Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials
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CRD summary
This review assessed the effectiveness of antibiotic-based lock solutions in preventing catheter-related bloodstream infection and concluded they were effective in haemodialysis patients; in oncology patients the evidence was weak. Study quality and methodological issues mean the conclusions may be over optimistic and should be interpreted with caution.

Authors' objectives
To assess the effects of antibiotic-based lock solutions to prevent catheter-related bloodstream infection (CRBSI).

Searching
MEDLINE (from inception) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies published until April 2009. Search terms were reported. No language restrictions were applied. Reference lists of included studies were searched.

Study selection
Eligible trials had to: use a randomised or quasi-randomised design; study the effects of one or more preventative antibiotic-based lock solutions; study patients who used central venous catheters intermittently; and present sufficient data for calculation of risks of CRBSI in treatment and control groups.

Within included studies, baseline incidence density (defined as incidences of CRBSI or bloodstream infections per 1,000 catheter days) ranged from 0.3 to 27.1. Most types of central venous catheter were tunnelled or cuffed; other types included indwelling central venous catheters, peripherally inserted central catheters and non-tunnelled types. Treatments included heparin, gentamicin sulphate, minocycline, ethylenediamine tetra-acetic acid and vancomycin hydrochloride. Nine studies were of haemodialysis patients. Six studies were of oncology patients. One study was of high-risk neonates. All comparators were heparin. Some studies reported bloodstream infections rather than CRBSI more specifically. Most studies included febrile episodes as part of the definition of bloodstream infections/CRBSI/endoluminal CRBSI. Other criteria used in the definitions differed between studies.

Two reviewers independently screened the papers. Disagreements were resolved by consensus.

Assessment of study quality
Papers were assessed as either adequate or not adequate with respect to criteria of allocation concealment, outcome assessment and treatment blinding, drop-out description and whether intention-to-treat analysis was reported.

Two reviewers independently assessed trial quality. Disagreements were resolved by consensus.

Data extraction
Data required to calculate the incidence density (defined as total number of CRBSIs divided by total catheter days of follow-up) with 95% confidence intervals (CIs) were extracted. Authors were contacted for data where necessary.

Two reviewers independently extracted data. Discrepancies were resolved by consensus.

Methods of synthesis
Incidence density rate (defined as the number of CRBSIs per 1,000 catheter days) and incidence density difference (IDD, defined as the difference in incidence density rate between treatment and control arms), with 95% CIs, were pooled using random-effects models. Using the IDD, the number needed to treat (NNT) was calculated. Statistical heterogeneity was quantified using the $I^2$ statistic.

A number of subgroup analyses were planned where data allowed subgroup differentiation, but analyses were not
Results of the review

Sixteen studies (2,358 patients, range 36 to 153 patients) and 224,449 total catheter days were included in the review. The total number of episodes recorded in particular arms within trials ranged from zero to 78. Seven studies were assessed as adequate regarding allocation concealment. Two studies were double-blinded. Eight reported adequate description of drop-outs (where reported, study drop-out levels ranged from 2% to 6%). One study reported use of intention-to-treat analysis.

Haemodialysis patients (nine studies): Compared with standard heparin lock solution, antibiotic-based lock solutions had a statistically significantly lower CRBSI (IDD -1.96, 95% CI -2.63 to -1.30; I²=41.3%). This difference was also present in a subgroup of five studies in which heparin was compared with heparin plus antibiotics (IDD -2.08, 95% CI -2.64 to -1.53; I²=0%) and a subgroup of three studies in which heparin was compared with antibiotics plus citrate (IDD -2.88, 95% CI -4.34 to -1.41; I²=0%).

Oncology patients (six studies): Overall results were not pooled. Within a subgroup of five studies in which antibiotic flush was used in children with malignancies there was a borderline statistically significant effect that favoured treatment over control (IDD -0.52, 95% CI -1.07 to -0.02; I²=41.8%). One study investigated the effectiveness of antibiotic locks in adults with malignancies and found no statistically significant difference compared with heparin lock solution.

High-risk neonates (one study): A statistically significant effect favoured antibiotic locks over heparin locks (IDD -13.15, 95% CI -24.73 to -1.56).

A funnel plot of haemodialysis patient studies only was strongly asymmetrical (publication bias could not be ruled out). A funnel plot of oncology patient studies was broadly symmetrical (no publication bias detected).

Authors' conclusions

Antibiotic catheter lock solutions were effective in preventing CRBSI in haemodialysis patients. Evidence in oncology patients was weak and the estimated effect had marginal statistical significance.

CRD commentary

This review addressed a clear clinical question with appropriate study selection criteria. The search was clearly defined, although perhaps limited in terms of the number of databases searched and additional measures taken to identify additional relevant studies. The restriction to published studies only meant that publication bias could not be ruled out (as suggested by a funnel plot presented within the review). Primary study details were adequately reported. Quality assessment and method of synthesis appeared appropriate and clearly reported. Appropriate methods were used to reduce reviewer error and bias.

In general, the method of synthesis and reporting of results appeared clear and reasonable. But, the results of the synthesis may have been sensitive to a number of assumptions. The study selection suggested that only studies that reported CRBSIs were eligible for inclusion; based on the primary study details, it appeared that bloodstream infections, CRBSIs and endoluminal CRBSIs were extracted and combined. The results may have been sensitive to using incidences per catheter day (rather than patients) as the unit of observation. Many of the observations were taken of the same individuals, so they were not independent and the pooled results may have been unreliable.

Considering the limited quality of the trials of haemodialysis patients and some methodological issues in the review, the authors' conclusions appear somewhat over optimistic and should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors stated that routine use of antibiotic-based lock solutions should not be recommended. Benefits of antibiotic-based lock solutions should be weighed against possible disadvantages such as development of bacterial antibiotic resistance and patient side-effects.

Research: The authors stated that a well-designed trial that compared antibiotic lock solutions to non-antibiotic antimicrobial lock solutions should be conducted. The issue of development of antibiotic resistance should be addressed.
through long-term prospective studies.

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