Does duration of perioperative antibiotic prophylaxis matter in cardiac surgery? A systematic review and meta-analysis

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CRD summary
This review comparing long-term and short-term antibiotic prophylaxis regimens in patients undergoing cardiac surgery concluded that uncertainty was too high to determine comparative effectiveness. This conclusion reflects the evidence and is reliable.

Authors' objectives
To compare the relative effectiveness of short-term (less than 24 hours) and long-term (24 hours or more) antibiotic prophylaxis in open heart surgery

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to January 2010 using specified search terms. References, guidelines, existing reviews and congress abstracts were also checked for additional eligible trials. Trialists were asked to identify any ongoing work and the ClinicalTrials.gov website was also searched. No language restrictions were applied.

Study selection
Parallel group randomised controlled trials that enrolled adult (over 18 years) patients undergoing open heart surgery, that compared short-term (less than 24 hours) and long-term (24 hours or more) antibiotic prophylaxis were eligible, irrespective of drug regimen. Patients were excluded if they: were undergoing heart transplants; had active infections or were on systemic antibiotic treatment within 48 hours of surgery; had received immunosuppressive therapy or had known immunodeficiency syndromes; or had severe allergic reaction to antibiotics. The primary outcome was incidence of sternal surgical site infections. Secondary outcomes were deep sternal infections, overall infections and adverse events.

Drug regimens were variable and the comparison of short-term and long-term groups did not always include the same drug (details provided). Length of follow up varied from three to 540 days. Trials were conducted in North America, Europe or Australia between 1972 and 2008. The mean age of patients ranged between 40 and 70 years, where reported. Timing of first dose was 0 to 30 minutes before surgery in most trials. The short-term trials mainly gave one dose of antibiotic, while most long-term trials gave antibiotics for less than 48 or less than 72 hours. Short-term trials administered monotherapy while a few long-term trials involved combination therapy.

Two reviewers assessed study eligibility resolving discrepancies by consensus or with reference to a third reviewer.

Assessment of study quality
A GRADE approach was used to assess the validity of trials with risk of bias assessed in the following domains: sequence generation; allocation concealment; blinding of patients; blinding of care provider; blinding of outcome assessor; incomplete data addressed; free of other bias.

Two reviewers assessed study validity resolving discrepancies by consensus or with reference to a third reviewer.

Data extraction
The number of sternal surgical site infections, deep sternal infections, mortality, overall infections and adverse events were tabulated using intention-to-treat (where possible) to allow calculation of risk ratio's (RR) and associated 95% confidence intervals (CI). Authors were contacted for missing information.

Two reviewers extracted data resolving discrepancies by consensus or with reference to a third reviewer.

Methods of synthesis
Effects were pooled using Mantel-Haenszel random-effects meta-analysis. Heterogeneity was quantified using $I^2$ and tested for statistically using Cochrane's Q. Prespecified sensitivity analyses compared only trials using the same drug in each arm, and excluded trials administering a single dose of a once daily antibiotic in one of the trial arms.

Publication bias was assessed using funnel plots.

**Results of the review**

Twelve trials were eligible of which 11 reported the primary outcome (7,793 patients included in the main analysis, sample sizes ranged from 53 to 3,027). Trial quality appeared poor with eight of 12 studies at high risk of bias in more than two relevant domains and 11 studies with some potential for bias.

Longer term prophylaxis reduced the risk of sternal surgical site infections by 38% (RR 1.38; 95% CI 1.13 to 1.69; 11 trials at high risk of bias) with a greater reduction in risk when analysis was restricted to four trials comparing the same drug regimens (RR 2.07; 95% CI 1.25 to 3.43). Heterogeneity was minimal in both analyses as the low event rates resulted in large confidence intervals for most studies; and the pooled effect of the latter analysis depended on a single trial (providing 42.5% of weight) with high risk of bias in three domains. Effects were imprecise and crossed the line of no effect for the remaining outcomes except deep sternal surgical site infections where longer term prophylaxis reduced risk (RR 1.68. 95% CI 1.12 to 2.53, six RCTs). Heterogeneity was not statistically significant for these analyses.

**Authors' conclusions**

Long-term antibiotic prophylaxis may be more effective than short-term regimens in preventing sternal surgical site infections in patients undergoing cardiac surgery but this was uncertain because of heterogeneity in antibiotic regimen and risk of bias in the published studies, which meant no definite conclusion could be drawn.

**CRD commentary**

This review utilised appropriate methods to minimise bias in searching for studies and assessing their eligibility and validity. Trial validity was low resulting in high risk of bias. The methods of synthesis were appropriate and the authors' conclusions judiciously reflected the uncertainty resulting from synthesising a limited number of clinically heterogeneous studies.

Event rates were low in most studies included in analyses of sternal surgical site infections which resulted in high uncertainty. Where analysis was restricted to like for like comparison, only one study had more than four events per arm, exhibiting the largest and most precise point estimate of the pooled studies, but also associated with high risk of bias in at least three domains. Conclusions regarding effectiveness were therefore heavily dependent on a very limited evidence-base. The author's conclusion that high uncertainty merited further work reflects the evidence and is reliable.

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

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

**Research:** A large randomised controlled trial was required to address the deficiencies in the current evidence-base.

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