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Evidence Review 2009-002

Trisodium citrate for prevention of catheter-related infections

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Abstract

Background: Catheter locking solutions are used to prevent coagulation and infection in various clinical settings. Heparin is traditionally used, but there has been increasing utilisation of the antimicrobial, trisodium citrate, and combinations of trisodium citrate plus other antimicrobials. Southern Health has approved the restricted use of 46.7% trisodium citrate in haemodialysis. However, Southern Health wishes to establish the broader effectiveness of trisodium citrate, at any concentration and with or without other antimicrobials, for preventing infections in vascular access catheters in any clinical setting.

Clinical Questions: In patients with a central venous access device (catheter), does the use of trisodium citrate, with or without other antimicrobials, compared to heparin solutions, with or without antimicrobials, as a locking solution reduce the incidence of infection?

Methods: We included all relevant studies published in English. We searched All EBM, including The Cochrane Database of Systematic Reviews, DARE, CENTRAL and HTA. We also searched Medline, EMBASE and CINAHL. Database searches were conducted in February 2009. Searches for guidelines were undertaken in December 2008. Studies were selected and appraised by two reviewers in consultation with colleagues, using inclusion, exclusion and appraisal criteria established a priori.

Results: Three studies were included – one systematic review, one randomised controlled trial (RCT), and one historical cohort study.

The systematic review included RCTs that used antimicrobials for catheter lock solutions for patients undergoing haemodialysis through central catheters. It included eight RCTs that used sodium citrate as the interventional treatment – four used citrate alone, three trials used citrate and antibiotics, one used citrate and another antimicrobial. The control treatments were all heparin. The systematic review has a moderate risk of bias. The search strategy and appraisal and summary of included studies were limited. We only report the results of 3 sets of meta-analysis (citrate alone, citrate combined with antibiotics, and citrate combined with a non-antibiotic antimicrobial) as we have concerns about the appropriateness of the combined analysis. Meta-analysis of the three citrate alone trials (using citrate at concentrations of 4%, 30% and 46.7%) demonstrated statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.48; 95%CI 0.31, 0.76), and per catheter day (RR 0.50; 95%CI 0.31, 0.81). Meta-analysis of the three citrate combined with antibiotics trials (citrate concentrations of 3.13% in two studies and 4.6% in the third; gentamicin doses of 4mg/ml, 18mg/l, 40 mg/ml) demonstrated statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.13; 95%CI 0.03, 0.51), and per catheter day (RR 0.09; 95%CI 0.02, 0.41). However, for both meta-analyses, when the trials using supplementary infection control measures were not included, the effectiveness of citrate was not significant. The trial examining the effectiveness of 4% citrate combined with 1.35%

taurolidine found non-statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.12; 95%CI 0.01, 2.11), and per catheter day (RR 0.14; 95%CI 0.01, 2.56).

The RCT conducted in 30 patients with end-stage renal disease undergoing haemodialysis compared 4% trisodium citrate to solutions of 1mL (5,000IU) unfractionated heparin plus 2mL saline. This study has a high risk of bias based on lack of reporting of conflict of interest, exclusion criteria, method of randomisation, allocation concealment or blinding. This study found that the incidence of sepsis was similar for citrate and heparin catheter locks, however it may not have included enough patients to establish a difference between the groups on this outcome.

The historical cohort study was conducted in 179 paediatric cancer patients. The intervention was 4% sodium citrate with 1.35% taurolidine and the control was 200IE heparin lock in 2mL sterile normal saline 0.9%. The study has a moderate risk of bias with no information on similarity of groups at baseline or blinding of outcome assessor and analysts. It reports a significantly lower number and incidence density of coagulase-negative staphylococci (CoNS) and methicillin resistant isolates of CoNS (MRSE) blood stream infections in paediatric oncology patients receiving citrate and taurolidine locking solutions compared to those receiving heparin. There is no difference in number or incidence density for all blood stream infections.

Conclusions: The combined evidence for the use of trisodium citrate at any concentration, with or without other antimicrobials, compared to heparin, with or without antimicrobials, for central venous catheter locking for the prevention of catheter-related infections is inconclusive. The quality of the evidence of the included studies is moderate to poor, and there are some important differences between the treatments used in the studies, substantial potential for confounding and important methodological weaknesses present.

Background

Central vascular access devices such as catheters are commonly used in various healthcare settings such as haemodialysis units and intensive care units. However, infection is one of the leading complications that prevent the long-term functional viability of central catheters, with catheter-related infections being common and serious complications of vascular access that can result in morbidity and mortality[1, 2, 3].

Solutions with anticoagulant actions, such as heparin, or antimicrobial actions, such as taurolidine, are sometimes used as locking solutions and are put into the lumen of the catheter between uses to prevent complications such as blood clotting or bacterial colonisation[3].Trisodium citrate is another potential locking solution, which is purported to have both anticoagulant and antimicrobial actions.

Many other methods are also used to reduce the incidence of bloodstream and/or exit-site infections. These interventions include skin cleansing, antimicrobials (oral, intravenous, or topical), non-medicated and medicated dressings, and varying the techniques of vascular access[4].

Current methods for locking vascular access catheters at Southern Health use heparin with or without antibiotic lock solutions. Recently, the restricted use of 46.7% trisodium citrate solutions was approved by the Technology/Clinical Practice Committee and introduced as a locking solution for catheters to reduce the incidence of thrombosis and infection in haemodialysis. This was based on randomised controlled trial (RCT) and cohort study results that showed the effectiveness of trisodium citrate as a locking solution in haemodialysis vascular access catheters[5, 6]. Southern Health wishes to establish the broader effectiveness of trisodium citrate, at any concentration and with or without other antimicrobials, for preventing infections in central vascular access catheters in any clinical setting.

Clinical Question

In patients with a central venous access device (catheter), does the use of trisodium citrate, with or without other antimicrobials, compared to heparin solutions, with or without antimicrobials, as a locking solution reduce the incidence of infection?

