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# Pharmacological interventions for acute pancreatitis (Review)

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# Pharmacological interventions for acute pancreatitis

Elisabetta Moggia[1], Rahul Koti[2], Ajay P Belgaumkar[3], Federico Fazio[4], Stephen P Pereira[5], Brian R Davidson[2], Kurinchi Selvan Gurusamy[2]

[1]Department of General and Digestive Surgery, IRCCS Humanitas Research Hospital, Milan, Italy. [2]Department of Surgery, Royal Free Campus, UCL Medical School, London, UK. [3]Dept of Upper GI Surgery, Ashford and St Peter's NHS Trust, Chertsey, UK. [4]HPB and Liver Transplant Surgery, Royal Free Hospital, NHS Foundation Trust, London, UK. [5]UCL Institute for Liver and Digestive Health, Royal Free Hospital Campus, London, UK

**Contact:** Kurinchi Selvan Gurusamy, Department of Surgery, Royal Free Campus, UCL Medical School, Royal Free Hospital, Pond Street, London, NW3 2QG, UK. k.gurusamy@ucl.ac.uk.

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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. Summary of findings (mortality)

**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<br>Inactive control | Corresponding risk<br>Various treatments | | | |
| **Short-term mortality**<br>Follow-up: up to 3 months | **Antibiotics** | | **OR 0.81**<br>(0.57 to 1.15) | 1058<br>(17 studies) | ⊕⊖⊖⊖<br>**Very low** [a,b,c] |
| | **120 per 1000** | **99 per 1000**<br>(72 to 135) | | | |
| | **Antioxidants** | | **OR 2.01**<br>(0.53 to 7.56) | 163<br>(4 studies) | ⊕⊖⊖⊖<br>**Very low** [a,b,c] |
| | **120 per 1000** | **215 per 1000**<br>(68 to 508) | | | |
| | **Aprotinin** | | **OR 0.68**<br>(0.40 to 1.14) | 651<br>(7 studies) | ⊕⊖⊖⊖<br>**Very low** [a,b,c] |
| | **120 per 1000** | **85 per 1000**<br>(52 to 135) | | | |
| | **Calcitonin** | | **OR 0.55**<br>(0.15 to 2.00) | 125<br>(2 studies) | ⊕⊖⊖⊖<br>**Very low** [1,2,3] |
| | **120 per 1000** | **69 per 1000**<br>(20 to 214) | | | |
| | **Cimetidine** | | **OR 1.00**<br>(0.06 to 17.18) | 40<br>(1 study) | ⊕⊖⊖⊖<br>**Very low** [a,b,c] |
| | **120 per 1000** | **120 per 1000**<br>(8 to 701) | | | |
| | **EDTA** | | **OR 0.94**<br>(0.12 to 7.08) | 64<br>(1 study) | ⊕⊖⊖⊖<br>**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 $I^2$.

## Summary of findings 2. Summary of findings (other primary outcomes)

| **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)**<br><br>Follow-up: up to 3 months | **Antibiotics** | | **OR 0.65**<br>(0.37 to 1.15) | 304<br>(5 studies) | ⊕⊖⊖⊖<br>**Very low** a,b,c |
| | **147 per 1000** | **101 per 1000**<br>(60 to 166) | | | |
| | **Antioxidants** | | **OR 1.98**<br>(0.48 to 8.13) | 82<br>(2 studies) | ⊕⊖⊖⊖<br>**Very low** a,b,c |
| | **147 per 1000** | **255 per 1000**<br>(77 to 584) | | | |
| | **EDTA** | | **OR 0.52**<br>(0.11 to 2.39) | 64<br>(1 study) | ⊕⊖⊖⊖<br>**Very low** a,b,c |
| | **147 per 1000** | **83 per 1000**<br>(19 to 292) | | | |
| | **Gabexate** | | **OR 1.31**<br>(0.31 to 5.60) | 201<br>(2 studies) | ⊕⊖⊖⊖<br>**Very low** a,b,c |
| | **147 per 1000** | **185 per 1000**<br>(51 to 492) | | | |
| | **Glucagon** | | **OR 0.29**<br>(0.01 to 7.46) | 127<br>(2 studies) | ⊕⊖⊖⊖<br>**Very low** a,b,c |
| | **147 per 1000** | **48 per 1000**<br>(2 to 563) | | | |
| | **Octreotide** | | **OR 1.73**<br>(0.61 to 4.93) | 58<br>(1 study) | ⊕⊖⊖⊖<br>**Very low** a,b,c,d |
| | **147 per 1000** | **230 per 1000**<br>(95 to 460) | | | |
| | **Somatostatin** | | **OR 1.07**<br>(0.35 to 3.27) | 111<br>(2 studies) | ⊕⊖⊖⊖<br>**Very low** a,b,c,d |
| | **147 per 1000** | **156 per 1000** | | | |

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| | | (57 to 361) | | | |
| **Serious adverse events (number)**<br><br>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 |

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|---|---|---|---|---|---|
| | **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**<br>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**<br><br>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**<br><br>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 $I^2$.

# 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.
   a. Short-term mortality (in-hospital mortality or mortality within six months).
   b. 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).
   a. 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).
   b. Organ failure (however reported by authors).
   c. Infected necrotising pancreatitis (cytology or positive culture).
   d. Sepsis (however reported by authors).
3. Health-related quality of life (using any validated scale).
   a. Short-term (four weeks to three months).
   b. Medium-term (three months to one year).
   c. Long-term (more than one year).
4. Health-related quality of life (using any validated scale).
   a. Short-term (four weeks to three months).

b. Medium-term (three months to one year).
c. 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).
   a. Length of hospital stay (including the index admission for acute pancreatitis and any disease-related or intervention-related readmissions including those for recurrent episodes).
   b. Length of intensive care unit (ICU) stay (including the index admission for acute pancreatitis and any disease- or intervention-related readmissions).
   c. Requirement for additional invasive intervention such as necrosectomy for pancreatic necrosis, endoscopic or radiological drainage of collections.
   d. Time to return to normal activity (return to pre-acute pancreatitis episode mobility without any additional caregiver support).
   e. 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.

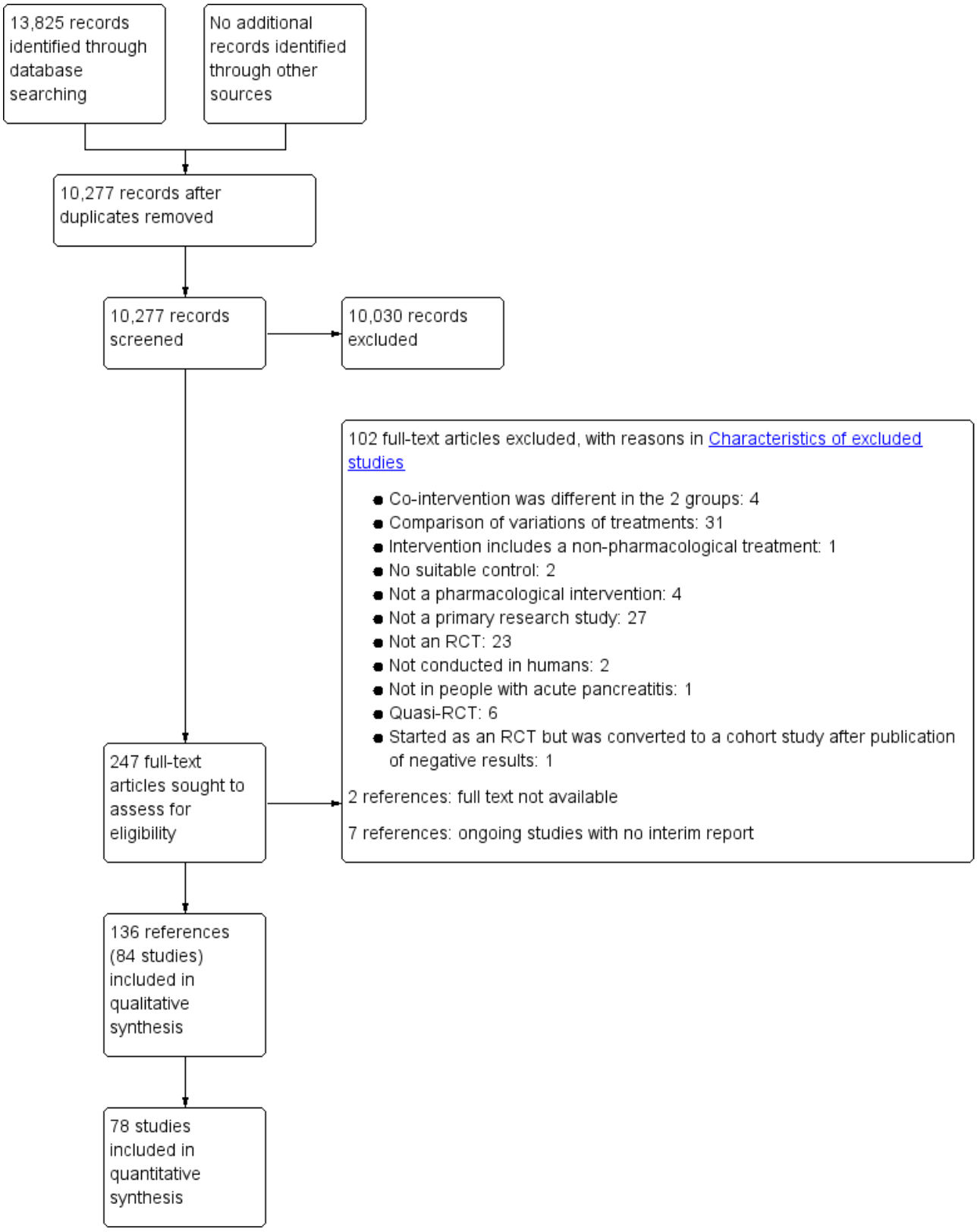
We searched for errata or retractions from eligible trials on www.ncbi.nlm.nih.gov/pubmed on 7 October 2016.

## 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.**

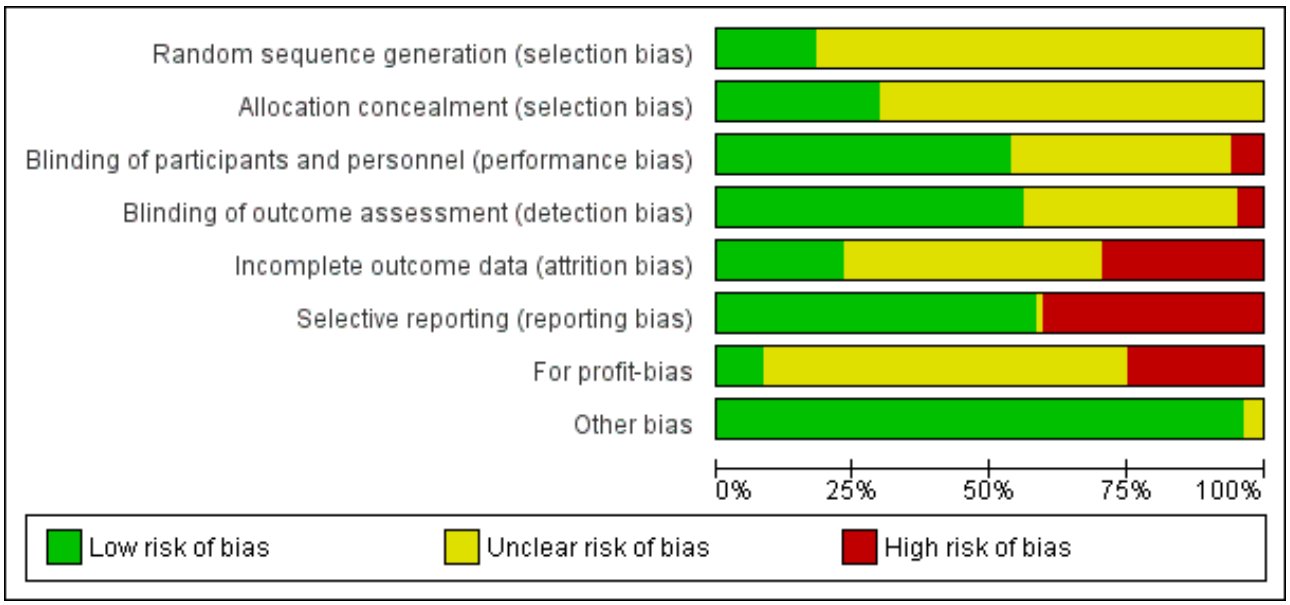


**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

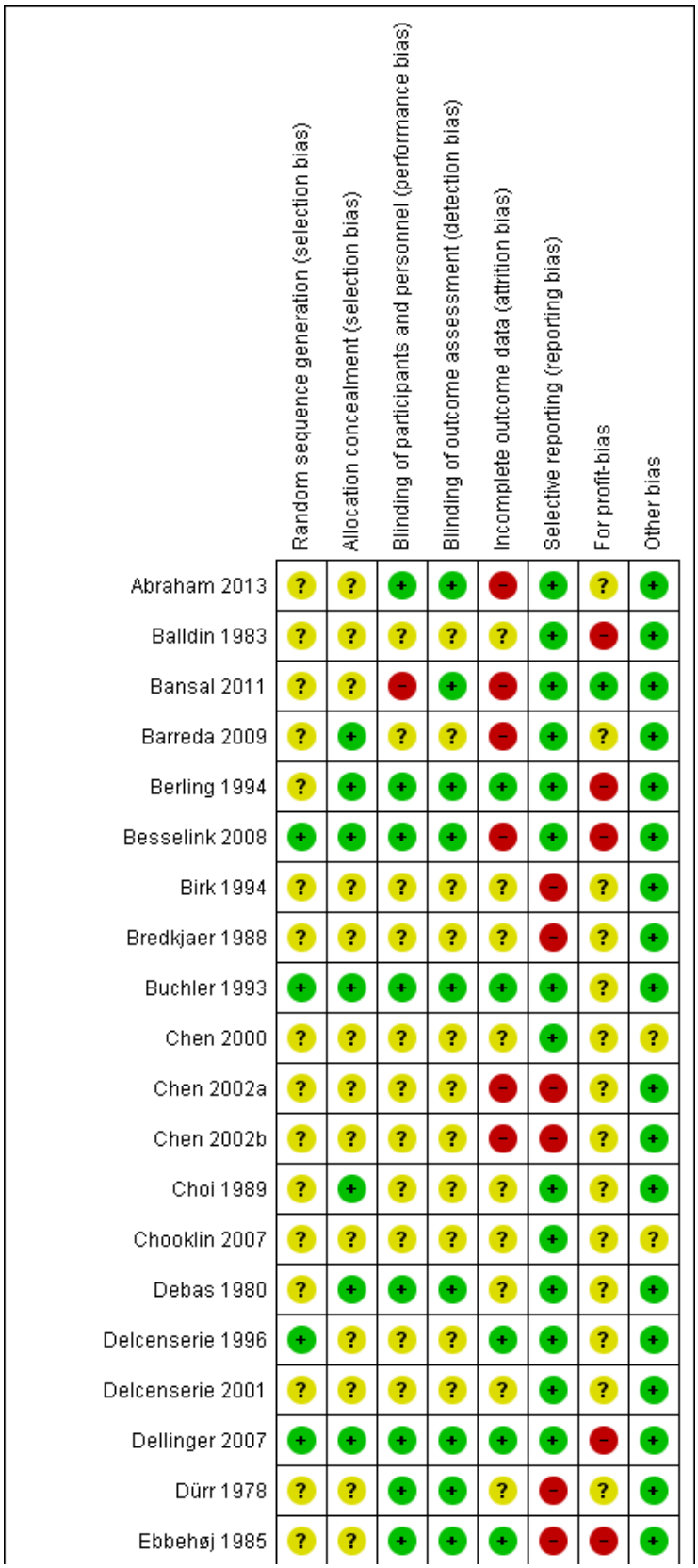


**Figure 3. (Continued)**

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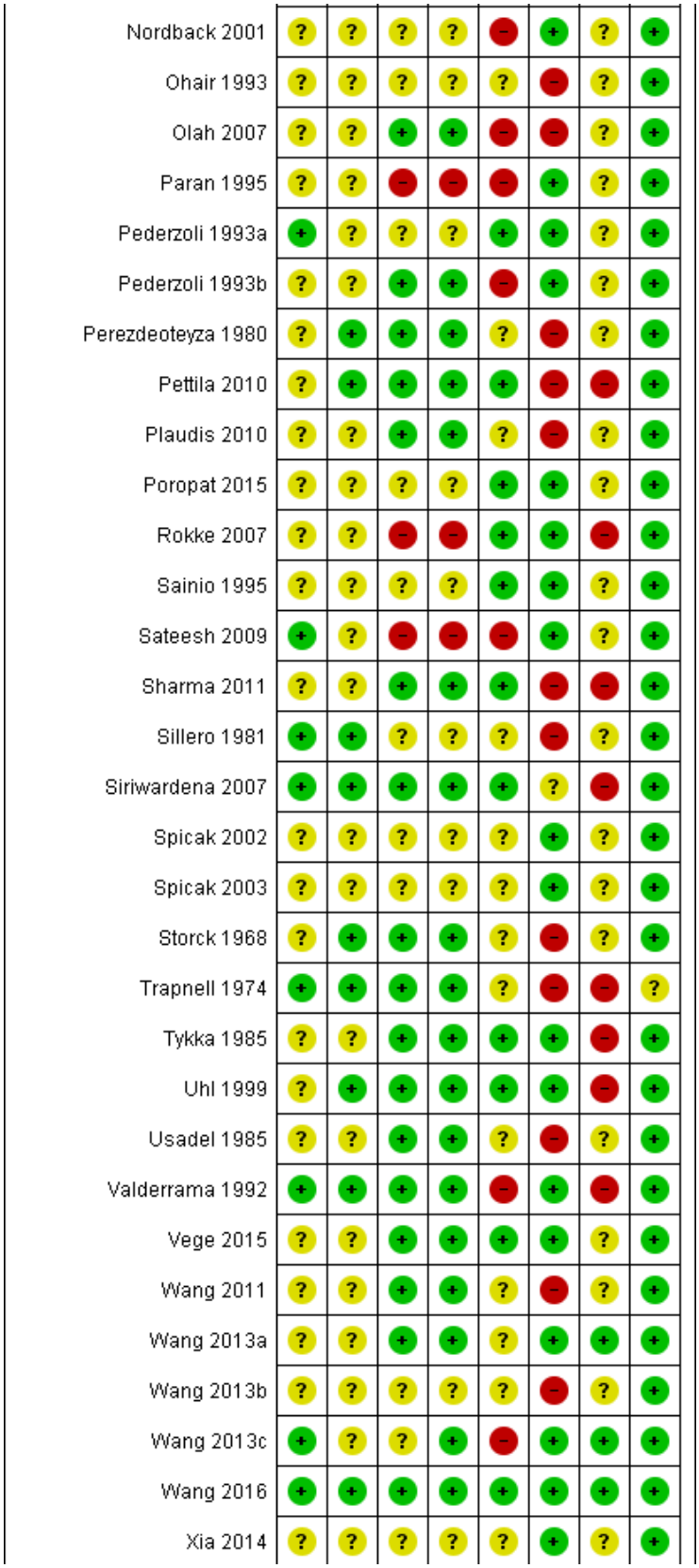
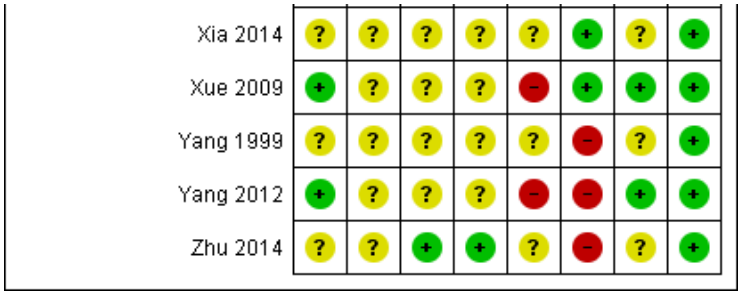


**Figure 3. (Continued)**




### 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.**

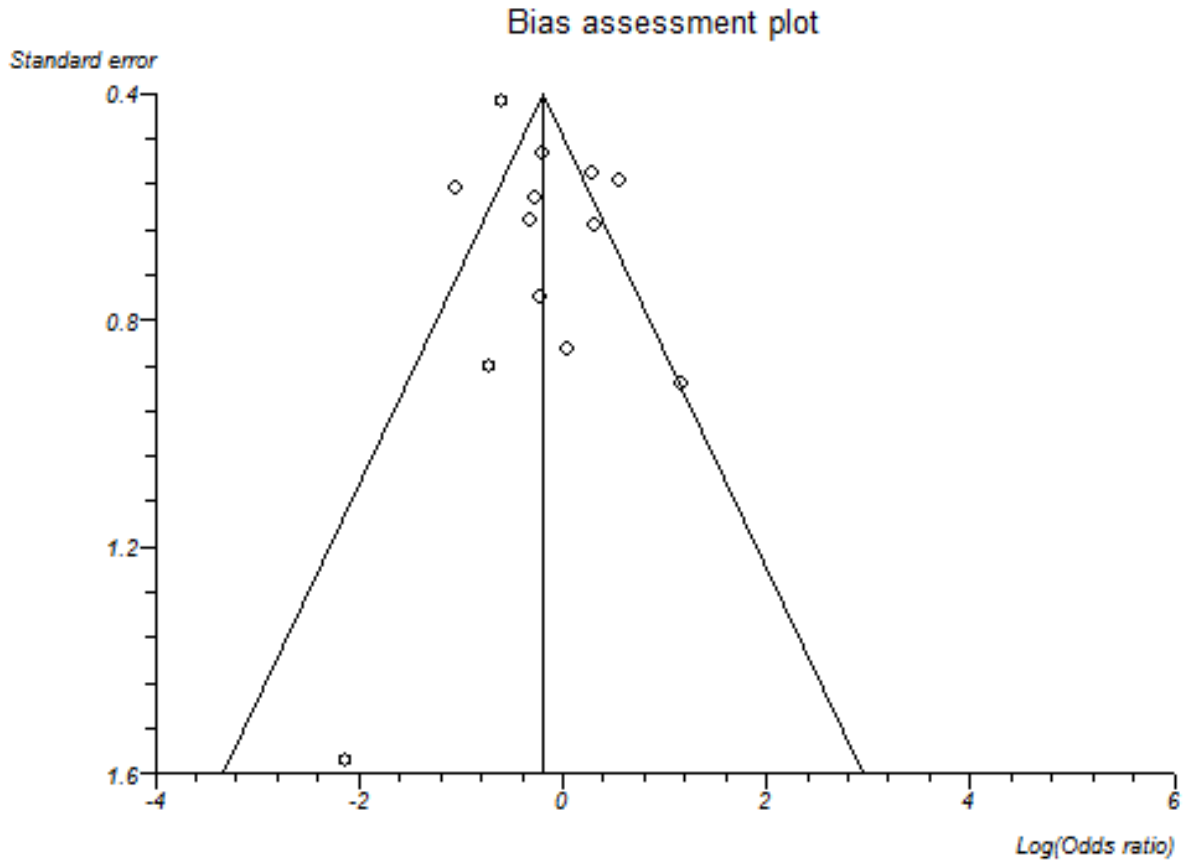


**Figure 7. Funnel plot of serious adverse events (number) indicating that trials with lower precision favoured antibiotics without matching trials with lower precision which showed no effect or favouring control.**

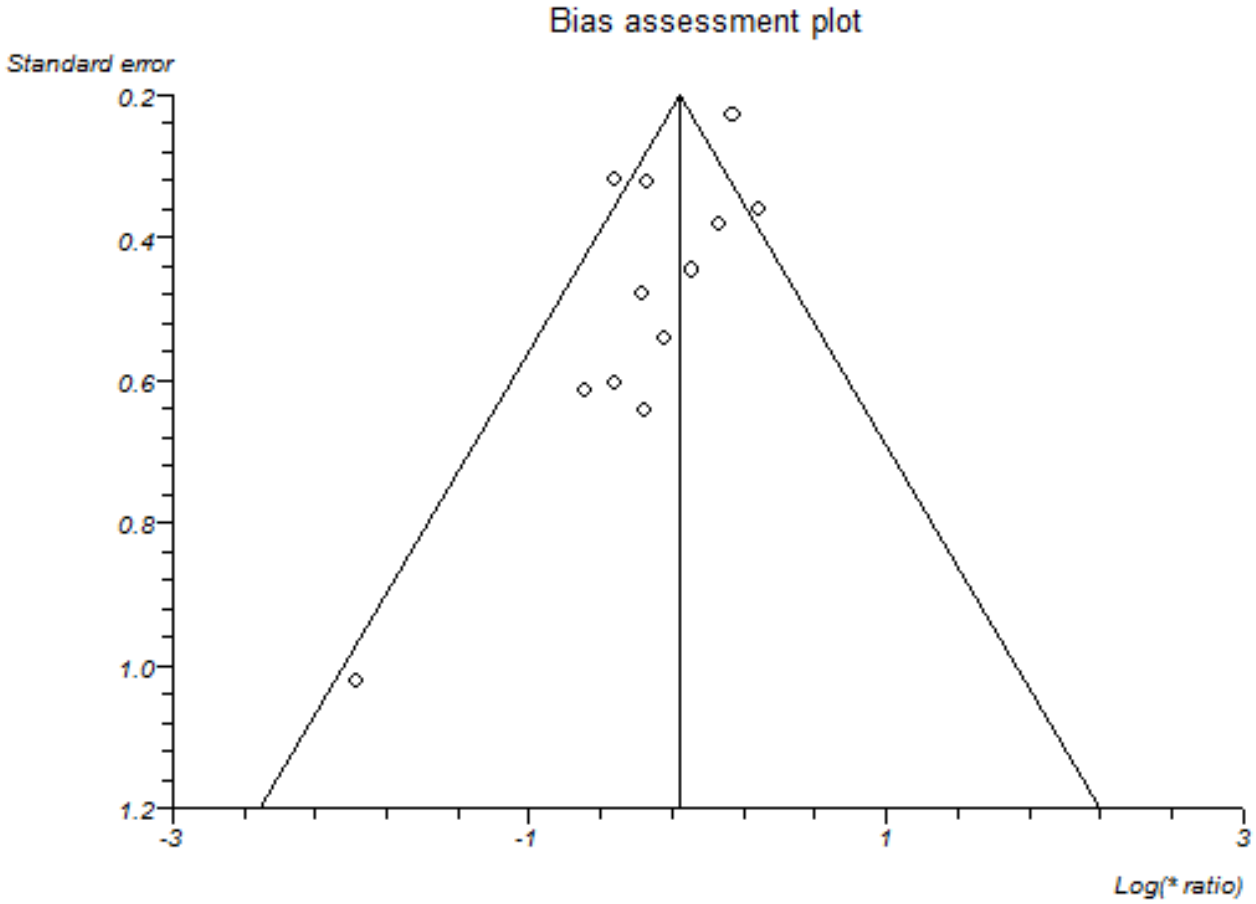
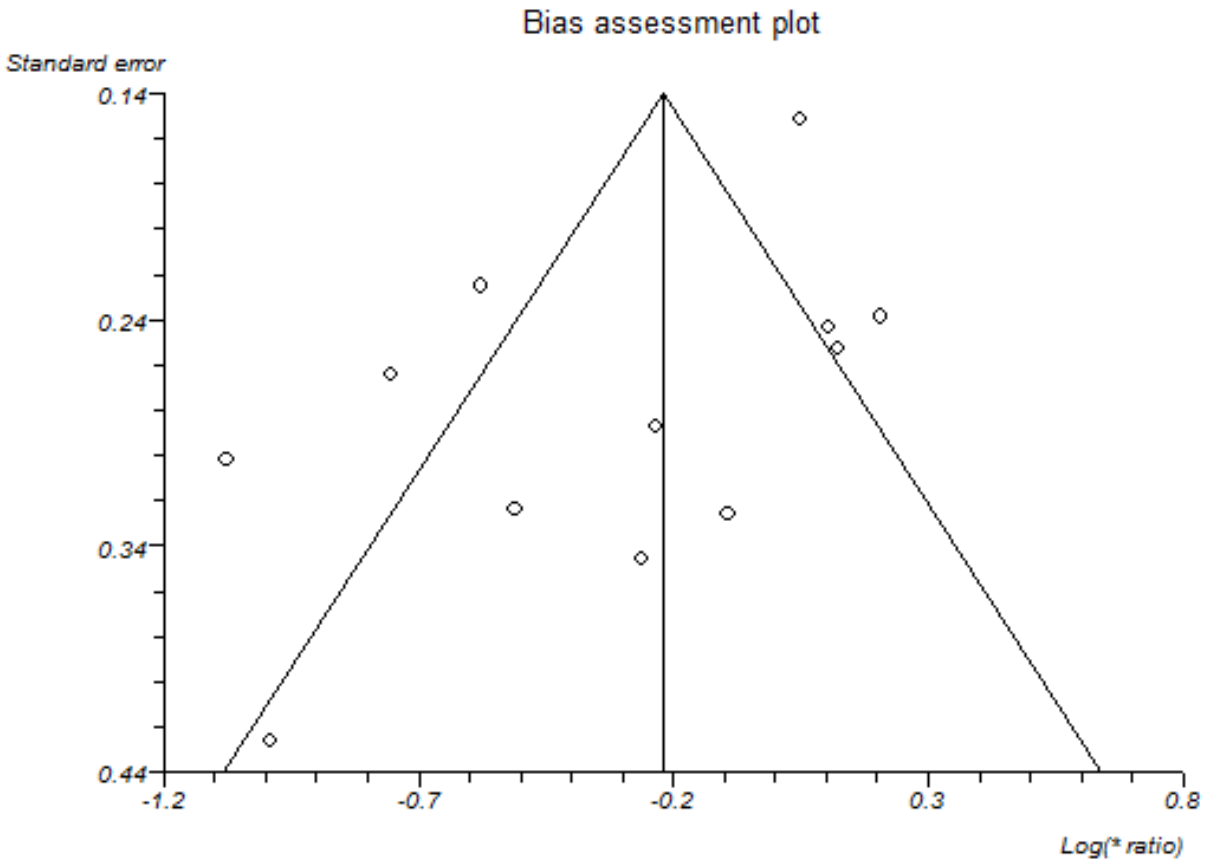


**Figure 8. Funnel plot of adverse events (number) indicating that trials with lower precision favoured antibiotics while trials with greater precision favoured control.**




## 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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**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<br>Number randomised: 135<br>Postrandomisation dropouts: 6 (4.4%)<br>Revised sample size: 129<br>Average age: 39 years<br>Women: 13 (10.1%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 62 (48.1%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 67 (51.9%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: 0<br>Inclusion criteria<br>1. Adults (18-70 years)<br>2. Acute pancreatitis (mild or severe)<br>3. Elevated C-reactive protein |
| Interventions | Group 1: ulinastatin (n = 30), 200,000 IU twice daily for 5 days |

**Abraham 2013** *(Continued)*

| | |
|---|---|
| | Group 2: placebo (n = 32) |
| Outcomes | Mortality, adverse events, organ failure, hospital stay<br>Follow-up: until discharge or maximum of 22 days |
| Notes | Reasons for postrandomisation dropouts: withdrew consent, screening error, died |

