 (P = 0.00024)				

Analysis 3.4. Comparison 3 Severe acute pancreatitis, Outcome 4 Organ failure.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 3 Severe acute pancreatitis

Outcome: 4 Organ failure



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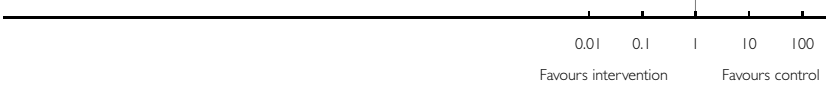
Study or subgroup	Intervention n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**124**	**122**		**100.0 %**	**0.58 [0.23, 1.45]**
Total events: 8 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.17 (P = 0.24)					
7 Somatostatin plus ulinastatin plus gabexate versus somatostatin					
Wang 2016	6/116	13/122		100.0 %	0.46 [0.17, 1.25]
Subtotal (95% CI)	**116**	**122**		**100.0 %**	**0.46 [0.17, 1.25]**
Total events: 6 (Intervention), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
8 Somatostatin plus ulinastatin versus somatostatin plus gabexate					
Wang 2016	8/124	11/130		100.0 %	0.75 [0.29, 1.92]
Subtotal (95% CI)	**124**	**130**		**100.0 %**	**0.75 [0.29, 1.92]**
Total events: 8 (Intervention), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
9 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate					
Wang 2016	6/116	11/130		100.0 %	0.59 [0.21, 1.65]
Subtotal (95% CI)	**116**	**130**		**100.0 %**	**0.59 [0.21, 1.65]**
Total events: 6 (Intervention), 11 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
10 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin					
Wang 2016	6/116	8/124		100.0 %	0.79 [0.27, 2.35]
Subtotal (95% CI)	**116**	**124**		**100.0 %**	**0.79 [0.27, 2.35]**
Total events: 6 (Intervention), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					

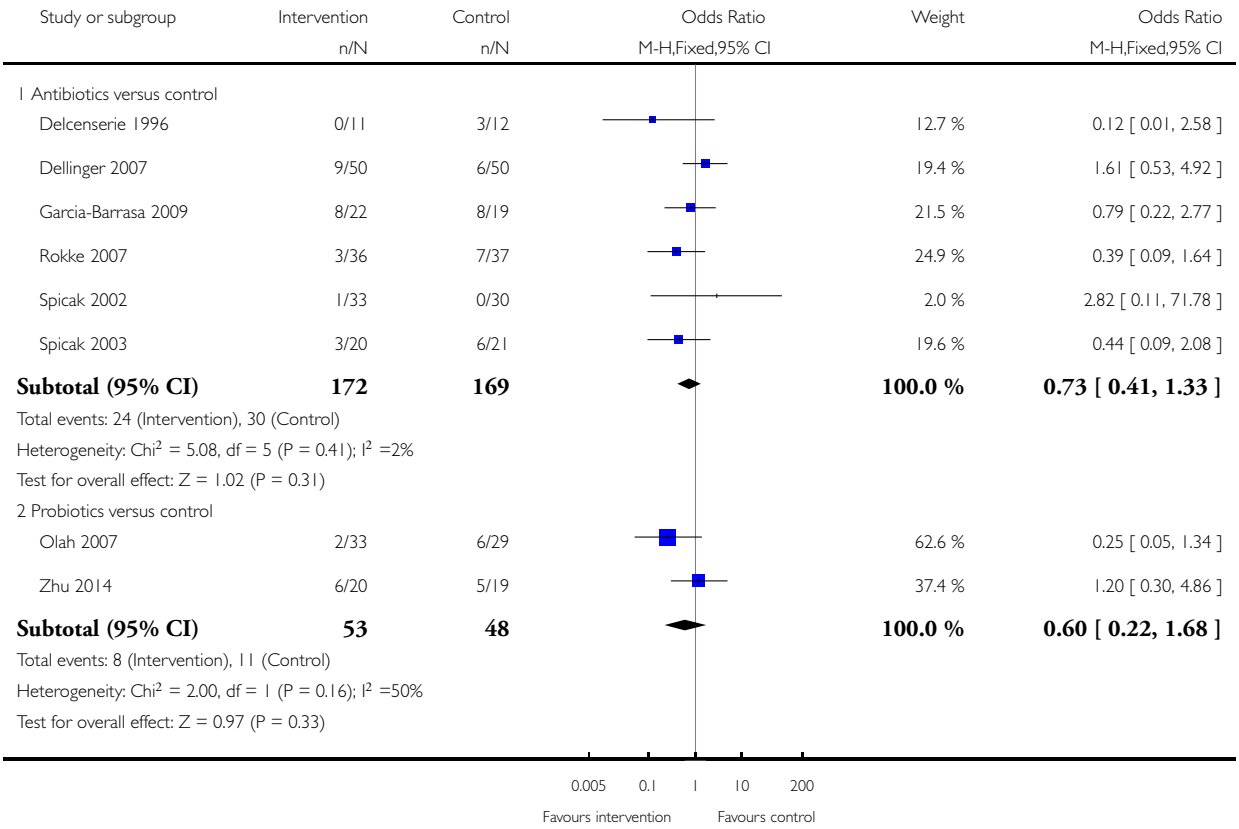


Analysis 3.5. Comparison 3 Severe acute pancreatitis, Outcome 5 Infected pancreatic necrosis.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 3 Severe acute pancreatitis

Outcome: 5 Infected pancreatic necrosis

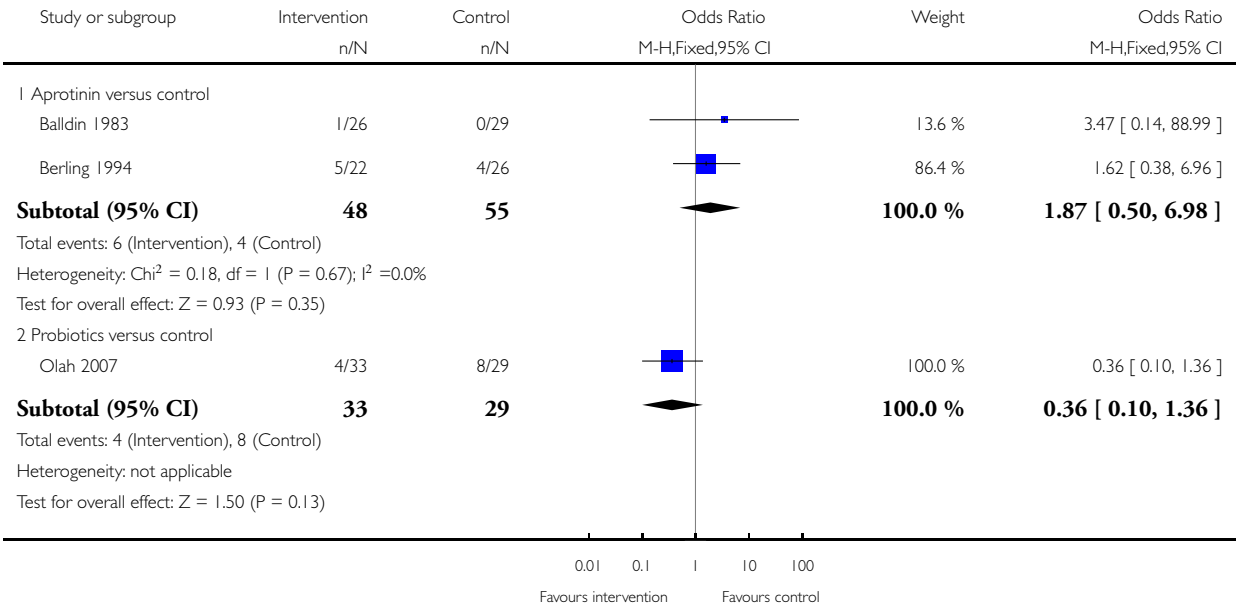


Analysis 3.6. Comparison 3 Severe acute pancreatitis, Outcome 6 Sepsis.

