Antibiotic prophylaxis is not protective in severe acute pancreatitis: a systematic review and meta-analysis
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CRD summary
The review assessed the clinical outcomes of patients with severe acute pancreatitis treated with antibiotics compared to placebo. Antibiotics did not reduce mortality or protect against infected necrosis or frequency of surgical intervention. The review was based on limited evidence; therefore, the conclusions should be treated with caution.

Authors’ objectives
To assess the clinical outcomes of patients with severe acute pancreatitis treated with prophylactic antibiotics compared to patients treated without antibiotics

Searching
MEDLINE, EMBASE, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases and Ovid and Google Scholar were searched from 1966 to May 2008 without language restrictions. Search terms were reported. Bibliographies of retrieved articles, reviews, evaluated symposia proceedings, poster presentations and abstracts from gastrointestinal and surgical meetings were handsearched for additional material.

Study selection
Randomised controlled trials (RCTs) that compared prophylactic antibiotics with placebo in patients with severe acute pancreatitis and evidence of necrosis on computed tomography were eligible for inclusion in the review. Prophylactic antibiotics had to be administered intravenously for a defined treatment length.

Severe acute pancreatitis was diagnosed with contrast enhanced computed tomography and one of Acute Physiology and Chronic Health Care Evaluation II, Imrie classification and increased C-reactive protein levels (>120mg/mL) were eligible for inclusion. Morbidity and mortality outcomes were required inclusion criteria. Reported morbidity outcomes were surgical intervention, infected necrosis and non-pancreatic infections.

Most included studies were performed in Europe. Participants were aged between 43 and 59 years. Causes of severe acute pancreatitis were alcoholic pancreatitis (56% of patients), biliary pancreatitis (24% of patients) and other causes (20%). Duration of antibiotic treatments was five to 21 days. Duration of hospital stay was 18 to 95 days. Included antibiotics were Imipenem, Cefuroxime, Ofloxacin, Meropenem and Ciprofloxacin. Dosing regimens varied between studies.

Three reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Trial quality assessment was conducted using the Jadad scale of randomisation, blinding and description of withdrawals. Maximum achievable score was 5. Trials graded 3 or more were considered high quality.

Three reviewers independently assessed quality.

Data extraction
Data were extracted on event rates for each outcome in treatment and control groups. Extracted data were used to calculate relative risk (RR) and/or absolute risk (AR), with 95% confidence intervals (CI).

Three reviewers independently extracted data. Disagreements were resolved by discussion.

Methods of synthesis
A fixed-effect model (Mantel-Haenszel methods) was used to combine relative risk and 95% confidence intervals. Heterogeneity was assessed using the $I^2$ test; a value of greater than 50% indicated significant heterogeneity. Sensitivity analyses were performed to assess the influence of infected necrosis, surgical intervention, non-pancreatic infection, type of antibiotic and study quality. Funnel plots, Egger tests and Begg and Mazumdar tests were used to assess publication bias.

**Results of the review**

Eight RCTs ($n=502$) were included in the meta-analysis. Two trials received a Jadad score of 5, three scored 3, two scored 2 and one scored 1. Six studies were single-blinded. Two studies were double-blinded.

Overall, antibiotic treatment did not significantly improve mortality rates in severe acute pancreatitis patients in comparison with placebo (RR 0.76, 95% CI 0.49 to 1.16). No significant heterogeneity was measured between the studies ($I^2=8.8\%$).

Antibiotic treatment did not significantly protect against infected necrosis (seven studies, $n=429$) or surgical interventions (seven studies, $n=476$). Antibiotic treatment significantly reduced non-pancreatic infections (RR 0.6, 95% CI 0.44 to 0.82; six studies, $n=407$). However, there was significant heterogeneity ($I^2=50.1\%$). Relative risk reduction (RRR) was 40% (95% CI 18% to 56%). Absolute risk reduction (ARR) was 15% (95% CI 6% to 23%). Number needed to treat was 7 (95% CI 4 to 17).

Sensitivity analysis of β-lactam antibiotics (four studies, $n=305$) found that they did not protect against mortality, infected necrosis and surgical interventions, but they provided significant protection against non pancreatic infections (RR 0.38, 95% CI 0.22 to 0.68, RRR 62%, 95% CI 32 to 78, ARR 12%, 95% CI 3 to 20, NNT=8, 95% CI 5 to 33).

Subanalysis of high-quality studies (five studies, $n=381$) found that use of antibiotics in severe acute pancreatitis patients did not protect against mortality, infected necrosis, surgical interventions and non-pancreatic infections. Publication bias was found for the five high-quality studies through uses of funnels plots, Egger tests ($p=0.031$) and Begg and Mazumdar tests ($p=0.027$).

**Authors' conclusions**

Antibiotic treatment of severe acute pancreatitis did not reduce mortality or protect against infected necrosis and frequency of surgical intervention.

**CRD commentary**

This review addressed a clear research question supported by clear inclusion criteria. The authors searched several databases without language restrictions, which reduced the chances of relevant studies being omitted and language bias. There were limited searches for unpublished material, so relevant trials may have been missed and publication bias was found for the high quality studies. Studies were assessed for quality and this was investigated further by sensitivity analyses. Some steps were taken throughout the review process to minimise errors and bias. Use of heterogeneous studies in the review suggested that use of a fixed-effect model may not have been appropriate. Use of sensitivity analysis was not always clear. There were limited studies of small population sizes and low quality, which further constrained the analyses. The authors' conclusions reflected the evidence presented. This review was generally well conducted, but given the described flaws the authors' conclusions should be treated with caution.

**Implications of the review for practice and research**

**Practice**: The authors did not state any implications for practice.

**Research**: The authors did not state any implications for research.

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