***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)<br>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)<br>All outcomes | Low risk | Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India". |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 55<br>Postrandomisation dropouts: not stated<br>Revised sample size: 55<br>Average age: not stated<br>Women: 15 (27.3%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 55 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: acute pancreatitis undergoing peritoneal lavage |

**Balldin 1983** *(Continued)*

| | |
|---|---|
| Interventions | Group 1: aprotinin (n = 26), 500,000 KIU in lavage fluid every 2 h for an average of 2.7 days<br>Group 2: no intervention (n = 29) |
| Outcomes | Mortality, serious adverse events, adverse events, sepsis, hospital stay<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 44<br>Postrandomisation dropouts: 5 (11.4%)<br>Revised sample size: 39<br>Average age: 39 years<br>Women: 9 (23.1%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated |

**Bansal 2011** *(Continued)*

| | |
|---|---|
| | Mild pancreatitis: not stated<br><br>Moderate pancreatitis: not stated<br><br>Severe pancreatitis: not stated<br><br>Persistent organ failure: not stated<br><br>Infected pancreatitis: not stated<br><br>Inclusion criteria: people with acute pancreatitis within 96 h of onset of symptoms<br><br>Exclusion criteria<br><br>1. Age <18 or >75 years<br>2. Pregnancy<br>3. Acute pancreatitis secondary to surgery, trauma, or malignancy<br>4. Psychosis (except alcoholic delirium)<br>5. Need for urgent therapeutic intervention (endoscopic papillotomy, cholecystectomy, and/or choledochotomy)<br>6. Those enrolled in any other trial<br>7. People with serious diseases of the heart, brain, liver, or kidney<br>8. Peptic ulcer<br>9. Autoimmune disease |
| 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<br>Group 2: no intervention (n = 20) |
| Outcomes | Mortality, serious adverse events, adverse events, organ failure, hospital stay<br><br>Follow-up: until discharge |
| Notes | Reasons for postrandomisation dropouts: lost to follow-up, withdrew consent |

***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)<br>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)<br>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)<br>All outcomes | High risk | Comment: there were postrandomisation dropouts. |

**Bansal 2011** *(Continued)*

| | | |
|---|---|---|
| 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<br>Number randomised: 80<br>Postrandomisation dropouts: 22 (27.5%)<br>Revised sample size: 58<br>Average age: 50 years<br>Women: 24 (41.4%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 58 (100%)<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with necrotising pancreatitis<br>Exclusion criteria<br>1. Treated in other institutions for more than 4 days<br>2. Received other prophylactic antibiotics |
| Interventions | Group 1: antibiotics (n = 24): imipenem 500 mg 4 times daily for 14 days<br>Group 2: no intervention (n = 34) |
| Outcomes | Mortality, serious adverse events, adverse events, infected pancreatic necrosis, requirement for additional intervention, length of hospital stay<br>Follow-up: 2 months |
| Notes | Reasons for postrandomisation dropouts: protocol violations |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Barreda 2009** *(Continued)*

| | | |
|---|---|---|
| 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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 48<br>Postrandomisation dropouts: not stated<br>Revised sample size: 48<br>Average age: 56 years<br>Women: 17 (35.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 48 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: participants with acute severe pancreatitis with circulatory insufficiency or peritonitis<br>Exclusion criteria |

**Berling 1994** *(Continued)*

| | |
|---|---|
| | 1. People who had several surgeries before<br>2. Renal failure<br>3. Previous allergy to aprotinin or history of severe allergies<br>4. Age < 15 years<br>5. Pregnant women |
| Interventions | Group 1: aprotinin (n = 22), 20 million KIU in 7 lavages over 30 h<br>Group 2: no intervention (n = 26) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay, ICU stay<br><br>Follow-up: 1 month |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "prospective double-blind randomized multicenter trial" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "prospective double-blind randomized multicenter trial" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 298<br>Postrandomisation dropouts: 2 (0.7%)<br>Revised sample size: 296<br>Average age: 60 years<br>Women: 122 (41.2%) |

**Besselink 2008** *(Continued)*

| | |
|---|---|
| | Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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)<br>Group 2: placebo (n = 144) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, organ failure, infected pancreatic necrosis, hospital stay, ICU stay<br><br>Follow-up: 3 months |
| Notes | Reasons for postrandomisation dropouts: did not receive drug, wrong diagnosis of acute pancreatitis |

***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.". |
| 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)<br>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)<br>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)<br>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<br>Number randomised: 20<br>Postrandomisation dropouts: not stated |

**Birk 1994** *(Continued)*

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

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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 |

**Bredkjaer 1988** *(Continued)*

| | |
|---|---|
| | Number randomised: 66<br>Postrandomisation dropouts: 9 (13.6%)<br>Revised sample size: 57<br>Average age: not stated<br>Women: 26 (45.6%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br>Exclusion criteria:<br>1. Chronic pancreatitis<br>2. Previous pseudocyst<br>3. Malignancy<br>4. Gastroduodenal ulcer<br>5. Coagulation disease |
| Interventions | Group 1: NSAID (n = 27): indomethacin 100 mg rectal for 7 days<br>Group 2: placebo (n = 30) |
| Outcomes | The outcomes reported were: hospital stay<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: chronic pancreatitis, wrong diagnosis, death |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |

**Bredkjaer 1988** *(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 |

**Buchler 1993**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: Germany<br>Number randomised: 223<br>Postrandomisation dropouts: not stated<br>Revised sample size: 223<br>Average age: 50 years<br>Women: 87 (39%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with moderate or severe acute pancreatitis<br>Exclusion criteria<br>1. Pre-existing renal insufficiency<br>2. Age < 18 years<br>3. Pregnancy<br>4. Psychosis<br>5. Previous treatment with aprotinin, glucagon, calcitonin, or somatostatin<br>6. Previous participation in the study |
| Interventions | Group 1: gabexate mesilate (n = 115), 53 mg/kg/day for 7 days<br>Group 2: placebo (n = 108) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay<br>Follow-up: 3 months |

**Buchler 1993** *(Continued)*

| | |
|---|---|
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "randomized, double-blind trial" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "randomized, double-blind trial" |
| Incomplete outcome data (attrition bias)<br>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 |

**Chen 2000**

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

**Chen 2000** *(Continued)*

| | |
|---|---|
| | Follow-up: 3 months |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 68<br>Postrandomisation dropouts: 6 (8.8%)<br>Revised sample size: 62<br>Average age: 53 years<br>Women: 33 (53.2%)<br>Acute interstitial oedematous pancreatitis: 62 (100%)<br>Necrotising pancreatitis: 0 (0%)<br>Mild pancreatitis: 62 (100%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 0 (0%)<br>Persistent organ failure: 0 (0%)<br>Infected pancreatitis: not stated<br>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<br>Group 2: gabexate mesilate (n = 14), 100 mg twice daily for 3 days followed by once daily for 5 days |

**Chen 2002a** *(Continued)*

| | |
|---|---|
| Outcomes | Serious adverse events, adverse events<br>Follow-up: not stated (probably 2 weeks) |
| Notes | Reasons for postrandomisation dropouts: recent or current treatment with other drugs |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 26<br>Postrandomisation dropouts: 1 (3.8%)<br>Revised sample size: 25<br>Average age: 59 years<br>Women: 12 (48%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 15 (60%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 25 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with severe necrotising pancreatitis |

**Chen 2002b** *(Continued)*

| | |
|---|---|
| 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<br>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<br><br>Follow-up: not stated (probably 2 weeks) |
| Notes | Reasons for postrandomisation dropouts: death after starting treatment |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 71<br>Postrandomisation dropouts: not stated<br>Revised sample size: 71<br>Average age: 61 years<br>Women: 39 (54.9%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 15 (21.1%)<br>Persistent organ failure: not stated |

**Choi 1989** *(Continued)*

| | |
|---|---|
| | Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br><br>Exclusion criteria: people with acute pancreatitis caused by trauma, iatrogenic, or malignancy |
| Interventions | Group 1: somatostatin (n = 35), 250 µg bolus followed by 100 µg/h for 48 h<br>Group 2: no intervention (n = 36) |
| Outcomes | Mortality, serious adverse events, adverse events<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 34<br>Postrandomisation dropouts: not stated<br>Revised sample size: 34<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated |

**Chooklin 2007** *(Continued)*

| | |
|---|---|
| | Moderate pancreatitis: not stated<br>Severe pancreatitis: 34 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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)<br>Group 2: no intervention (n = 18) |
| Outcomes | None of the outcomes of interest were reported.<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 66<br>Postrandomisation dropouts: not stated<br>Revised sample size: 66<br>Average age: 53 years<br>Women: 25 (37.9%)<br>Acute interstitial oedematous pancreatitis: not stated |

**Debas 1980** *(Continued)*

| | |
|---|---|
| | Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: glucagon (n = 33), 1 mg every 3 h (duration not stated)<br>Group 2: placebo (n = 33) |
| Outcomes | Mortality, serious adverse events, adverse events, hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "[p]rospective randomized double-blind study" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "[p]rospective randomized double-blind study" |
| Incomplete outcome data (attrition bias)<br>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 |

**Delcenserie 1996**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: France<br><br>Number randomised: 23<br><br>Postrandomisation dropouts: 0 (0%) |

**Delcenserie 1996** *(Continued)*

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<br>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<br><br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias) | Unclear risk | Comment: this information was not available. |

**Delcenserie 1996** *(Continued)*

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

**Delcenserie 2001** *(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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 100<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 100<br>Average age: 50 years<br>Women: 30 (30%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 100 (100%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 100 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: 0<br>Inclusion criteria |

**Dellinger 2007** *(Continued)*

1. People with necrotising pancreatitis
2. Within 5 days of onset of symptoms

Exclusion criteria

1. People with concurrent pancreatic or peripancreatic infection
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)<br>Group 2: placebo (n = 50) |
| Outcomes | Mortality, serious adverse events, adverse events, infected pancreatic necrosis<br>Follow-up: 1.5 months |
| Notes | — |

***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)<br>All outcomes | Low risk | Quote: "[r]andomized, double-blind, placebo-controlled study" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "[r]andomized, double-blind, placebo-controlled study" |
| Incomplete outcome data (attrition bias)<br>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" |
| Other bias | Low risk | Comment: no other risk of bias |

**Dürr 1978**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: Germany<br>Number randomised: 69<br>Postrandomisation dropouts: not stated<br>Revised sample size: 69<br>Average age: 49 years<br>Women: 27 (39.1%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: placebo (n = 36) |
| Outcomes | Mortality, requirement for surgery, hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 30<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 30<br>Average age: 55 years<br>Women: 10 (33.3%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: NSAID (n = 14), indomethacin 50 mg PR twice daily for 7 days<br>Group 2: placebo (n = 16) |
| Outcomes | Hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Low risk | Quote: "[c]ontrolled double-blind trial". |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "[c]ontrolled double-blind trial". |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 62<br>Postrandomisation dropouts: 4 (6.5%)<br>Revised sample size: 58<br>Average age: 36 years<br>Women: 24 (41.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br>Exclusion criteria<br>1. History of blunt trauma<br>2. Previous history compatible with gallstones<br>3. Medications: steroids, thorazine, thiaziole diuretics<br>4. Parathyroid disease<br>5. Duodenal peptic ulcer disease<br>6. A source of fever, independent of the pancreatitis<br>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)<br>Group 2: no intervention (n = 27) |
| Outcomes | Mortality, adverse events, hospital stay<br>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***

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

**Finch 1976** *(Continued)*

| | | |
|---|---|---|
| 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."<br>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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 50<br>Postrandomisation dropouts: not stated<br>Revised sample size: 50<br>Average age: not stated<br>Women: 17 (34%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br>Exclusion criteria |

**Freise 1986** *(Continued)*

| | |
|---|---|
| | 1. Duration of symptoms more than 48 h<br>2. < 18 years<br>3. Pregnancy<br>4. Chronic renal insufficiency |
| Interventions | Group 1: gabexate mesilate (n = 25), 150 mg IV 3 times daily for 7 days<br>Group 2: placebo (n = 25) |
| Outcomes | Mortality, serious adverse events, adverse events, organ failure, sepsis<br>Follow-up: not stated |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 116<br>Postrandomisation dropouts: not stated<br>Revised sample size: 116<br>Average age: 57 years |

**Frulloni 1994** *(Continued)*

| | |
|---|---|
| | Women: 49 (42.2%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 116 (100%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with acute necrotising pancreatitis<br>2. Within 72 h of onset of symptoms<br>3. No skin sensitivity to aprotinin |
| Interventions | Group 1: gabexate mesilate (n = 65), 3 g/day for 7 days<br>Group 2: aprotinin (n = 51), 1.5 million KIU/day for 7 days |
| Outcomes | Mortality, serious adverse events, adverse events, sepsis<br>Follow-up: 3 months |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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 |

### Garcia-Barrasa 2009

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

***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)<br>All outcomes | Low risk | Quote: "[p]rospective, randomized, placebo-controlled, double-blind study" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "[p]rospective, randomized, placebo-controlled, double-blind study" |
| Incomplete outcome data (attrition bias)<br>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". |

**Garcia-Barrasa 2009** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | Comment: no other risk of bias |

**Gilsanz 1978**

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

***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" |

**Gilsanz 1978** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 63<br>Postrandomisation dropouts: not stated<br>Revised sample size: 63<br>Average age: 49 years<br>Women: 22 (34.9%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with first attack of acute pancreatitis<br>2. Within 24 h of onset of symptoms |
| Interventions | Group 1: somatostatin (n = 33), 250 µg/h for 3 days<br>Group 2: placebo (n = 30) |
| Outcomes | Mortality, serious adverse events, adverse events, hospital stay |

**Gjørup 1992** *(Continued)*

| | |
|---|---|
| | Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blinded trial" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blinded trial" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 94<br>Postrandomisation dropouts: not stated<br>Revised sample size: 94<br>Average age: 55 years<br>Women: 37 (39.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 29 (30.9%)<br>Moderate pancreatitis: 49 (52.1%)<br>Severe pancreatitis: 16 (17%) |

**Goebell 1979** *(Continued)*

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

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 162<br>Postrandomisation dropouts: 11 (6.8%) |

**Goebell 1988** *(Continued)*

| | |
|---|---|
| | Revised sample size: 151<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: placebo (n = 75) |
| Outcomes | Mortality, serious adverse events, requirement for surgery<br><br>Follow-up: 3 months |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 70 |

**Grupo Español 1996** *(Continued)*

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

***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)<br>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)<br>All outcomes | Low risk | Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India" |
| Incomplete outcome data (attrition bias)<br>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 |

**Guo 2015**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: China |

**Guo 2015** *(Continued)*

| | |
|---|---|
| | Number randomised: 120<br>Postrandomisation dropouts: not stated<br>Revised sample size: 120<br>Average age: 46 years<br>Women: 58 (48.3%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 120 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>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<br><br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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 |

**Hansky 1969**

| | |
|---|---|
| Methods | Randomised clinical trial |

**Hansky 1969** *(Continued)*

| | |
|---|---|
| Participants | Country: Australia<br>Number randomised: 24<br>Postrandomisation dropouts: not stated<br>Revised sample size: 24<br>Average age: not stated<br>Women: 7 (29.2%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 3 (12.5%)<br>Moderate pancreatitis: 15 (62.5%)<br>Severe pancreatitis: 6 (25%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: no intervention (n = 9) |
| Outcomes | Mortality, hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | High risk | Quote: "[t]he drug was not evaluated in a double-blind manner". |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "[t]he drug was not evaluated in a double-blind manner". |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 41<br>Postrandomisation dropouts: not stated<br>Revised sample size: 41<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 41 (100%).<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with severe acute pancreatitis |
| Interventions | Group 1: antibiotics (n = 20): meropenem 500 mg 3 times daily for 10 days<br>Group 2: no intervention (n = 21) |
| Outcomes | Mortality, adverse events, requirement for surgery, hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 161<br>Postrandomisation dropouts: not stated<br>Revised sample size: 161<br>Average age: 51 years<br>Women: 92 (57.1%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 60 (37.3%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br>Exclusion criteria<br>1. Post-traumatic pancreatitis<br>2. Postsurgical pancreatitis<br>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<br>Group 2: placebo (n = 81) |
| Outcomes | Mortality, serious adverse events, adverse events<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind trial". |
| Blinding of outcome assessment (detection bias) | Low risk | Quote: "double-blind trial". |

**Imrie 1978** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 50<br>Postrandomisation dropouts: not stated<br>Revised sample size: 50<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 29 (58%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 21 (42%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: aprotinin (n = 25), 2 million units KIU bolus followed by 400,000 KIU 4 h later<br>Group 2: placebo (n = 25) |
| Outcomes | Mortality<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind trial" |

**Imrie 1980** *(Continued)*

| | | |
|---|---|---|
| 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<br>Number randomised: 119<br>Postrandomisation dropouts: 5 (4.2%)<br>Revised sample size: 114<br>Average age: 47 years<br>Women: 27 (23.7%)<br>Acute interstitial oedematous pancreatitis: 38 (33.3%)<br>Necrotising pancreatitis: 76 (66.7%)<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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)<br>Group 2: placebo (n = 56) |
| Outcomes | Serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis, hospital stay, ICU stay<br><br>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***

| 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". |

**Isenmann 2004** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "double-blind trial" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind trial" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 291<br>Postrandomisation dropouts: 1 (0.3%)<br>Revised sample size: 290<br>Average age: 63 years<br>Women: 124 (42.8%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with predicted severe acute pancreatitis<br>2. Premenopausal women in whom pregnancy could not be excluded<br>3. Pancreatitis secondary to trauma, surgery, malignancy, or ERCP<br>4. Person unsuitable for ventilation<br>5. Other investigational agents in the last 3 years<br>6. People receiving oral anti-coagulant therapy |

**Johnson 2001** *(Continued)*

| | |
|---|---|
| | 7. People who had received lexipafant previously<br><br>Exclusion criteria: age < 18 or > 80 years |
| Interventions | Group 1: lexipafant (n = 151), 100 mg daily for 7 days<br>Group 2: placebo (n = 139) |
| Outcomes | Mortality, serious adverse events, adverse events, organ failure, sepsis, hospital stay, ICU stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: withdrew from the study |

***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)<br>All outcomes | Low risk | Quote: "double blind, placebo controlled, randomised, parallel group" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind, placebo controlled, randomised, parallel group" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 80<br>Postrandomisation dropouts: 9 (11.3%)<br>Revised sample size: 71<br>Average age: 46 years<br>Women: 28 (39.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated |

**Kalima 1980** *(Continued)*

| | |
|---|---|
| | Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: glucagon (n = 32), 7.5 mg twice daily for 4-5 days<br>Group 2: placebo (n = 29) |
| Outcomes | Mortality, serious adverse events, adverse events<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: underwent surgery, wrong diagnosis |

***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)<br>All outcomes | Unclear risk | Comment: although placebo was used, there was no mention of blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: although placebo was used, there was no mention of blinding. |
| Incomplete outcome data (attrition bias)<br>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<br><br>Number randomised: 83<br><br>Postrandomisation dropouts: not stated<br><br>Revised sample size: 83 |

**Kingsnorth 1995** *(Continued)*

| | |
|---|---|
| | Average age: 59 years<br>Women: 41 (49.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 54 (65.1%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 29 (34.9%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis within 48 h of onset of symptoms<br>Exclusion criteria<br>1. Age < 18 years<br>2. Unsterilised premenopausal women<br>3. Concomitant anticoagulant therapy |
| Interventions | Group 1: lexipafant (n = 42), 15 mg 4 times daily for 3 days<br>Group 2: placebo (n = 41) |
| Outcomes | Mortality, adverse events<br>Follow-up: 1 week |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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. |

**Kingsnorth 1995** *(Continued)*

| | | |
|---|---|---|
| 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<br>Number randomised: 150<br>Postrandomisation dropouts: not stated<br>Revised sample size: 150<br>Average age: 53 years<br>Women: 78 (52%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 35 (23.3%)<br>Moderate pancreatitis: 61 (40.7%)<br>Severe pancreatitis: 54 (36%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: glucagon (n = 75), 10 mg/day for 4 days<br>Group 2: atropine (n = 75), 4 days (dose not stated) |
| Outcomes | Mortality, serious adverse events, adverse events<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |

**Kirsch 1978** *(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 |

**Kronborg 1980**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: Denmark<br>Number randomised: 22<br>Postrandomisation dropouts: not stated<br>Revised sample size: 22<br>Average age: not stated<br>Women: 4 (18.2%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: 11 (50%)<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with acute pancreatitis (first attack only)<br>2. Deteriorating clinical condition or in shock<br>3. No suspected biliary disease |
| Interventions | Group 1: glucagon (n = 10), 1 mg IV followed by 6 mg/day for 3 days<br>Group 2: placebo (n = 12) |
| Outcomes | Mortality, adverse events<br>Follow-up: until discharge |
| Notes | Reasons for postrandomisation dropouts: not stated |

***Risk of bias***

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

**Kronborg 1980** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Comment: this information was not available. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 80<br>Postrandomisation dropouts: not stated<br>Revised sample size: 80<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 80 (100%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: 0<br>Inclusion criteria: people with non-infected necrotising pancreatitis |
| Interventions | Group 1: antibiotics (n = 40): imipenem 750 mg IV twice daily for 7 days<br>Group 2: placebo (n = 40) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis<br><br>Follow-up: 1 month |
| Notes | Reasons for postrandomisation dropouts: not stated |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Llukacaj 2012** *(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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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 |

**Luengo 1994**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: Spain<br>Number randomised: 100<br>Postrandomisation dropouts: not stated<br>Revised sample size: 100<br>Average age: 55 years<br>Women: 39 (39%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 78 (78%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 22 (22%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br>Exclusion criteria |

**Luengo 1994** *(Continued)*

| | |
|---|---|
| | 1. Pancreatitis following trauma, surgery, endoscopy, malignancy, drugs, or pregnancy<br>2. Allergy to one of the antibiotics<br>3. < 18 years of age<br>4. Postoperative pancreatitis<br>5. Infected pancreatic necrosis |
| Interventions | Group 1: somatostatin (n = 50), 250 µg/h for 48 h following a 250 µg bolus<br>Group 2: no intervention (n = 50) |
| Outcomes | Mortality, requirement for surgery, hospital stay<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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". |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 109<br>Postrandomisation dropouts: 7 (6.4%)<br>Revised sample size: 102<br>Average age: 55 years<br>Women: 42 (41.2%)<br>Acute interstitial oedematous pancreatitis: not stated |

**Luiten 1995** *(Continued)*

| | |
|---|---|
| | Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 102 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: 0<br>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<br>Group 2: no intervention (n = 52) |
| Outcomes | Mortality, adverse events, requirement for surgery, hospital stay<br><br>Follow-up: until discharge |
| Notes | Reasons for postrandomisation dropouts: perioperatively proven infected pancreatic necrosis or wrong clinical diagnosis |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 73 |

**Marek 1999** *(Continued)*

| | |
|---|---|
| | Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 73<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 56 (76.7%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 17 (23.3%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: antioxidants (n = 35): vitamin C 500 mg IV 3 times daily for 5 days<br>Group 2: placebo (n = 38) |
| Outcomes | None of the outcomes of interest were reported.<br><br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Unclear risk | Comment: although a placebo was used, it was not clear blinding was performed. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: although a placebo was used, it was not clear blinding was performed. |
| Incomplete outcome data (attrition bias)<br>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 |

**Martinez 1984** *(Continued)*

| | |
|---|---|
| | Number randomised: 31<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 31<br>Average age: 48 years<br>Women: 6 (19.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 31 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: placebo (n = 17) |
| Outcomes | Mortality, requirement for surgery, hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 58<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 58<br>Average age: 69 years<br>Women: 32 (55.2%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with moderate or severe pancreatitis<br>Exclusion criteria<br>1. < 18 years of age<br>2. Women in whom pregnancy could not be excluded<br>3. People with acute pancreatitis following pregnancy |
| Interventions | Group 1: octreotide (n = 28), 1 mg/day IV for 5 days<br>Group 2: placebo (n = 30) |
| Outcomes | Mortality, serious adverse events, adverse events, organ failure, infected pancreatic necrosis, hospital stay<br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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) | Low risk | Quote: "[p]atients, investigators, and medical staff were blinded regarding the nature of the trial infusion". |

**McKay 1997a** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| 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<br>Number randomised: 51<br>Postrandomisation dropouts: 1 (2%)<br>Revised sample size: 50<br>Average age: 65 years<br>Women: 21 (42%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with predicted severe pancreatitis<br>Exclusion criteria<br>1. Pregnancy<br>2. ERCP induced pancreatitis<br>3. Oral anticoagulant use<br>4. Other trial drugs within 3 months of study<br>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<br>Group 2: placebo (n = 24) |

**McKay 1997b** *(Continued)*

| | |
|---|---|
| Outcomes | Mortality, organ failure, hospital stay<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: incorrect diagnosis |

***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]acks were numbered sequentially and prepared in advance by British Biotech (Oxford, UK)". |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "[i]nvestigators and patients were unaware of the nature of the trial infusion." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "[i]nvestigators and patients were unaware of the nature of the trial infusion." |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 87<br>Postrandomisation dropouts: 3 (3.4%)<br>Revised sample size: 84<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated |

**Moreau 1986** *(Continued)*

| | |
|---|---|
| | Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br>Exclusion criteria<br>1. Acute pancreatitis following surgery or ERCP<br>2. Duration of symptoms for more than 48 h |
| Interventions | Group 1: somatostatin (n = 44), 400 µg for first 3 days, tapered and stopped on 4th day<br>Group 2: placebo (n = 41) |
| Outcomes | None of the outcomes of interest were reported.<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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 |

**MRC Multicentre Trial 1977** *(Continued)*

| | |
|---|---|
| Participants | Country: UK<br>Number randomised: 264<br>Postrandomisation dropouts: 7 (2.7%)<br>Revised sample size: 257<br>Average age: not stated<br>Women: 153 (59.5%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: glucagon (n = 68), 2 mg IV followed by 2 mg every 6 h for 5 days<br>Group 3: placebo (n = 123) |
| Outcomes | Mortality, requirement for surgery<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: initial amylase was too low |

***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)<br>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)<br>All outcomes | Low risk | Quote: "[r]andomized, double-blind, placebo-controlled, multi-centre trial across 15 centres in India" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 90<br>Postrandomisation dropouts: 32 (35.6%)<br>Revised sample size: 58<br>Average age: 46 years<br>Women: 7 (12.1%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 58 (100%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: 0 (0%)<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute necrotising pancreatitis<br>Exclusion criteria<br>1. People who had already been started on antibiotics<br>2. Those admitted to intensive care unit with multiorgan failure<br>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<br>Group 2: placebo (n = 33) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, ICU stay<br>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***

| 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)<br>All outcomes | Unclear risk | Comment: although a placebo was used, it was not clear blinding was performed. |

**Nordback 2001** *(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 | 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<br>Number randomised: 180<br>Postrandomisation dropouts: not stated<br>Revised sample size: 180<br>Average age: 37 years<br>Women: 41 (22.8%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: octreotide (n = 90), 100 µg 3 times daily SC for duration of hospital stay<br>Group 2: placebo (n = 90) |
| Outcomes | Requirement for surgery, hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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) | Unclear risk | Comment: although a placebo was used, it was not clear blinding was performed. |

**Ohair 1993** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: although a placebo was used, it was not clear blinding was performed. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 83<br>Postrandomisation dropouts: 21 (25.3%)<br>Revised sample size: 62<br>Average age: 47 years<br>Women: 10 (16.1%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 62 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with severe acute pancreatitis<br>Exclusion criteria: people with acute exacerbation of chronic pancreatitis. |
| Interventions | Group 1: probiotics (n = 33): Synbiotic 2000 once daily for at least 1 week<br>Group 2: no intervention (n = 29)<br>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<br><br>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***

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

**Olah 2007** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Comment: this information was not available. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 51<br>Postrandomisation dropouts: 13 (25.5%)<br>Revised sample size: 38<br>Average age: 61 years<br>Women: 18 (47.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: octreotide (n = 19), 01. mg SC 3 times daily for 14 days<br>Group 2: no intervention (n = 19) |
| Outcomes | Mortality, serious adverse events, adverse events, sepsis, hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: failure to meet inclusion criteria, incomplete data, incorrect diagnosis |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Paran 1995** *(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)<br>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)<br>All outcomes | High risk | Quote: "[a]s placebo vials were not available to us, the study was double blinded". |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 74<br>Postrandomisation dropouts: not stated<br>Revised sample size: 74<br>Average age: 52 years<br>Women: 30 (40.5%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 74 (100%)<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: antibiotics (n = 41): imipenem 0.5 g every 8 h for 2 weeks<br>Group 2: no intervention (n = 33) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, organ failure, infected pancreatic necrosis<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |
| ***Risk of bias*** | |

**Pederzoli 1993a** *(Continued)*

| 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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 199<br>Postrandomisation dropouts: 17 (8.5%)<br>Revised sample size: 182<br>Average age: 58 years<br>Women: 78 (42.9%)<br>Acute interstitial oedematous pancreatitis: 66 (36.3%)<br>Necrotising pancreatitis: 116 (63.7%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: gabexate mesilate (n = 91), 3 g/day for 7 days<br>Group 2: aprotinin (n = 91), 1,500,000 KIU/day for 7 days |
| Outcomes | Mortality, adverse events, requirement for surgery<br><br>Follow-up: 3 months for mortality; all other complications - 2 weeks |
| Notes | Reasons for postrandomisation dropouts: major protocol violations |

**Pederzoli 1993b** *(Continued)*

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 40<br>Postrandomisation dropouts: not stated<br>Revised sample size: 40<br>Average age: 56 years<br>Women: 24 (60%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated |

**Perezdeoteyza 1980** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: people with acute pancreatitis<br><br>Exclusion criteria<br><br>1. Post-traumatic pancreatitis<br>2. Postsurgical pancreatitis<br>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<br>Group 2: placebo (n = 20) |
| Outcomes | Mortality<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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 |

**Pettila 2010**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: Finland<br><br>Number randomised: 32<br><br>Postrandomisation dropouts: 0 (0%) |

**Pettila 2010** *(Continued)*

| | |
|---|---|
| | Revised sample size: 32<br>Average age: 45 years<br>Women: 3 (9.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 32 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with acute severe pancreatitis<br>2. Admitted to hospital < 4 days of onset of pain<br>3. At least one organ dysfunction<br>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<br>Group 2: placebo (n = 16) |
| Outcomes | Mortality, hospital stay<br>Follow-up: not stated (probably 2 weeks) |
| Notes | — |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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. |

**Pettila 2010** *(Continued)*

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

***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)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |

**Plaudis 2010** *(Continued)*

| | | |
|---|---|---|
| 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<br>Number randomised: 43<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 43<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with acute pancreatitis<br>2. APACHE II score ≥ 8 |
| Interventions | Group 1: antibiotics (n = 23): imipenem 500 mg IV 3 times daily for 10 days<br>Group 2: no intervention (n = 24) |
| Outcomes | Mortality, serious adverse events, adverse events, infected pancreatic necrosis, and organ failure<br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***Risk of bias***