Review: Pharmacological interventions for acute pancreatitis

Comparison: 3 Severe acute pancreatitis

Outcome: 6 Sepsis



ADDITIONAL TABLES

Table 1. Characteristics of included studies (ordered by comparisons)

Study name	No of participants randomised	Postrandomisation dropouts	No of participants for whom outcome was reported	Treatment 1	Treatment 2	Selection bias	Performance and detection bias	Attrition bias	Selective reporting bias	Other bias
Pettila 2010	32	0	32	Activated protein C	Placebo	Unclear	Low	Low	High	High
Barreda 2009	80	22	58	Antibiotics	No active intervention	Unclear	Unclear	High	Low	Unclear

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Del-censerie 1996	23	0	23	Antibi-otics	No ac-tive inter-vention	Unclear	Unclear	Low	Low	Unclear
Del-censerie 2001	81	Not stated	81	Antibi-otics	No ac-tive inter-vention	Unclear	Unclear	Unclear	Low	Unclear
Dellinger 2007	100	0	100	Antibi-otics	Placebo	Low	Low	Low	Low	High
Finch 1976	62	4	58	Antibi-otics	No ac-tive inter-vention	Unclear	Unclear	High	Low	Unclear
Garcia-Barrasa 2009	46	5	41	Antibi-otics	Placebo	Unclear	Low	High	Low	Low
Hejt-mankova 2003	41	Not stated	41	Antibi-otics	No ac-tive inter-vention	Unclear	Unclear	Unclear	Low	Unclear
Isen-mann 2004	119	5	114	Antibi-otics	Placebo	Unclear	Low	High	High	High
Llukacaj 2012	80	Not stated	80	Antibi-otics	Placebo	Unclear	Low	Unclear	High	Unclear
Luiten 1995	109	7	102	Antibi-otics	No ac-tive inter-vention	Unclear	Unclear	High	Low	Unclear
Nord-back 2001	90	32	58	Antibi-otics	Placebo	Unclear	Unclear	High	Low	Unclear
Poropat 2015	47	0	47	Antibi-otics	No ac-tive inter-vention	Unclear	Unclear	Low	Low	Unclear
Pederzoli 1993a	74	Not stated	74	Antibi-otics	No ac-tive inter-vention	Unclear	Unclear	Low	Low	Unclear
Rokke 2007	73	0	73	Antibi-otics	No ac-tive inter-vention	Unclear	High	Low	Low	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Sainio 1995	60	0	60	Antibiotics	No active intervention	Unclear	Unclear	Low	Low	Unclear
Spicak 2002	63	Not stated	63	Antibiotics	No active intervention	Unclear	Unclear	Unclear	Low	Unclear
Spicak 2003	41	Not stated	41	Antibiotics	No active intervention	Unclear	Unclear	Unclear	Low	Unclear
Xue 2009	59	3	56	Antibiotics	No active intervention	Unclear	Unclear	High	Low	Low
Bansal 2011	44	5	39	Antioxidants	No active intervention	Unclear	High	High	Low	Low
Birk 1994	20	Not stated	20	Antioxidants	No active intervention	Unclear	Unclear	Unclear	High	Unclear
Marek 1999	73	0	73	Antioxidants	Placebo	Unclear	Unclear	Low	High	Unclear
Sateesh 2009	56	3	53	Antioxidants	No active intervention	Unclear	High	High	Low	Unclear
Siriwardena 2007	43	0	43	Antioxidants	Placebo	Low	Low	Low	Low	High
Vege 2015	28	Not stated	28	Antioxidants	Placebo	Unclear	Low	Low	Low	Unclear
Chooklin 2007	34	Not stated	34	Antioxidants plus Corticosteroids	No active intervention	Unclear	Unclear	Unclear	High	Unclear
MRC Multicentre Trial 1977 (this is a 3-armed	264	7	257	Aprotinin	Placebo	Unclear	Low	High	High	High

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

trial; the numbers stated included all 3 arms)										
Balldin 1983	55	Not stated	55	Aprotinin	No active intervention	Unclear	Unclear	Unclear	Low	High
Berling 1994	48	Not stated	48	Aprotinin	No active intervention	Unclear	Low	Low	Low	High
Imrie 1978	161	Not stated	161	Aprotinin	Placebo	Unclear	Low	Unclear	Low	High
Imrie 1980	50	Not stated	50	Aprotinin	Placebo	Unclear	Low	Unclear	High	Unclear
Storck 1968	43	Not stated	43	Aprotinin	Placebo	Unclear	Low	Unclear	High	Unclear
Trapnell 1974	105	Not stated	105	Aprotinin	Placebo	Low	Low	Unclear	High	High
MRC Multicentre Trial 1977 (this is a 3-armed trial; the numbers stated included all 3 arms)	264	7	257	Aprotinin	Glucagon	Unclear	Low	High	High	High
Goebell 1979	94	Not stated	94	Calcitonin	Placebo	Unclear	Low	Unclear	Low	Unclear
Martinez 1984	31	0	31	Calcitonin	Placebo	Unclear	Unclear	Low	High	Unclear
Perezdeotey 1980	40	Not stated	40	Cimetidine	Placebo	Unclear	Low	Unclear	High	Unclear

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Sillero 1981	60	Not stated	60	Cimetidine	Placebo	Low	Unclear	Unclear	High	Unclear
Tykka 1985	64	0	64	EDTA	Placebo	Unclear	Low	Low	Low	High
Frulloni 1994	116	Not stated	116	Gabexate	Aprotinin	Unclear	Unclear	Unclear	Low	Unclear
Pederzoli 1993b	199	17	182	Gabexate	Aprotinin	Unclear	Low	High	Low	Unclear
Buchler 1993	223	Not stated	223	Gabexate	Placebo	Low	Low	Low	Low	Unclear
Chen 2000	52	Not stated	52	Gabexate	Placebo	Unclear	Unclear	Unclear	Low	Unclear
Freise 1986	50	Not stated	50	Gabexate	Placebo	Unclear	Low	Unclear	Low	Unclear
Goebell 1988	162	11	151	Gabexate	Placebo	Unclear	Low	High	Low	Unclear
Valderrama 1992	105	5	100	Gabexate	Placebo	Low	Low	High	Low	High
Kirsch 1978	150	Not stated	150	Glucagon	Atropine	Unclear	Unclear	Unclear	Low	Unclear
MRC Multicentre Trial 1977 (this is a 3-armed trial; the numbers stated included all 3 arms)	264	7	257	Glucagon	Placebo	Unclear	Unclear	Unclear	Low	High
Debas 1980	66	Not stated	66	Glucagon	Placebo	Unclear	Low	Unclear	Low	Unclear
Dürr 1978	69	Not stated	69	Glucagon	Placebo	Unclear	Low	Unclear	High	Unclear

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Kalima 1980	80	9	71	Glucagon	Placebo	Unclear	Unclear	High	Low	Unclear
Kronborg 1980	22	Not stated	22	Glucagon	Placebo	Unclear	Low	Unclear	High	Unclear
Gilsanz 1978	62	Not stated	62	Glucagon	Oxyphenonium	Unclear	Low	Unclear	Low	Unclear
Hansky 1969	24	Not stated	24	Iniprol	No active intervention	Unclear	High	Unclear	High	High
Johnson 2001	291	1	290	Lexipafant	Placebo	Unclear	Low	High	Low	High
Kingsnorth 1995	83	Not stated	83	Lexipafant	Placebo	Unclear	Low	Unclear	High	High
McKay 1997b	51	1	50	Lexipafant	Placebo	Unclear	Low	High	High	High
Bredkjaer 1988	66	9	57	NSAID	Placebo	Unclear	Unclear	Unclear	High	Unclear
Ebbehøj 1985	30	0	30	NSAID	Placebo	Unclear	Low	Low	High	High
McKay 1997a	58	0	58	Octreotide	Placebo	Low	Low	Low	Low	Unclear
Ohair 1993	180	Not stated	180	Octreotide	Placebo	Unclear	Unclear	Unclear	High	Unclear
Paran 1995	51	13	38	Octreotide	No active intervention	Unclear	High	High	Low	Unclear
Uhl 1999	302	0	302	Octreotide	Placebo	Unclear	Low	Low	Low	High
Wang 2013c	372	Not stated	372	Octreotide	No active intervention	Unclear	Unclear	High	Low	Low
Yang 2012	163	6	157	Octreotide	No active intervention	Unclear	Unclear	High	High	Low