Methods

Study Selection Criteria

Patient	**Inclusion**: Patients with central vascular access catheters. **Exclusion:** Patients with peripheral or non-blood-contacting catheters.		
Intervention	**Inclusion:** Trisodium citrate at any concentration, with or without other antimicrobials, as the catheter lock solution. **Exclusion:** Catheter-lock solutions not using trisodium citrate.		
Comparison	**Inclusion:** Heparin, with or without antimicrobials, as the catheter lock solution. **Exclusion:** Catheter-lock solutions not using heparin.		
Outcomes	**Inclusion:** Catheter-related infection. **Exclusion:** Anticoagulant effectiveness; any results from *in vitro* studies.		
Study Type	For the specified outcomes, systematic reviews and RCTs addressing the outcomes are sought. If there are outcomes not addressed by RCTs, then evidence from lower quality comparative studies are sought.	**Publication Date** **Language**	Since January 1980. English

Search Strategy

Evidence Source	Date of Search or Issue searched
All EBM (Ovid) *	February 6th 2009.
Medline (Ovid)	February 6th 2009. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1950 to Present.
CINAHL (Ovid)	February 6th 2009. 1982 to December Week 2 2008.
EMBASE	February 6th 2009. 1980 to 2008 Week 51.

*(including The Cochrane Database of Systematic Reviews, DARE, CENTRAL, CMR, ACP Journal Club, HTA and NHSEED)

Search Terms in Medline*

Patient	-
Intervention	((citrate OR citric).mp OR (tricitrasol OR citra-lock OR taurolock).mp) AND (exp catheterization/ OR catheters, indwelling/ OR catheter*.mp)
Comparison	-
Outcomes	-

* Similar terms, appropriately translated, were used in other databases.

Selection and Appraisal of Studies

Studies from health databases were selected and appraised by two reviewers, using study selection and appraisal criteria established a priori. Disagreements were resolved by consensus or by consultation with a third reviewer if necessary.

Guidelines & Internet Search Strategies

A broad internet search using Google was undertaken to identify guidelines and websites of potentially relevant organisations such as government health departments, professional colleges, and peak bodies. These websites and guideline websites were then searched using appropriate terms. Details are provided in Appendix 2.

Guideline searches and application of selection criteria were conducted by one reviewer.

Results

Our searches in All EBM returned 57 references, Medline returned 154 references, CINAHL returned 15 references, and EMBASE returned 253 references. In total, there were 335 potentially relevant references. Most references were excluded because they were narrative reviews, letters or commentary, or did not meet inclusion criteria. Three articles met our study selection criteria. These are a systematic review in haemodialysis patients by Yahav et al 2008[7], an RCT in end-stage renal disease patients by Buturovic et al 1998[8], and a historical cohort study in paediatric oncology patients by Simon et al 2008[9]. Searches in guideline databases, relevant health websites, and Google yielded no additional relevant results.

Usually if we find a relevant systematic review we only search for studies published since the systematic review search date. However, given our concerns about the systematic review's search strategy, we also searched for RCTs published beforehand. One additional RCT not included in the systematic review was found.

The systematic review included eight relevant studies, two of which we did not find in our search. One study was a conference abstract and is not indexed in any of the databases that we used. The other study did not use the keyword 'citrate' alone in its title, abstract or keywords. It used 'gentamicin/citrate' which we did not pick up with our search terms because it is not common to do a wildcard search for "whole words" in front of the word 'citrate' (eg ' *citrate ').

The lower level evidence cohort study by Simon et al 2008 is included in our analysis because it investigates a population not analysed by the other included studies – paediatric oncology patients.

We found a moderate or high risk of bias in all included studies.

Systematic Review:

The systematic review included RCTs that used antimicrobials for catheter lock solutions for patients undergoing haemodialysis through central catheters. It included eight RCTs that used sodium citrate in various concentrations as the interventional treatment – four used citrate alone, three trials used citrate and antibiotics, one used citrate and another antimicrobial. The control treatments were all heparin. There were subgroup analyses for citrate-alone trials and for all citrate trials combined (eg citrate only, citrate plus antibiotics, and citrate plus other antimicrobials).

The systematic review has a moderate risk of bias. It is not reported if reviewers are blind to the authors, institutions and affiliations nor is it reported who did the appraisal of study quality. The search strategy is only partially adequate, with only a limited systematic search of a small number of bibliographic databases. Only a partial summary of results of the individual studies is provided. Reporting and discussion of the strengths and limitations of the included studies and on the potential impact on the results could be more detailed. Four different sets of meta-analyses were conducted however we have concerns about the variable quality of the studies included and the appropriateness of combining the results of studies that report use of widely varying concentrations of citrate, doses of antibiotics and additional infection control measures in the meta-analysis of all citrate trials, so we only report three of the four sets of meta-analyses here.

Meta-analysis of the three citrate alone trials (using citrate at concentrations of 4%, 30% and 46.7%) demonstrated statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.48; 95%CI 0.31, 0.76), and per catheter day (RR 0.50; 95%CI 0.31, 0.81). One of these three trials used additional infection control measures. When this study was excluded and results of the two trials which did not use additional infection control measures were meta-analysed (citrate concentrations of 4% and 46.7%), the reduction in infections was no longer statistically significant (RR 0.90; 95%CI 0.48, 1.69). It is not reported whether this data is per patient or per catheter day. Meta-analysis of the three citrate combined with antibiotics trials (citrate concentrations of 3.13% in two studies and 4.6% in the third; gentamicin doses of 4mg/ml, 18mg/ml, and 40 mg/ml) demonstrated statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.13; 95%CI 0.03, 0.51), and per catheter day (RR 0.09; 95%CI 0.02, 0.41). Two of these trials used additional infection control measures. A meta-analysis of the results of these two studies is not reported, however the individual results of these two studies were not statistically significant. The results of the single study which did not use additional infection control measures do not show a statistically significant reduction in infections per patient (RR 0.07; 95%CI 0.00, 1.32) or per catheter day (RR 0.06; 95%CI 0.00, 1.20).

The trial examining the effectiveness of 4% citrate combined with 1.35% taurolidine found non-statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.12; 95%CI 0.01, 2.11), and per catheter day (RR 0.14; 95%CI 0.01, 2.56).

Figure 2 from the systematic review shows meta-analysis of citrate plus antibiotic RCTs, while Figure 4 from the systematic review shows meta-analysis of citrate alone and citrate plus another antimicrobial RCTs. These figures are reproduced in Appendix 1.