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

**Poropat 2015** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Comment: this information was not available. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 73<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 73<br>Average age: 58 years<br>Women: 24 (32.9%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 73 (100%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 73 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with acute necrotising pancreatitis<br>2. Duration of symptoms < 72 h<br>Exclusion criteria |

**Rokke 2007** *(Continued)*

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<br>Group 2: no intervention (n = 37) |
| Outcomes | Mortality, adverse events, requirement for surgery, organ failure, infected pancreatic necrosis, hospital stay, ICU stay<br><br>Follow-up: not stated (probably 2 weeks) |
| Notes | — |

***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)<br>All outcomes | High risk | Quote: "[t]he study was unblinded to all attending physicians". |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "[t]he study was unblinded to all attending physicians". |
| Incomplete outcome data (attrition bias)<br>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<br><br>Number randomised: 60 |

**Sainio 1995** *(Continued)*

| | |
|---|---|
| | Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 60<br>Average age: 41 years<br>Women: 7 (11.7%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 60 (100%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with alcohol-induced necrotising pancreatitis<br>Exclusion criteria<br>1. Treatment elsewhere for more than 48 h of onset of symptoms<br>2. Continuing antimicrobial treatment<br>3. Previous severe episode of pancreatitis<br>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<br>Group 2: no intervention (n = 30) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay, ICU stay<br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |

**Sainio 1995** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 56<br>Postrandomisation dropouts: 3 (5.4%)<br>Revised sample size: 53<br>Average age: 39 years<br>Women: 33 (62.3%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 10 (18.9%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with acute pancreatitis<br>2. < 72 h of onset of symptoms<br>Exclusion criteria<br>1. Acute exacerbation of chronic pancreatitis<br>2. Prior antioxidant therapy<br>3. Delayed presentation to the ward<br>4. Severe comorbidity<br>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<br>Group 2: no intervention (n = 30) |
| Outcomes | Mortality, adverse events, organ failure, hospital stay |

**Sateesh 2009** *(Continued)*

| | |
|---|---|
| | Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: did not receive allocated treatment, discontinued medication |

***Risk of bias***

| 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)<br>All outcomes | High risk | Quote: "[t]he study was unblinded". |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Quote: "[t]he study was unblinded". |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 50<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 50<br>Average age: 41 years<br>Women: 27 (54%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 28 (56%)<br>Moderate pancreatitis: not stated |

**Sharma 2011** *(Continued)*

| | |
|---|---|
| | Severe pancreatitis: 22 (44%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with acute pancreatitis<br>2. < 72 h of onset of symptoms or had not been taking anything orally for up to 5 days<br>Exclusion criteria<br>1. Malignancy<br>2. Infection or sepsis related to source other than pancreatic bed<br>3. Intra-oeprative diagnosis of acute pancreatitis<br>4. Immunodeficiency<br>5. Earlier use of probiotics or prebiotics<br>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<br>Group 2: placebo (n = 26) |
| Outcomes | Hospital stay, ICU stay<br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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." |

**Sharma 2011** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | Comment: no other risk of bias |

**Sillero 1981**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: Spain<br>Number randomised: 60<br>Postrandomisation dropouts: not stated<br>Revised sample size: 60<br>Average age: 52 years<br>Women: 36 (60%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: placebo (n = 30) |
| Outcomes | Serious adverse events, adverse events, requirement for surgery<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: although a placebo was used, it was not clear blinding was performed. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: although a placebo was used, it was not clear blinding was performed. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 43<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 43<br>Average age: 67 years<br>Women: 28 (65.1%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with predicted severe pancreatitis<br>2. Within 72 h of admission to hospital<br>3. 16 years of older<br>4. Not enrolled in other trials<br>5. No history of allergy to intravenous antioxidant therapy<br>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<br>Group 2: placebo (n = 21) |
| Outcomes | Mortality, serious adverse events, organ failure, hospital stay, ICU stay<br>Follow-up: until discharge |
| Notes | — |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Siriwardena 2007** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "random number generation"<br>Comment: probably computer-generated |
| 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)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 63<br>Postrandomisation dropouts: not stated<br>Revised sample size: 63<br>Average age: 55 years<br>Women: 25 (39.7%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 63 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with severe acute pancreatitis |

**Spicak 2002** *(Continued)*

| | |
|---|---|
| | 2. Within 4 days of onset of symptoms<br><br>Exclusion criteria<br><br>1. < 18 years of age<br>2. More than 48 h from onset of symptoms<br>3. Iatrogenic pancreatitis<br>4. Infectious complications<br>5. Already receiving antibiotics for previous 2 weeks |
| Interventions | Group 1: antibiotics (n = 33): metronidazole 500 mg 3 times daily and ciprofloxacin 200 mg twice daily for 2 weeks<br>Group 2: no intervention (n = 30) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis, hospital stay, ICU stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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 |

**Spicak 2003** *(Continued)*

| | |
|---|---|
| | Number randomised: 41<br>Postrandomisation dropouts: not stated<br>Revised sample size: 41<br>Average age: 58 years<br>Women: 10 (24.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%).<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 41 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis<br>Exclusion criteria<br>1. < 18 years of age<br>2. More than 48 h from onset of symptoms<br>3. Pancreatitis following surgery or ERCP<br>4. Infectious complications<br>5. Already receiving antibiotics for previous 2 weeks |
| Interventions | Group 1: antibiotics (n = 20): meropenem 0.5 mg 3 times daily for 10 days<br>Group 2: no intervention (n = 21) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, infected pancreatic necrosis, hospital stay<br>Follow-up: not stated |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | This information was not available. |
| Blinding of outcome assessment (detection bias) | Unclear risk | This information was not available. |

**Spicak 2003** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 43<br>Postrandomisation dropouts: not stated<br>Revised sample size: 43<br>Average age: 59 years<br>Women: 28 (65.1%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: placebo (n = 22) |
| Outcomes | Mortality<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double blind" |

**Storck 1968** *(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 | 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<br>Number randomised: 105<br>Postrandomisation dropouts: not stated<br>Revised sample size: 105<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with first attack of acute pancreatitis<br>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<br>Group 2: placebo (n = 52) |
| Outcomes | Mortality<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

**Trapnell 1974** *(Continued)*

***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)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 64<br>Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 64<br>Average age: 51 years<br>Women: 23 (35.9%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated |

**Tykka 1985** *(Continued)*

| | |
|---|---|
| | Infected pancreatitis: not stated<br><br>Inclusion criteria: people with acute pancreatitis<br><br>Exclusion criteria<br><br>1. Post-traumatic pancreatitis<br>2. Postsurgical pancreatitis |
| Interventions | Group 1: EDTA (n = 33), dose and duration not reported<br>Group 2: placebo (n = 31)<br><br>Follow-up: not stated (probably until discharge) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery |
| Notes | — |

***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)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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."<br>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<br><br>Number randomised: 302 |

**Uhl 1999** *(Continued)*

| | |
|---|---|
| | Postrandomisation dropouts: 0 (0%)<br>Revised sample size: 302<br>Average age: 50 years<br>Women: 104 (34.4%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: 108 (35.8%)<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with moderate to severe acute pancreatitis<br>2. Duration of symptoms < 4 days<br>Exclusion criteria<br>1. Known chronic renal failure<br>2. < 18 years of age<br>3. Pregnancy<br>4. Psychosis (except alcoholic delirium)<br>5. Previous treatment with aprotinin, glucagon, calcitonin, pirenzepine, atropine, or native somatostatin<br>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<br>Group 2: placebo (n = 103) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, sepsis, hospital stay<br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Low risk | Quote: "double blind" |

**Uhl 1999** *(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) | 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<br>Number randomised: 77<br>Postrandomisation dropouts: not stated<br>Revised sample size: 77<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: somatostain (n = 36), 250 ng/h for 7 days<br>Group 2: placebo (n = 41) |
| Outcomes | Mortality<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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. |

**Usadel 1985** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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 |

**Valderrama 1992**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: Spain<br>Number randomised: 105<br>Postrandomisation dropouts: 5 (4.8%)<br>Revised sample size: 100<br>Average age: 57 years<br>Women: 53 (53%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>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<br>Group 2: placebo (n = 49) |
| Outcomes | Mortality, serious adverse events, adverse events, sepsis<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: protocol violations |

***Risk of bias***

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

**Valderrama 1992** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Quote: "consecutively numbered boxes containing FOY or placebo" |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 28<br>Postrandomisation dropouts: not stated<br>Revised sample size: 28<br>Average age: not stated<br>Women: not stated<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with predicted severe acute pancreatitis<br>2. < 72 h of onset of symptoms |

**Vege 2015** *(Continued)*

| | |
|---|---|
| Interventions | Group 1: antioxidant (n = 14): pentoxifylline 400 mg oral 3 times daily for 3 days<br>Group 2: placebo (n = 14) |
| Outcomes | Mortality, serious adverse events, organ failure, hospital stay, ICU stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 24<br>Postrandomisation dropouts: not stated<br>Revised sample size: 24<br>Average age: 46 years<br>Women: 15 (62.5%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 24 (100%).<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated |

**Wang 2011** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: people with severe acute pancreatitis. |
| Interventions | Group 1: thymosin alpha (n = 12), 3.2 mg twice daily for 7 days<br>Group 2: placebo (n = 12) |
| Outcomes | Mortality, hospital stay, ICU stay<br>Follow-up: 1 month |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 183<br>Postrandomisation dropouts: not stated<br>Revised sample size: 183<br>Average age: 42 years<br>Women: 89 (48.6%)<br>Acute interstitial oedematous pancreatitis: not stated |

**Wang 2013a** *(Continued)*

| | |
|---|---|
| | Necrotising pancreatitis: not stated<br><br>Mild pancreatitis: not stated<br><br>Moderate pancreatitis: not stated<br><br>Severe pancreatitis: 159 (86.9%)<br><br>Persistent organ failure: not stated<br><br>Infected pancreatitis: not stated<br><br>Inclusion criteria<br><br>1. People with severe acute pancreatitis<br>2. Age: 18 to 45 years<br>3. < 2 days from onset of symptoms<br>4. Presence of gastrointestinal ileus or distension<br><br>Exclusion criteria<br><br>1. History of renal dysfunction<br>2. Pregnant or lactating<br>3. Expected to receive extracorporeal removal<br>4. Inflammatory bowel disease<br>5. Infections at the time of hospital admission<br>6. Received recent NSAID |
| Interventions | Group 1: somatostatin plus ulinastatin (n = 62)<br>Group 2: somatostatin (n = 61)<br>Group 3: no intervention (n = 60)<br>Somatostatin: 250 µg/h IV for 10 days.<br>Ulinastatin: 10,000 units IV twice daily for 10 days |
| Outcomes | Mortality, serious adverse events<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double blind" |

**Wang 2013a** *(Continued)*

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

***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) | Unclear risk | Comment: this information was not available. |

**Wang 2013b** *(Continued)*

| | | |
|---|---|---|
| All outcomes | | |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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 2013c**

| | |
|---|---|
| Methods | Randomised clinical trial |
| Participants | Country: China<br>Number randomised: 372<br>Postrandomisation dropouts: not stated<br>Revised sample size: 372<br>Average age: 45 years<br>Women: 174 (46.8%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 0 (0%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with predicted severe acute pancreatitis or acute pancreatitis<br>2. Age 18 to 70 years<br>3. Admission in < 48 h of onset of symptoms<br>4. No other severe diseases such as cirrhosis, chronic obstructive airway disease, chronic renal insufficiency, malignant tumours<br>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) |

**Wang 2013c** *(Continued)*

| | |
|---|---|
| | 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<br><br>Follow-up: some outcomes were measured on 8th day and others at 1 month |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>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".<br>Comment: there is no mention of participant blinding. |
| Blinding of outcome assessment (detection bias)<br>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)<br>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<br><br>Number randomised: 492<br><br>Postrandomisation dropouts: not stated<br><br>Revised sample size: 492<br><br>Average age: 41 years<br><br>Women: 238 (48.4%)<br><br>Acute interstitial oedematous pancreatitis: not stated |

**Wang 2016** *(Continued)*

| | |
|---|---|
| | Necrotising pancreatitis: not stated<br><br>Mild pancreatitis: 0 (0%)<br><br>Moderate pancreatitis: 0 (0%)<br><br>Severe pancreatitis: 492 (100%)<br><br>Persistent organ failure: not stated<br><br>Infected pancreatitis: not stated<br><br>Inclusion criteria: people with severe acute pancreatitis<br><br>Exclusion criteria<br><br>1. Evidence or a known history of renal dysfunction<br>2. Pregnancy<br>3. Malignancy<br>4. Immunodeficiency<br>5. Pre-existing chronic kidney diseases requiring regular hemodialysis |
| Interventions | Group 1: somatostatin plus ulinastatin plus gabexate (n = 116)<br>Group 2: somatostatin plus ulinastatin (n = 124)<br>Group 3: somatostatin plus gabexate (n = 130)<br>Group 4: somatostatin (n = 122)<br>Somatostatin: 3 mg IV for 10 days<br>Ulinastatin: 10,000 units IV twice daily for 10 days<br>Gabexate: 0.1 g IV 3 times daily for 10 days |
| Outcomes | Mortality, adverse events, organ failure, length of hospital stay<br><br>Follow-up: not stated (probably until discharge) |
| Notes | — |

***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)<br>All outcomes | Low risk | Quote: "[t]his was a prospective and double-blind study"<br>Comment: a placebo was used to achieve blinding. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "[t]his was a prospective and double-blind study"<br>Comment: a placebo was used to achieve blinding. |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Comment: there were no postrandomisation dropouts. |

**Wang 2016** *(Continued)*

| | | |
|---|---|---|
| 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<br>Number randomised: 140<br>Postrandomisation dropouts: not stated<br>Revised sample size: 140<br>Average age: 43 years<br>Women: 48 (34.3%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: 140 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with severe acute pancreatitis<br>2. No associated severe liver disease or biliary diseases<br>3. Pancreatitis not resulting from trauma, malignancy<br>4. No contraindications or allergies to somatostatin<br>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)<br>Group 2: no intervention (n = 70) |
| Outcomes | Mortality, serious adverse events, adverse events<br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |
| ***Risk of bias*** | |

**Xia 2014** *(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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 59<br>Postrandomisation dropouts: 3 (5.1%)<br>Revised sample size: 56<br>Average age: 48 years<br>Women: 28 (50%)<br>Acute interstitial oedematous pancreatitis: 0 (0%)<br>Necrotising pancreatitis: 56 (100%)<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 56 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: 0<br>Inclusion criteria |

**Xue 2009** *(Continued)*

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<br>Group 2: no intervention (n = 27) |
| Outcomes | Mortality, serious adverse events, adverse events, requirement for surgery, hospital stay<br>Follow-up: 1 month |
| Notes | Reasons for postrandomisation dropouts: death after starting treatment, transferred to operation |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 48<br>Postrandomisation dropouts: not stated<br>Revised sample size: 48<br>Average age: 45 years<br>Women: 26 (54.2%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: not stated<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria: people with acute pancreatitis |
| Interventions | Group 1: somatostatin (n = 25), 250 µg/h for 3-4 days<br>Group 2: no intervention (n = 23) |
| Outcomes | Serious adverse events, adverse events<br><br>Follow-up: not stated (probably until discharge) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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<br>Number randomised: 163<br>Postrandomisation dropouts: 6 (3.7%)<br>Revised sample size: 157<br>Average age: 46 years<br>Women: 71 (45.2%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 157 (100%)<br>Moderate pancreatitis: not stated<br>Severe pancreatitis: not stated<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria<br>1. People with mild pancreatitis<br>2. Aged between 18 and 70 years<br>3. < 48 h of symptoms<br>4. People with a BMI > 25 kg/$m^2$<br>Exclusion criteria<br>1. People with alcohol dependence<br>2. Pregnancy<br>3. Drug abuse<br>4. Psychosis<br>5. Cirrhosis<br>6. Chronic obstructive pulmonary disease<br>7. Chronic renal insufficiency<br>8. Malignancy |
| Interventions | Group 1: octreotide (n = 80), 50 µg/h for 3 days<br>Group 2: no intervention (n = 77) |
| Outcomes | Mortality, hospital stay<br>Follow-up: 1 month |
| Notes | Reasons for postrandomisation dropouts: loss to follow-up; lack of data |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Yang 2012** *(Continued)*

| | | |
|---|---|---|
| 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)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Comment: this information was not available. |
| Incomplete outcome data (attrition bias)<br>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 | 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<br>Number randomised: 39<br>Postrandomisation dropouts: not stated<br>Revised sample size: 39<br>Average age: 43 years<br>Women: 18 (46.2%)<br>Acute interstitial oedematous pancreatitis: not stated<br>Necrotising pancreatitis: not stated<br>Mild pancreatitis: 0 (0%)<br>Moderate pancreatitis: 0 (0%)<br>Severe pancreatitis: 39 (100%)<br>Persistent organ failure: not stated<br>Infected pancreatitis: not stated<br>Inclusion criteria |

**Zhu 2014** *(Continued)*

| | |
|---|---|
| | 1. People with severe acute pancreatitis<br>2. < 48 h from onset of symptoms<br>3. < 65 years of age<br><br>Exclusion criteria<br><br>1. Chronic pancreatitis<br>2. Associated with primary infection, tumours, low immunity |
| Interventions | Group 1: probiotics (n = 20), 2 tablets twice daily for 14 days (Japanese preparation)<br>Group 2: placebo (n = 19) |
| Outcomes | Serious adverse events, adverse events, requirement for endoscopic or radiological drainage, infected pancreatic necrosis<br><br>Follow-up: not stated (probably 2 weeks) |
| Notes | Reasons for postrandomisation dropouts: not stated |

***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)<br>All outcomes | Low risk | Quote: "double-blind" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "double-blind" |
| Incomplete outcome data (attrition bias)<br>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 |
| 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 |

| Study | Reason for exclusion |
|---|---|
| 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 |
| 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 |

| Study | Reason for exclusion |
|---|---|
| Jiang 1988 | Not an RCT |
| 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 |
| 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) |

| Study | Reason for exclusion |
|---|---|
| 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 |
| 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 | — |

**Hansen 1966** *(Continued)*

| | |
|---|---|
| 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 |
| 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 |

**EUCTR2014-004844-37-ES** *(Continued)*

| | |
|---|---|
| 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 |

**NCT02212392** *(Continued)*

| | |
|---|---|
| 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 |
| 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] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 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] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 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] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 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] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 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] |

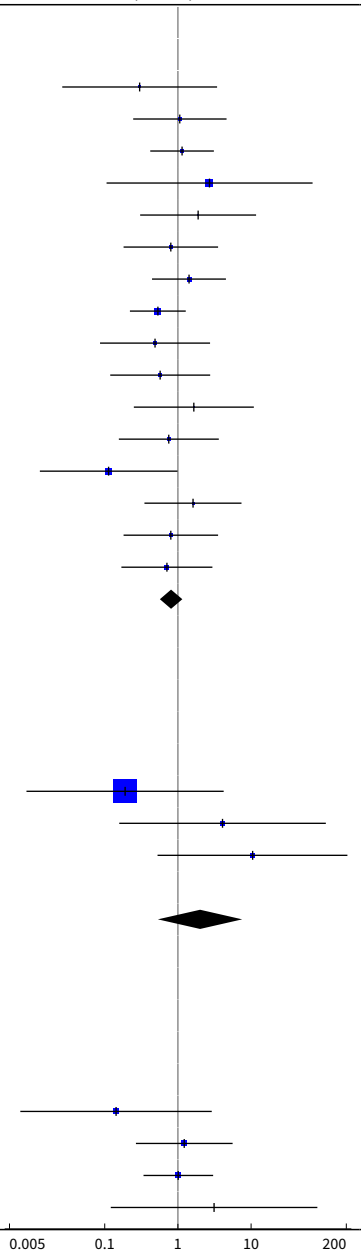
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.13 Ulinastatin versus gabexate | 1 | 62 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 7.14 Ulinastatin versus octreotide | 1 | 25 | Odds Ratio (M-H, Fixed, 95% CI) | 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] |

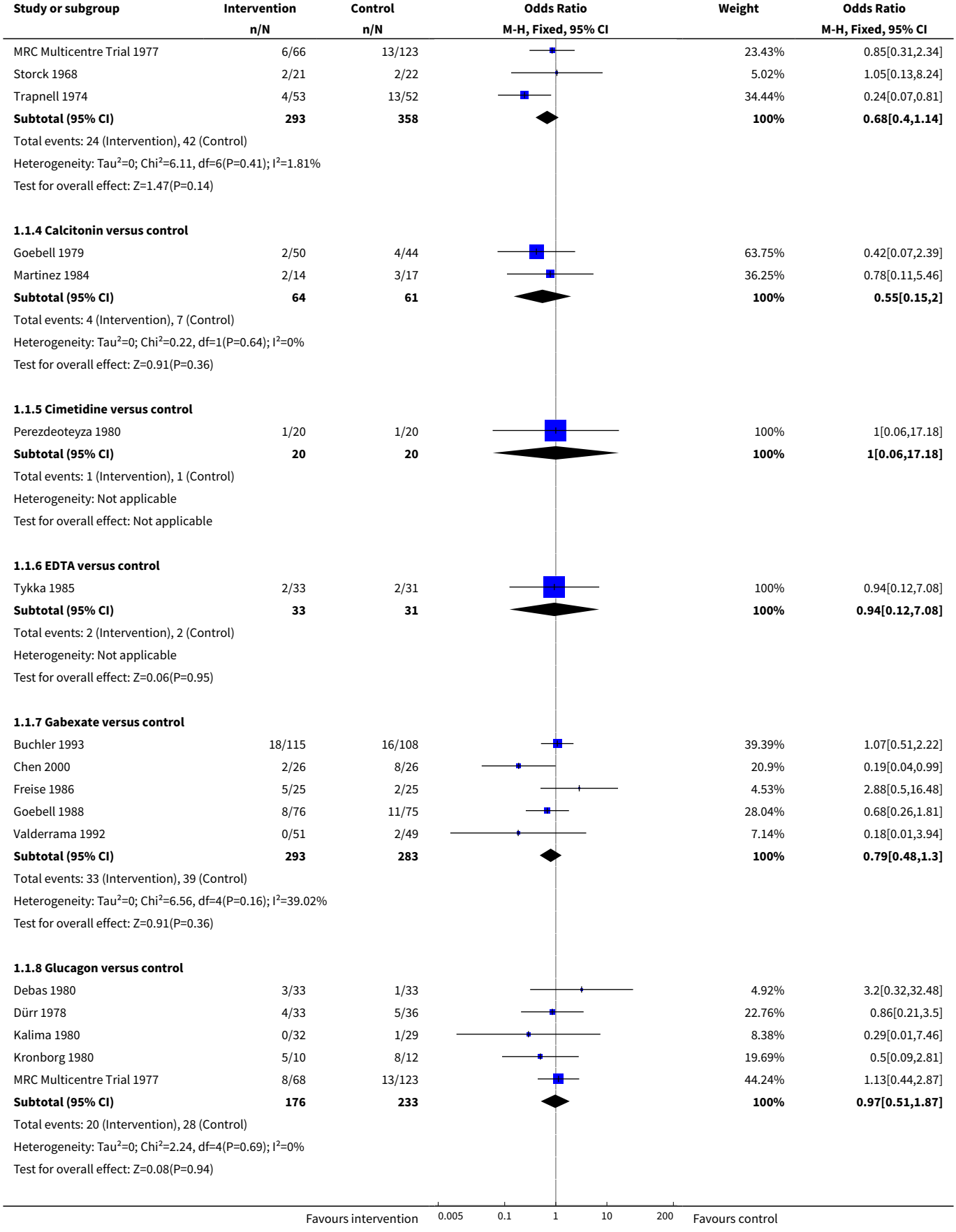
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.15 Glucagon versus atropine | 1 | 150 | Rate Ratio (Random, 95% CI) | 0.79 [0.36, 1.73] |
| 8.16 Oxyphenonium versus glucagon | 1 | 62 | Rate Ratio (Random, 95% CI) | 0.93 [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] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 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] |

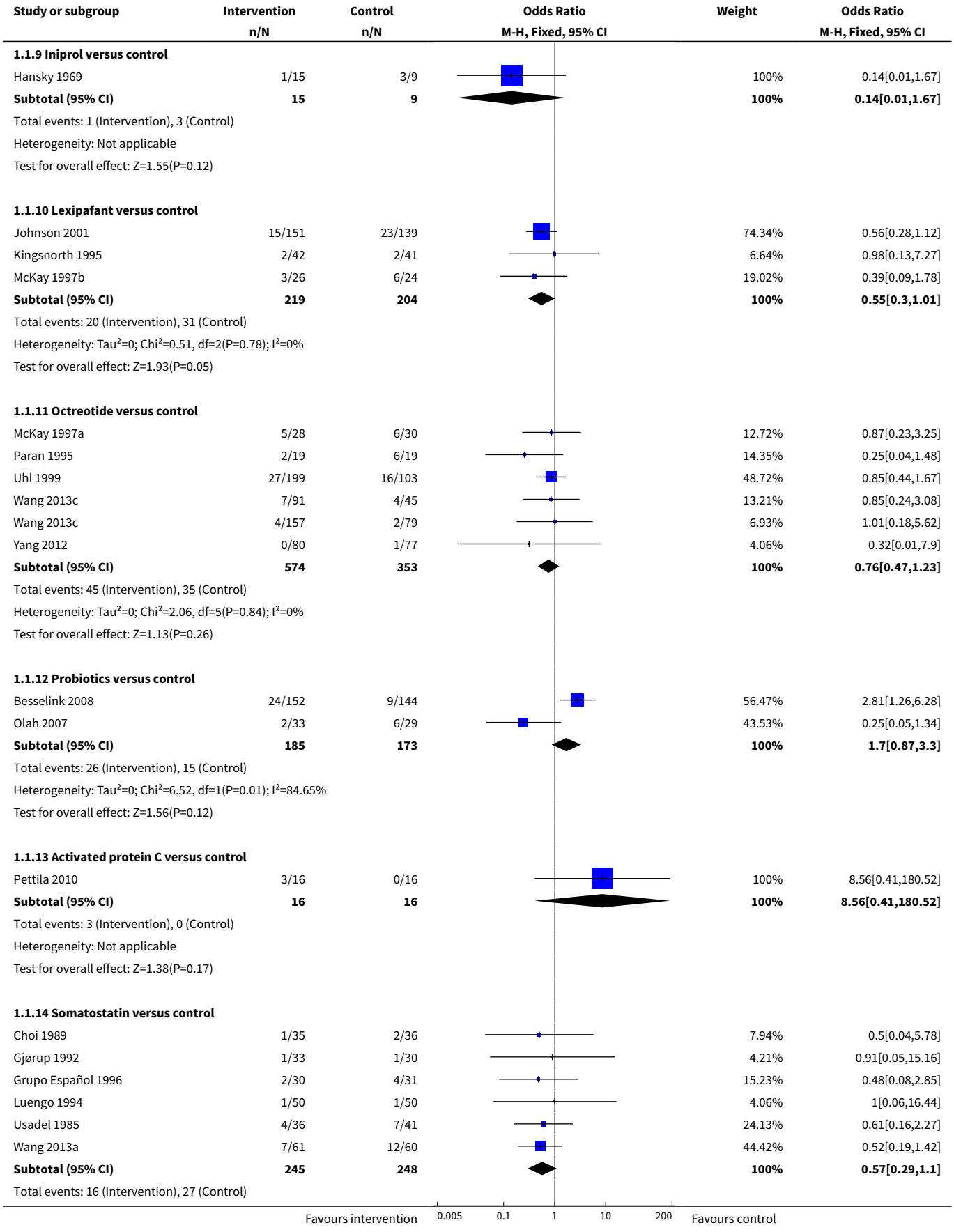
**Analysis 1.1. Comparison 1 Acute pancreatitis, Outcome 1 Short-term mortality.**