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Wang 2013b	354	Not stated	354	Octreotide plus NSAID	Octreotide	Unclear	Unclear	Unclear	High	Unclear
Guo 2015	120	Not stated	120	Octreotide plus ulinastatin	Octreotide	Unclear	Unclear	Unclear	Low	Unclear
Besselink 2008	298	2	296	Probiotics	Placebo	Low	Low	High	Low	High
Olah 2007	83	21	62	Probiotics	No active intervention	Unclear	Low	High	High	Unclear
Plaudis 2010	90	Not stated	58	Probiotics	No active intervention	Unclear	Low	Unclear	High	Unclear
Sharma 2011	50	0	50	Probiotics	Placebo	Unclear	Low	Low	High	High
Zhu 2014	39	Not stated	39	Probiotics	Placebo	Unclear	Low	Unclear	High	Unclear
Grupo Español 1996	70	9	61	Somatostatin	Placebo	Unclear	Low	High	High	Unclear
Choi 1989	71	Not stated	71	Somatostatin	No active intervention	Unclear	Unclear	Unclear	Low	Unclear
Gjørup 1992	63	Not stated	63	Somatostatin	Placebo	Unclear	Low	Unclear	Low	Unclear
Luengo 1994	100	Not stated	100	Somatostatin	No active intervention	Unclear	Low	Unclear	High	Unclear
Moreau 1986	87	3	84	Somatostatin	Placebo	Unclear	Low	Unclear	High	High
Usadel 1985	77	Not stated	77	Somatostatin	Placebo	Unclear	Low	Unclear	High	Unclear

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Wang 2013a (this is a 3-armed trial; the numbers stated included all 3 arms)	183	Not stated	183	Somatostatin	No active intervention	Unclear	Low	Unclear	Low	Low
Yang 1999	48	Not stated	48	Somatostatin	No active intervention	Unclear	Unclear	Unclear	High	Unclear
Xia 2014	140	Not stated	140	Somatostatin plus omeprazole	No active intervention	Unclear	Unclear	Unclear	Low	Unclear
Wang 2013a (this is a 3-armed trial; the numbers stated included all 3 arms)	183	Not stated	183	Somatostatin plus ulinastatin	Placebo	Unclear	Unclear	Unclear	High	Unclear
Wang 2013a (this is a 3-armed trial; the numbers stated included all 3 arms)	183	Not stated	183	Somatostatin plus ulinastatin	Somatostatin	Unclear	Low	Unclear	Low	Low
Wang 2016 (this is a 4-armed trial; the numbers stated included all 4 arms)	492	0	492	Somatostatin plus ulinastatin	Somatostatin	Low	Low	Low	Low	Low

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Wang 2016 (this is a 4-armed trial; the numbers stated included all 4 arms)	492	0	492	Somatostatin plus gabexate	Somatostatin	Low	Low	Low	Low	Low
Wang 2016 (this is a 4-armed trial; the numbers stated included all 4 arms)	492	0	492	Somatostatin plus ulinastatin plus gabexate	Somatostatin	Low	Low	Low	Low	Low
Wang 2016 (this is a 4-armed trial; the numbers stated included all 4 arms)	492	0	492	Somatostatin plus ulinastatin	Somatostatin plus gabexate	Low	Low	Low	Low	Low
Wang 2016 (this is a 4-armed trial; the numbers stated included all 4 arms)	492	0	492	Somatostatin plus ulinastatin plus gabexate	Somatostatin plus gabexate	Low	Low	Low	Low	Low
Wang 2016 (this is a 4-armed trial; the numbers stated included all 4 arms)	492	0	492	Somatostatin plus ulinastatin plus gabexate	Somatostatin plus ulinastatin	Low	Low	Low	Low	Low

Table 1. Characteristics of included studies (ordered by comparisons) *(Continued)*

Wang 2011	24	Not stated	24	Thymosin	Placebo	Unclear	Low	Unclear	High	Unclear
Abraham 2013	135	6	129	Ulinastatin	Placebo	Unclear	Low	High	Low	Unclear
Chen 2002a	68	6	62	Ulinastatin	Gabexate	Unclear	Unclear	High	High	Unclear
Chen 2002b	26	1	25	Ulinastatin	Octreotide	Unclear	Unclear	High	High	Unclear

Table 2. Potential effect modifiers (ordered by comparisons)

Study name	Treatment 1	Treatment 2	Severe pancreatitis	Necrotising pancreatitis	Organ failure	Infection
Pettila 2010	Activated protein C	Placebo	yes	not stated	not stated	not stated
Barreda 2009	Antibiotics	No active intervention	not stated	yes	not stated	not stated
Delcenserie 1996	Antibiotics	No active intervention	yes	not stated	not stated	not stated
Delcenserie 2001	Antibiotics	No active intervention	not stated	yes	not stated	not stated
Dellinger 2007	Antibiotics	Placebo	yes	yes	not stated	no
Finch 1976	Antibiotics	No active intervention	not stated	not stated	not stated	not stated
Garcia-Barrasa 2009	Antibiotics	Placebo	yes	yes	not stated	not stated
Hejtmankova 2003	Antibiotics	No active intervention	yes	not stated	not stated	not stated
Isenmann 2004	Antibiotics	Placebo	not stated	not stated	not stated	not stated
Llukacaj 2012	Antibiotics	Placebo	not stated	yes	not stated	no
Luiten 1995	Antibiotics	No active intervention	yes	not stated	not stated	no
Nordback 2001	Antibiotics	Placebo	not stated	yes	no	not stated

Table 2. Potential effect modifiers (ordered by comparisons) (*Continued*)

Pederzoli 1993a	Antibiotics	No active intervention	not stated	yes	not stated	not stated
Rokke 2007	Antibiotics	No active intervention	yes	yes	not stated	not stated
Sainio 1995	Antibiotics	No active intervention	not stated	yes	not stated	not stated
Spicak 2002	Antibiotics	No active intervention	yes	not stated	not stated	not stated
Spicak 2003	Antibiotics	No active intervention	yes	not stated	not stated	not stated
Xue 2009	Antibiotics	No active intervention	yes	yes	not stated	no
Bansal 2011	Antioxidants	No active intervention	not stated	not stated	not stated	not stated
Birk 1994	Antioxidants	No active intervention	yes	not stated	not stated	not stated
Marek 1999	Antioxidants	Placebo	not stated	not stated	not stated	not stated
Sateesh 2009	Antioxidants	No active intervention	not stated	not stated	not stated	not stated
Siriwardena 2007	Antioxidants	Placebo	not stated	not stated	not stated	not stated
Vege 2015	Antioxidants	Placebo	not stated	not stated	not stated	not stated
Chooklin 2007	Antioxidants plus corticosteroids	No active intervention	yes	not stated	not stated	not stated
Balldin 1983	Aprotinin	No active intervention	yes	not stated	not stated	not stated
Berling 1994	Aprotinin	No active intervention	yes	not stated	not stated	not stated
Imrie 1978	Aprotinin	Placebo	not stated	not stated	not stated	not stated
Imrie 1980	Aprotinin	Placebo	not stated	not stated	not stated	not stated

Table 2. Potential effect modifiers (ordered by comparisons) (*Continued*)

MRC Multicentre Trial 1977	Aprotinin	Placebo	not stated	not stated	not stated	not stated
Storck 1968	Aprotinin	Placebo	not stated	not stated	not stated	not stated
Trapnell 1974	Aprotinin	Placebo	not stated	not stated	not stated	not stated
Goebell 1979	Calcitonin	Placebo	not stated	not stated	not stated	not stated
Martinez 1984	Calcitonin	Placebo	yes	not stated	not stated	not stated
Perezdeoteyza 1980	Cimetidine	Placebo	not stated	not stated	not stated	not stated
Sillero 1981	Cimetidine	Placebo	not stated	not stated	not stated	not stated
Tykka 1985	EDTA	Placebo	not stated	not stated	not stated	not stated
Buchler 1993	Gabexate	Placebo	not stated	not stated	not stated	not stated
Chen 2000	Gabexate	Placebo	yes	not stated	yes	not stated
Freise 1986	Gabexate	Placebo	not stated	not stated	not stated	not stated
Goebell 1988	Gabexate	Placebo	not stated	not stated	not stated	not stated
Valderrama 1992	Gabexate	Placebo	not stated	not stated	not stated	not stated
Debas 1980	Glucagon	Placebo	not stated	not stated	not stated	not stated
Dürr 1978	Glucagon	Placebo	not stated	not stated	not stated	not stated
Kalima 1980	Glucagon	Placebo	not stated	not stated	not stated	not stated
Kronborg 1980	Glucagon	Placebo	not stated	not stated	not stated	not stated
MRC Multicentre Trial 1977	Glucagon	Placebo	not stated	not stated	not stated	not stated
Hansky 1969	Iniprol	No active intervention	not stated	not stated	not stated	not stated
Johnson 2001	Lexipafant	Placebo	not stated	not stated	not stated	not stated