RCT:

The RCT by Buturovic et al 1998[8] was conducted in 30 patients with end-stage renal disease undergoing haemodialysis but was not included in the systematic review. There were three arms to this study. Only two arms of the trial are relevant to this evidence review (n=20). The intervention of interest was 4% sodium citrate, and the control treatment was a mixture of 5000IU of unfractionated heparin and saline. The primary outcome of this study is catheter function time, which is not relevant to this evidence review, however sepsis and exit site infection were secondary outcomes.

The RCT has a high risk of bias. There are no explicit exclusion criteria reported. Conflict of interest, method of randomisation, allocation concealment, blinding of patients, and blinding of investigators, care providers and assessors were not reported. It is not reported if groups were treated the same (besides the interventions). It was not reported if outcomes were measured in standard, valid and reliable ways. Some outcomes were assessed objectively. It is not reported if outcomes were assessed independently. There is no power calculation reported and there is no statistical analysis undertaken for our outcome of interest. Most baseline characteristics are not reported, so we cannot be sure if the groups were similar at baseline. The paper has some selective outcome reporting. These results are extracted from Table 2 (p947) of the paper:

Case of catheter removal	Heparin (n=10)	Citrate (n=10)
Sepsis:	2	2
Exit site infection:	2	0

As the study was designed to examine catheter function time, the fact that we see no significant difference in the infection rates does not rule out the existence of a difference, particularly given the small number of patients included.

Historical cohort study:

The historical cohort study by Simon et al 2008 was conducted in 179 paediatric cancer patients[9]. This study compared patient groups from two time periods. The control treatment data was collected from April 2003 to March 2005, and the intervention treatment data was collected from April 2005 to March 2007. The control treatment was 200IE heparin lock in 2mL sterile normal saline 0.9%. The intervention treatment was 4% sodium citrate with 1.35% taurolidine.

The historical cohort study has a moderate risk of bias. A historical cohort study provides lower level evidence than either a prospective cohort study or a RCT, because changes in clinical practice other than the intervention may be introduced between the control and intervention periods. The outcomes of this study are not clearly stated which also makes it difficult to assess it follow up was an appropriate length. The study has limited specified inclusion/exclusion criteria. It is unclear if the groups are selected from similar populations. It is not reported if outcome assessors were blind to the exposure nor can we be sure the paper is free of selective outcome reporting. No power calculation was reported. There is also some dissimilarity of groups at baseline.

There was no significant difference between the groups in the number of patients with at least one bloodstream infection. There was however a significant reduction in the number of BSI events caused by CoNS and MRSE using the sodium citrate and taurolidine solution (47% vs 11%; p=0.004). There is no difference in the incidence density for all bloodstream infections. The results table is reproduced in Appendix 1.

As well as CoNS and MRSE infections, this paper presents the distribution of bacterial isolates identified (Figure 1, p106, not reproduced in appraisal). The profile of bacteria isolates found in each time period is quite different and while it is unclear if the study was powered to detect differences in isolates other than CoNS or MRSE, the differences in bacterial profiles in the unit during the control and intervention periods may well contribute to any differences seen on other outcomes.

Discussion

The methodological weaknesses of the studies included in this review affect our ability to interpret their results.

Systematic review:

The systematic review has a moderate risk of bias.

In their discussion, the authors say "evidence does not show the efficacy of citrate or citrate-taurolidine catheter lock solutions as single agents, when applied without other preventive measures." Some studies used other infection control measures in both the treatment and comparison groups. In this systematic review, when the studies investigating citrate alone in the presence of other infection control measures are combined with the studies investigating citrate alone without other infection control measures, a significant benefit of citrate is seen. However analysed separately, neither citrate alone in the presence of other infection control measures nor citrate alone without other infection control measures, is effective.

Similarly, when the studies investigating citrate and antibiotics in the presence of other infection control measures are combined with the studies investigating citrate and antibiotics without other infection control measures, a significant benefit of citrate is seen. However analysed separately, neither citrate and antibiotics in the presence of other infection control measures nor citrate and antibiotics without other infection control measures, is effective. In these studies we also cannot separate the effect of citrate from the effect of the antibiotics.

Given the multiple factors involved in these studies, it is difficult to conclude whether citrate is effective in reducing central venous catheter related infections. Taking these factors into account we cannot be confident that the conclusions of this systematic review, regarding the use of citrate for preventing catheter-related bloodstream infections, can be attributed to using trisodium citrate alone.

RCT:

As discussed in our results section the RCT by Buturovic et al 1998[8] has a high risk of bias. Since there are many unreported details in this study, we cannot be sure of the quality of this study, and we cannot be confident that the conclusions for catheter-related infection are justified.

The primary outcome of this study was to assess catheter patency. It is unclear if the study was adequately powered to detect any differences in the primary outcome, let alone any secondary outcomes. Therefore, though numbers of infections were reported we cannot conclude from this study if there is any difference in infection rates between the heparin and citrate groups.

Historical cohort study:

In the historical cohort study by Simon et al 2008[9] we found a moderate risk of bias. As suggested by the authors of this study, an adequately powered RCT would provide more conclusive evidence about the effectiveness of a taurolidine/citrate lock solution for preventing catheter-related blood stream infections in paediatric oncology patients (p107). Though this study shows a significant decrease in CoNS and MRSE it did not reduce overall numbers or

incidence density of all bloodstream infections. It is possible that the different time periods in which these two treatments were applied (2003-2005 versus 2005-2007) may have influenced the outcomes. From Figure 1 it appears that different strains of bacterial species are present for each time period. The control period (2003-2005) had seven strains that were not present in the intervention period (2005-2007). The intervention period had five strains that were not present previously. Since the treatments were not given during the same time period, it is possible that factors other than the catheter-lock solution may have changed the presence of bacterial species in this unit. These factors might be changes in infection control procedures (eg hand washing), changes in staff members and their respective catheter care techniques, or changes in other hospital policies that could influence infection control. The presence of different bacterial species may influence the effectiveness of the catheter lock solution and hence the results of this study.