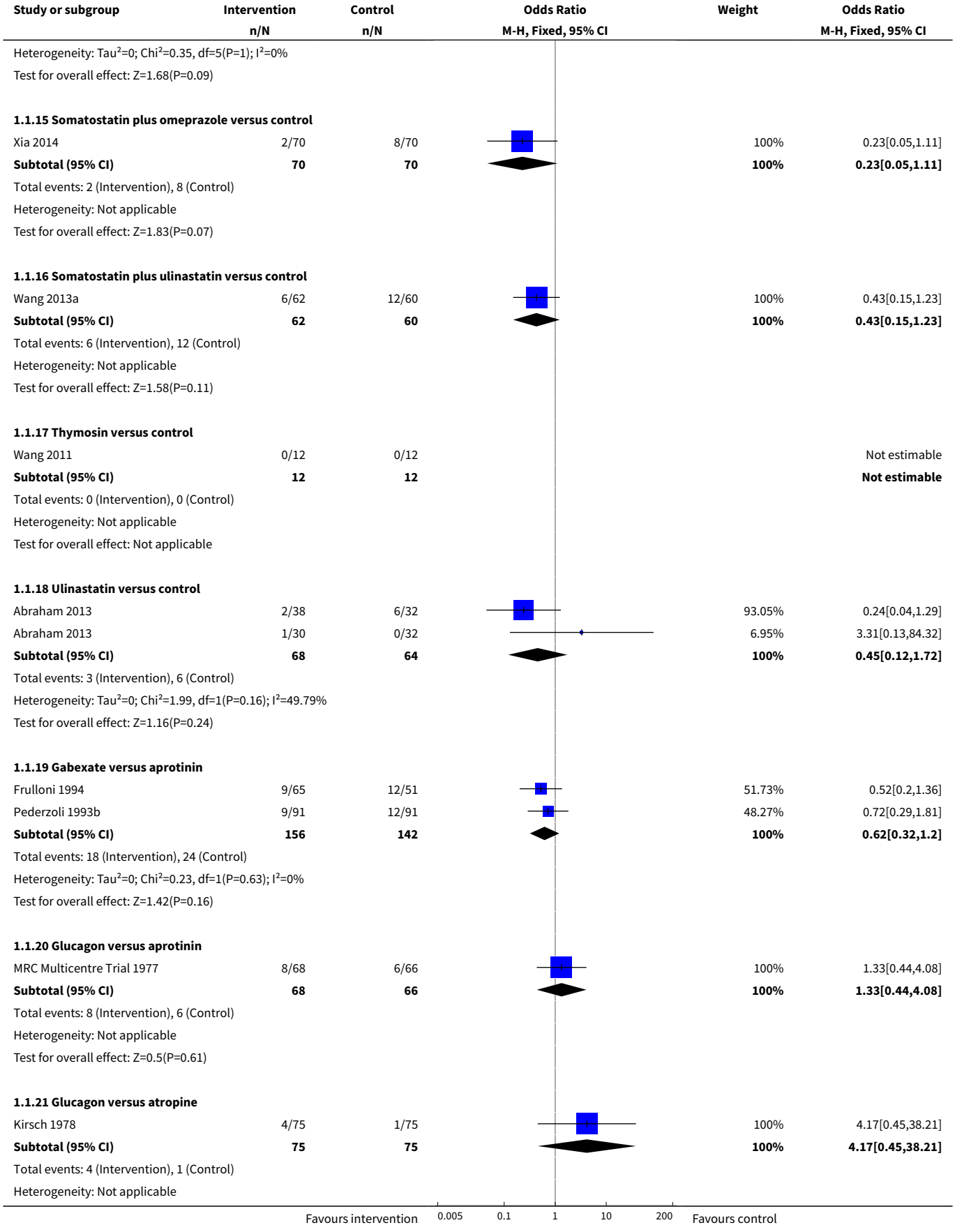
| Study or subgroup | Intervention n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **1.1.1 Antibiotics versus control** | | | | | |
| Barreda 2009 | 0/24 | 0/34 | | | Not estimable |
| Delcenserie 1996 | 1/11 | 3/12 | | 3.77% | 0.3[0.03,3.43] |
| Delcenserie 2001 | 6/53 | 3/28 | | 5.03% | 1.06[0.24,4.62] |
| Dellinger 2007 | 10/50 | 9/50 | | 10.4% | 1.14[0.42,3.1] |
| Finch 1976 | 1/31 | 0/27 | | 0.73% | 2.7[0.11,69.19] |
| Garcia-Barrasa 2009 | 4/22 | 2/19 | | 2.54% | 1.89[0.31,11.68] |
| Hejtmankova 2003 | 4/20 | 5/21 | | 5.64% | 0.8[0.18,3.54] |
| Llukacaj 2012 | 8/40 | 6/40 | | 6.93% | 1.42[0.44,4.53] |
| Luiten 1995 | 11/50 | 18/52 | | 19.88% | 0.53[0.22,1.28] |
| Nordback 2001 | 2/25 | 5/33 | | 5.73% | 0.49[0.09,2.75] |
| Pederzoli 1993a | 3/41 | 4/33 | | 5.93% | 0.57[0.12,2.76] |
| Poropat 2015 | 3/23 | 2/24 | | 2.46% | 1.65[0.25,10.91] |
| Rokke 2007 | 3/36 | 4/37 | | 5.22% | 0.75[0.16,3.62] |
| Sainio 1995 | 1/30 | 7/30 | | 9.77% | 0.11[0.01,0.99] |
| Spicak 2002 | 5/33 | 3/30 | | 3.85% | 1.61[0.35,7.39] |
| Spicak 2003 | 4/20 | 5/21 | | 5.64% | 0.8[0.18,3.54] |
| Xue 2009 | 4/30 | 5/28 | | 6.47% | 0.71[0.17,2.96] |
| **Subtotal (95% CI)** | **539** | **519** | | **100%** | **0.81[0.57,1.15]** |
| Total events: 70 (Intervention), 81 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=9.4, df=15(P=0.86); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.2(P=0.23) | | | | | |
| **1.1.2 Antioxidants versus control** | | | | | |
| Bansal 2011 | 0/19 | 2/20 | | 74.35% | 0.19[0.01,4.22] |
| Sateesh 2009 | 1/23 | 0/30 | | 12.79% | 4.07[0.16,104.53] |
| Siriwardena 2007 | 4/22 | 0/21 | | 12.85% | 10.46[0.53,207.4] |
| Vege 2015 | 0/14 | 0/14 | | | Not estimable |
| **Subtotal (95% CI)** | **78** | **85** | | **100%** | **2.01[0.53,7.56]** |
| Total events: 5 (Intervention), 2 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=3.58, df=2(P=0.17); $I^2$=44.07% | | | | | |
| Test for overall effect: Z=1.03(P=0.3) | | | | | |
| **1.1.3 Aprotinin versus control** | | | | | |
| Balldin 1983 | 0/26 | 3/29 | | 9.24% | 0.14[0.01,2.9] |
| Berling 1994 | 4/22 | 4/26 | | 8.52% | 1.22[0.27,5.59] |
| Imrie 1978 | 7/80 | 7/81 | | 18.02% | 1.01[0.34,3.03] |
| Imrie 1980 | 1/25 | 0/25 | | 1.34% | 3.12[0.12,80.39] |

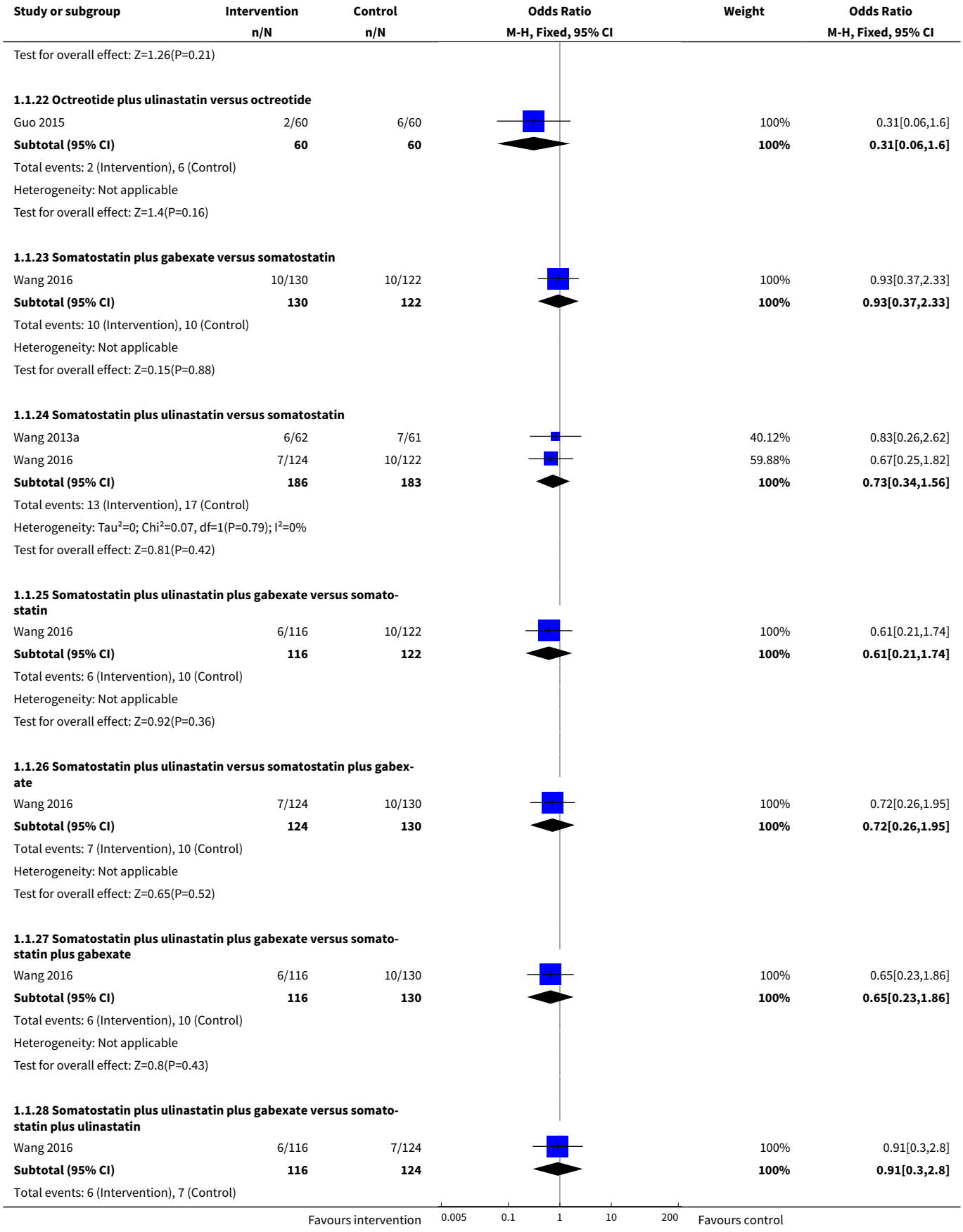




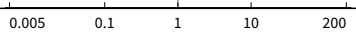
| Study or subgroup | Intervention n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| MRC Multicentre Trial 1977 | 6/66 | 13/123 | | 23.43% | 0.85[0.31,2.34] |
| Storck 1968 | 2/21 | 2/22 | | 5.02% | 1.05[0.13,8.24] |
| Trapnell 1974 | 4/53 | 13/52 | | 34.44% | 0.24[0.07,0.81] |
| **Subtotal (95% CI)** | **293** | **358** | | **100%** | **0.68[0.4,1.14]** |
| Total events: 24 (Intervention), 42 (Control) | | | | | |
| Heterogeneity: Tau²=0; Chi²=6.11, df=6(P=0.41); I²=1.81% | | | | | |
| Test for overall effect: Z=1.47(P=0.14) | | | | | |
| **1.1.4 Calcitonin versus control** | | | | | |
| Goebell 1979 | 2/50 | 4/44 | | 63.75% | 0.42[0.07,2.39] |
| Martinez 1984 | 2/14 | 3/17 | | 36.25% | 0.78[0.11,5.46] |
| **Subtotal (95% CI)** | **64** | **61** | | **100%** | **0.55[0.15,2]** |
| Total events: 4 (Intervention), 7 (Control) | | | | | |
| Heterogeneity: Tau²=0; Chi²=0.22, df=1(P=0.64); I²=0% | | | | | |
| Test for overall effect: Z=0.91(P=0.36) | | | | | |
| **1.1.5 Cimetidine versus control** | | | | | |
| Perezdeoteyza 1980 | 1/20 | 1/20 | | 100% | 1[0.06,17.18] |
| **Subtotal (95% CI)** | **20** | **20** | | **100%** | **1[0.06,17.18]** |
| Total events: 1 (Intervention), 1 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **1.1.6 EDTA versus control** | | | | | |
| Tykka 1985 | 2/33 | 2/31 | | 100% | 0.94[0.12,7.08] |
| **Subtotal (95% CI)** | **33** | **31** | | **100%** | **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) | | | | | |
| **1.1.7 Gabexate versus control** | | | | | |
| Buchler 1993 | 18/115 | 16/108 | | 39.39% | 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 | | 4.53% | 2.88[0.5,16.48] |
| Goebell 1988 | 8/76 | 11/75 | | 28.04% | 0.68[0.26,1.81] |
| Valderrama 1992 | 0/51 | 2/49 | | 7.14% | 0.18[0.01,3.94] |
| **Subtotal (95% CI)** | **293** | **283** | | **100%** | **0.79[0.48,1.3]** |
| Total events: 33 (Intervention), 39 (Control) | | | | | |
| Heterogeneity: Tau²=0; Chi²=6.56, df=4(P=0.16); I²=39.02% | | | | | |
| Test for overall effect: Z=0.91(P=0.36) | | | | | |
| **1.1.8 Glucagon versus control** | | | | | |
| Debas 1980 | 3/33 | 1/33 | | 4.92% | 3.2[0.32,32.48] |
| Dürr 1978 | 4/33 | 5/36 | | 22.76% | 0.86[0.21,3.5] |
| Kalima 1980 | 0/32 | 1/29 | | 8.38% | 0.29[0.01,7.46] |
| Kronborg 1980 | 5/10 | 8/12 | | 19.69% | 0.5[0.09,2.81] |
| MRC Multicentre Trial 1977 | 8/68 | 13/123 | | 44.24% | 1.13[0.44,2.87] |
| **Subtotal (95% CI)** | **176** | **233** | | **100%** | **0.97[0.51,1.87]** |
| Total events: 20 (Intervention), 28 (Control) | | | | | |
| Heterogeneity: Tau²=0; Chi²=2.24, df=4(P=0.69); I²=0% | | | | | |
| Test for overall effect: Z=0.08(P=0.94) | | | | | |







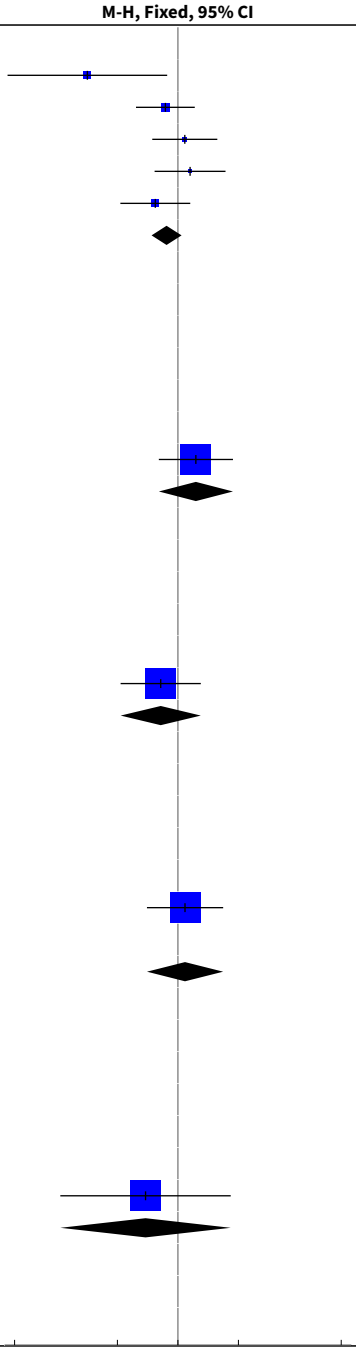
| Study or subgroup | Intervention n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100% | | | | | |
| Test for overall effect: Z=0.16(P=0.87) | | | | | |



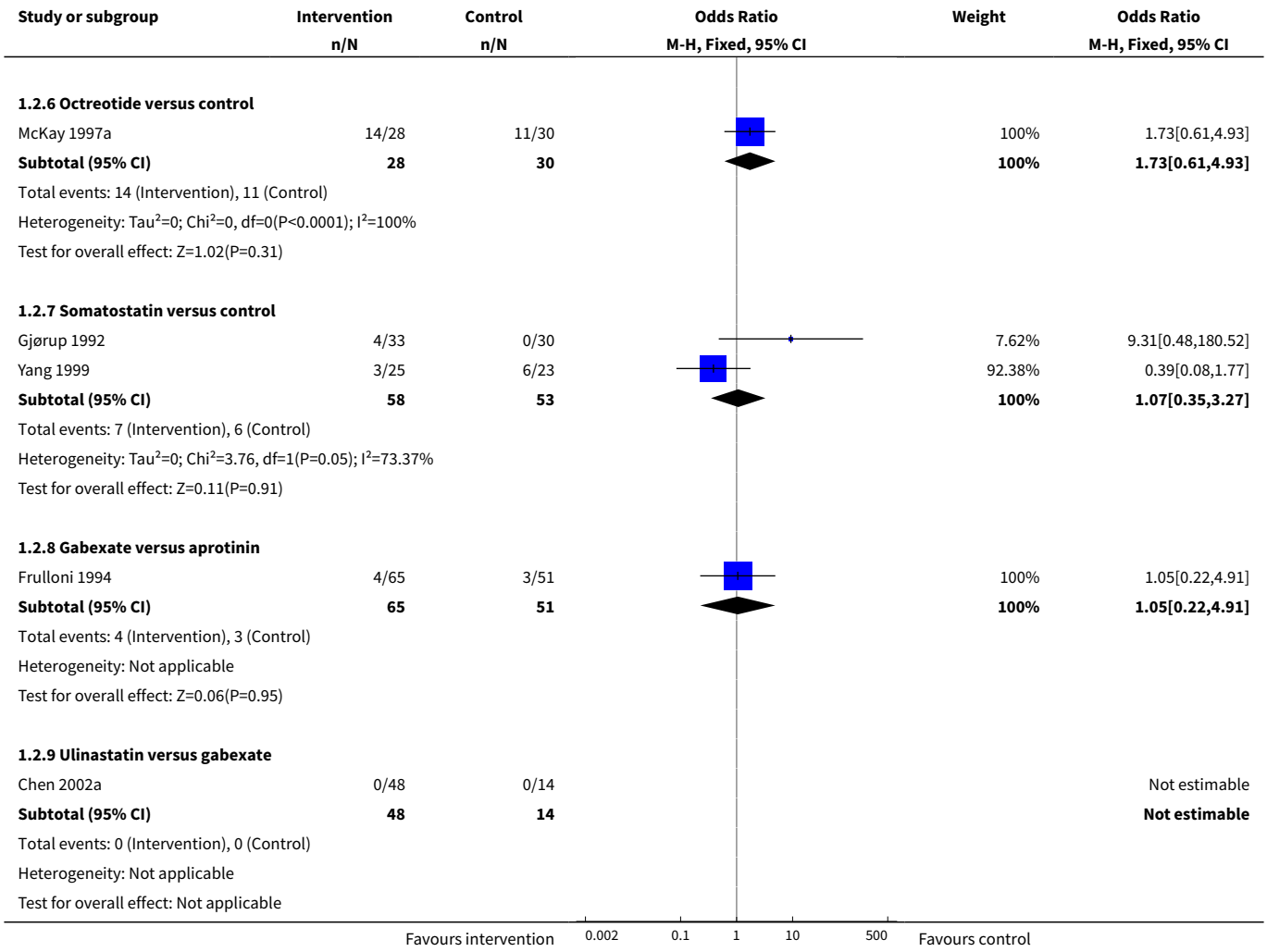

Favours intervention — Favours control

## Analysis 1.2. Comparison 1 Acute pancreatitis, Outcome 2 Serious adverse events (proportion).

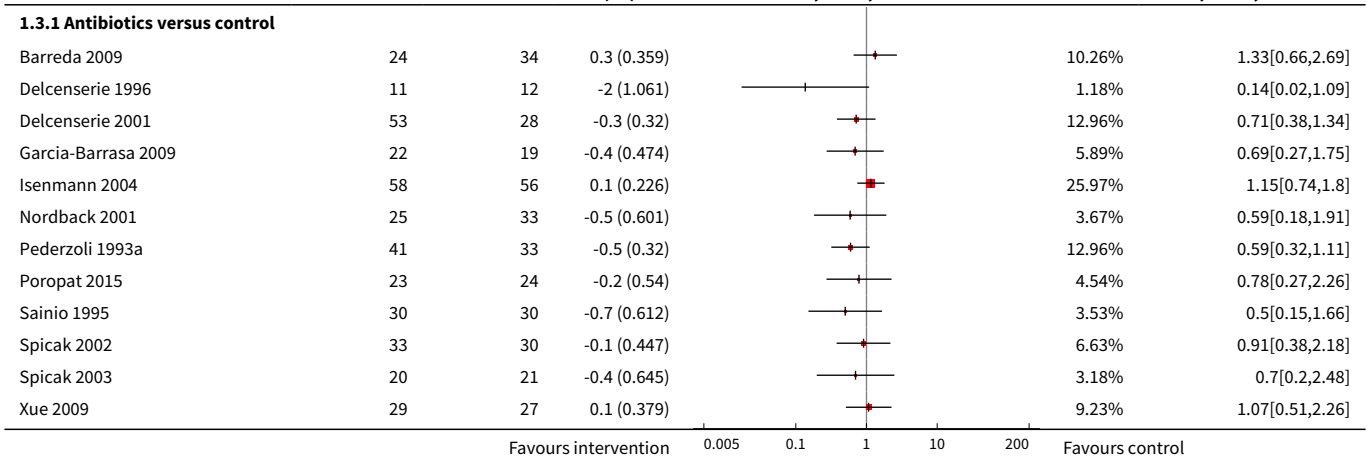
| Study or subgroup | Intervention n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **1.2.1 Antibiotics versus control** | | | | | |
| Delcenserie 1996 | 0/11 | 7/12 | | 23.36% | 0.03[0,0.67] |
| Dellinger 2007 | 6/50 | 9/50 | | 26.81% | 0.62[0.2,1.9] |
| Garcia-Barrasa 2009 | 13/22 | 10/19 | | 14.86% | 1.3[0.38,4.48] |
| Llukacaj 2012 | 6/40 | 4/40 | | 11.51% | 1.59[0.41,6.12] |
| Sainio 1995 | 4/30 | 8/30 | | 23.47% | 0.42[0.11,1.6] |
| **Subtotal (95% CI)** | **153** | **151** | | **100%** | **0.65[0.37,1.15]** |
| Total events: 29 (Intervention), 38 (Control) | | | | | |
| Heterogeneity: Tau²=0; Chi²=7.08, df=4(P=0.13); I²=43.53% | | | | | |
| Test for overall effect: Z=1.49(P=0.14) | | | | | |
| **1.2.2 Antioxidants versus control** | | | | | |
| Bansal 2011 | 0/19 | 0/20 | | | Not estimable |
| Siriwardena 2007 | 7/22 | 4/21 | | 100% | 1.98[0.48,8.13] |
| **Subtotal (95% CI)** | **41** | **41** | | **100%** | **1.98[0.48,8.13]** |
| Total events: 7 (Intervention), 4 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.95(P=0.34) | | | | | |
| **1.2.3 EDTA versus control** | | | | | |
| Tykka 1985 | 3/33 | 5/31 | | 100% | 0.52[0.11,2.39] |
| **Subtotal (95% CI)** | **33** | **31** | | **100%** | **0.52[0.11,2.39]** |
| Total events: 3 (Intervention), 5 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.84(P=0.4) | | | | | |
| **1.2.4 Gabexate versus control** | | | | | |
| Freise 1986 | 5/25 | 4/25 | | 100% | 1.31[0.31,5.6] |
| Goebell 1988 | 0/76 | 0/75 | | | Not estimable |
| **Subtotal (95% CI)** | **101** | **100** | | **100%** | **1.31[0.31,5.6]** |
| Total events: 5 (Intervention), 4 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.37(P=0.71) | | | | | |
| **1.2.5 Glucagon versus control** | | | | | |
| Debas 1980 | 0/33 | 0/33 | | | Not estimable |
| Kalima 1980 | 0/32 | 1/29 | | 100% | 0.29[0.01,7.46] |
| **Subtotal (95% CI)** | **65** | **62** | | **100%** | **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) | | | | | |