Table 2. Potential effect modifiers (ordered by comparisons) (*Continued*)

Kingsnorth 1995	Lexipafant	Placebo	not stated	not stated	not stated	not stated
McKay 1997b	Lexipafant	Placebo	not stated	not stated	not stated	not stated
Bredkjaer 1988	NSAID	Placebo	not stated	not stated	not stated	not stated
Ebbehøj 1985	NSAID	Placebo	not stated	not stated	not stated	not stated
McKay 1997b	Octreotide	Placebo	not stated	not stated	not stated	not stated
Ohair 1993	Octreotide	Placebo	not stated	not stated	not stated	not stated
Paran 1995	Octreotide	No active intervention	not stated	not stated	not stated	not stated
Uhl 1999	Octreotide	Placebo	not stated	not stated	not stated	not stated
Wang 2013c (mild pancreatitis)	Octreotide	No active intervention	no	not stated	not stated	not stated
Wang 2013c (severe pancreatitis)	Octreotide	No active intervention	yes	not stated	not stated	not stated
Yang 2012	Octreotide	No active intervention	no	not stated	not stated	not stated
Besselink 2008	Probiotics	Placebo	not stated	not stated	not stated	not stated
Olah 2007	Probiotics	No active intervention	yes	not stated	not stated	not stated
Plaudis 2010	Probiotics	No active intervention	yes	not stated	not stated	not stated
Sharma 2011	Probiotics	Placebo	not stated	not stated	not stated	not stated
Zhu 2014	Probiotics	Placebo	yes	not stated	not stated	not stated
Choi 1989	Somatostatin	No active intervention	not stated	not stated	not stated	not stated
Gjørup 1992	Somatostatin	Placebo	not stated	not stated	not stated	not stated
Grupo Español 1996	Somatostatin	Placebo	yes	not stated	not stated	not stated

Table 2. Potential effect modifiers (ordered by comparisons) (*Continued*)

Luengo 1994	Somatostatin	No active intervention	not stated	not stated	not stated	not stated
Moreau 1986	Somatostatin	Placebo	not stated	not stated	not stated	not stated
Usadel 1985	Somatostatin	Placebo	not stated	not stated	not stated	not stated
Wang 2013a	Somatostatin	No active intervention	yes	not stated	not stated	not stated
Yang 1999	Somatostatin	No active intervention	not stated	not stated	not stated	not stated
Xia 2014	Somatostatin plus omeprazole	No active intervention	yes	not stated	not stated	not stated
Wang 2013a	Somatostatin plus ulinastatin	No active intervention	yes	not stated	not stated	not stated
Wang 2011	Thymosin	Placebo	yes	not stated	not stated	not stated
Abraham 2013 (mild pancreatitis)	Ulinastatin	Placebo	no	not stated	not stated	no
Abraham 2013 (severe pancreatitis)	Ulinastatin	Placebo	yes	not stated	not stated	not stated
Frulloni 1994	Gabexate	Aprotinin	not stated	yes	not stated	not stated
Pederzoli 1993b	Gabexate	Aprotinin	not stated	not stated	not stated	not stated
Kirsch 1978	Glucagon	Atropine	not stated	not stated	not stated	not stated
Chen 2002a	Ulinastatin	Gabexate	no	no	no	not stated
MRC Multicentre Trial 1977	Aprotinin	Glucagon	not stated	not stated	not stated	not stated
Guo 2015	Octerotide plus ulinastatin	Octreotide	yes	not stated	not stated	not stated
Wang 2013b	Octreotide plus NSAID	Octreotide	not stated	not stated	not stated	not stated
Chen 2002b	Ulinastatin	Octreotide	yes	yes	not stated	not stated

Table 2. Potential effect modifiers (ordered by comparisons) (*Continued*)

Gilsanz 1978	Glucagon	Oxyphenonium	not stated	not stated	not stated	not stated
Poropat 2015	Antibiotics	No active intervention	not stated	not stated	not stated	no
Wang 2016	Somatostatin plus gabexate	Somatostatin	yes	not stated	not stated	not stated
Wang 2013a	Somatostatin plus ulinastatin	Somatostatin	yes	not stated	not stated	not stated
Wang 2016	Somatostatin plus ulinastatin	Somatostatin	yes	not stated	not stated	not stated
Wang 2016	Somatostatin plus ulinastatin plus gabexate	Somatostatin	yes	not stated	not stated	not stated
Wang 2016	Somatostatin plus ulinastatin	Somatostatin plus gabexate	yes	not stated	not stated	not stated
Wang 2016	Somatostatin plus ulinastatin plus gabexate	Somatostatin plus gabexate	yes	not stated	not stated	not stated
Wang 2016	Somatostatin plus ulinastatin plus gabexate	Somatostatin plus ulinastatin	yes	not stated	not stated	not stated

Table 3. Length of hospital stay (days)

Study name	Intervention	Comparator	Number of participants in intervention	Number of participants in control	Mean or median (standard deviation or interquartile range, if reported) hospital stay in intervention group	Mean or median (standard deviation or interquartile range, if reported) hospital stay in control group	Difference	Statistical significance (P-value if reported)
Barreda 2009	Antibiotics	No active intervention	24	34	54	45	9	Not significant

Table 3. Length of hospital stay (days) (*Continued*)

Delcenserie 1996	Antibiotics	No active intervention	11	12	27.8	22	5.8	Not significant
Finch 1976	Antibiotics	No active intervention	31	27	10.4	11.3	−0.9	Not significant
Garcia-Barrasa 2009	Antibiotics	Placebo	22	19	21	19	2	Not significant (0.80)
Hejtmankova 2003	Antibiotics	No active intervention	20	21	18 (7.2)	25 (14.8)	−7	Not significant
Isenmann 2004	Antibiotics	Placebo	58	56	21	18	3	Not significant
Luiten 1995	Antibiotics	No active intervention	50	52	30	32	−2	Not significant
Rokke 2007	Antibiotics	No active intervention	36	37	18	22	−4	Not significant (0.32)
Sainio 1995	Antibiotics	No active intervention	30	30	33.2 (22.1)	43.8 (43.1)	−10.6	Not significant (0.24)
Spicak 2002	Antibiotics	No active intervention	33	30	18.9 (8.1)	23.8 (19.3)	−4.9	Not significant
Spicak 2003	Antibiotics	No active intervention	20	21	18 (7.2)	25 (14.8)	−7	Not significant
Xue 2009	Antibiotics	No active intervention	29	27	28.3	30.7	−2.4	Not significant
Bansal 2011	Antioxidants	No active intervention	19	20	12.8	15.1	−2.3	Not significant
Sateesh 2009	Antioxidants	No active intervention	23	30	7.2 (5)	10.3 (7)	−3.1	Not significant (0.07)
Siriwardena 2007	Antioxidants	Placebo	22	21	20.4 (24.4)	14.3 (15.7)	6.1	Not significant (0.34)
Vege 2015	Antioxidants	Placebo	14	14	3	5	−2	Not significant (0.06)

Table 3. Length of hospital stay (days) (*Continued*)

Balldin 1983	Aprotinin	No active intervention	26	29	17.3	16.5	0.8	Not significant
Berling 1994	Aprotinin	No active intervention	22	26	25 (15-32)	33 (17-38)	−8	Not significant (0.24)
Goebell 1979	Calcitonin	Placebo	50	44	18.3 (6.4)	20.2 (7.5)	−1.9	Not significant
Martinez 1984	Calcitonin	Placebo	14	17	24 (20.2)	30 (21.7)	−6	Not significant
Buchler 1993	Gabexate	Placebo	115	108	26 (20-43)	23 (28-34)	3	Not significant
Debas 1980	Glucagon	Placebo	33	33	26 (28.7)	20 (19.2)	6	Not significant
Dürr 1978	Glucagon	Placebo	33	36	32.6	26.9	5.7	Not significant
Hansky 1969	Iniprol	No active intervention	15	9	14.7 (9.3)	18.7 (10.2)	−4	Not significant
Johnson 2001	Lexipafant	Placebo	151	139	9	10	−1	Not significant
McKay 1997b	Lexipafant	Placebo	26	24	13.3	14.9	−1.6	Not significant
Bredkjaer 1988	NSAID	Placebo	27	30	9	10	−1	Not significant
Ebbehøj 1985	NSAID	Placebo	14	16	13	15	−2	Not significant
McKay 1997a	Octreotide	Placebo	28	30	10	10	0	Not significant
Ohair 1993	Octreotide	Placebo	90	90	7.3	8.2	−0.9	Not significant
Paran 1995	Octreotide	No active intervention	19	19	17.9 (13.2)	34.1 (22.7)	−16.2	Significant (0.02)
Uhl 1999	Octreotide	Placebo	199	103	21.5	21	0.5	Not significant