Other reviews and studies:

There is a Cochrane systematic review protocol entitled “Interventions for preventing infectious complications in haemodialysis patients with central venous lines”[10]. In this protocol the authors noted a Cochrane systematic review entitled “Antibiotic lock therapy for preventing dialysis catheter-related infections in haemodialysis patients”. This should be relevant to this review, but we could not find it as a protocol nor as a review on the Cochrane Library (searched March 2009). In our database search, we also found a RCT by Abdalla 2005 entitled “Trisodium citrate versus Heparin for locking tunneled haemodialysis catheters: a randomised controlled trial” that was registered in 2005 on the UK National Research Register (http://www.nrr.nhs.uk/) however we do not know the status of this trial at the present time[11].

Conclusions

The combined evidence for the use of trisodium citrate at any concentration, with or without other antimicrobials, compared to heparin, with or without antimircobials, for central venous catheter locking for the prevention of catheter-related infections is inconclusive. The quality of the evidence of the included studies is variable, and there are some important differences between the treatments used in the studies, substantial potential for confounding and important methodological weaknesses present. More studies are needed.

References

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Appendix 1 – Appraisal of Included Studies

Study: Yahav D, Rozen-Zvi, B, Gafter-Gvili A, Leibovici L, Gafter U, and Paul M, 2008, Clinical Infectious Diseases, 47: 83-93.

Description of study: systematic review

Patient/population	"Randomized controlled trials that assessed antimicrobial catheter lock solutions for the prevention of catheter-related infections in patients undergoing hemodialysis" (p84) through central venous catheters.
N	Sixteen trials were included in the review. Eight of these trials included citrate in the intervention and are relevant to this evidence review.
Setting	Haemodialysis units in teaching hospitals, tertiary haemodialysis referral centers and satellite dialysis units, and renal and transplant units, in The Netherlands, Australia, Belgium, Canada, and USA.

Intervention/indicator

Reference	Intervention
Weijmer et al 2005.	Citrate 30%. Also used nasal mupirocin, and exit site topical iodine/chlorhexidine.
Duncan et al 2005.	Citrate 46.7%.
Hendrickx et al 2001.	Citrate 5%.
MacRae et al 2006.	Citrate 4%.
Nori et al 2006.	Citrate 3.13% and gentamicin 4mg/mL
Pervez et al 2002.	Citrate 4.6% and gentamicin 18mg/mL Also used exit site topical iodine, and plastic bag over catheter hub.
Dogra et al 2002.	Citrate 3.13% and gentamicin 40mg/mL.Also used nasal mupirocin and exit site topical iodine/chlorhexidine.
Betjes and von Agteren 2004.	Citrate 4% + taurolidine 1.35%. Also used nasal mupirocin, and exit site topical iodine/chlorhexidine.

Comparison/control

Reference	Comparison
Weijmer et al 2005.	Heparin 5000U/mL. Also used nasal mupirocin, and exit site topical iodine/chlorhexidine.
Duncan et al 2005.	Heparin 5000U/mL.
Hendrickx et al 2001.	Heparin 5000U/mL.
MacRae et al 2006.	Heparin 5000U/mL.
Nori et al 2006.	Heparin 5000U/mL.
Pervez et al 2002.	Heparin 5000U/mL. Also used exit site topical iodine, and plastic bag over catheter hub.
Dogra et al 2002.	Heparin 5000U/mL. Also used nasal mupirocin and exit site topical iodine/chlorhexidine.
Betjes and von Agteren 2004.	Heparin 5000U/mL. Also used nasal mupirocin, and exit site topical iodine/chlorhexidine.

Outcomes	The primary outcomes assessed were: (1) clinically significant bacteremia of any cause, and (2) catheter-related bloodstream infections. (p84) Secondary infections outcomes included: (1) exit site infections, (2) tunnel infections, and (3) fungal infections. (p84)
Inclusion Criteria	RCTs that "assessed adults or children with end-stage renal disease undergoing hemodialysis through central catheters." "Up to 30% of patients with acute renal failure" were included in this systematic review. "Trials that compared any single or combination antimicrobial (antibiotic, citrate, taurolidine, or alcohol) catheter lock solution with heparin or another catheter lock solution" were also included. "All antimicrobial solutions could be given with heparin or EDTA." (p84)
Exclusion Criteria	None reported.

Study Validity

Were there any conflicts of interest in the writing or funding of this review?	No.	See p92 for conflict of interest statement.
Were reviewers blind to authors, institutions and affiliations?	Not reported.	
Does the review have a clearly-focused question?	Yes.	The authors state "The objective of our systematic review was to assess the efficacy of antimicrobial lock solutions for the prevention of catheter-associated infections in patients undergoing hemodialysis." (p89) The population studied was specific - "adults or children with end-stage renal disease undergoing hemodialysis through central venous catheters", including up to 30% of patients with acute renal failure. (p84) The interventions were focused - the interventions were either "any single or combination antimicrobial (antibiotic, citrate, taurolidine, or alcohol) catheter lock solution with heparin or another antimicrobial catheter lock solution", with heparin or EDTA allowed with the antimicrobial solutions. (p84) The comparisons were to heparin or any antimicrobial solution. The outcomes were focused - all were related to bacterial infection. This included "clinically significant bacteremia of any cause, catheter-related bloodstream infections … exit site infections, tunnel infections … fungal infections …" (p84). However, the other outcomes of "removal of catheter for any cause", "all-cause mortality", "catheter thrombosis", "the need for hospitalization and hospitalization duration", and "adverse events" may not necessarily be related to bacterial infections.
Does the review have specified inclusion/exclusion criteria?	Yes.	Inclusion criteria were well defined. There was no explicit exclusion criteria reported.
Were 2 or more independent reviewers used for: **1. application of inclusion criteria to assess eligibility of studies?**	Yes.	"Two reviewers (D.Y. and B.R.-Z) independently performed the search, applied inclusion criteria, and extracted the data" (p84).