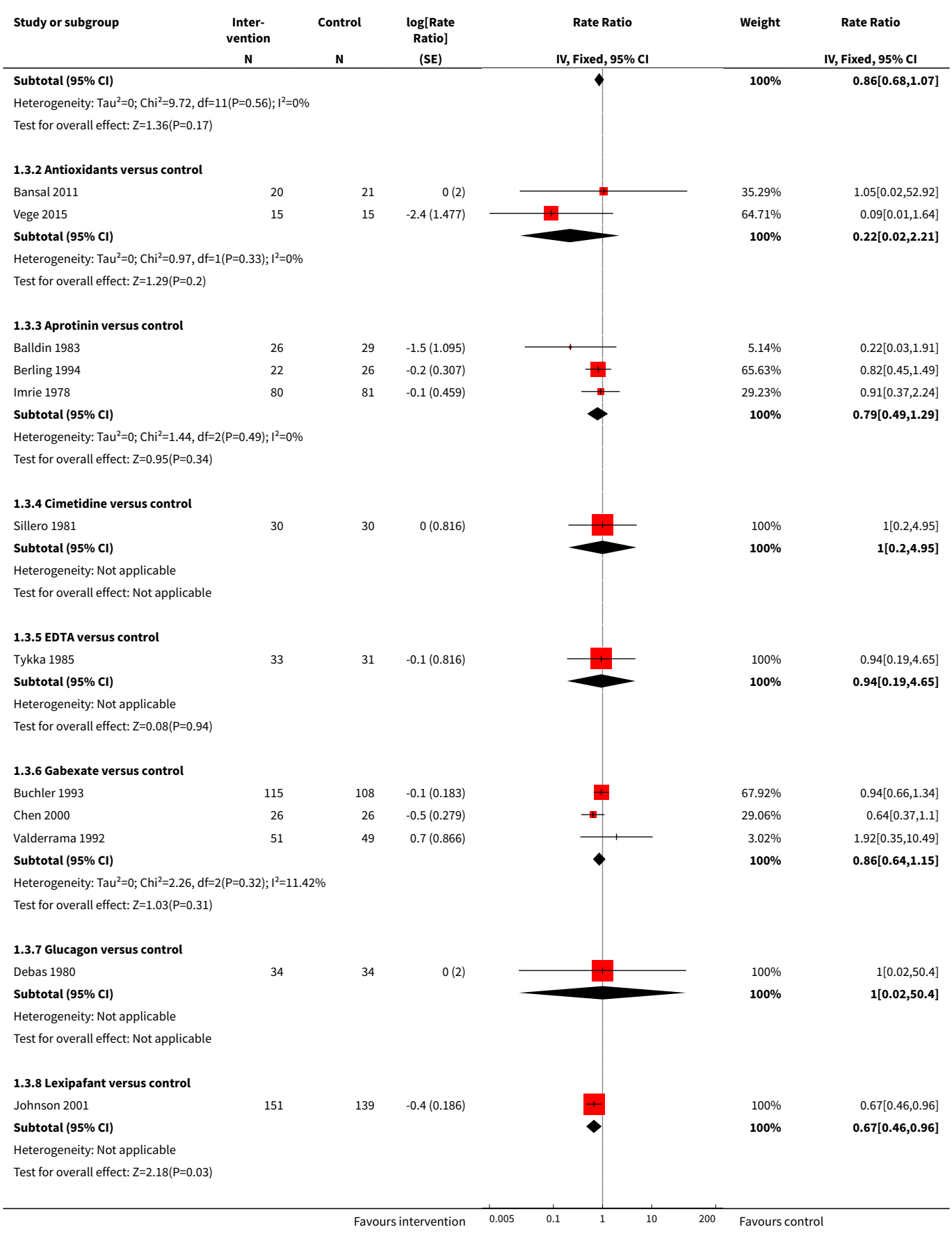


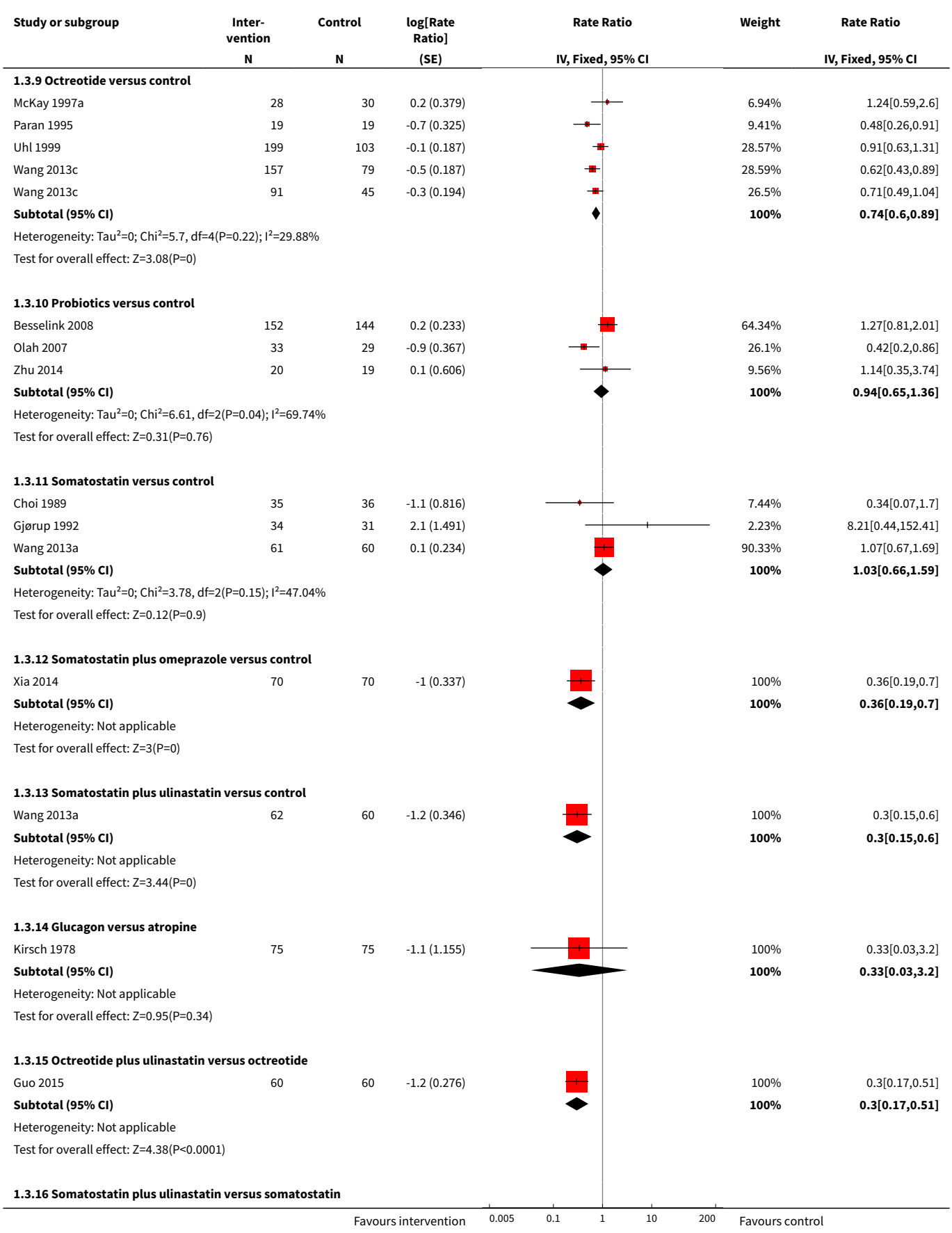

Favours intervention — Favours control

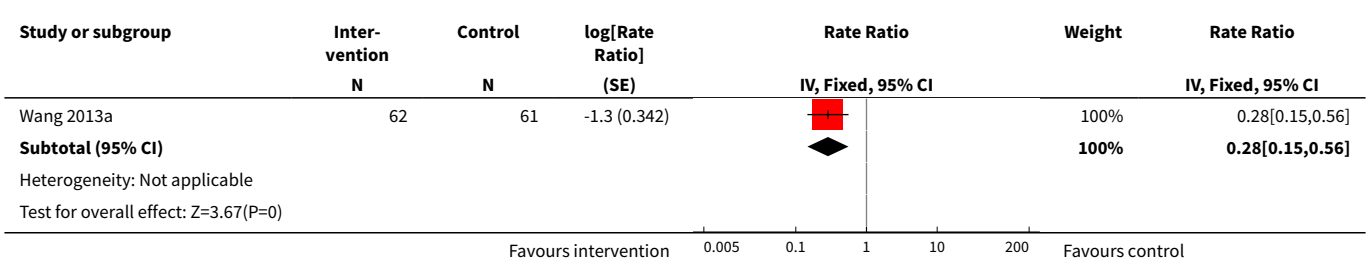



## Analysis 1.3. Comparison 1 Acute pancreatitis, Outcome 3 Serious adverse events (number).

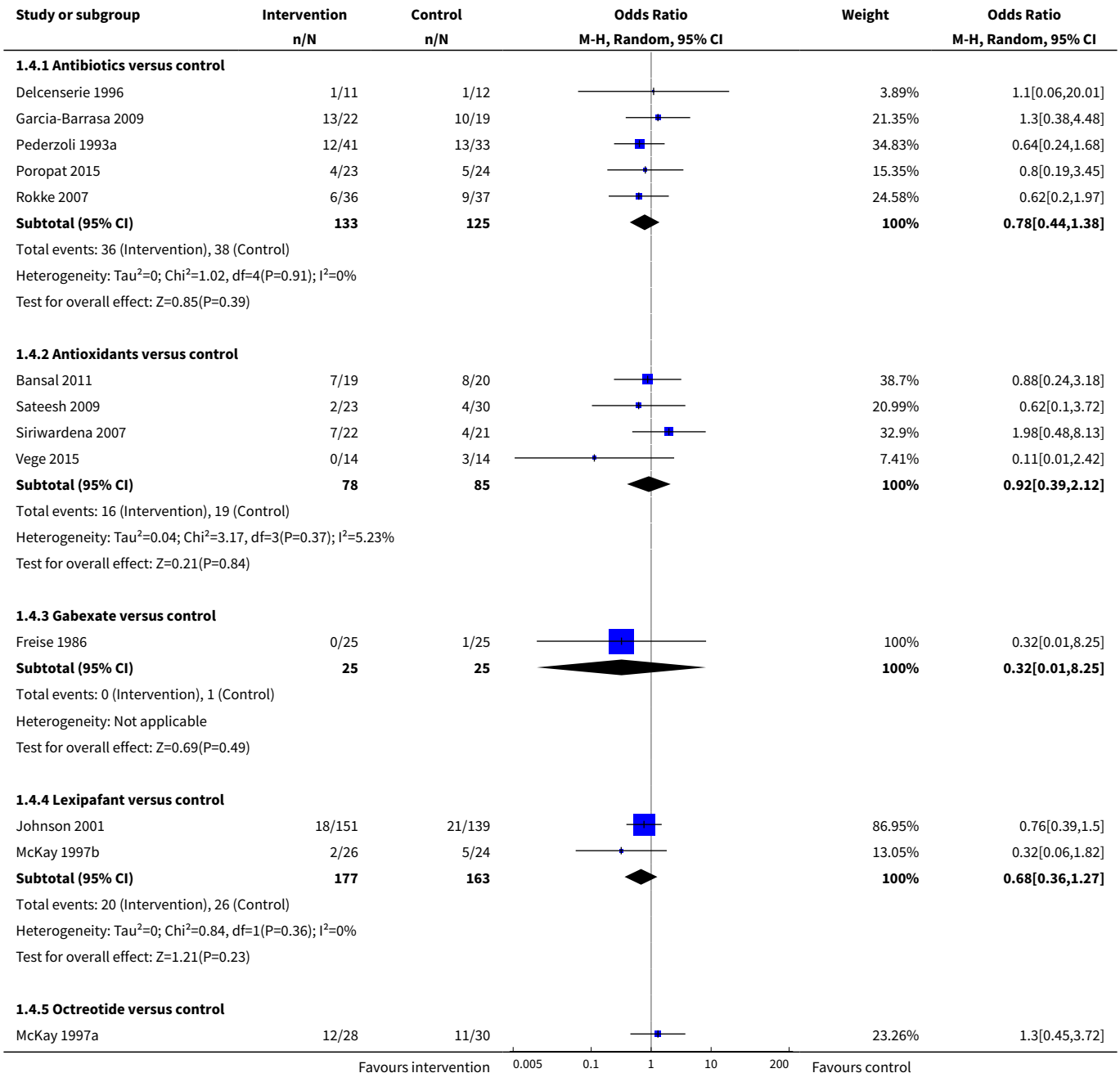


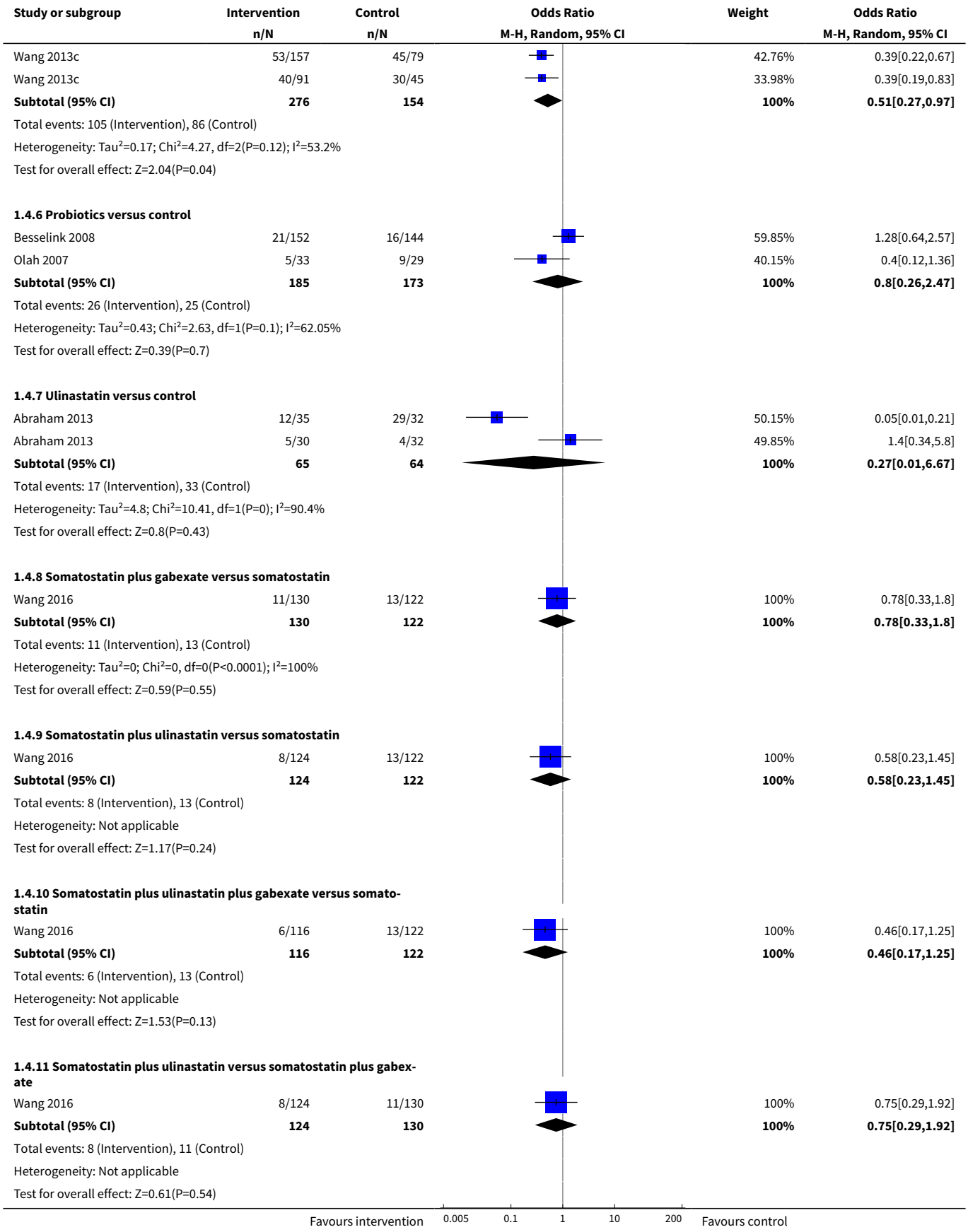


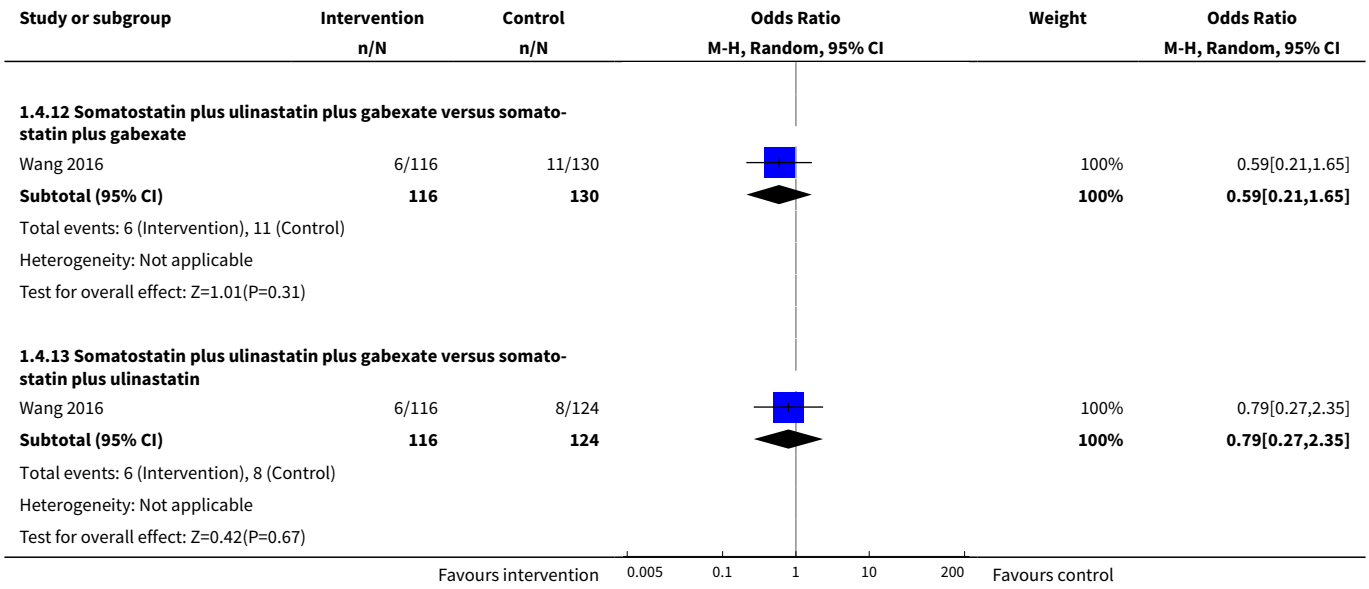




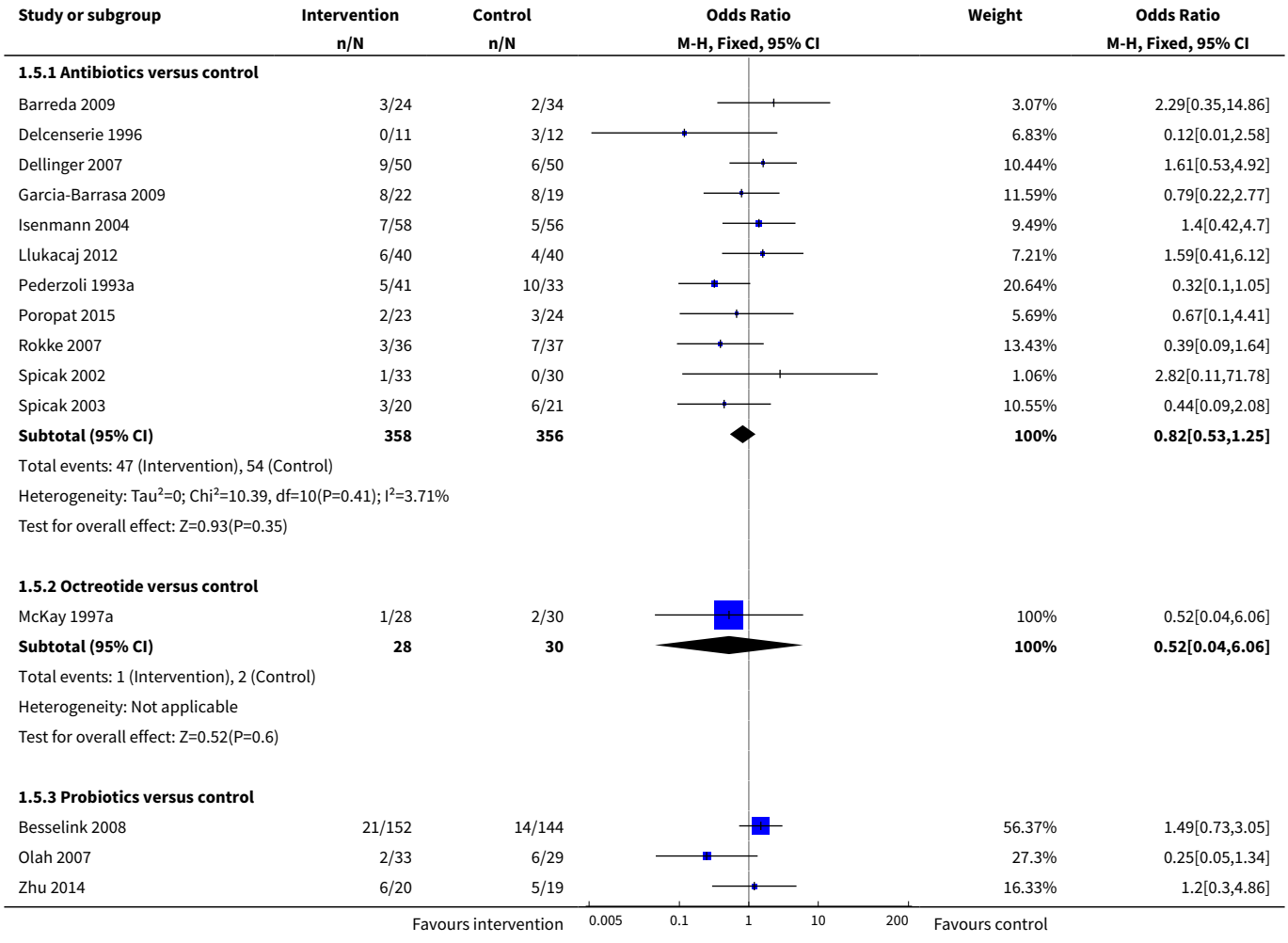

## Analysis 1.4. Comparison 1 Acute pancreatitis, Outcome 4 Organ failure.

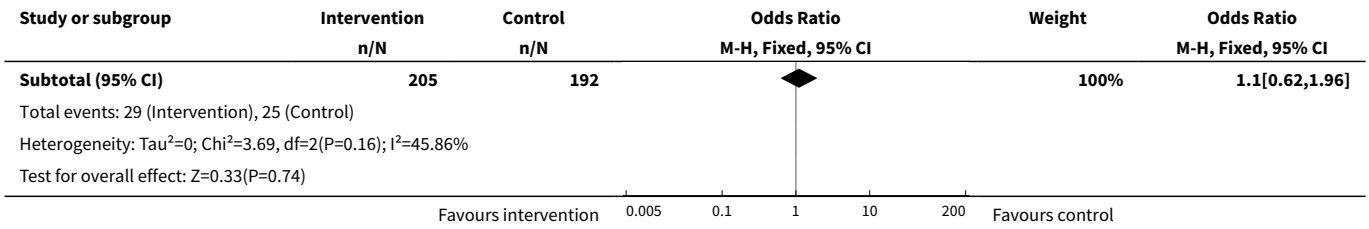




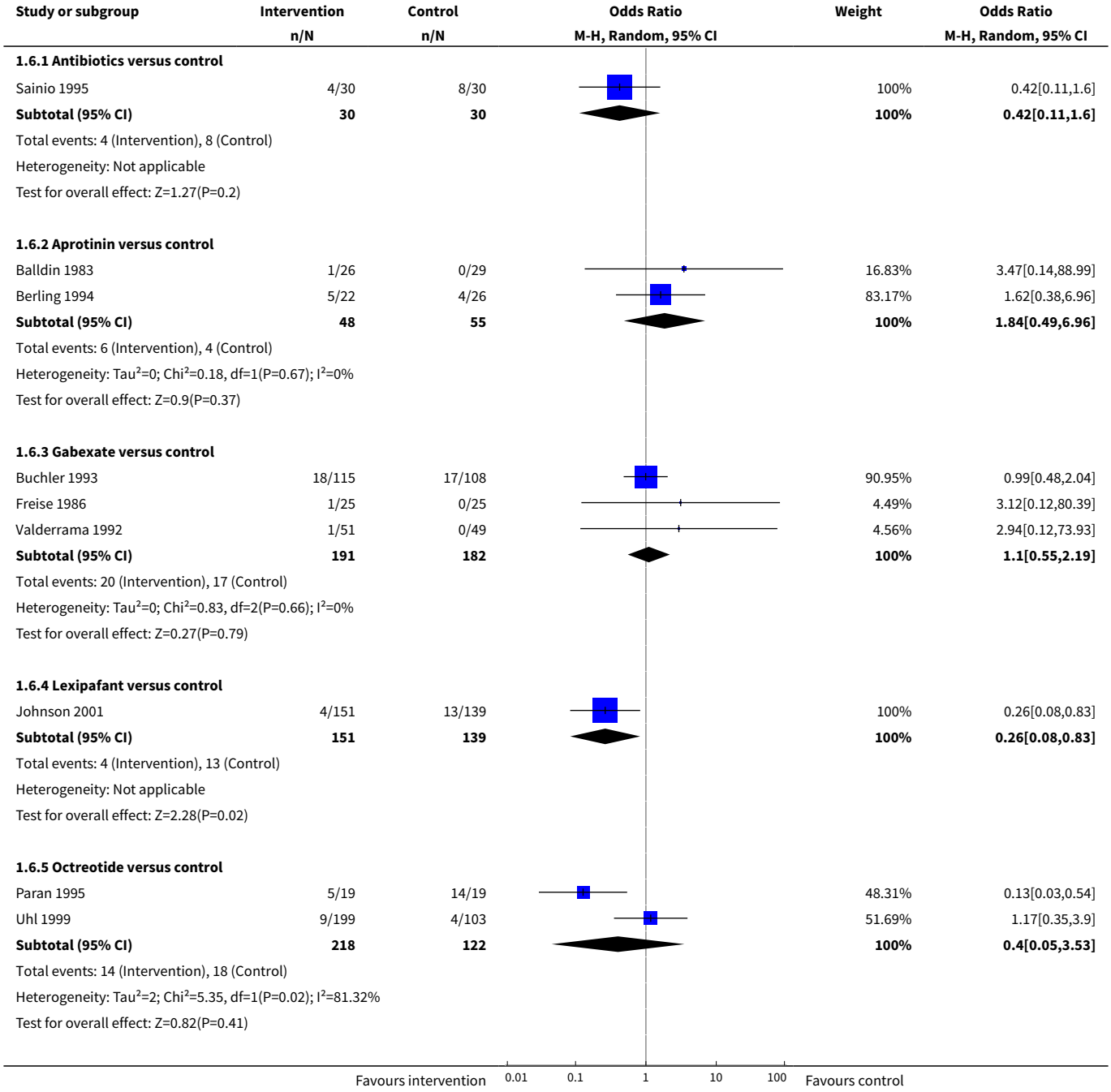


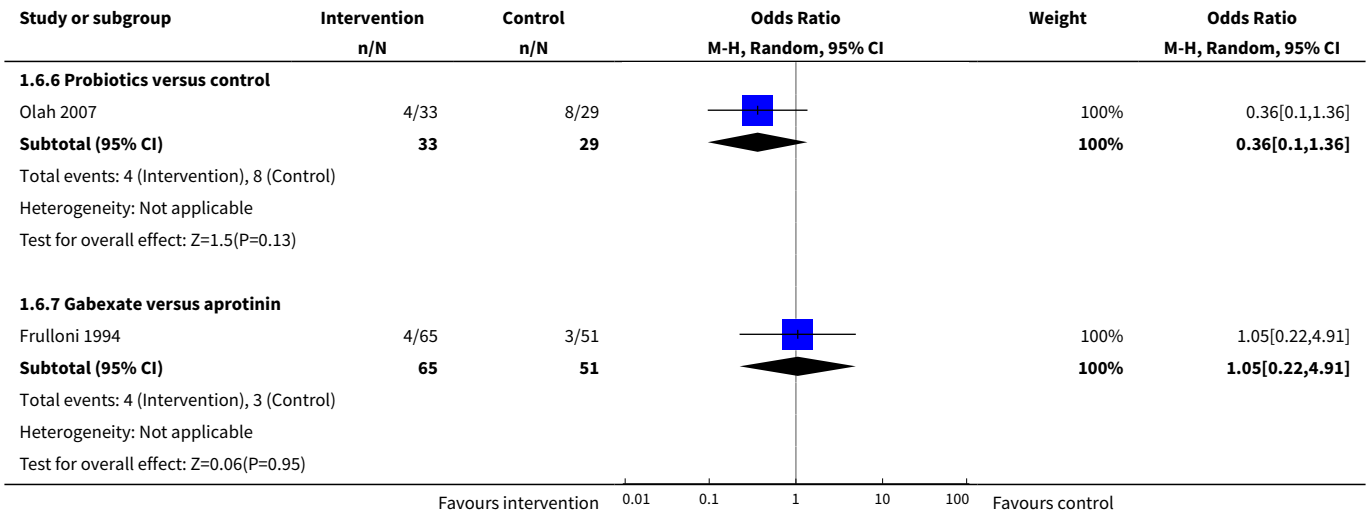

## Analysis 1.5. Comparison 1 Acute pancreatitis, Outcome 5 Infected pancreatic necrosis.



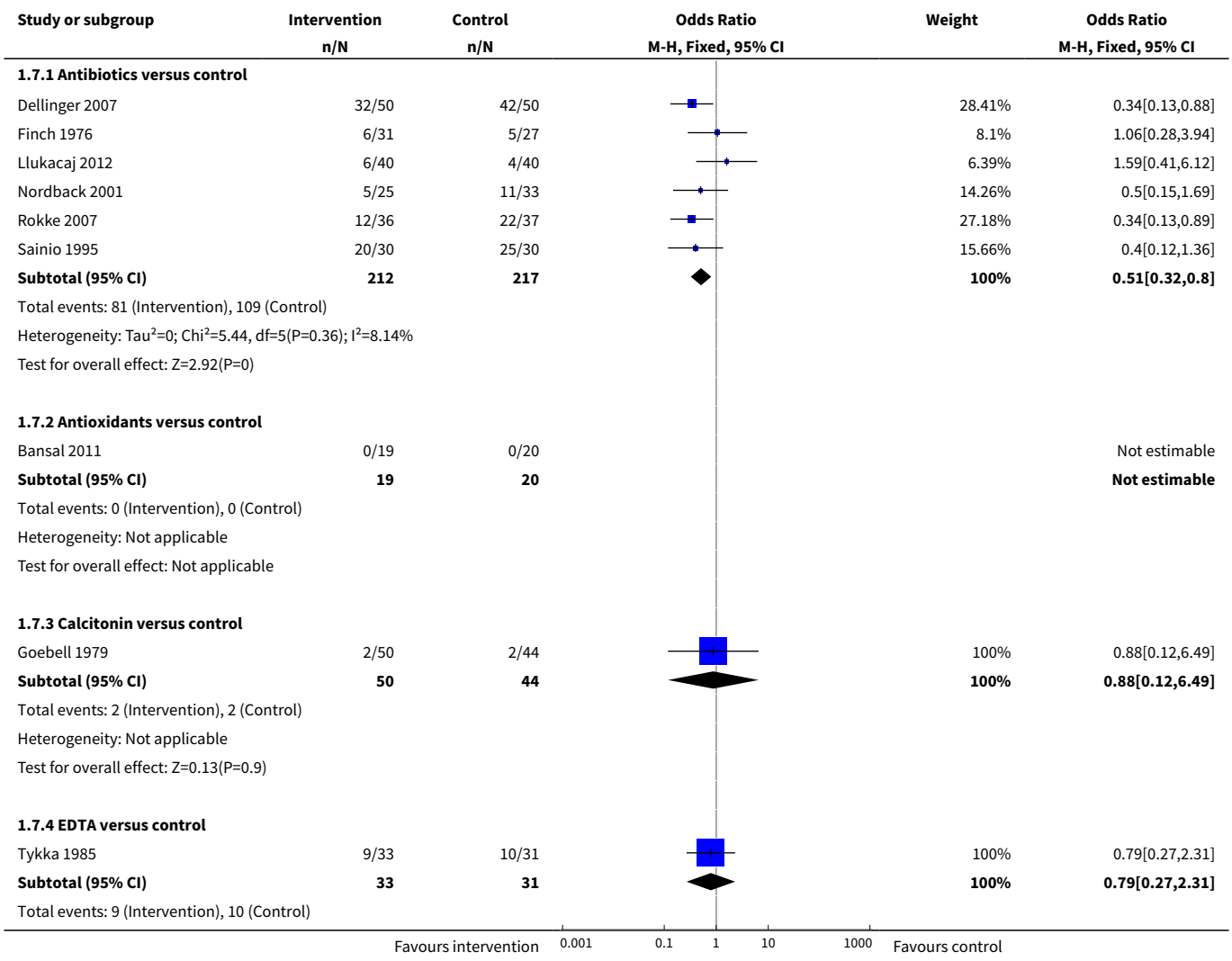


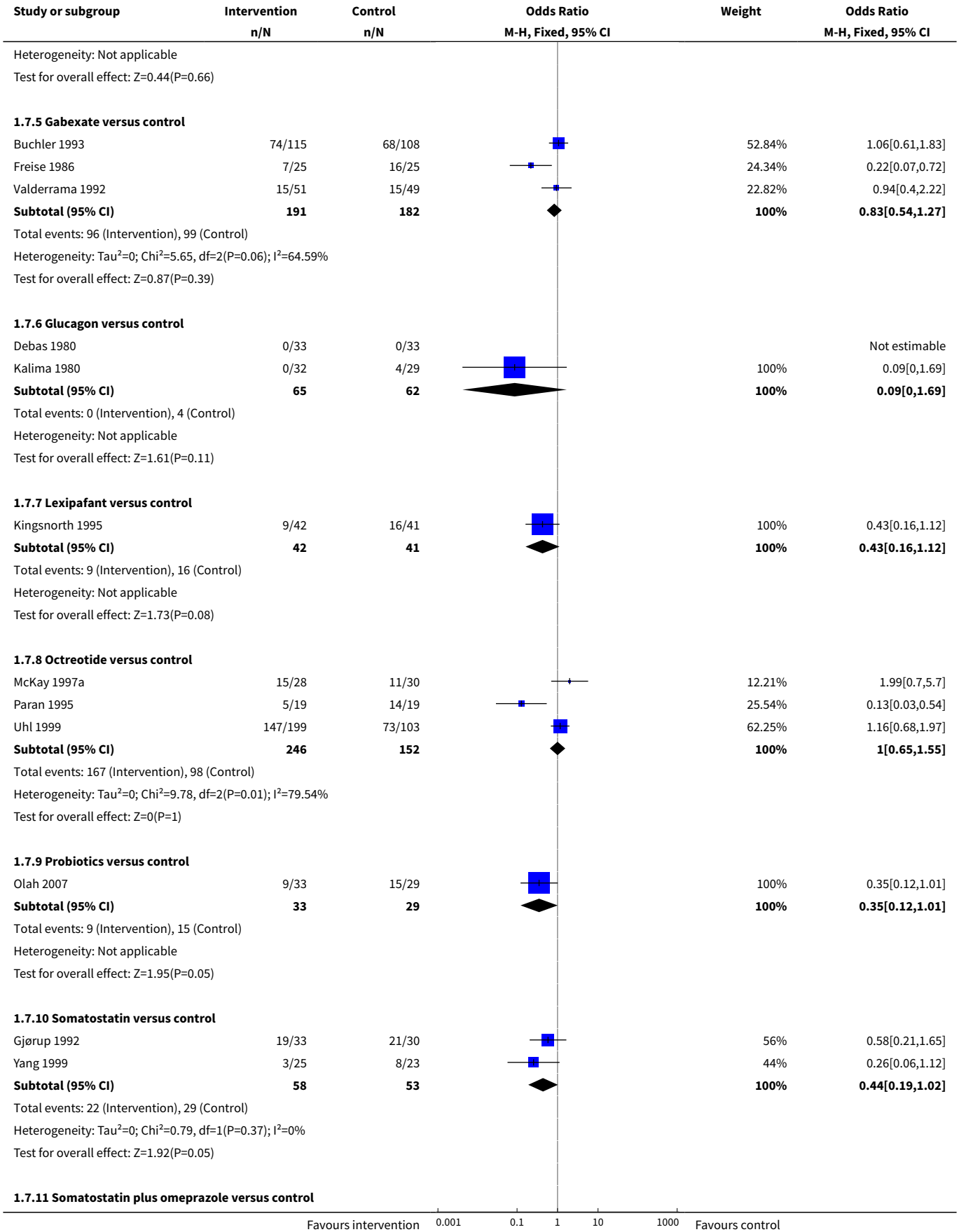

## Analysis 1.6. Comparison 1 Acute pancreatitis, Outcome 6 Sepsis.

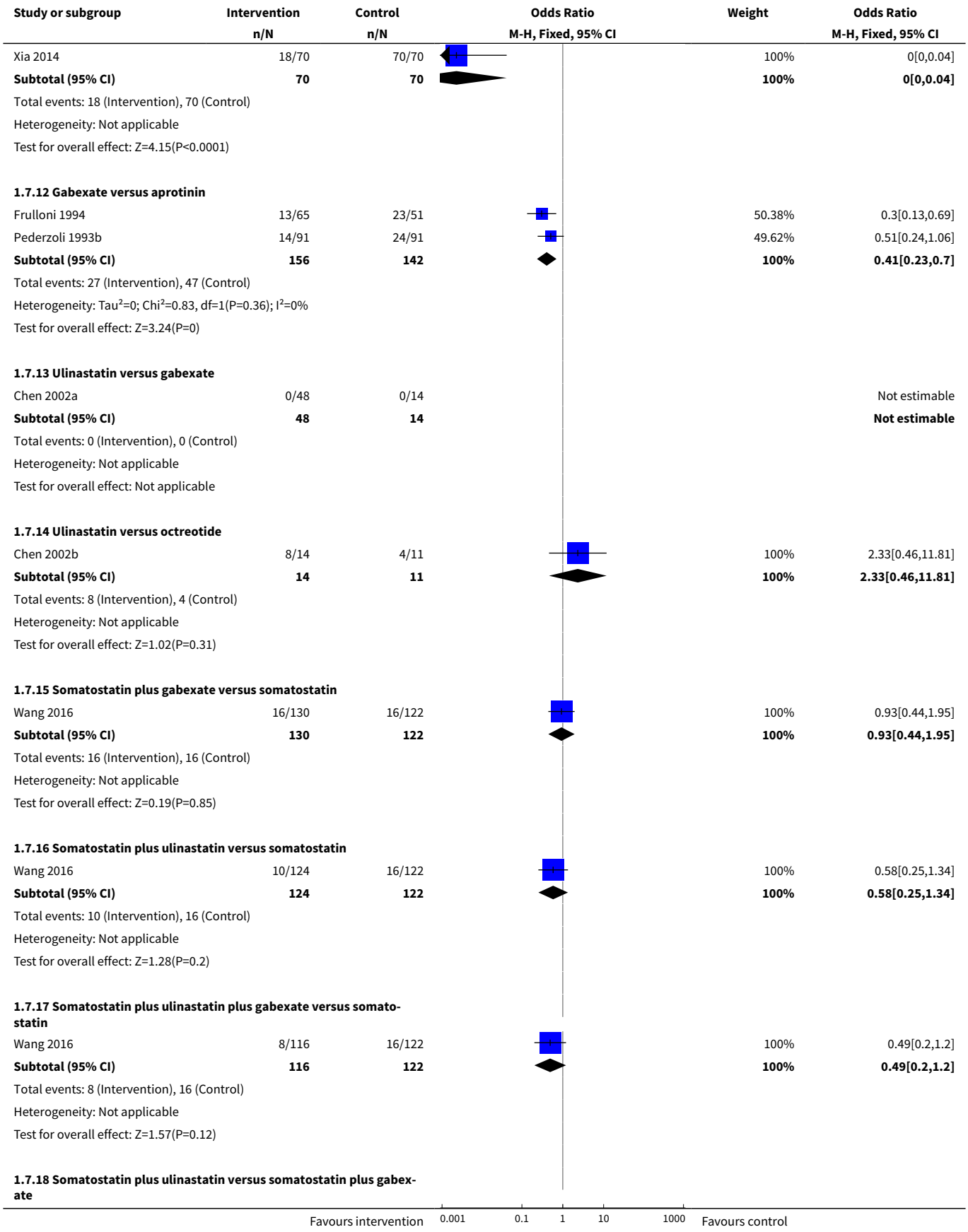


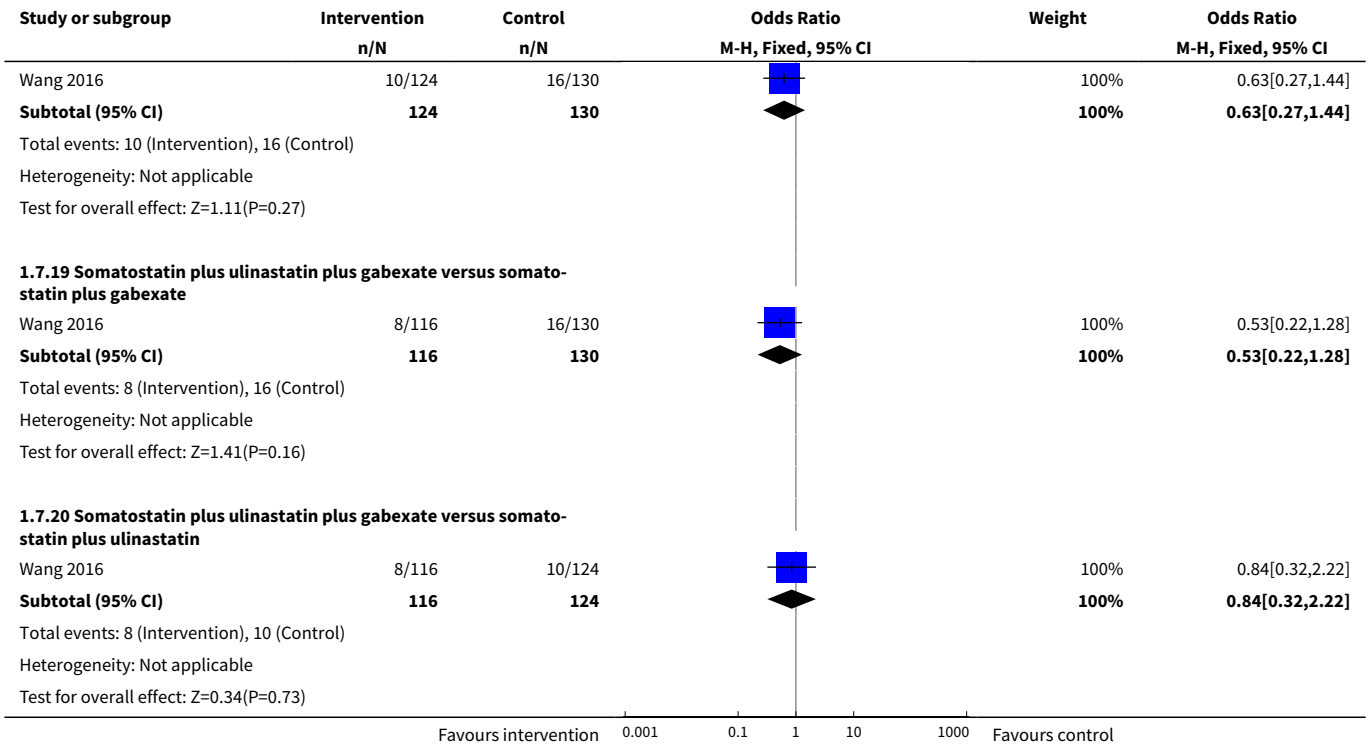



## Analysis 1.7. Comparison 1 Acute pancreatitis, Outcome 7 Adverse events (proportion).





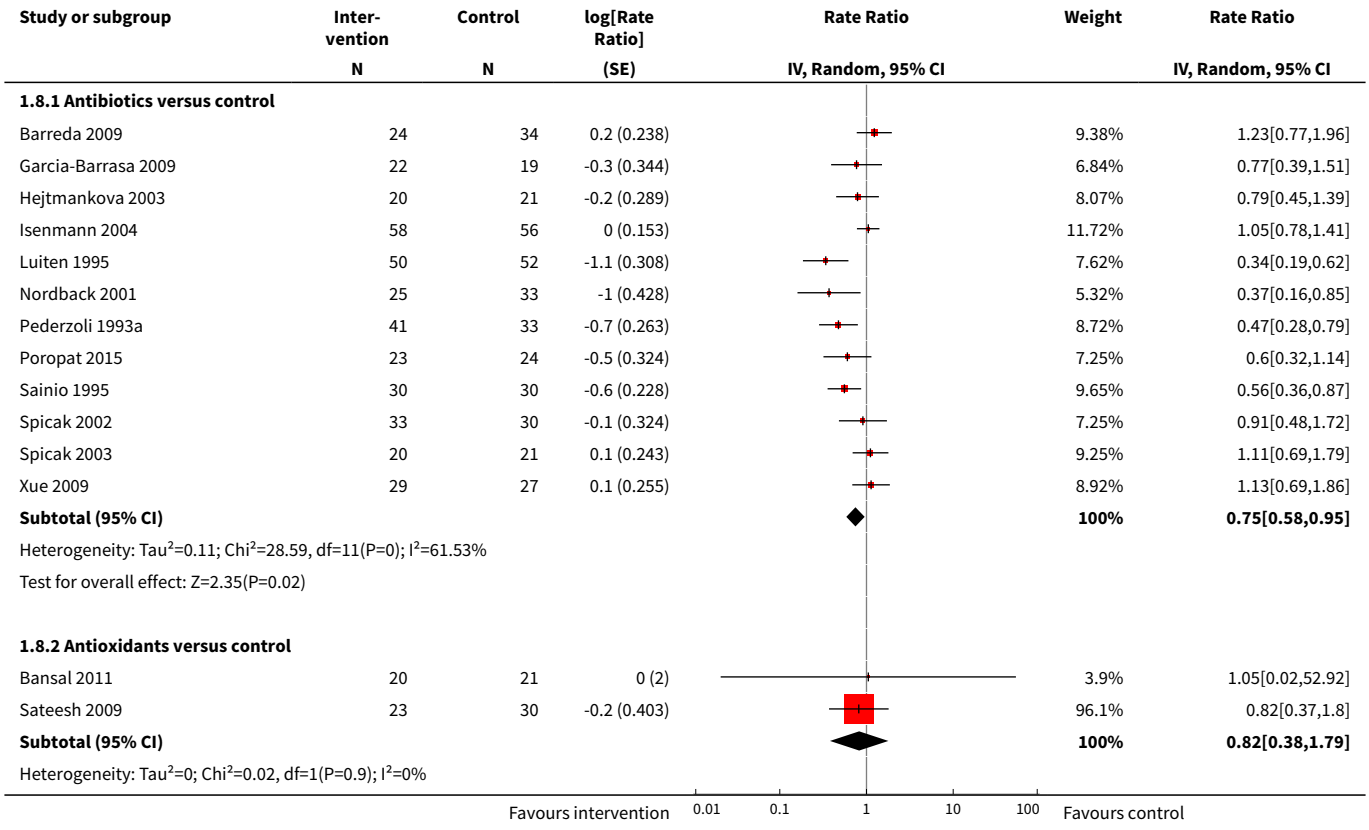




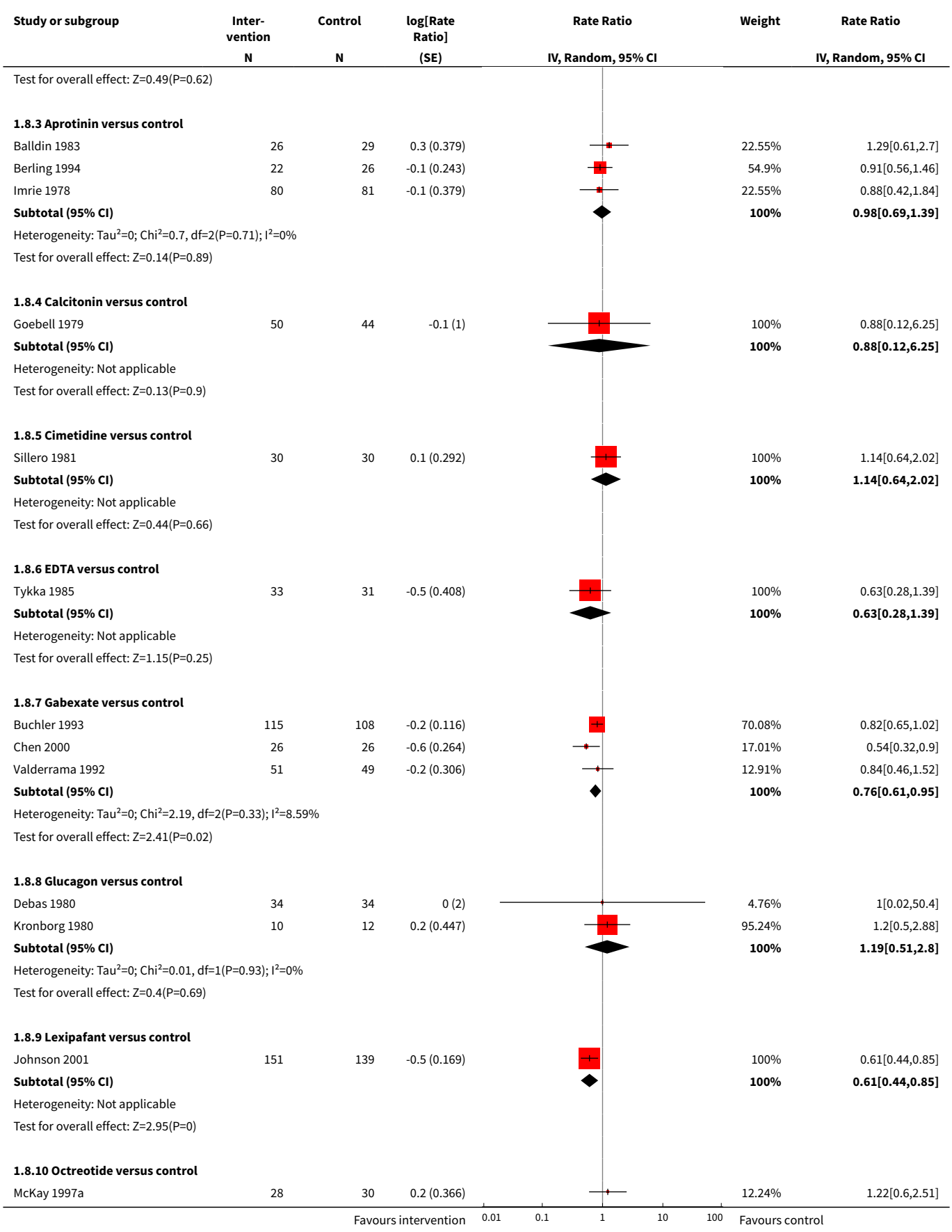
| Study or subgroup | Intervention n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Wang 2016 | 10/124 | 16/130 | | 100% | 0.63[0.27,1.44] |
| **Subtotal (95% CI)** | **124** | **130** | | **100%** | **0.63[0.27,1.44]** |
| Total events: 10 (Intervention), 16 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.11(P=0.27) | | | | | |
| **1.7.19 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus gabexate** | | | | | |
| Wang 2016 | 8/116 | 16/130 | | 100% | 0.53[0.22,1.28] |
| **Subtotal (95% CI)** | **116** | **130** | | **100%** | **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) | | | | | |
| **1.7.20 Somatostatin plus ulinastatin plus gabexate versus somatostatin plus ulinastatin** | | | | | |
| Wang 2016 | 8/116 | 10/124 | | 100% | 0.84[0.32,2.22] |
| **Subtotal (95% CI)** | **116** | **124** | | **100%** | **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) | | | | | |

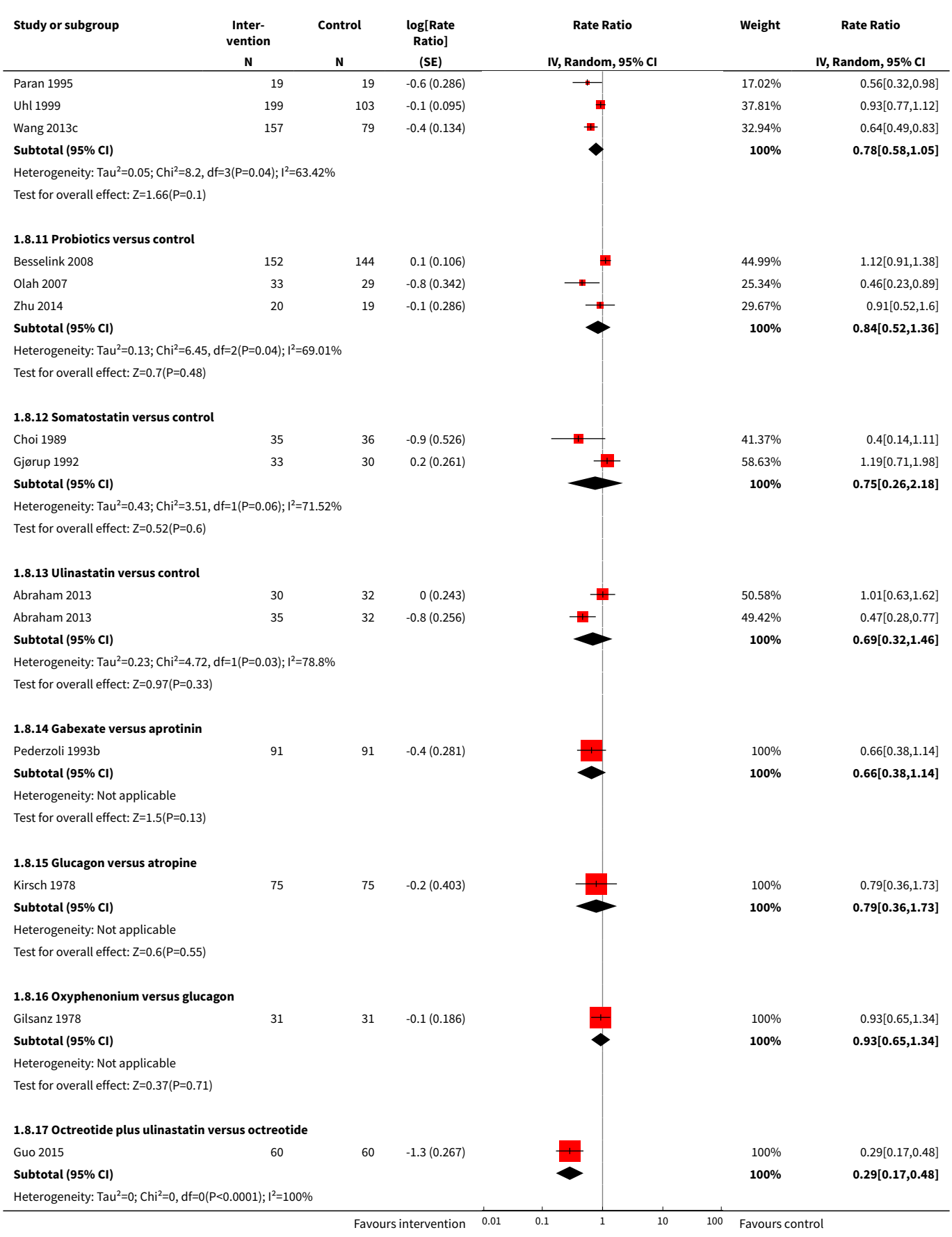


## Analysis 1.8. Comparison 1 Acute pancreatitis, Outcome 8 Adverse events (number).

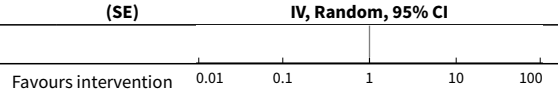


| Study or subgroup | Intervention N | Control N | log[Rate Ratio] (SE) | Rate Ratio IV, Random, 95% CI | Weight | Rate Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **1.8.1 Antibiotics versus control** | | | | | | |
| Barreda 2009 | 24 | 34 | 0.2 (0.238) | | 9.38% | 1.23[0.77,1.96] |
| Garcia-Barrasa 2009 | 22 | 19 | -0.3 (0.344) | | 6.84% | 0.77[0.39,1.51] |
| Hejtmankova 2003 | 20 | 21 | -0.2 (0.289) | | 8.07% | 0.79[0.45,1.39] |
| Isenmann 2004 | 58 | 56 | 0 (0.153) | | 11.72% | 1.05[0.78,1.41] |
| Luiten 1995 | 50 | 52 | -1.1 (0.308) | | 7.62% | 0.34[0.19,0.62] |
| Nordback 2001 | 25 | 33 | -1 (0.428) | | 5.32% | 0.37[0.16,0.85] |
| Pederzoli 1993a | 41 | 33 | -0.7 (0.263) | | 8.72% | 0.47[0.28,0.79] |
| Poropat 2015 | 23 | 24 | -0.5 (0.324) | | 7.25% | 0.6[0.32,1.14] |
| Sainio 1995 | 30 | 30 | -0.6 (0.228) | | 9.65% | 0.56[0.36,0.87] |
| Spicak 2002 | 33 | 30 | -0.1 (0.324) | | 7.25% | 0.91[0.48,1.72] |
| Spicak 2003 | 20 | 21 | 0.1 (0.243) | | 9.25% | 1.11[0.69,1.79] |
| Xue 2009 | 29 | 27 | 0.1 (0.255) | | 8.92% | 1.13[0.69,1.86] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.75[0.58,0.95]** |
| Heterogeneity: $Tau^2$=0.11; $Chi^2$=28.59, df=11(P=0); $I^2$=61.53% | | | | | | |