Table 3. Length of hospital stay (days) (*Continued*)

Wang 2013c (mild acute pancreatitis)	Octreotide	No active intervention	157	79	14.4	15.37	−0.97	Not significant
Wang 2013c (severe acute pancreatitis)	Octreotide	No active intervention	91	45	16	16	0	Not significant
Yang 2012	Octreotide	No active intervention	80	77	7.4 (2)	11.8 (4)	−4.4	Significant
Besselink 2008	Probiotics	Placebo	152	144	28.9 (41.5)	23.5 (25.9)	5.4	Not significant (0.98)
Olah 2007	Probiotics	No active intervention	33	29	14.9	19.7	−4.8	Not significant
Sharma 2011	Probiotics	Placebo	24	26	13.23 (18.19)	9.69 (9.69)	3.54	Not significant (0.76)
Pettila 2010	Activated protein C	Placebo	16	16	17.1	34.4	−17.3	Significant (P < 0.05)
Gjørup 1992	Somatostatin	Placebo	33	30	12	10	2	Not significant
Luengo 1994	Somatostatin	No active intervention	50	50	14.92 (11.46)	20.28 (15)	−5.36	Significant
Wang 2011	Thymosin	Placebo	12	12	37.1 (22.7)	60.6 (32.9)	−23.5	Not significant (0.06)
Abraham 2013 (mild acute pancreatitis)	Ulinastatin	Placebo	30	32	7 (5-22)	8 (5-15)	−1	Not significant (0.07)
Abraham 2013 (severe acute pancreatitis)	Ulinastatin	Placebo	35	32	9 (6-22)	10 (6-22)	−1	Not significant (0.21)
Guo 2015	Octerotide plus ulinastatin	Octreotide	60	60	11.8 (3.9)	23.7 (16.3)	−11.9	Significant
Wang 2016	Somatostatin plus	Somatostatin	116	122	17.7 (32.1)	31.3 (37.6)	-13.6	Significant

Table 3. Length of hospital stay (days) (*Continued*)

	uli-nastatin plus gabexate							
Wang 2016	Somato-statin plus ulinastatin	Somato-statin	124	122	22.6 (34.5)	31.3 (37.6)	-8.7	Significant
Wang 2016	Somato-statin plus gabexate	Somato-statin	130	122	23.2 (29.6)	31.3 (37.6)	-8.1	Significant
Wang 2016	Somato-statin plus uli-nastatin plus gabexate	Somato-statin plus gabexate	116	130	17.7 (32.1)	23.2 (29.6)	−5.5	Significant
Wang 2016	Somato-statin plus ulinastatin	Somato-statin plus gabexate	124	130	22.6 (34.5)	23.2 (29.6)	−0.6	Significant
Wang 2016	Somato-statin plus uli-nastatin plus gabexate	Somato-statin plus ulinastatin	116	124	17.7 (32.1)	22.6 (34.5)	−4.9	Significant

NSAID: non-steroidal anti-inflammatory drug.

Table 4. Length of intensive care unit (ICU) stay (days)

Study name	Intervention	Control	Number of participants in intervention	Number of participants in control	Mean or median (standard deviation or interquartile range, if reported) intensive care stay in intervention group	Mean or median (standard deviation or interquartile range, if reported) intensive care stay in control group	Difference	Statistical significance (P-value, reported)
Garcia-Barrasa 2009	Antibiotics	Placebo	22	19	17	18	-1	Not significant (P-value

Table 4. Length of intensive care unit (ICU) stay (days) (*Continued*)

								= 0.83)
Isenmann 2004	Antibiotics	Placebo	58	56	8	6	2	Not significant
Nordback 2001	Antibiotics	Placebo	25	33	8	8	0	Not significant
Rokke 2007	Antibiotics	No active intervention	36	37	8	7	1	Not significant (P-value = 0.78)
Sainio 1995	Antibiotics	No active intervention	30	30	12.7 (10.7)	23.6 (28.7)	-10.9	Not significant (P-value = 0.06)
Spicak 2002	Antibiotics	No active intervention	33	30	11.4 (5.4)	15.9 (12)	-4.5	Not significant
Siriwardena 2007	Antioxidants	Placebo	22	21	4 (10.3)	0 (0)	4	Not significant (P-value = 0.08)
Vege 2015	Antioxidants	Placebo	14	14	0	0	0	Significant (P-value = 0.03)
Berling 1994	Aprotinin	No active intervention	22	26	9.5 (4 - 10)	12 (3-20)	-2.5	Not significant (P-value = 0.47)
Johnson 2001	Lexipafant	Placebo	151	139	9.5	11	-1.5	Not significant
Besselink 2008	Probiotics	Placebo	152	144	6.6 (17.1)	3 (9.3)	3.6	Not significant (P-value = 0.08)
Sharma 2011	Probiotics	Placebo	24	26	4.94 (9.54)	4 (5.86)	0.94	Not significant (P-value = 0.94)
Wang 2011	Thymosin	Placebo	12	12	24.6 (19.6)	50.5 (25.7)	-25.9	Significant (P-value = 0.01)

APPENDICES

Appendix 1. Glossary of terms

Acute: sudden.
Analogues: a substance that is similar to another substance.
Antioxidants: substances that inhibit oxidation.
Autodigestion: Breakdown of the same organ that secretes the substance.
Bacterial colonisation: growth and multiplication of bacteria.
Cholangiopancreatography: fully known as endoscopic retrograde cholangiopancreatography (ERCP); a procedure carried out on the pancreatic and bile ducts using an endoscope and x-rays.
Colonisation: presence of bacteria without causing illness (in this context).
Endoscopic sphincterotomy: endoscopic operation to cut the muscle surrounding the common bile duct and the pancreatic duct.
Endoscopic: with the help of an endoscope, a tube inserted into body (in this context, through the mouth and into the stomach and upper part of the small intestine).
Enzyme: substances that enable and speed up chemical reactions that are necessary for the normal functioning of the body.
Epigastric: upper central abdomen.
Epigastric pain: upper central abdominal pain.
Heterogeneity: variability.
Insulin: substance which helps regulate blood sugar.
Interstitial: space in between.
Morbidity: illness (in this context, it means complications).
Mortality: death.
Necrosectomy: removal of dead tissue.
Necrosis: death and decomposition of living tissue usually caused by lack of blood supply but can be caused by other pathological insult.
Necrotising : causing necrosis.
Oedematous: excessive accumulation of serous fluid in the intercellular spaces of tissues.
Pancreatic pseudocysts: fluid collections in the pancreas or the tissues surrounding the pancreas, surrounded by a well defined wall and contain only fluid with little or no solid material.
Pancreatitis: inflammation of the pancreas.
Pathologic insult: substance or mechanism that causes the condition.
Percutaneous: through the skin.
Peripancreatic tissues: tissues surrounding the pancreas.
Pharmacological: medicinal drugs.
Platelet activating factor: substance that causes platelets (cells responsible for clotting of blood) to clump together and is an intermediary substance in the inflammatory pathway.
Probiotics: microorganisms that are believed to provide health benefits when consumed.
Prognostic: to predict the likely outcome.
Protease inhibitors: substances that inhibit proteases.
Protease: an enzyme that digests protein.
Pseudocyst: a fluid-filled cavity that resembles a cyst but lacks a wall or lining.
Radiology guided percutaneous treatments: treatments carried out by insertion of needle from the external surface of the body which are guided by a scan (usually an ultrasound or CT (computed tomography) scan).
Randomisation: using chance methods to assign people to treatments.
Retrograde: moving backwards.
Sepsis: life-threatening illness due to blood infection with bacteria, fungus, or virus.
Serum: clear fluid that separates out when blood clots.
Sphincterotomy: a surgical procedure of the internal anal sphincter muscle.
Transabdominal: through the abdomen.
Transient: temporary.
Tumour necrosis factor-alpha antibody: antibody to tumour necrosis factor-alpha, an intermediary substance in the inflammatory pathway.