2. extraction of data from study reports?	Yes.	“Two reviewers (D.Y. and B.R.-Z) independently performed the search, applied inclusion criteria, and extracted the data” (p84).
3. appraisal of study quality?	Not reported.	The authors state that "Methodologic quality assessment was performed" (p84), but it is not reported who did it.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes.	
Does the review document a comprehensive search strategy?	Partial.	The bibliographic databases searched were limited. Only the Cochrane Register of Controlled Trials (CENTRAL) and PubMed databases were used. Appropriate keywords - "lock*, flush, solution*, antibiotic*, and specific lock solutions" - were used. The subject headings used seemed appropriate - "dialysis or kidney disease and intravascular catheters" (p84). However, we question why "catheterization" wasn't used as a subject heading for the Medline search. There was follow-up from reference lists (p84). There was correspondence with investigators of included trials. The reviewers stated that "unpublished trials were sought in references of all selected studies, relevant conference proceedings, trial registries, ongoing trial databases, new drug application documents, and personal contacts with the investigators of included trials" (p84).
Was the validity of included trials appraised using appropriate criteria?	Yes.	"Methodological quality assessment was performed using the individual component approach, and its direct effect was assessed through sensitivity analyses. Allocation concealment and generation were graded as adequate, unclear, or inadequate, by use of criteria suggested in the Cochrane handbook" (p84). Table 1 reports on the assessment of allocation generation, concealment and blinding (p86).
Is there a summary of the results of individual studies?	Partial.	The study presents Table 1 for summarising baseline data of individual studies (p86). Primary results are presented for individual studies only when they are used in the meta-analyses (Figures 2 and 4). Tables 2 and 3 summarise various outcome data, but we do not know the contribution to these outcomes from the individual studies as only combined results are provided.
Were the strengths and limitations of included studies and potential impact on the results discussed?	Partial.	There is only limited analysis of the strengths or limitations of the included trials, with Table 1 reporting on allocation generation, concealment and blinding.

If meta-analyses were conducted, was it reasonable to do so?	Partial.	Several different analyses were undertaken. The analyses relevant to this study include: • Effectiveness of citrate alone (three trials); • Effectiveness of citrate combined with antibiotics (three trials); • Effectiveness of citrate combined with non-antibiotic antimicrobials (one trial); • Effectiveness of citrate alone or in combination with antibiotics or other antimicrobials (seven trials). The three citrate alone trials used citrate at concentrations of 4%, 30% and 46.7%; one of these studies also undertook additional infection control measures. The authors report that there was heterogeneity in the results of these studies which was explained by the additional infection control measures. The validity of combining of these trials in meta-analysis is questionable. A fourth study of citrate alone was identified, but not included in the meta-analysis. Correspondence with the review author clarified that this was because it did not report the relevant outcome. The three citrate and antibiotic studies used similar concentrations of citrate (3.13% in two studies and 4.6% in the third). In all studies the antibiotic was gentamicin, however the dose of the antibiotic varied from 4mg/ml to 40 mg/ml. Two of the studies used additional infection control measures. There was no significant heterogeneity in the results of these studies. Only one trial of citrate combined with a non-antibiotic antimicrobial was reported. The fourth analysis combines all seven of the above studies. Given our concerns about combining the different doses of citrate, we have questions about the appropriateness of this meta-analysis, which combines these already heterogeneous results with results from studies reporting on combinations of citrate with antibiotics and other antimicrobials. The authors do not report the level of heterogeneity in this meta-analysis, and a forest plot is not presented so we cannot assess this. In light of this, and the fact that the two out of the three separate analyses already report statistically significant results, we have not reported the results of this meta-analysis.
If meta-analyses were conducted, was it done appropriately?	Yes.	The meta-analysis was done appropriately using RevMan 4.2 (p84). But, as mentioned previously, there are questions about the appropriateness of grouping certain trials together for meta-analysis.
Other		
What is the overall risk of bias?	Moderate.	This review has some methodological issues which may affect its conclusions. It is not reported if reviewers are blind to the authors, institutions and affiliations nor is it reported who did the appraisal of study quality. The search strategy is only partially adequate - there is a limited systematic search of bibliographic databases. There is a partial summary of results of the individual studies and limited reporting and discussion of the strengths and limitations of the included studies and on the potential impact on the results. Meta-analysis is conducted but only some of the analyses are appropriate. This is mainly due to concerns about the variable quality of the studies included and the appropriateness of combining the results of studies that report use of widely varying concentrations of citrate, doses of antibiotics and additional infection control measures.

Results

Effectiveness of citrate alone (three trials):
Meta-analysis of the three citrate alone trials (using citrate at concentrations of 4%, 30% and 46.7%) demonstrated statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.48; 95%CI 0.31, 0.76), and per catheter day (RR 0.50; 95%CI 0.31, 0.81).
One of these three trials used additional infection control measures. When this study was excluded and results of the two trials which did not use additional infection control measures were meta-analysed (citrate concentrations of 4% and 46.7%), the reduction in infections was no longer statistically significant (RR 0.90; 95%CI 0.48, 1.69). (It is not reported whether this data is per patient or per catheter day).

Effectiveness of citrate combined with antibiotics (three trials):
Meta-analysis of the three citrate combined with antibiotics trials (citrate concentrations of 3.13% in two studies and 4.6% in the third; gentamicin doses of 4mg/ml, 18mg/ml, and 40 mg/ml) demonstrated statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.13, 95%CI 0.03, 0.51), and per catheter day (RR 0.09, 95%CI 0.02, 0.41).
Two of these trials used additional infection control measures. A meta-analysis of the results of these two studies is not reported, however the individual results of these two studies were not statistically significant. The results of the single study which did not use additional infection control measures do not show a statistically significant reduction in infections per patient (RR 0.07; 95%CI 0.00, 1.32) or per catheter day (RR 0.06; 95%CI 0.00, 1.20).

Effectiveness of citrate combined with non-antibiotic antimicrobials (one trial):
The trial examining the effectiveness of 4% citrate combined with 1.35% taurolidine found non-statistically significant reductions in catheter-related bloodstream infections per patient (RR 0.12; 95%CI 0.01, 2.11), and per catheter day (RR 0.14; 95%CI 0.01, 2.56).