| Test for overall effect: Z=2.35(P=0.02) | | | | | | |
| **1.8.2 Antioxidants versus control** | | | | | | |
| Bansal 2011 | 20 | 21 | 0 (2) | | 3.9% | 1.05[0.02,52.92] |
| Sateesh 2009 | 23 | 30 | -0.2 (0.403) | | 96.1% | 0.82[0.37,1.8] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.82[0.38,1.79]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.02, df=1(P=0.9); $I^2$=0% | | | | | | |



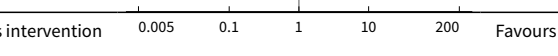


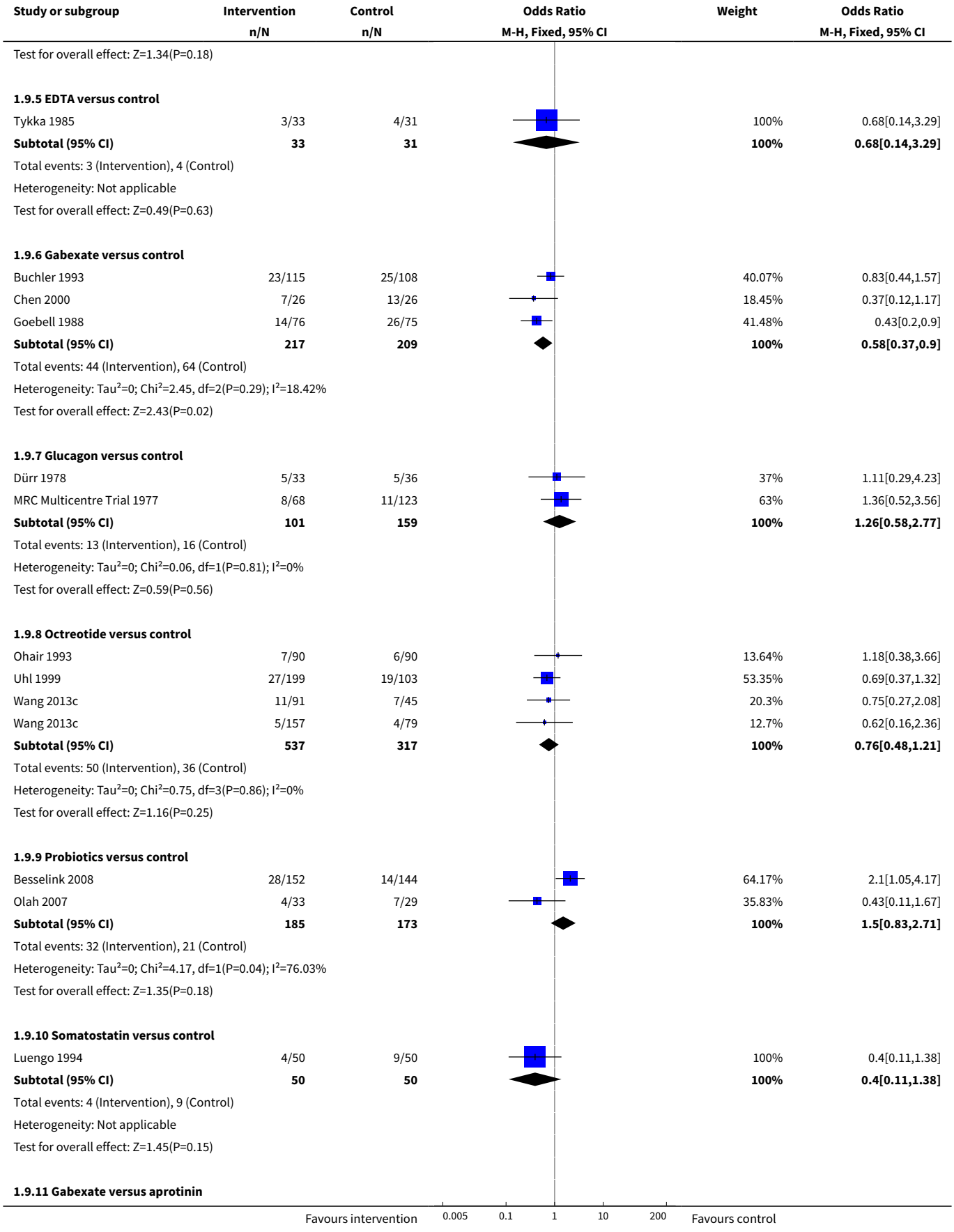
| Study or subgroup | Inter-vention | Control | log[Rate Ratio] | Rate Ratio | Weight | Rate Ratio |
|---|---|---|---|---|---|---|
| | N | N | (SE) | IV, Random, 95% CI | | IV, Random, 95% CI |
| Test for overall effect: Z=4.69(P<0.0001) | | | | | | |

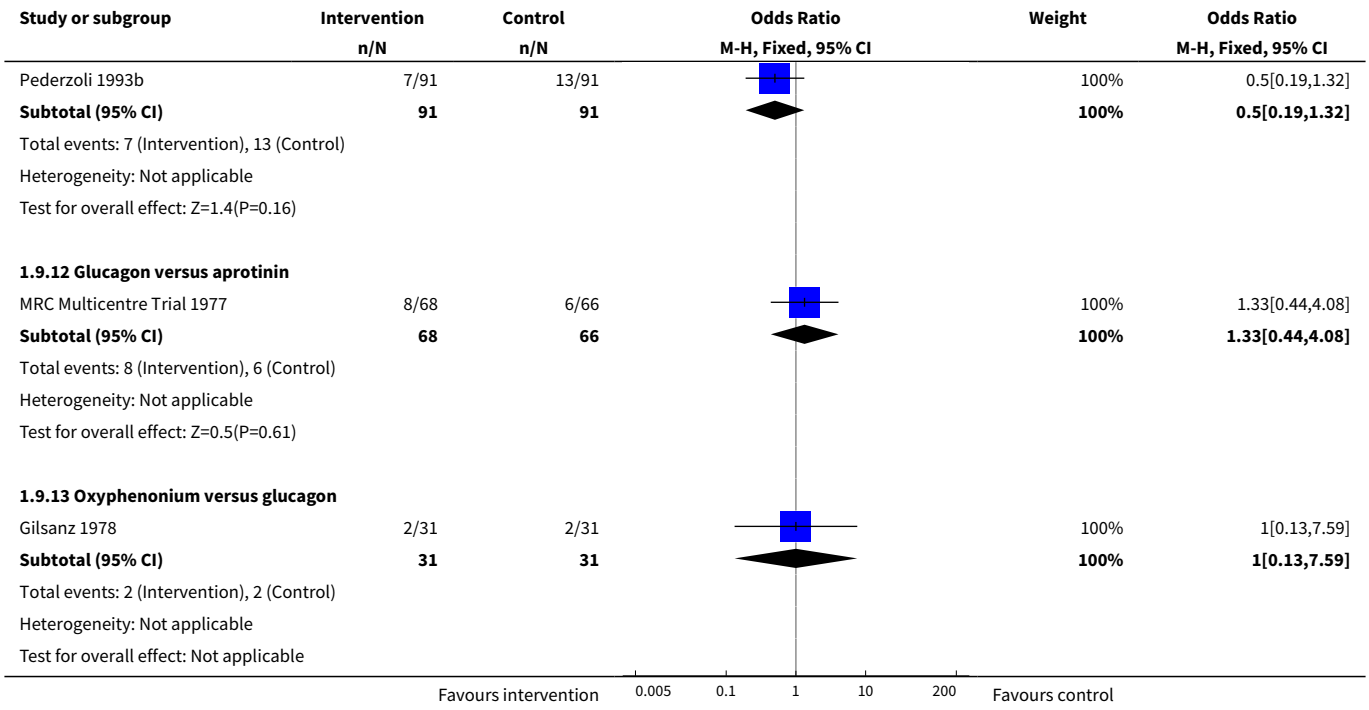



## Analysis 1.9. Comparison 1 Acute pancreatitis, Outcome 9 Requirement for additional invasive intervention.

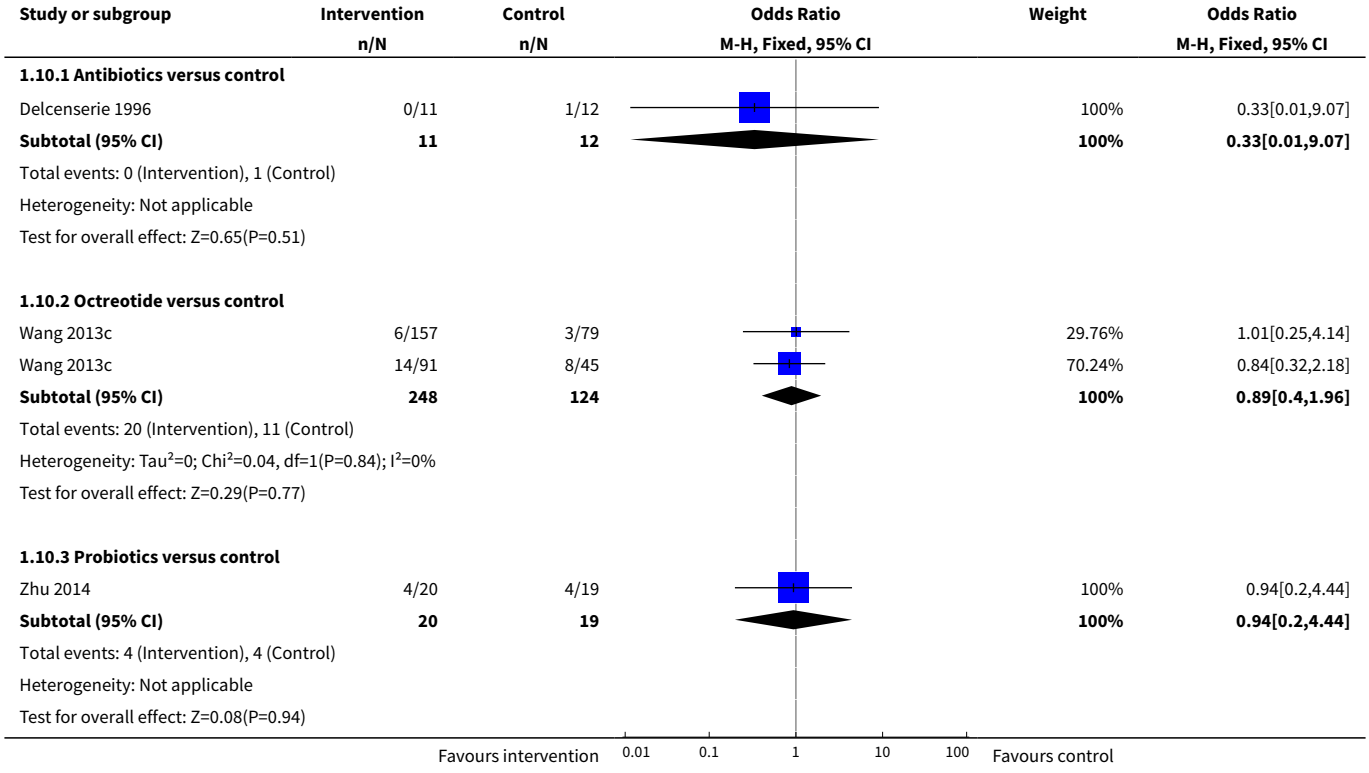
| Study or subgroup | Intervention | Control | Odds Ratio | Weight | Odds Ratio |
|---|---|---|---|---|---|
| | n/N | n/N | M-H, Fixed, 95% CI | | M-H, Fixed, 95% CI |
| **1.9.1 Antibiotics versus control** | | | | | |
| Barreda 2009 | 4/24 | 2/34 | | 1.67% | 3.2[0.54,19.11] |
| Delcenserie 1996 | 0/11 | 3/12 | | 3.9% | 0.12[0.01,2.58] |
| Garcia-Barrasa 2009 | 11/22 | 8/19 | | 5.2% | 1.38[0.4,4.73] |
| Hejtmankova 2003 | 4/20 | 5/21 | | 4.73% | 0.8[0.18,3.54] |
| Isenmann 2004 | 10/58 | 6/56 | | 6.12% | 1.74[0.59,5.15] |
| Llukacaj 2012 | 10/40 | 8/40 | | 7.27% | 1.33[0.46,3.83] |
| Luiten 1995 | 16/50 | 24/52 | | 19.39% | 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 | | 10.45% | 0.83[0.31,2.22] |
| Rokke 2007 | 3/36 | 3/37 | | 3.29% | 1.03[0.19,5.48] |
| Sainio 1995 | 7/30 | 14/30 | | 13.01% | 0.35[0.11,1.05] |
| Spicak 2002 | 6/33 | 7/30 | | 7.27% | 0.73[0.21,2.48] |
| Spicak 2003 | 4/20 | 5/21 | | 4.73% | 0.8[0.18,3.54] |
| Xue 2009 | 8/29 | 9/27 | | 8.18% | 0.76[0.24,2.39] |
| **Subtotal (95% CI)** | **439** | **445** | | **100%** | **0.82[0.59,1.13]** |
| Total events: 97 (Intervention), 110 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=10.79, df=13(P=0.63); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.22(P=0.22) | | | | | |
| **1.9.2 Aprotinin versus control** | | | | | |
| Berling 1994 | 0/22 | 6/26 | | 45.58% | 0.07[0,1.32] |
| MRC Multicentre Trial 1977 | 6/66 | 11/123 | | 54.42% | 1.02[0.36,2.89] |
| **Subtotal (95% CI)** | **88** | **149** | | **100%** | **0.59[0.23,1.47]** |
| Total events: 6 (Intervention), 17 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=3.08, df=1(P=0.08); $I^2$=67.58% | | | | | |
| Test for overall effect: Z=1.14(P=0.25) | | | | | |
| **1.9.3 Calcitonin versus control** | | | | | |
| Goebell 1979 | 2/50 | 5/44 | | 60.35% | 0.33[0.06,1.77] |
| Martinez 1984 | 1/14 | 4/17 | | 39.65% | 0.25[0.02,2.55] |
| **Subtotal (95% CI)** | **64** | **61** | | **100%** | **0.3[0.08,1.16]** |
| Total events: 3 (Intervention), 9 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.03, df=1(P=0.86); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.75(P=0.08) | | | | | |
| **1.9.4 Cimetidine versus control** | | | | | |
| Sillero 1981 | 0/30 | 3/30 | | 100% | 0.13[0.01,2.61] |
| **Subtotal (95% CI)** | **30** | **30** | | **100%** | **0.13[0.01,2.61]** |
| Total events: 0 (Intervention), 3 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |