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Pancreatitis, Acute Necrotizing] this term only
#2 MeSH descriptor: [Pancreatitis] this term only and with qualifier(s): [Etiology - ET]
#3 MeSH descriptor: [Pancreas] this term only and with qualifier(s): [Abnormalities - AB, Pathology - PA, Physiopathology - PP]
#4 (acute near/3 pancrea*)
#5 (necro* near/3 pancrea*)
#6 (inflam* near/3 pancrea*)
#7 ((interstitial or edema* or oedema*) near/2 pancrea*)
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

Appendix 3. MEDLINE search strategy

1. Pancreatitis, Acute Necrotizing/
2. Pancreatitis/et
3. Pancreas/ab, pa, pp
4. (acute adj3 pancrea*).mp.
5. (necro* adj3 pancrea*).mp.
6. (inflam* adj3 pancrea$).mp.
7. ((interstitial or edema* or oedema*) adj2 pancrea*).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. drug therapy.fs.
14. randomly.ab.
15. trial.ab.
16. groups.ab.
17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp animals/ not humans.sh.
19. 17 not 18
20. 8 and 19

Appendix 4. Embase search strategy

1. acute hemorrhagic pancreatitis/
2. Pancreatitis/et
3. acute pancreatitis/
4. (acute adj3 pancrea*).mp.
5. (necro* adj3 pancrea*).mp.
6. (inflam* adj3 pancrea*).mp.
7. ((interstitial or edema* or oedema*) adj2 pancrea*).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Clinical trial/
10. Randomized controlled trial/
11. Randomization/
12. Single-Blind Method/
13. Double-Blind Method/
14. Cross-Over Studies/
15. Random Allocation/
16. Placebo/

17. Randomi?ed controlled trial*.tw.
18. Rct.tw.
19. Random allocation.tw.
20. Randomly allocated.tw.
21. Allocated randomly.tw.
22. (allocated adj2 random).tw.
23. Single blind*.tw.
24. Double blind*.tw.
25. ((treble or triple) adj blind*).tw.
26. Placebo*.tw.
27. Prospective study/
28. or/9-27
29. Case study/
30. Case report.tw.
31. Abstract report/ or letter/
32. or/29-31
33. 28 not 32
34. 8 and 33

Appendix 5. Science Citation Index search strategy

1 TS=((acute or necro* or inflam* or interstitial or edema* or oedema*) near/3 pancrea*)
2 TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)
3 #2 AND #1

Appendix 6. ClinicalTrials.gov search strategy

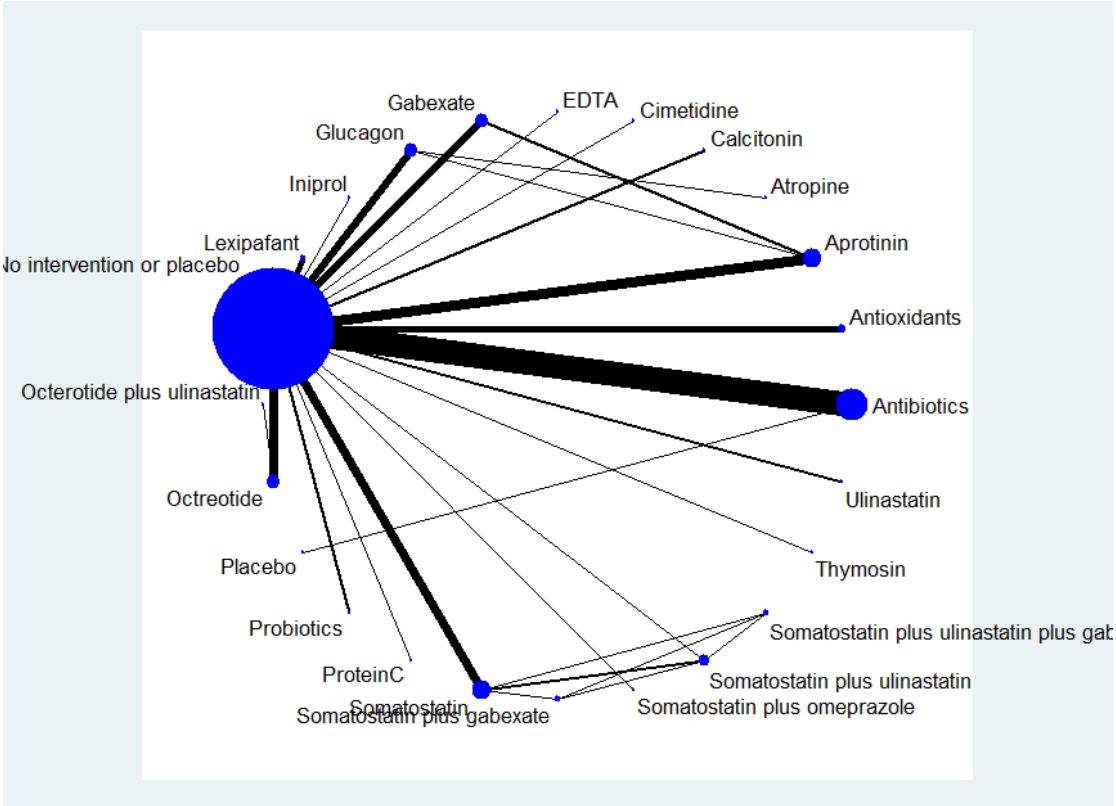
"Interventional" [STUDY-TYPES] AND acute pancreatitis [DISEASE] AND ("Phase 2" OR "Phase 3" OR "Phase 4") [PHASE]

Appendix 7. Planned methods

We planned to conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes when there was direct and indirect evidence for at least one comparison. Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012).
We planned to obtain a network plot (Figure 9) to ensure that the trials were connected by treatments using Stata/IC 11 (StataCorp LP) (see Appendix 9 for the Stata commands used). We planned to apply network meta-analysis to each connected network. We planned to conduct a Bayesian network meta-analysis using the Markov chain Monte Carlo method in WinBUGS 1.4. We planned to model the treatment contrast (e.g. log OR for binary outcomes, MD or SMD for continuous outcomes, rate ratio for count outcomes, HR for time-to-event outcomes) for any two interventions ('functional parameters') as a function of comparisons between each individual intervention and an arbitrarily selected reference group ('basic parameters') (Lu 2004). We planned to use inactive control (combination of placebo and no-intervention) as the reference group. We planned to perform the network analysis as per the guidance from the NICE DSU documents (Dias 2013). We planned to perform the network meta-analysis using arm level data. Further details of the codes we planned to use and the technical details of how we planned to perform the analysis are shown in Appendix 10 and Appendix 11. In short, we planned to use three chains and a burn in of 10,000 simulations to ensure convergence, and to obtain the posterior estimates after a further 20,000 simulations. We planned to run the fixed-effect and random-effects models (assuming homogeneous between-trial variance across comparisons) for each outcome. We planned to choose the fixed-effect model if it resulted in an equivalent or better fit (assessed by residual deviances, number of effective parameters, and deviance information criterion (DIC)) than the random-effects model. A lower DIC indicates a better model fit. We planned to use the random-effects model if it resulted in a better model fit as indicated by a DIC lower than that of the fixed-effect model by at least three. In addition, we planned to perform a random-effects inconsistency model suggested by NICE DSU (Dias 2012b). We planned to consider the inconsistency model to be better than the

random-effects consistency model (standard random-effects network meta-analysis model) if the model fit of the inconsistency model (as indicated by DIC) was at least three lower than the random-effects consistency model.

Figure 9. Network plot showing the treatment comparisons that included short-term mortality. The circles represent treatments while the lines represent the comparisons between the treatments.



For multi-arm trials, one can enter the data from all the arms in a trial as: the number of people with events and the number of people exposed to the event, using the binomial likelihood and logit link for binary outcomes; the mean and standard error using the normal likelihood and identity link for continuous outcomes requiring calculation of the mean difference; the mean and standard error of the treatment differences using the normal likelihood and identity link for continuous outcomes requiring calculation of the standardised mean difference; the number of events and the number of people exposed to the event using the Poisson likelihood and log link for count outcomes; the follow-up time in the study, number of people with the event and the number of people exposed to the event using the binomial likelihood and cloglog link for time-to-event outcomes. We planned to report the treatment contrasts (e.g. log ORs for binary outcomes, MDs for continuous outcomes, and so on) of the different treatments in relation to the reference treatment (inactive intervention i.e. combined placebo and no-intervention), the residual deviances, number of effective parameters, and DIC for the fixed-effect model and the random-effects model for each outcome. We also planned to report the parameters used to assess the model fit (i.e. residual deviances, number of effective parameters, and DIC) for the inconsistency model for all the outcomes and the between-trial variance for the random-effects model (Dias 2012a; Dias 2012b). If the inconsistency model resulted in a better model fit than consistency models, the transitivity assumption is likely to be untrue and the effect estimates obtained may not be reliable. We planned to highlight such outcomes where the inconsistency model results in a better model fit than consistency models.