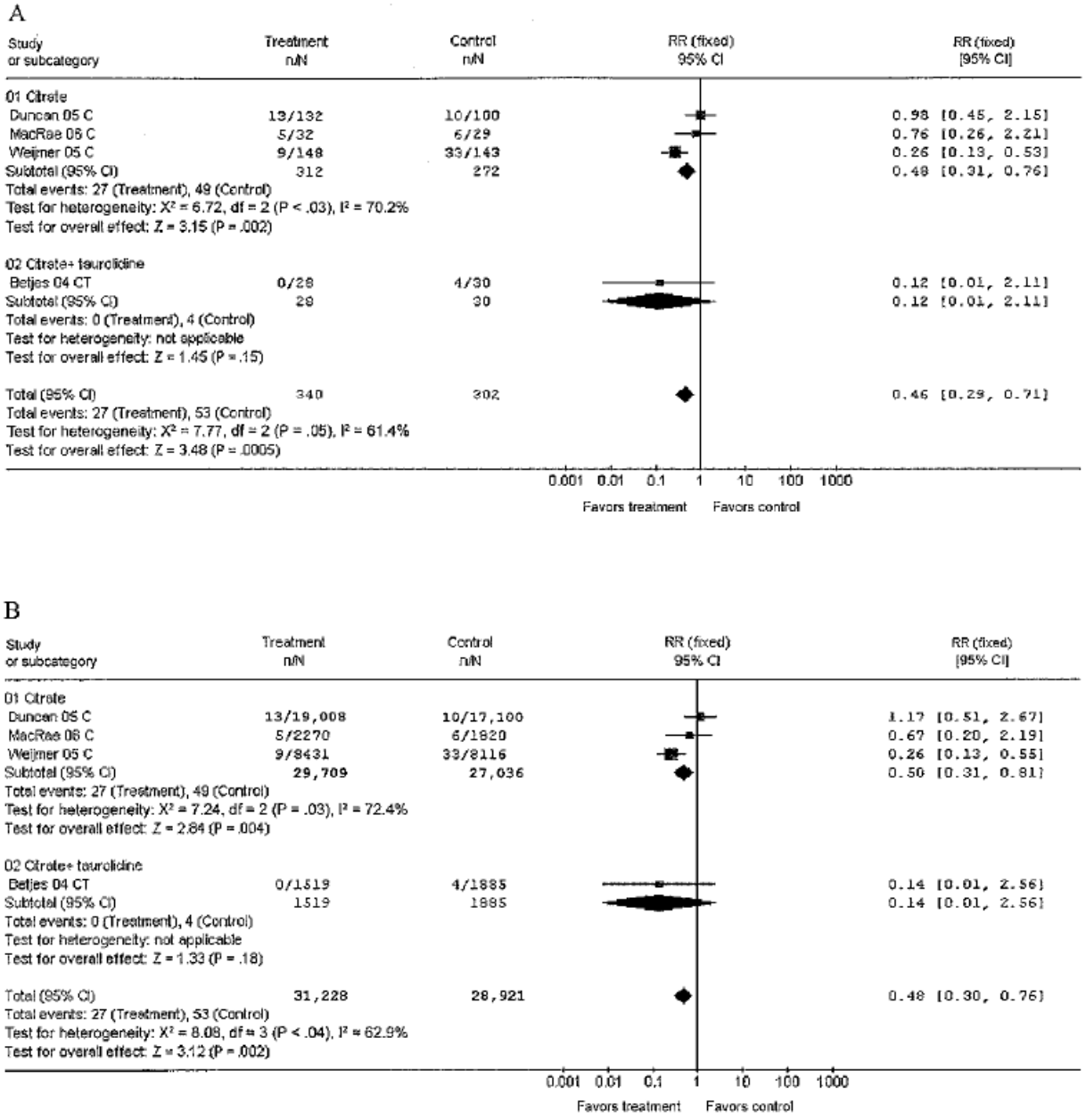

Figure 4. Catheter-related bloodstream infections per patient (*A*) and per catheter-day (*B*) for trials comparing nonantibiotic antimicrobial catheter lock solution with heparin. The analysis is subcategorized by the type of antimicrobial. Studies are given as the first author's surname followed by the last 2 digits of the year published and an abbreviation for the substance studied: C, citrate; CT, citrate-taurolidine. RR, relative risk.