## Analysis 1.10. Comparison 1 Acute pancreatitis, Outcome 10 Endoscopic or radiological drainage of collections.

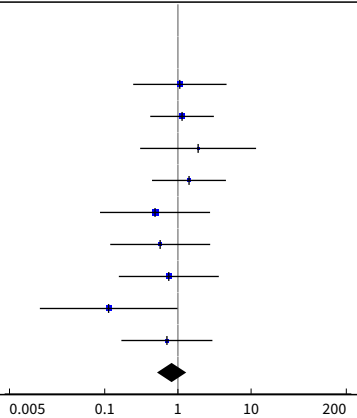


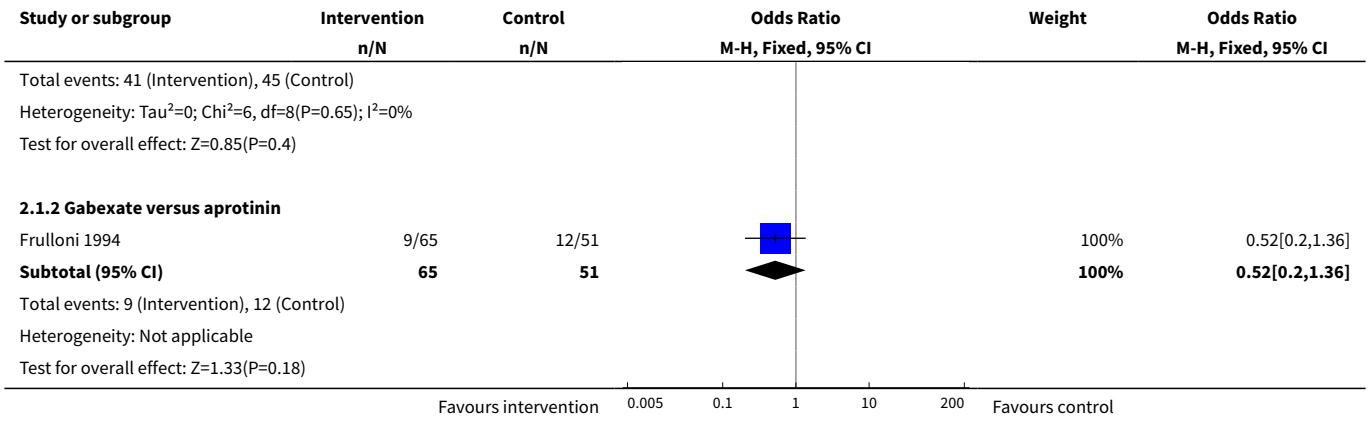
## Comparison 2. Acute necrotising pancreatitis

| 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] |

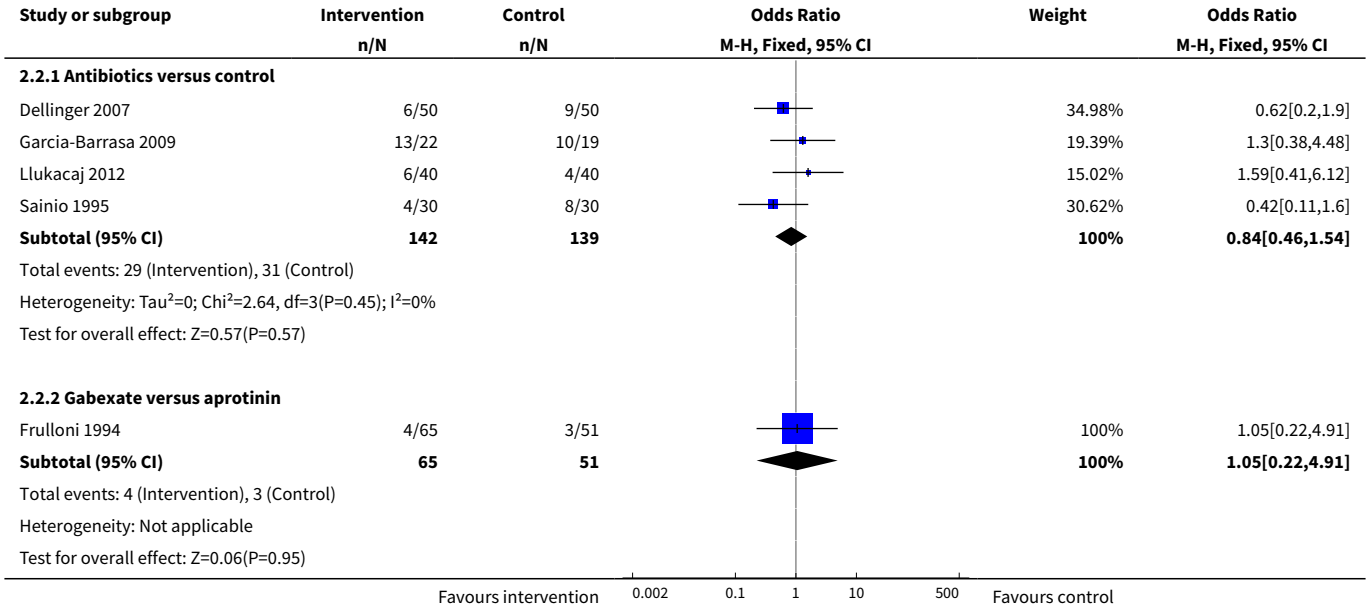
### Analysis 2.1. Comparison 2 Acute necrotising pancreatitis, Outcome 1 Short-term mortality.

| Study or subgroup | Intervention n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.1.1 Antibiotics versus control** | | | | | |
| Barreda 2009 | 0/24 | 0/34 | | | Not estimable |
| Delcenserie 2001 | 6/53 | 3/28 | | 8.67% | 1.06[0.24,4.62] |
| Dellinger 2007 | 10/50 | 9/50 | | 17.92% | 1.14[0.42,3.1] |
| Garcia-Barrasa 2009 | 4/22 | 2/19 | | 4.37% | 1.89[0.31,11.68] |
| Llukacaj 2012 | 8/40 | 6/40 | | 11.95% | 1.42[0.44,4.53] |
| Nordback 2001 | 2/25 | 5/33 | | 9.87% | 0.49[0.09,2.75] |
| Pederzoli 1993a | 3/41 | 4/33 | | 10.23% | 0.57[0.12,2.76] |
| Rokke 2007 | 3/36 | 4/37 | | 9% | 0.75[0.16,3.62] |
| Sainio 1995 | 1/30 | 7/30 | | 16.84% | 0.11[0.01,0.99] |
| Xue 2009 | 4/30 | 5/28 | | 11.16% | 0.71[0.17,2.96] |
| **Subtotal (95% CI)** | **351** | **332** | | **100%** | **0.82[0.52,1.3]** |

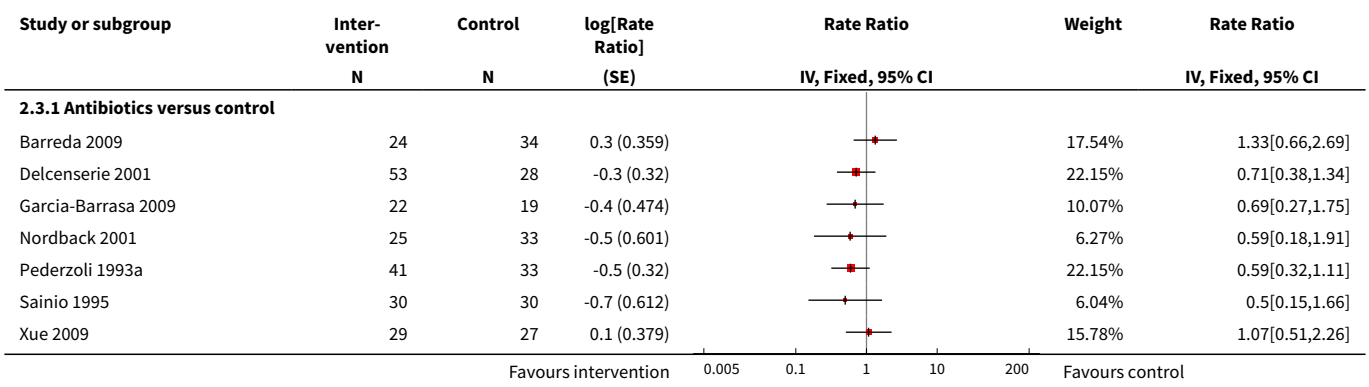


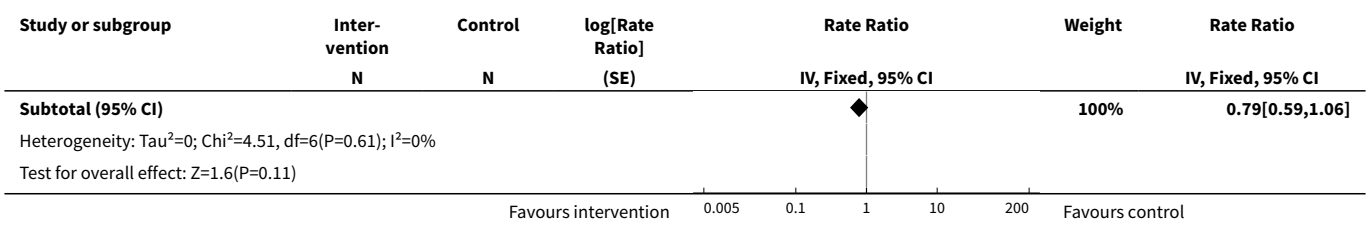



## Analysis 2.2. Comparison 2 Acute necrotising pancreatitis, Outcome 2 Serious adverse events (proportion).

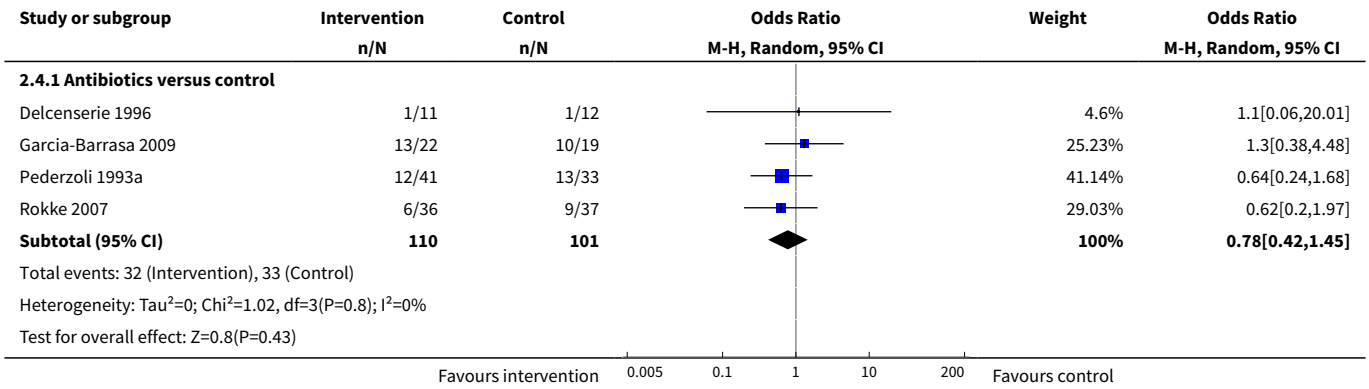



## Analysis 2.3. Comparison 2 Acute necrotising pancreatitis, Outcome 3 Serious adverse events (number).

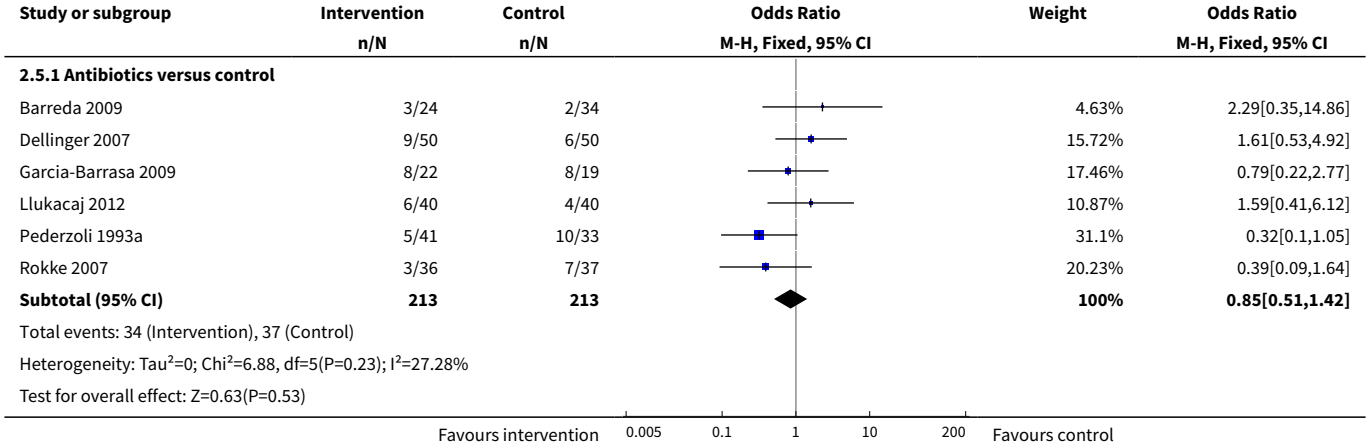




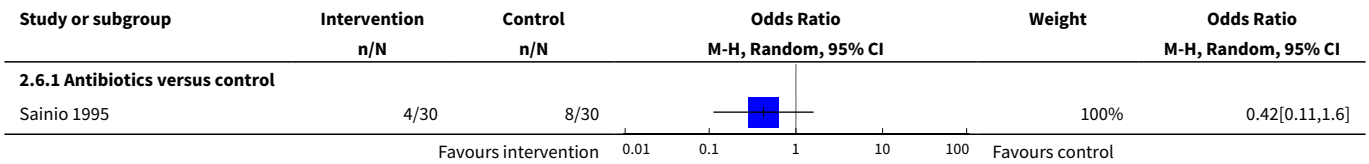

## Analysis 2.4. Comparison 2 Acute necrotising pancreatitis, Outcome 4 Organ failure.

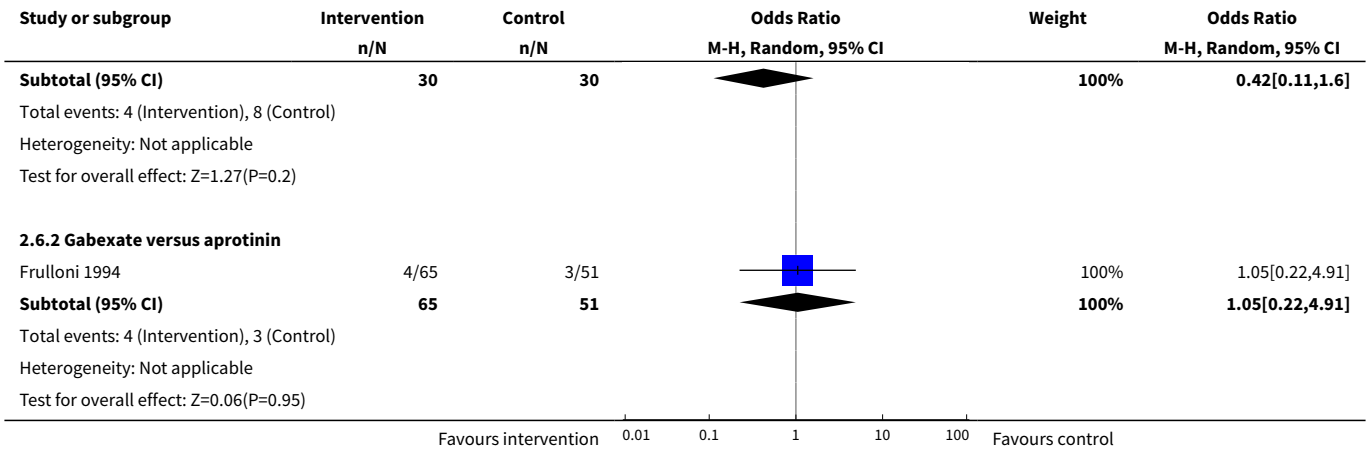



## Analysis 2.5. Comparison 2 Acute necrotising pancreatitis, Outcome 5 Infected pancreatic necrosis.




## Analysis 2.6. Comparison 2 Acute necrotising pancreatitis, Outcome 6 Sepsis.






## 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] |

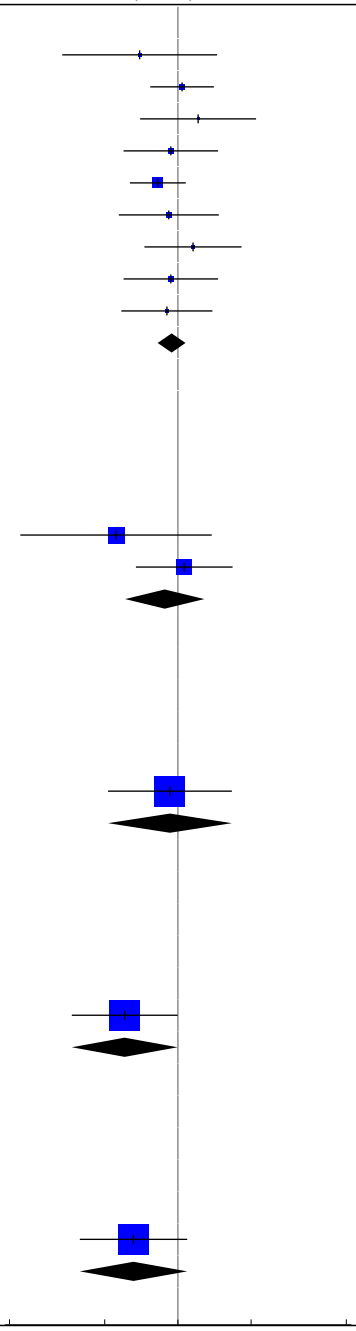
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.11 Ulinastatin versus control | 1 | 70 | Odds Ratio (M-H, Fixed, 95% CI) | 0.24 [0.04, 1.29] |
| 1.12 Octreotide plus ulinastatin versus octreotide | 1 | 120 | Odds Ratio (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] |

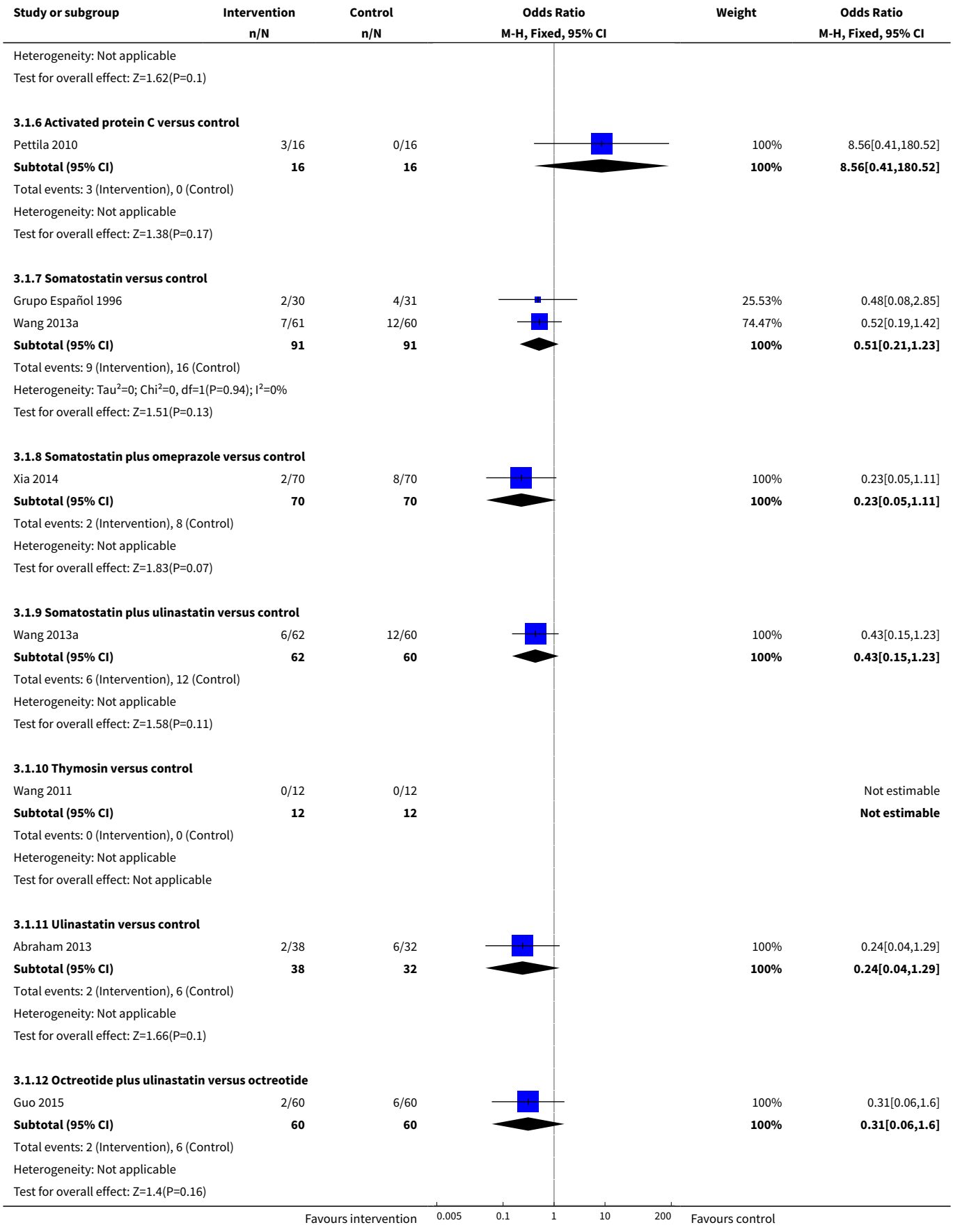
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.8 Octreotide plus ulinastatin versus octreotide | 1 | | Rate Ratio (Random, 95% CI) | 0.30 [0.17, 0.51] |
| 3.9 Somatostatin plus ulinastatin versus somatostatin | 1 | | Rate 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] |

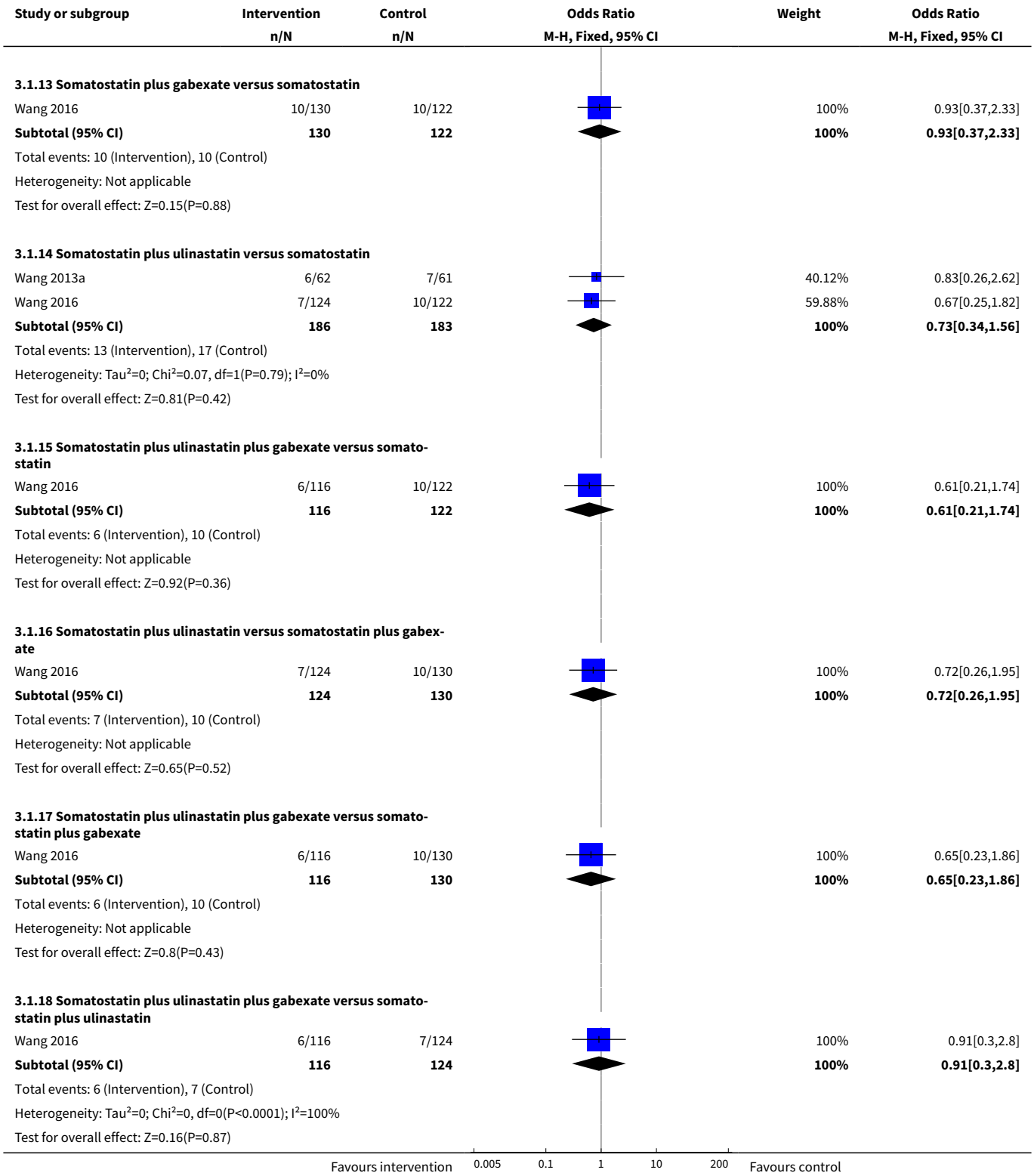
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6.2 Probiotics versus control | 1 | 62 | Odds Ratio (M-H, Fixed, 95% CI) | 0.36 [0.10, 1.36] |

## Analysis 3.1. Comparison 3 Severe 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 |
|---|---|---|---|---|---|
| **3.1.1 Antibiotics versus control** | | | | | |
| Delcenserie 1996 | 1/11 | 3/12 | | 5.94% | 0.3[0.03,3.43] |
| Dellinger 2007 | 10/50 | 9/50 | | 16.4% | 1.14[0.42,3.1] |
| Garcia-Barrasa 2009 | 4/22 | 2/19 | | 4% | 1.89[0.31,11.68] |
| Hejtmankova 2003 | 4/20 | 5/21 | | 8.89% | 0.8[0.18,3.54] |
| Luiten 1995 | 11/50 | 18/52 | | 31.35% | 0.53[0.22,1.28] |
| Rokke 2007 | 3/36 | 4/37 | | 8.24% | 0.75[0.16,3.62] |
| Spicak 2002 | 5/33 | 3/30 | | 6.07% | 1.61[0.35,7.39] |
| Spicak 2003 | 4/20 | 5/21 | | 8.89% | 0.8[0.18,3.54] |
| Xue 2009 | 4/30 | 5/28 | | 10.21% | 0.71[0.17,2.96] |
| **Subtotal (95% CI)** | **272** | **270** | | **100%** | **0.82[0.53,1.27]** |
| Total events: 46 (Intervention), 54 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=3.6, df=8(P=0.89); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.88(P=0.38) | | | | | |
| **3.1.2 Aprotinin versus control** | | | | | |
| Balldin 1983 | 0/26 | 3/29 | | 52.03% | 0.14[0.01,2.9] |
| Berling 1994 | 4/22 | 4/26 | | 47.97% | 1.22[0.27,5.59] |
| **Subtotal (95% CI)** | **48** | **55** | | **100%** | **0.66[0.19,2.3]** |
| Total events: 4 (Intervention), 7 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.62, df=1(P=0.2); $I^2$=38.39% | | | | | |
| Test for overall effect: Z=0.65(P=0.51) | | | | | |
| **3.1.3 Calcitonin versus control** | | | | | |
| Martinez 1984 | 2/14 | 3/17 | | 100% | 0.78[0.11,5.46] |
| **Subtotal (95% CI)** | **14** | **17** | | **100%** | **0.78[0.11,5.46]** |
| Total events: 2 (Intervention), 3 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.25(P=0.8) | | | | | |
| **3.1.4 Gabexate versus control** | | | | | |
| Chen 2000 | 2/26 | 8/26 | | 100% | 0.19[0.04,0.99] |
| **Subtotal (95% CI)** | **26** | **26** | | **100%** | **0.19[0.04,0.99]** |
| Total events: 2 (Intervention), 8 (Control) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.97(P=0.05) | | | | | |
| **3.1.5 Probiotics versus control** | | | | | |
| Olah 2007 | 2/33 | 6/29 | | 100% | 0.25[0.05,1.34] |
| **Subtotal (95% CI)** | **33** | **29** | | **100%** | **0.25[0.05,1.34]** |
| Total events: 2 (Intervention), 6 (Control) | | | | | |

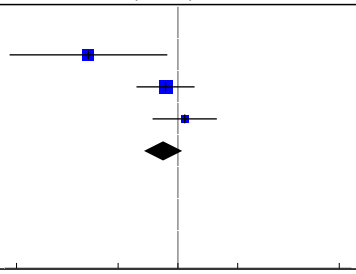






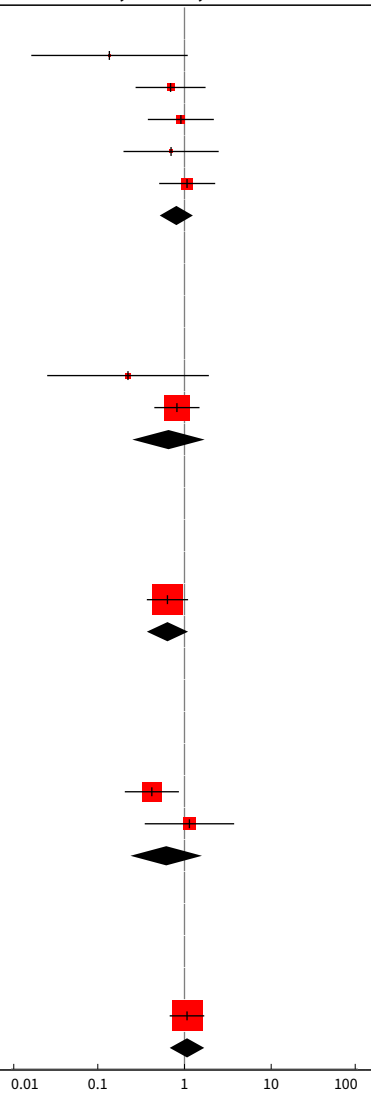
## Analysis 3.2. Comparison 3 Severe acute pancreatitis, Outcome 2 Serious adverse events (proportion).