We found significant clinical heterogeneity in the type of participants included under the different comparisons. To overcome the heterogeneity in the type of people included in different comparisons (See 'Included studies') we planned to perform a separate network

meta-analysis for interventions for mild pancreatitis separately from moderately severe or severe pancreatitis. This is because mild pancreatitis has no local or systemic complications and combining participants with mild and severe acute pancreatitis in the same network meta-analysis may violate the transitivity assumption (the assumption that the participants included in the different studies with different treatments can be considered to be a part of a multi-arm randomised controlled trial - i.e. they should be reasonably similar in characteristics). We then planned to assess inconsistency again. However, this was not appropriate in the subgroup of severe acute pancreatitis because of the absence of any comparison in which direct and indirect comparison was available. If there was no evidence of inconsistency in the revised analysis, we planned to present the results of the analysis for mild and moderate or severe acute pancreatitis separately. If there was persistent evidence of inconsistency, we planned to present the results from the direct comparison in the 'Summary of findings' table.

We planned to calculate the 95% CrIs of treatment effects (e.g. ORs for binary outcomes, MDs for continuous outcomes, and so on) in the Bayesian meta-analysis, which is similar in use to the 95% confidence intervals in the frequentist meta-analysis. These are the 2.5^{th} percentile and 97.5^{th} percentiles of the simulations. We planned to report the mean effect estimate and the 95% CrI for each pair-wise comparison in a table. We also planned to estimate the probability that each intervention ranks at one of the possible positions, and have presented this information in graphs. It should be noted that a less than 90% probability that the treatment is the best treatment is unreliable (i.e. one should not conclude that the treatment is the best treatment for that outcome if the probability of it being the best treatment is less than 90%) (Dias 2012a). We also planned to present the cumulative probability of the treatment ranks (i.e. the probability that the treatment is within the top two, the probability that the treatment is within the top three, etc.) in graphs. We also planned to plot the probability that each treatment is best for each of the different outcomes (rankograms) which are generally considered more informative (Dias 2012a; Salanti 2011). We planned to perform direct comparisons using the same codes. This would have allowed us to assess the heterogeneity in the comparisons and provide additional information in the 'Summary of findings' table. We also planned to use the Tau^2 statistic to measure heterogeneity among the trials in each analysis. The Tau^2 statistic provides a measure of the variability of the effect estimate across studies in a random-effects model (Higgins 2011). If we identified substantial heterogeneity, we planned to explore it by meta-regression. We also planned to assess the differences in the effect estimates between the subgroups using meta-regression for each source of heterogeneity (i.e. one analysis for each source of heterogeneity) with the help of the code shown in Appendix 12. We planned to perform the following subgroup analyses regardless of heterogeneity. We planned to calculate the interaction term (Dias 2012c). If the 95% CrI of the regression coefficient of the interaction term does not overlap zero, we considered this statistically significant.

In the presence of adequate data where authors report the outcomes of participants at multiple follow-up time points, we planned to follow the methods suggested by Lu 2007 to perform the meta-analysis.

We planned to use methods and recommendations described for grading network meta-analysis (Puhan 2014). This includes grading the quality for direct comparison, indirect comparison, and network meta-analysis and presenting the information in tabular format.

Appendix 8. WHO ICTRP search strategy

Acute pancreatitis

Appendix 9. Stata code for network plot

networkplot t1 t2, labels(T1 T2 T3 ..)

Appendix 10. Winbugs code

Binary outcome

Binary outcome - fixed-effect model

```
# Binomial likelihood, logit link
# Fixed effects model
model{ # *** PROGRAM STARTS
```

```
for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor
logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Binary outcome - random-effects model

```
# Binomial likelihood, logit link
# Random effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }
# summed residual deviance contribution for this trial
```

```
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}

} # *** PROGRAM ENDS
```

Binary outcome - inconsistency model (random-effects)

```
# Binomial likelihood, logit link, inconsistency model
# Random effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH trials
delta[i,1]<-0 # treatment effect is zero in control arm
mu[i] ~ dnorm(0,.0001) # vague priors for trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
logit(p[i,k]) <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
```

```
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(d[t[i,1],t[i,k]] ,tau)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
for (c in 1:(nt-1)) { # priors for all mean treatment effects
for (k in (c+1):nt) { d[c,k] ~ dnorm(0,.0001) }
}
sd ~ dunif(0,5) # vague prior for between-trial standard deviation
var <- pow(sd,2) # between-trial variance
tau <- 1/var # between-trial precision
} # *** PROGRAM ENDS
```

Continuous outcome (mean difference)

Continuous outcome (mean difference) - fixed-effect model

```
# Normal likelihood, identity link
# Fixed effect model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k])
# model for linear predictor
theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes lower is better
# rk[k] <- nt+1-rank(d[],k) # assumes lower outcome is worse
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Continuous outcome (mean difference) - random-effects model

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
y[i,k] ~ dnorm(theta[i,k],prec[i,k])
theta[i,k] <- mu[i] + delta[i,k] # model for linear predictor
#Deviance contribution
dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
}
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific MD distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of MD distributions, with multi-arm trial correction
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of MD distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- rank(d[],k) # assumes lower is better
# rk[k] <- nt+1-rank(d[],k) # assumes lower outcome is worse
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Continuous outcome (standardised mean difference)

The standardised mean difference and its standard error for each treatment comparison will be calculated using the statistical algorithms used by RevMan.

Continuous outcome (standardised mean difference) - fixed-effect model

```
# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns2) { # LOOP THROUGH 2-ARM STUDIES
y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
#Deviance contribution for trial i
resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
}
for(i in (ns2+1):(ns2+ns3)) { # LOOP THROUGH THREE-ARM STUDIES
for (k in 1:(na[i]-1)) { # set variance-covariance matrix
for (j in 1:(na[i]-1)) {
Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
}
}
Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,]) #Precision matrix
# multivariate normal likelihood for 3-arm trials
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
for (k in 1:(na[i]-1)){ # multiply vector & matrix
ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
}
resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
}
for(i in 1:(ns2+ns3)){ # LOOP THROUGH ALL STUDIES
for (k in 2:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
delta[i,k] <- d[t[i,k]] - d[t[i,1]]
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- nt+1-rank(d[],k) # assumes higher HRQoL is "good"
#rk[k] <- rank(d[],k) # assumes higher outcome is "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Continuous outcome (standardised mean difference) - random-effects model

```
# Normal likelihood, identity link
# Trial-level data given as treatment differences
# Random effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns2) { # LOOP THROUGH 2-ARM STUDIES
y[i,2] ~ dnorm(delta[i,2],prec[i,2]) # normal likelihood for 2-arm trials
```

```
#Deviance contribution for trial i
resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2]
}
for(i in (ns2+1):(ns2+ns3)) { # LOOP THROUGH THREE-ARM STUDIES
for (k in 1:(na[i]-1)) { # set variance-covariance matrix
for (j in 1:(na[i]-1)) {
Sigma[i,j,k] <- V[i]*(1-equals(j,k)) + var[i,k+1]*equals(j,k)
}
}
Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,]) #Precision matrix
# multivariate normal likelihood for 3-arm trials
y[i,2:na[i]] ~ dmnorm(delta[i,2:na[i]],Omega[i,1:(na[i]-1),1:(na[i]-1)])
#Deviance contribution for trial i
for (k in 1:(na[i]-1)){ # multiply vector & matrix
ydiff[i,k]<- y[i,(k+1)] - delta[i,(k+1)]
z[i,k]<- inprod2(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
}
resdev[i]<- inprod2(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)])
}
for(i in 1:(ns2+ns3)){ # LOOP THROUGH ALL STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
for (k in 2:na[i]) { # LOOP THROUGH ARMS
var[i,k] <- pow(se[i,k],2) # calculate variances
prec[i,k] <- 1/var[i,k] # set precisions
}
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific SMD distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of random effects distributions, with multi-arm trial correction
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of random effects distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# ranking on relative scale
for (k in 1:nt) {
rk[k] <- nt+1-rank(d[],k) # assumes higher HRQoL is "good"
# rk[k] <- rank(d[],k) # assumes higher outcome is "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Count outcome

