Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: a meta-analysis of prospective randomized trials

Labriola L, Crott R, Jadoul M

CRD summary
The authors concluded that antimicrobial lock solution reduced catheter-related bacteraemia in haemodialysis patients by a factor of about three. The longer term risk of adverse events or bacterial resistance was unknown. Due to the uncertain quality of most of the primary studies and limited reporting of review methods, a degree of caution may be necessary in interpreting these conclusions.

Authors' objectives
To evaluate the use of antimicrobial lock solutions (ALS) for prevention of haemodialysis catheter-related bacteraemia.

Searching
MEDLINE, Web of Science, The Cochrane Library and major nephrology journals were searched from 1990 to March 2007. Search terms were reported. The search was restricted to published studies in peer-reviewed journals. There was no restriction by language. Conference abstracts were not included.

Study selection
Randomised controlled trials (RCTs) comparing an ALS with or without antibiotics versus a standard heparin lock solution (5,000 units per mL) were eligible for inclusion, provided they used tunnelled (TCC) or non-tunnelled (NTC) haemodialysis catheters and reported catheter-related bacteraemia (CRB) as the primary outcome. CRB was defined in the review as bacteraemia without other obvious cause and with signs of systemic infection. Studies were required to define CRB clearly and state the planned course of action should it be suspected. It was not planned to report endpoints other than CRB (for example, catheter colonisation) in the review. Studies of the treatment of CRB (rather than prophylaxis) were excluded.

Most studies in the review included only newly inserted catheters and used TCCs or a combination of TCCs and NTCs. A wide variety of lock solutions was used (the commonest were combinations of gentamycin, minocycline, cefotaxime, citrate and heparin in various concentrations). Most studies failed to give details of the preparation and installation of the lock solution. Intranasal mupirocin was also used in some studies. The diagnostic criteria for CRB varied, the most commonly used being the criteria for probable or definite bloodstream infection defined by the Center for Disease Control; other studies used less restrictive definitions. Occurrence of CRB within two or three weeks of stopping antibiotic treatment was defined in some studies either as a new CRB episode or as a relapse (most studies did not define CRB relapse). Adverse events were also reported as a review outcome. Median duration of follow up was 288 days (range 60 to 400 days).

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Validity assessment included evaluation of randomisation and blinding procedures. The authors did not state how the assessment was performed.

Data extraction
The ratio of the incidence rate of CRB per 1,000 catheter-days in the two groups was calculated and expressed as a natural logarithm. Confidence rates for the incidence rate ratio were calculated using bootstrapping. The results were then re-transformed and expressed as relative risks (RRs) with 95% CIs. In studies where no events occurred, a value of 0.5 was assigned to facilitate analysis. Apart from noting that an Excel data form was used, the authors did not state how the data were extracted for the review or how many reviewers performed the data extraction.
Methods of synthesis
Data were combined using both fixed- and random-effects models to calculate pooled RRs of CRB incidence, with 95% CIs. The Q statistic was used to assess heterogeneity. Predefined subgroup analyses were conducted using random-effects models to examine the effects of clinical and methodological differences between the studies. Sensitivity analyses were also conducted, substituting alternative data relating to one of the included RCTs and excluding one RCT with poorly reported data. Publication bias was assessed by visual inspection of a funnel plot and explored using fail-safe Ns.

Results of the review
Eight RCTs were included (n=829 patients (range 40 to 291); 882 catheters; 90,191 catheter days). Five RCTs described their method of random sequence generation. Only two gave details of allocation concealment (of which only one used an optimal method). Four were double-blinded, but only two provided detail on blinding procedures.

ALS versus standard heparin lock (eight RCTs)
CRB incidence was significantly lower in the ALS group (RR 0.32, 95% CI: 0.10, 0.42), with heterogeneity of borderline statistical significance (p=0.071). Random-effects analysis also significantly favoured the ALS group (RR 0.20, 95% CI: 0.09, 0.32). Sensitivity analyses did not change the significance of these results.

Subgroup analyses
The four studies evaluating an ALS containing gentamycin showed a significantly greater reduction in the RR of a CRB (RR of 0.08 compared with 0.38, p=0.003). No other variables were found to significantly influence outcomes.

The funnel plot suggested potential publication bias. However, fail-safe N tests suggested that at least 42 studies would be required to negate the statistical significance of the main (fixed-effect) findings.

Adverse events (nine RCTs)
No serious adverse event related to ALS was reported, nor did any RCTs report CRB caused by bacteria resistant to the antibiotic in the lock solution. One study reported that gentamycin was detected in the plasma when a high concentration of gentamycin was used in the ALS. The most commonly reported adverse events were dizziness, paraesthesia and metallic taste.

Authors’ conclusions
ALS reduced CRB in haemodialysis patients by a factor of about three. The achieved incidence was similar to published figures from the units with the lowest incidence. The longer term risk of adverse events or bacterial resistance was unknown.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without language restriction. However, the restriction to published studies meant that the review was subject to publication bias. It was unclear whether steps were taken to minimise the risk of bias and error by having more than one reviewer independently select studies, assess study validity and extract data. Some relevant quality criteria were assessed, but no details were provided about other aspects of validity (for example, follow-up rates, baseline equality of groups). The reporting of the results showed some confusion between what was an incidence rate ratio and a relative risk and it was unclear why the results were not just presented as incidence rate ratios. However, both fixed- and random-effect model results were presented, heterogeneity was explored and publication bias was assessed, so the statistical techniques appeared to have been appropriate. Other limitations in the data, such as the limited duration of follow-up in the primary studies, were well addressed in the text. The authors’ conclusions appeared to be well-supported by the data presented, but due to the uncertain quality of most of the primary studies and limited reporting of review methods, a degree of caution may be necessary in interpreting these conclusions.

Implications of the review for practice and research
Practice: the authors stated that all dialysis unit staff should receive intensive education on catheter care. ALS could be useful as an additional preventative measure for patients at high risk of infection or for whom CRB would have drastic consequences.
Research: the authors did not make any recommendations for research

**Funding**
Not stated.

**Bibliographic details**

**PubMedID**
18065789

**DOI**
10.1093/ndt/gfm847

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anti-Bacterial Agents /administration & dosage; Bacteremia /etiology /prevention & control; Catheters, Indwelling /adverse effects /microbiology; Gentamicins /administration & dosage; Humans; Prospective Studies; Randomized Controlled Trials as Topic; Renal Dialysis /adverse effects /methods; Risk Factors; Risk Reduction Behavior

**AccessionNumber**
12008104049

**Date bibliographic record published**
23/12/2008

**Date abstract record published**
06/05/2009

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.