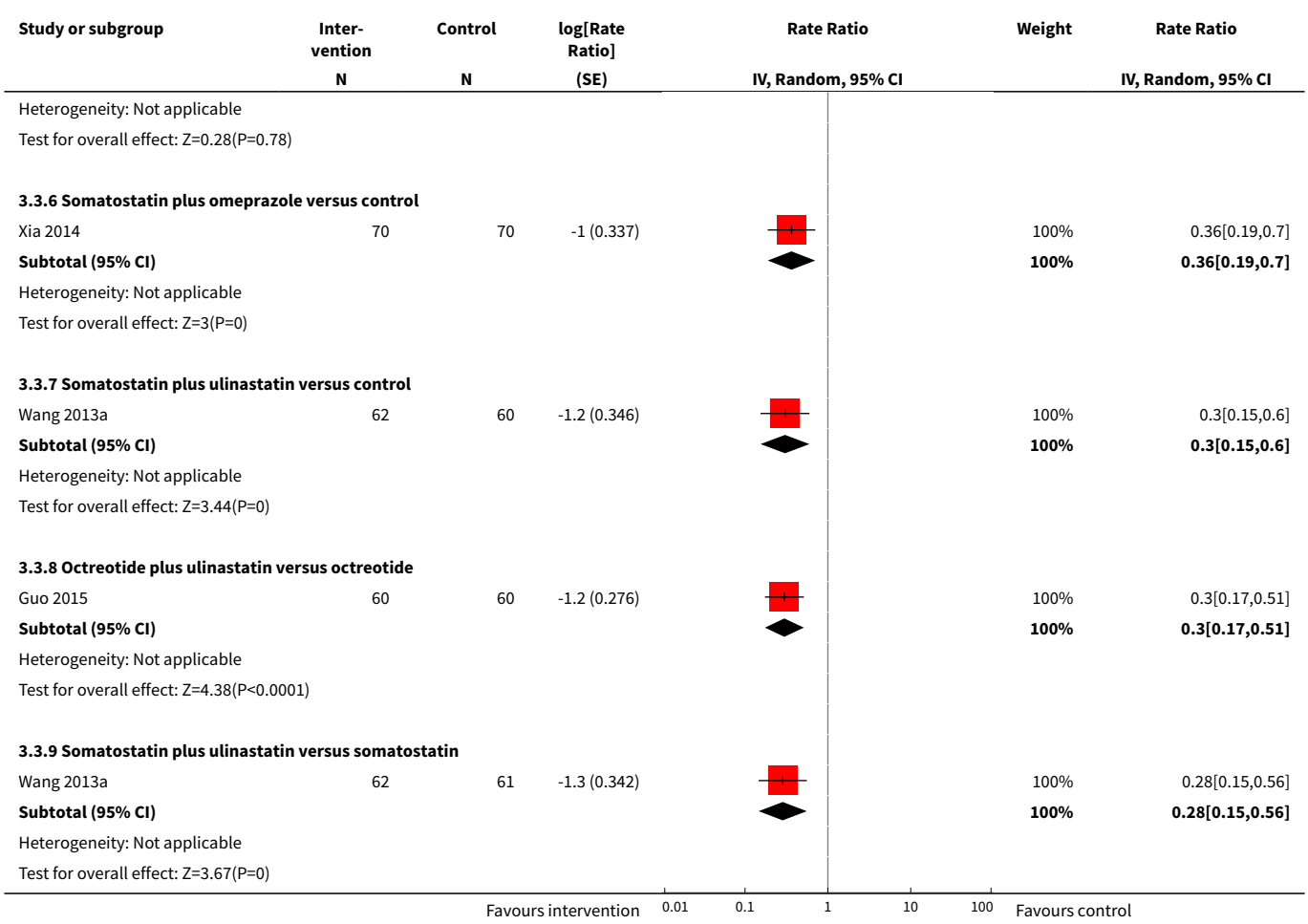
| Study or subgroup | Intervention n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **3.2.1 Antibiotics versus control** | | | | | |
| Delcenserie 1996 | 0/11 | 7/12 | | 35.92% | 0.03[0,0.67] |
| Dellinger 2007 | 6/50 | 9/50 | | 41.23% | 0.62[0.2,1.9] |
| Garcia-Barrasa 2009 | 13/22 | 10/19 | | 22.85% | 1.3[0.38,4.48] |
| **Subtotal (95% CI)** | **83** | **81** | | **100%** | **0.56[0.27,1.18]** |
| Total events: 19 (Intervention), 26 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=5.21, df=2(P=0.07); $I^2$=61.61% | | | | | |
| Test for overall effect: Z=1.53(P=0.13) | | | | | |



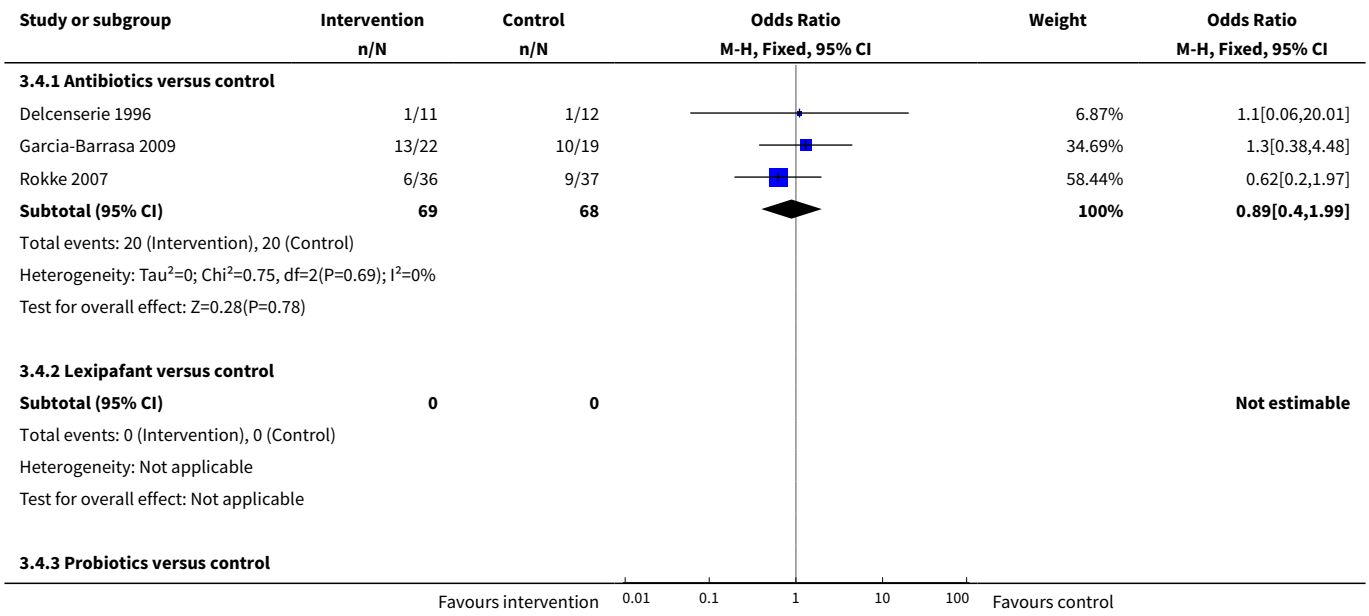

## Analysis 3.3. Comparison 3 Severe acute pancreatitis, Outcome 3 Serious adverse events (number).

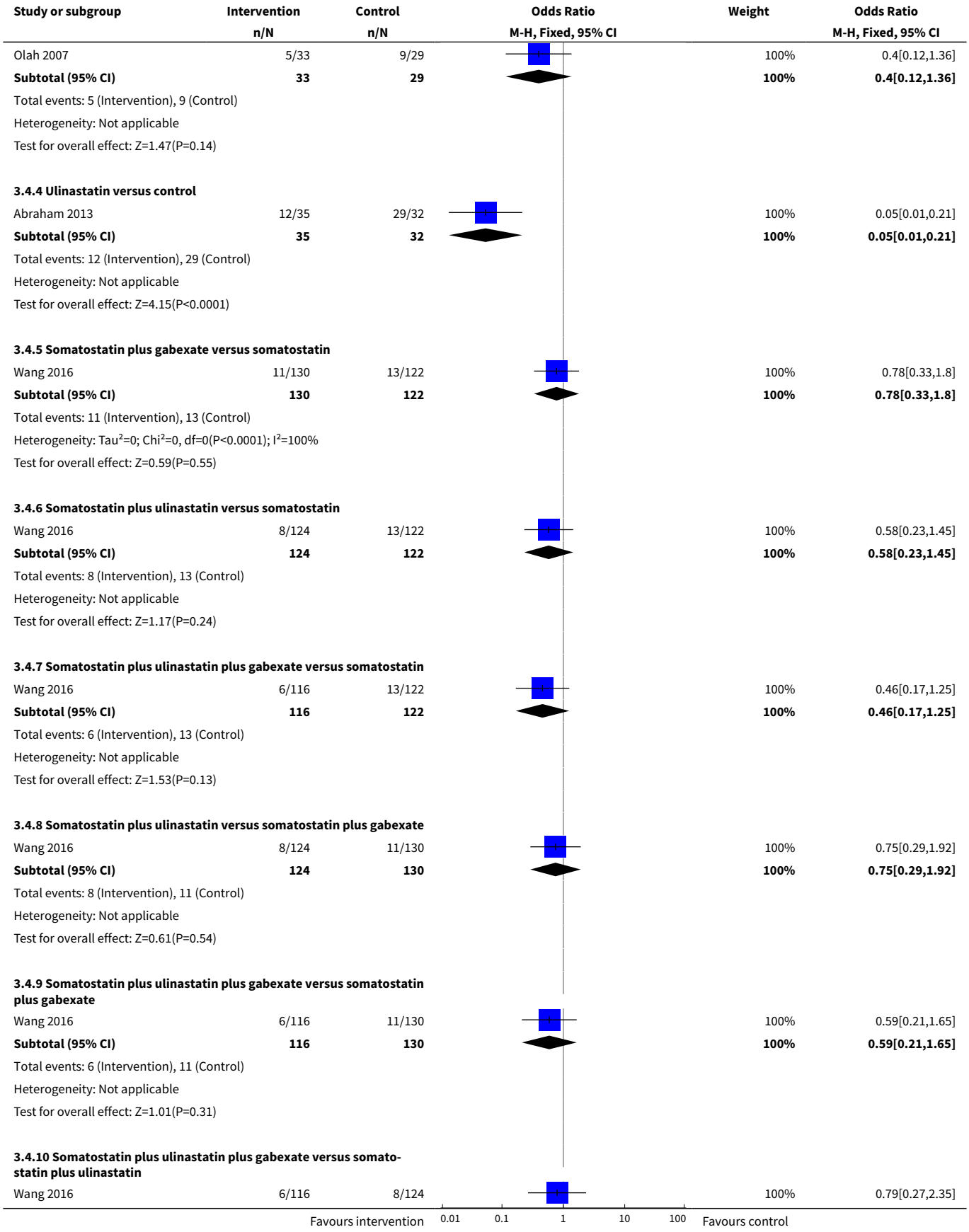
| Study or subgroup | Inter-vention N | Control N | log[Rate Ratio] (SE) | Rate Ratio IV, Random, 95% CI | Weight | Rate Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.3.1 Antibiotics versus control** | | | | | | |
| Delcenserie 1996 | 11 | 12 | -2 (1.061) | | 4.51% | 0.14[0.02,1.09] |
| Garcia-Barrasa 2009 | 22 | 19 | -0.4 (0.474) | | 22.56% | 0.69[0.27,1.75] |
| Spicak 2002 | 33 | 30 | -0.1 (0.447) | | 25.38% | 0.91[0.38,2.18] |
| Spicak 2003 | 20 | 21 | -0.4 (0.645) | | 12.18% | 0.7[0.2,2.48] |
| Xue 2009 | 29 | 27 | 0.1 (0.379) | | 35.36% | 1.07[0.51,2.26] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.81[0.52,1.25]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=3.61, df=4(P=0.46); $I^2$=0% | | | | | | |
| Test for overall effect: Z=0.96(P=0.34) | | | | | | |
| **3.3.2 Aprotinin versus control** | | | | | | |
| Balldin 1983 | 26 | 29 | -1.5 (1.095) | | 17.26% | 0.22[0.03,1.91] |
| Berling 1994 | 22 | 26 | -0.2 (0.307) | | 82.74% | 0.82[0.45,1.49] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.65[0.25,1.71]** |
| Heterogeneity: $Tau^2$=0.2; $Chi^2$=1.31, df=1(P=0.25); $I^2$=23.38% | | | | | | |
| Test for overall effect: Z=0.87(P=0.39) | | | | | | |
| **3.3.3 Gabexate versus control** | | | | | | |
| Chen 2000 | 26 | 26 | -0.5 (0.279) | | 100% | 0.64[0.37,1.1] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.64[0.37,1.1]** |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z=1.62(P=0.11) | | | | | | |
| **3.3.4 Probiotics versus control** | | | | | | |
| Olah 2007 | 33 | 29 | -0.9 (0.367) | | 61.66% | 0.42[0.2,0.86] |
| Zhu 2014 | 20 | 19 | 0.1 (0.606) | | 38.34% | 1.14[0.35,3.74] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.62[0.24,1.59]** |
| Heterogeneity: $Tau^2$=0.25; $Chi^2$=1.99, df=1(P=0.16); $I^2$=49.68% | | | | | | |
| Test for overall effect: Z=1(P=0.32) | | | | | | |
| **3.3.5 Somatostatin versus control** | | | | | | |
| Wang 2013a | 61 | 60 | 0.1 (0.234) | | 100% | 1.07[0.67,1.69] |
| **Subtotal (95% CI)** | | | | | **100%** | **1.07[0.67,1.69]** |

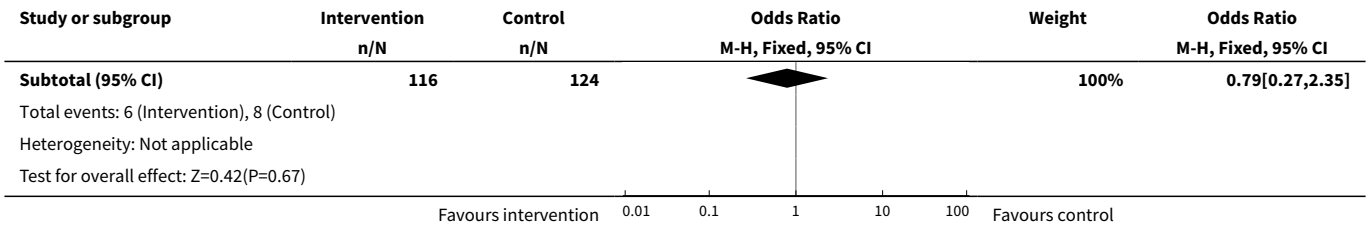




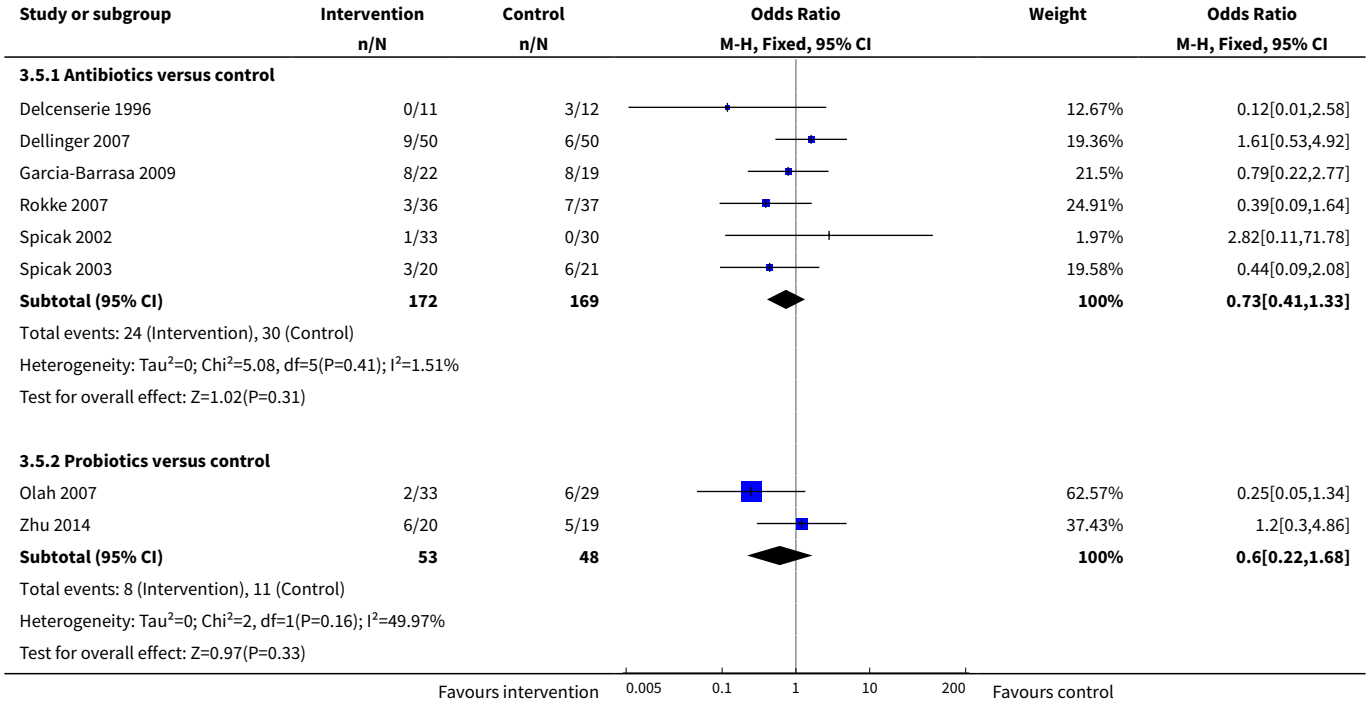

## Analysis 3.4. Comparison 3 Severe acute pancreatitis, Outcome 4 Organ failure.



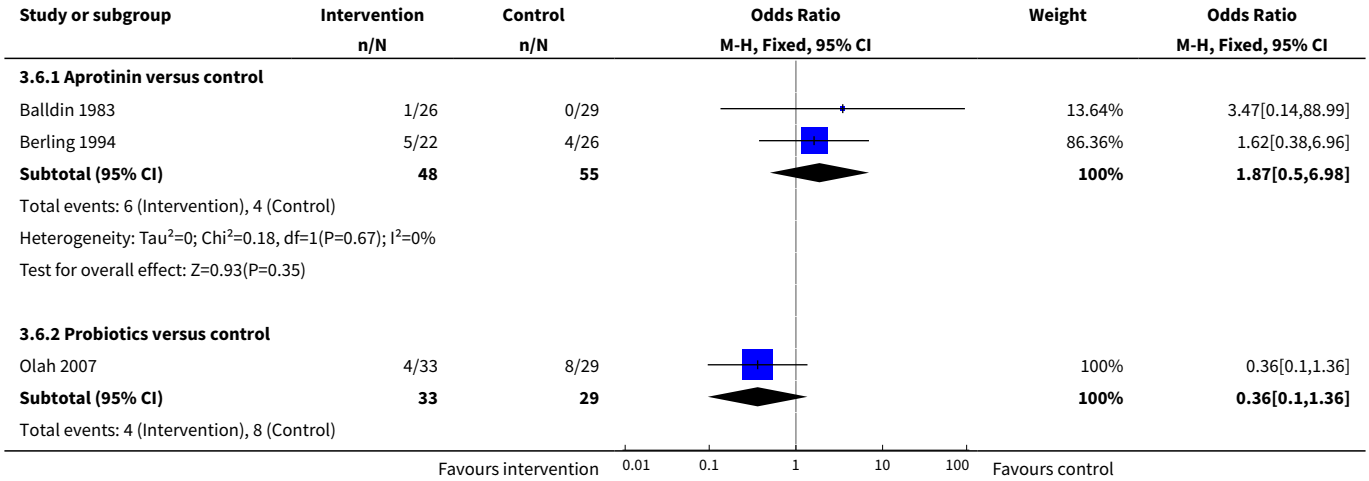


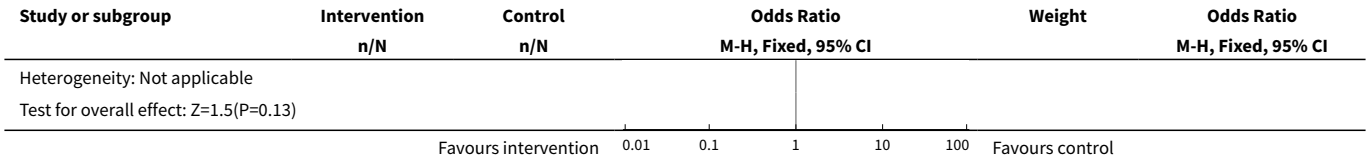



## Analysis 3.5. Comparison 3 Severe acute pancreatitis, Outcome 5 Infected pancreatic necrosis.




## Analysis 3.6. 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 |
| Delcenserie 1996 | 23 | 0 | 23 | Antibiotics | No active intervention | Unclear | Unclear | Low | Low | Unclear |
| Delcenserie 2001 | 81 | Not stated | 81 | Antibiotics | No active intervention | Unclear | Unclear | Unclear | Low | Unclear |
| Dellinger 2007 | 100 | 0 | 100 | Antibiotics | Placebo | Low | Low | Low | Low | High |
| Finch 1976 | 62 | 4 | 58 | Antibiotics | No active intervention | Unclear | Unclear | High | Low | Unclear |
| Garcia-Barrasa 2009 | 46 | 5 | 41 | Antibiotics | Placebo | Unclear | Low | High | Low | Low |
| Hejtmankova 2003 | 41 | Not stated | 41 | Antibiotics | No active intervention | Unclear | Unclear | Unclear | Low | Unclear |
| Isenmann 2004 | 119 | 5 | 114 | Antibiotics | Placebo | Unclear | Low | High | High | High |
| Llukacaj 2012 | 80 | Not stated | 80 | Antibiotics | Placebo | Unclear | Low | Unclear | High | Unclear |
| Luiten 1995 | 109 | 7 | 102 | Antibiotics | No active intervention | Unclear | Unclear | High | Low | Unclear |
| Nordback 2001 | 90 | 32 | 58 | Antibiotics | Placebo | Unclear | Unclear | High | Low | Unclear |
| Poropat 2015 | 47 | 0 | 47 | Antibiotics | No active intervention | Unclear | Unclear | Low | Low | Unclear |

**Table 1. Characteristics of included studies (ordered by comparisons)** *(Continued)*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pederzoli 1993a | 74 | Not stated | 74 | Antibiotics | No active intervention | Unclear | Unclear | Low | Low | Unclear |
| Rokke 2007 | 73 | 0 | 73 | Antibiotics | No active intervention | Unclear | High | Low | Low | High |
| 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<br><br>(this is a 3-armed trial; the numbers stated included all 3 arms) | 264 | 7 | 257 | Aprotinin | Placebo | Unclear | Low | High | High | High |

**Table 1. Characteristics of included studies (ordered by comparisons)** *(Continued)*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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<br><br>(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 |
| Perezdeoteyza 1980 | 40 | Not stated | 40 | Cimetidine | Placebo | Unclear | Low | Unclear | High | Unclear |
| 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 |

**Table 1. Characteristics of included studies (ordered by comparisons)** *(Continued)*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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<br><br>(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 |
| 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 |

**Table 1. Characteristics of included studies (ordered by comparisons)** *(Continued)*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 |
| 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 |
| 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 |

**Table 1. Characteristics of included studies (ordered by comparisons)** *(Continued)*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 |
| 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 |

**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 ulinastatin plus gabexate | Somatostatin plus ulinastatin | Low | Low | Low | Low | Low |
| 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 |
| 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 |

**Table 2. Potential effect modifiers (ordered by comparisons)** *(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| 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 |
| 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 |
| Kingsnorth 1995 | Lexipafant | Placebo | not stated | not stated | not stated | not stated |

**Table 2. Potential effect modifiers (ordered by comparisons)** *(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| 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 |
| 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 |

**Table 2. Potential effect modifiers (ordered by comparisons)** *(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| 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 |
| 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 |
| 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 |

**Table 3. Length of hospital stay (days)** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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) |
| 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 |

**Table 3. Length of hospital stay (days)** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 |
| 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) |

**Table 3. Length of hospital stay (days)** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 ulinastatin plus gabexate | Somatostatin | 116 | 122 | 17.7 (32.1) | 31.3 (37.6) | -13.6 | Significant |
| Wang 2016 | Somatostatin plus ulinastatin | Somatostatin | 124 | 122 | 22.6 (34.5) | 31.3 (37.6) | -8.7 | Significant |
| Wang 2016 | Somatostatin plus gabexate | Somatostatin | 130 | 122 | 23.2 (29.6) | 31.3 (37.6) | -8.1 | Significant |
| Wang 2016 | Somatostatin plus ulinastatin plus gabexate | Somatostatin plus gabexate | 116 | 130 | 17.7 (32.1) | 23.2 (29.6) | −5.5 | Significant |
| Wang 2016 | Somatostatin plus ulinastatin | Somatostatin plus gabexate | 124 | 130 | 22.6 (34.5) | 23.2 (29.6) | −0.6 | Significant |
| Wang 2016 | Somatostatin plus ulinastatin plus gabexate | Somatostatin 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) |
|---|---|---|---|---|---|---|---|---|

**Table 4. Length of intensive care unit (ICU) stay (days)** *(Continued)*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Garcia-Barrasa 2009 | Antibiotics | Placebo | 22 | 19 | 17 | 18 | -1 | Not significant (P-value = 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

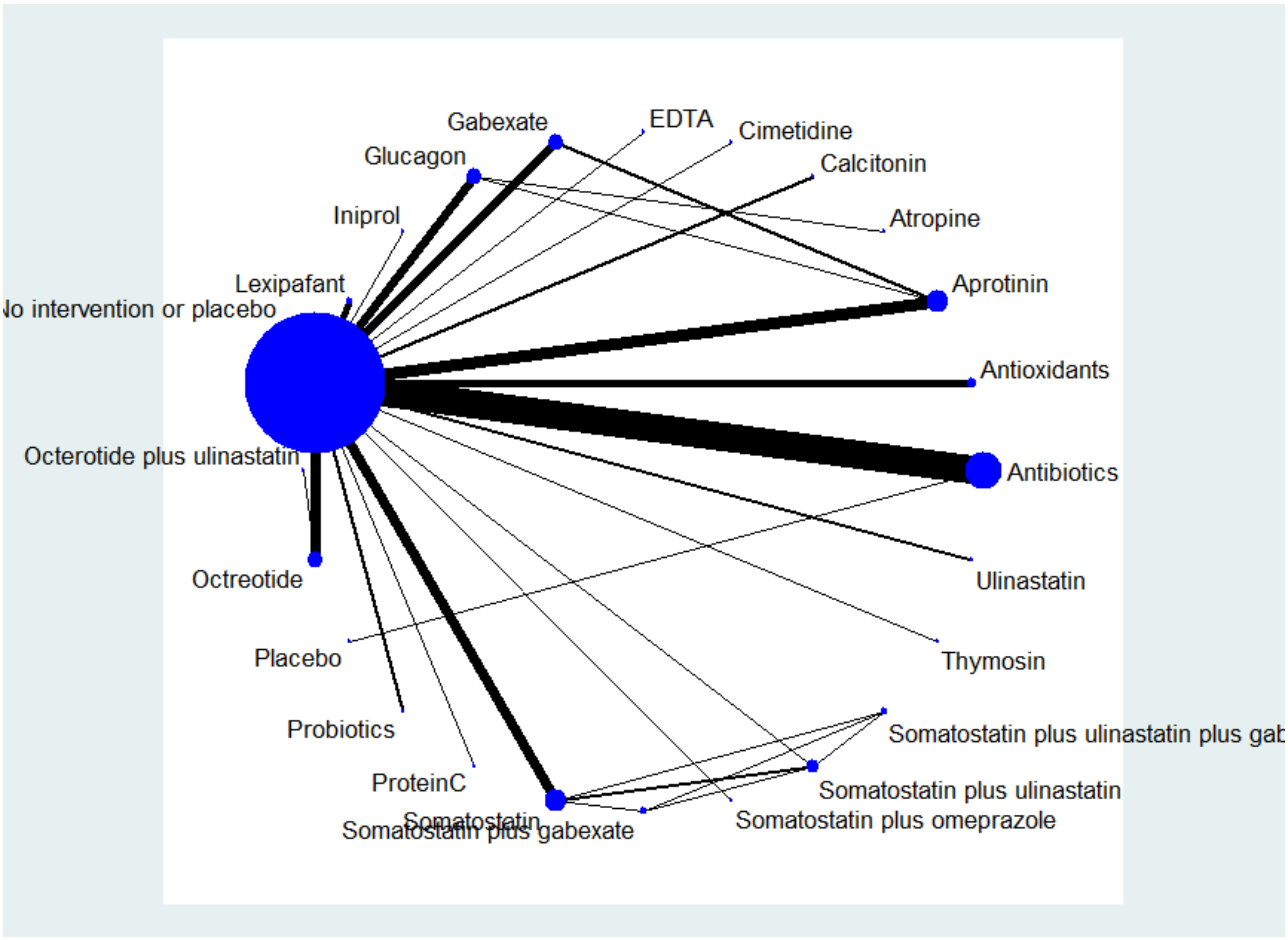
"Interventional" [STUDY-TYPES] AND acute pancreatitis [DISEASE] AND ( "Phase 2" OR "Phase 3" OR "Phase 4" ) [PHASE]

## 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.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [adverse effects] [therapeutic use]; Antioxidants [adverse effects] [therapeutic use]; Confidence Intervals; Gastrointestinal Agents [adverse effects] [therapeutic use]; Pancreatitis [*drug therapy] [mortality]; Pancreatitis, Acute Necrotizing [drug therapy] [mortality]; Probiotics [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic

### MeSH check words

Humans