Count outcome - fixed-effect model

```
# Poisson likelihood, log link
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dpois(theta[i,k]) # Poisson likelihood
theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
# model for linear predictor
log(lambda[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k])) }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }

# pairwise RRs and LRRs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
rater[c,k] <- exp(d[k] - d[c])
lrater[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are “good”
rk[k] <- rank(d[],k) # assumes events are “bad”
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Count outcome - random-effects model

```
# Poisson likelihood, log link
# Random effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dpois(theta[i,k]) # Poisson likelihood
theta[i,k] <- lambda[i,k]*E[i,k] # failure rate * exposure
# model for linear predictor
```

```
log(lambda[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
dev[i,k] <- 2*((theta[i,k]-r[i,k]) + r[i,k]*log(r[i,k]/theta[i,k])) }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)

# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- nt+1-rank(d[],k) # assumes events are "good"
rk[k] <- rank(d[],k) # assumes events are "bad"
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}

} # *** PROGRAM ENDS
```

Time-to-event outcome

Time-to-event outcome - fixed-effect model

```
# Binomial likelihood, cloglog link
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
```

```
r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
cloglog(p[i,k]) <- log(time[i]) + mu[i] + d[t[i,k]] - d[t[i,1]]
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))  }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- rank(d[],k) # assumes lower is better
rk[k] <- nt+1-rank(d[],k) # assumes lower outcome is worse
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Time-to-event outcome - random-effects model

```
# Binomial likelihood, cloglog link
# Random effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))  }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
```

```
}
}
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# ranking on relative scale
for (k in 1:nt) {
# rk[k] <- rank(d[],k) # assumes lower is better
rk[k] <- nt+1-rank(d[],k) # assumes lower outcome is worse
best[k] <- equals(rk[k],1) #calculate probability that treat k is best
for (h in 1:nt){ prob[h,k] <- equals(rk[k],h) } # calculates probability that treat k is h-th best
}
} # *** PROGRAM ENDS
```

Appendix 11. Technical details of network meta-analysis

The posterior probabilities (effect estimates or values) of the treatment contrast (i.e. log odds ratio, mean difference, standardised mean difference, rate ratio, or hazard ratio) may vary depending on the initial values to start the simulations. In order to control the random error due to the choice of initial values, we performed the network analysis for three different initial values (priors) as per the guidance from The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) documents (Dias 2013). If the results from three different priors are similar (convergence), then the results are reliable. It is important to discard the results of the initial simulations as they can be significantly affected by the choice of the priors and only include the results of the simulations obtained after the convergence. The discarding of the initial simulations is called 'burn in'. We ran the models for all outcomes for 10,000 simulations for 'burn in' for three different chains (a set of initial values). We ran the models for another 20,000 simulations to obtain the effect estimates. We obtained the effect estimates from the results of all the three chains (different initial values). We also ensured that the results in the three different chains are similar in order to control for random error due to the choice of initial values. This was done in addition to the visual inspection of convergence obtained after simulations in the burn in.

We ran three different models for each outcome. The fixed-effect model assumes that the treatment effect is the same across studies. The random-effects consistency model assumes that the treatment effect is distributed normally across the studies but assumes that the transitivity assumption is satisfied (i.e. the population studied, the definition of outcomes, and the methods used were similar across studies and that there is consistency between the direct comparison and indirect comparison). A random-effects inconsistency model does not make the transitivity assumption. If the inconsistency model resulted in a better model fit than the consistency model, the results of the network meta-analysis can be unreliable and so should be interpreted with extreme caution. If there is evidence of inconsistency, we planned to identify areas in the network where substantial inconsistency might be present in terms of clinical and methodological diversities between trials and, when appropriate, limit the network meta-analysis to a more compatible subset of trials. The choice of the model between fixed-effect and random-effects was based on the model fit as per the guidelines of the NICE TSU (Dias 2013). The model fit will be assessed by deviance residuals and Deviance Information Criteria (DIC) according to NICE TSU guidelines (Dias 2013). A difference of three or five in the DIC is not generally considered important (Dias 2012c). We used the simpler model, i.e. fixed-effect model if the DIC are similar between the fixed-effect and the random-effects models. We used the random-effects model if it results in a better model fit as indicated by a DIC lower than that of the fixed-effect model by at least three.

We planned to calculate the effect estimates of the treatment and the 95% credible intervals using the following additional code.

```
# pairwise ORs and MD for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
OR[c,k] <- exp(d[k] - d[c])
#MD[c,k] <- (d[k]-d[c])
}
}
```

where c indicates control group, k indicates intervention group, OR indicates odds ratio or other ratios, and MD indicates mean difference or other differences.

Appendix 12. Winbugs code for subgroup analysis

Categorical covariate

Only the code for random-effects model for a binary outcome is shown. The differences in the code are underlined. We planned to make similar changes for other outcomes.

```
# Binomial likelihood, logit link, subgroup
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor, covariate effect relative to treat in arm 1
logit(p[i,k]) <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]]) * x[i]
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
beta[1] <- 0 # covariate effect is zero for reference treatment
for (k in 2:nt){ # LOOP THROUGH TREATMENTS
d[k] ~ dnorm(0,.0001) # vague priors for treatment effects
beta[k] <- B[k] # exchangeable covariate effect
B[k] ~ dnorm(0,.0001) # vague prior for covariate effect
}
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# treatment effect when covariate = z[j]
for (k in 1:nt){ # LOOP THROUGH TREATMENTS
```

```
for (j in 1:nz) { dz[j,k] <- d[k] + (beta[k]-beta[1])*z[j] }
}
# *** PROGRAM ENDS
```

Continuous covariate

```
# Binomial likelihood, logit link, continuous covariate
# Random effects model for multi-arm trials
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
w[i,1] <- 0 # adjustment for multi-arm trials is zero for control arm
delta[i,1] <- 0 # treatment effect is zero for control arm
mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
for (k in 1:na[i]) { # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
# model for linear predictor, covariate effect relative to treat in arm 1
logit(p[i,k]) <- mu[i] + delta[i,k] + (beta[t[i,k]]-beta[t[i,1]]) * (x[i]-mx)
rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))) }
# summed residual deviance contribution for this trial
resdev[i] <- sum(dev[i,1:na[i]])
for (k in 2:na[i]) { # LOOP THROUGH ARMS
# trial-specific LOR distributions
delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
sw[i,k] <- sum(w[i,1:k-1])/(k-1)
}
}
totresdev <- sum(resdev[]) # Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
beta[1] <- 0 # covariate effect is zero for reference treatment
for (k in 2:nt){ # LOOP THROUGH TREATMENTS
d[k] ~ dnorm(0,.0001) # vague priors for treatment effects
beta[k] <- B[k] # exchangeable covariate effect
B[k] ~ dnorm(0,.0001) # vague prior for covariate effect
}
sd ~ dunif(0,5) # vague prior for between-trial SD
tau <- pow(sd,-2) # between-trial precision = (1/between-trial variance)
# treatment effect when covariate = z[j] (un-centring treatment effects)
for (k in 1:nt){
for (j in 1:nz) { dz[j,k] <- d[k] - (beta[k]-beta[1])*(mx-z[j]) }
}
# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
```

```
# at mean value of covariate
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
# at covariate=z[j]
for (j in 1:nz) {
orz[j,c,k] <- exp(dz[j,k] - dz[j,c])
lorz[j,c,k] <- (dz[j,k]-dz[j,c])
}
}
}
} # *** PROGRAM ENDS
```

CONTRIBUTIONS OF AUTHORS

EM selected studies and extracted the data for more than half the studies identified by screening and completed the tables detailing the characteristics of included and excluded studies. FF helped EM with data extraction. RK selected studies and extracted the data for the remaining studies. AB screened the references. SP and BRD critically commented on the review. KG screened the references, selected studies, extracted the data, analysed the data, and wrote the review.

DECLARATIONS OF INTEREST

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We did not combine somatostatin and somatostatin analogues. This is to avoid further clinical heterogeneity.
2. We reported sepsis separately under serious adverse events due to its importance as an important clinical outcome.