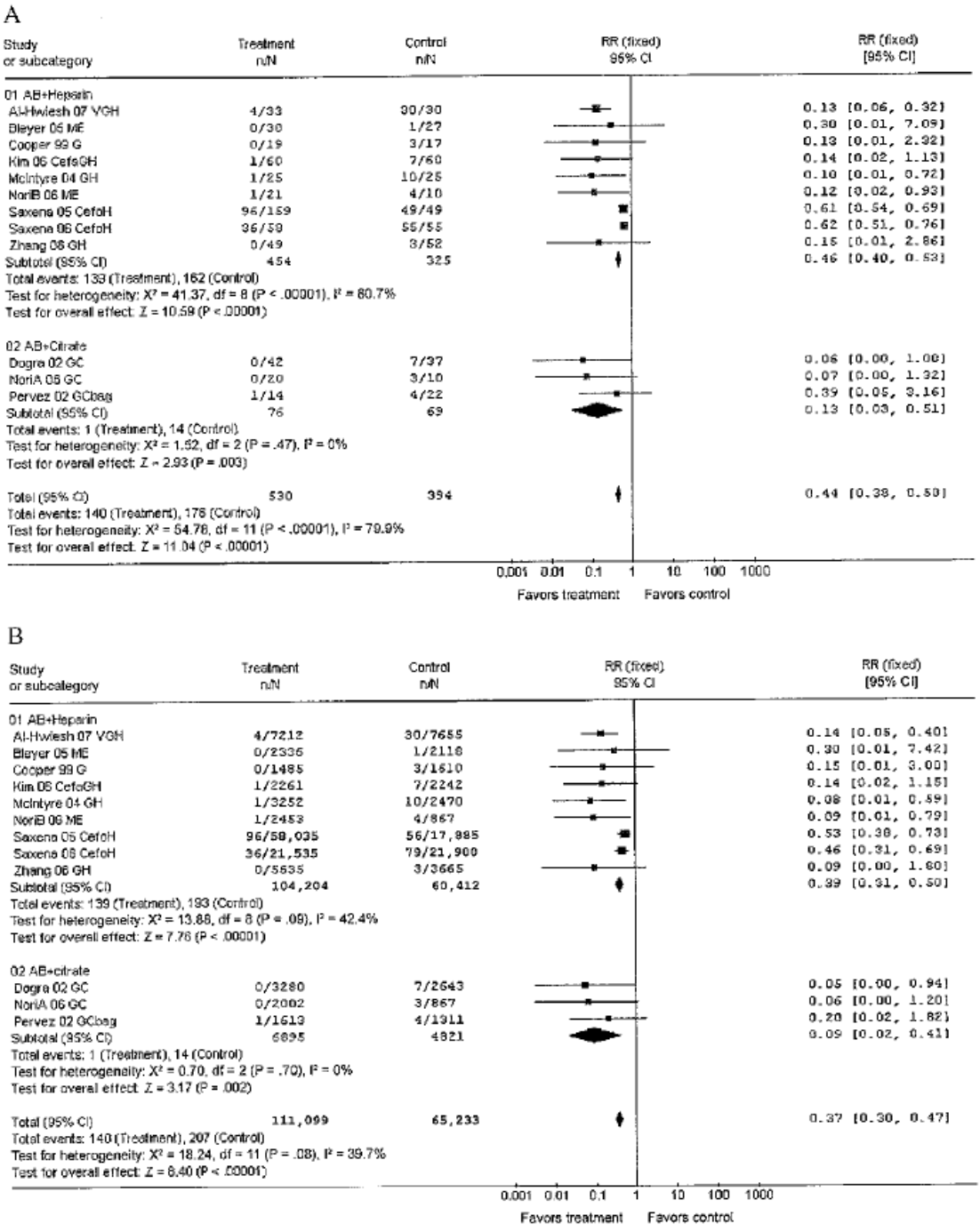

Figure 2. Catheter-related bloodstream infections per patient (*A*) and per catheter-day (*B*) for trials that compared any antibiotic catheter lock solution with heparin. The analysis is subcategorized by the concomitant use of citrate with the antibiotic. A relative risk (RR) of <1.0 favors the antimicrobial lock solution examined. Studies are given as the first author's surname followed by the last 2 digits of the year published and an abbreviation for the substance studied: CefaGH, cefazolin-gentamicin-heparin; CefoH, cefotaxime-heparin; G, gentamicin; GC, gentamicin-citrate; GCbag, gentamicin-citrate plastic bag over catheter hub; GH, gentamicin-heparin; ME, minocycline-EDTA; VGH, vancomycin-gentamicin-heparin.

Author's Conclusions

"Currently, evidence does not show the efficacy of citrate or citrate-taurolidine catheter lock solutions as single agents, when applied without other preventive measures." (p92)

Our comments/summary

This systematic review has a moderate risk of bias.

A concern in the methodological quality of this systematic review is the use of only two bibliographic databases for searching. This may be fine for this review because we did not find additional studies with our search. Also, the limited database use seems to have been partially compensated by the use of broad search terms, and a comprehensive search of reference lists, the 'grey literature', and other sources of information such as from personal correspondence with study authors. However, it is unclear how systematic and a priori this non-database searching is.

This systematic review found two studies that we did not find in our own search. The study by Duncan et al 2005 is a conference abstract and is not indexed in any of the databases that we used. The study by Nori et al 2006 did not use the word 'citrate' by itself. It did use 'gentamicin/citrate' which we did not pick up with our search terms because it is not common to do a wildcard search for "whole words" in front of the word 'citrate' (eg ' *citrate ').

There are concerns about the appropriateness of the meta-analysis. This is mainly due to concerns about the variable quality of the studies included and the appropriateness of combining the results of studies that report use of widely varying concentrations of citrate, doses of antibiotics and additional infection control measures. Some studies also used other infection control measures with the citrate treatments. From the results of this review it is unclear if citrate, used with or without other antimicrobials, may reduce the risk of catheter-related infection, when it is applied in combination with other infection control measures, such as nasal mupirocin and topical iodine. The meta-analyses report that only two out of the four studies that used additional infection control measures showed significant benefits of citrate treatments in catheter-related bloodstream infections per catheter-day (ie Dogra et al 2002 and Weijmer et al 2005).Only one out of the four studies showed significant benefits of citrate treatments in catheter-related bloodstream infections per patient (ie Weijmer et al 2005).

The varying methodological quality of the studies reported in this systematic review, along with the wide range of concentrations of citrate and the varying doses of antibiotics mean all results should be interpreted cautiously.

Study: Buturovic J, Ponikvar R, Kandus A, Boh M, Klinkmann J, and Ivanovich P, 1998, Artificial Organs, 22(11): 945-947.

Description of study: randomised controlled trial

Patient/population	End-stage renal disease patients, ages 59 to 77 years (mean 63 +/- 8).
N	Intervention n=10; Control n=10 (30 enrolled into trial, but 10 were enrolled into a group not relevant to this evidence review (polygeline)).
Setting	Not reported, but probably a dialysis unit.
Intervention/indicator	4% trisodium citrate.
Comparison/control	1mL (5,000IU) unfractionated heparin + 2mL saline.
Outcomes	Catheter patency. Causes of catheter removal - such as sepsis and exit site infection.
Inclusion Criteria	End-stage renal disease patients who are receiving haemodialysis. Patients have subclavian or jugular single lumen catheters in place for at least 7 days.
Exclusion Criteria	Not reported.

Study Validity

Were there any conflicts of interest in the writing or funding of this study?	Not reported.	
Does the study have a clearly focused question?	Yes.	The population studied was focused, using end-stage renal disease patients who needed haemodialysis. The intervention and control treatments and doses are clearly defined. The outcomes considered were adequate for the study (catheter patency).
Is a RCT the appropriate method to answer this question?	Yes.	
Does the study have specified inclusion/exclusion criteria?	Partial.	The inclusion criteria are adequate. There are no exclusion criteria.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Partial.	Patients with contraindications to citrate or heparin should perhaps have been mentioned in the exclusion criteria. It is unclear if the inclusion/exclusion criteria were formulated a priori because of the lack of detail given, especially since there are no exclusion criteria.
Did the study have an adequate method of randomisation?	Not reported.	This article only reports that "patients were randomly assigned" (p946).
Was allocation to intervention group concealed?	Not reported.	
Were patients blind to intervention group?	Not reported.	

Were investigators and care providers blind to intervention group?	Not reported.	
Were outcome assessors blind to intervention group?	Not reported.	
Aside from the experimental intervention, were the groups treated the same?	Not reported.	
Was there sufficient duration of follow-up?	Partial.	The follow-up period seems adequate. Patients were monitored until the endpoint of catheter removal. "The endpoint of the study was the removal of catheters when they were no longer required or had to be removed for complications" (p946). There was, however, no post-discharge follow-up. It is possible that an infection developing on discharge day may not be detected before discharge (eg if a patient develops an undetected infection the day before discharge, is then discharged, but has a detectable infection later).
All outcomes were measured in a standard, valid and reliable way?	Not reported.	Infection is a common laboratory-tested and validated outcome to measure in a clinical setting, but it is not reported how these were measured or by whom. Measurement of patency of catheters is a broad term and there is no clear definition of what was measured in the methods section.
Were outcomes assessed objectively?	Partial.	The identification of sepsis and exit site infection needs to be subjectively identified by clinical staff before objective laboratory analysis can confirm it. It is not reported how infection was initially identified and by whom.
Were outcomes assessed independently?	Not reported.	It is not reported if the outcomes were assessed independently, how these were measured or by whom.
Was the study sufficiently powered to detect any differences between the groups?	Partial.	The primary outcome for this paper is catheter patency, and there is a statistically significant longer patency of catheters that used citrate (Table 1, p946). There is no power calculations reported for the outcome of interest to our review: sepsis or exit site infection.
If statistical analysis was undertaken, was this appropriate?	No.	Student's t test is used to compare catheter function time (p946). However, for our outcomes of interest, there is no inferential statistical analysis. There is only summary statistics of basic results of frequency, mean, range, and volume for various measurements.
Were the groups similar at baseline with regards to key prognostic variables?	Partial.	The two groups have slightly different number of patients using different vein insertion sites. For the citrate group there were eight patients with subclavian vein and two with jugular vein insertion sites. For the heparin group, there were seven patients with subclavian vein and three with jugular vein insertion sites. Apart from this, other baseline characteristics for each group are not reported. The sex and mean and range of age are reported for the trial as a whole, but not for the groups (p945).
What percentage of the individuals recruited into each arm of the study dropped out?	0% treatment; 0% control.	There were no drop outs.
Were all the subjects analysed in the groups to which they were randomly allocated (ie intention to treat analysis)?	Yes.	The subjects are analysed in the groups to which they were allocated.

Is the paper free of selective outcome reporting?	Partial.	There is no previously published protocol to confirm if this paper did plan and measure all outcomes. Only in Table 2 do we find out what caused catheter removal (p946). It is unknown whether these items were planned to be measured a priori.
Were the outcomes measured appropriate?	Yes.	The authors list the causes of catheter removal in Table 2, including sepsis and exit site infection (p946). Sepsis and exit site infection are relevant outcomes for our review on catheter-related bloodstream infections. Though this paper reports on sepsis it is not powered to find a clinically important difference between groups for this outcome.
Other		
What is the overall risk of bias?	High.	There are no explicit exclusion criteria reported. Conflict of interest, method of randomisation, allocation concealment, blinding of patients, and blinding of investigators, care providers and assessors were not reported. It is not reported if groups were treated the same (besides the interventions). It was not reported if outcomes were measured in standard, valid and reliable ways. Outcomes were partially assessed objectively. It is not reported if outcomes were assessed independently. There is no power calculation reported. There is no statistical analysis undertaken for our outcome of interest. Most baseline characteristics are not reported, so we cannot be sure if the groups were similar at baseline. The paper has some selective outcome reporting.

Results

(Extracted from Table 2, p947)

Case of catheter removal	Heparin (n=10)	Citrate (n=10)
Sepsis:	2	2
Exit site infection:	2	0

Author's conclusions

"Our results indicate that citrate or polygeline can replace heparin effectively as a filling solution for single lumen temporary hemodialysis catheters." (p945)

Our comments/summary

This RCT has a high risk of bias. Due to many unreported details in this study, we cannot be sure of this study's methodology validity, and we cannot be confident that the conclusions for catheter-related infection are justified.

The primary outcome of this study was to assess catheter patency. There is very little detail reported about study methods and this means we cannot rule out substantial opportunity for bias. It is unclear if the study was adequately powered to detect any differences in the outcomes. Though numbers of infections are reported we cannot conclude from this study if there is any difference in infection rates between the heparin and citrate groups.

Study: Simon A, Ammann R, Wiszniewsky G, Bode U, Fleischhack G and Besuden M, 2008, Taurolidine-citrate lock solution (TauroLock) significantly reduces CVAD-associated grampositive infections in pediatric cancer. BMC Infectious Diseases, 8: 102-109.

Description of study: cohort study

Patient/population	Paediatric oncology patients with long term central venous access devices (CVADs).
N	Intervention n=89; Control n=90.
Setting	Paediatric oncology unit, University Children's Hospital, Bonn, Germany, between April 2003 and March 2007.
Intervention (exposure)	Catheter lock containing 1.35% Taurolidine and 4% Sodium Citrate (TauroLock^{TM}). Intervention was applied from 2005-2007.
Comparison/control	Catheter lock containing 200IU/ml heparin in 2ml sterile normal saline 0.9%. Control was used from 2003-2005.
Outcomes	Blood stream infections, particularly Coagulase-negative staphylococci (CoNS) and Methicillin Resistant isolates of CoNS (MRSE).
Inclusion Criteria	Patients with cancer and long term intravenous access device. All patients were receiving anti-cancer chemotherapy.
Exclusion Criteria	Patients with short-term non-tunnelled central venous catheters. Patients with haematological diseases without neutropenia. "Neutropenia was defined as an absolute neutrophil count <0.5x10^9/l or a leukocyte count <1x10^9/l in absence of a differential WBC." (p104).

Study Validity

Were there any conflicts of interest in the writing or funding of this study?	No.	The authors state that there are no competing interests (p108).
Does the study have a clearly focused question?	Partial.	The study has a clearly defined population, intervention and comparison, but the outcomes are not clearly stated. The aim was to investigate the impact of a CVAD lock containing taurolidine/citrate on catheter associated blood stream infections, with particular attention to CoNS and MRSE.
Is a cohort study the appropriate method to answer this question?	Partial.	A RCT would be the ideal design to answer this question. In this situation a historical cohort study was performed to examine a change in practice.
Does the study have specified inclusion/exclusion criteria?	Partial.	Whilst this study has specified inclusion and exclusion criteria the terms 'short term' and 'long term' are not defined.
If there were specified inclusion/ exclusion criteria, were these appropriate?	Yes.	The study selected a relatively defined age group (ie children) with a defined condition (ie cancer) and catheter use (ie long-term intravenous access device).
Other than the exposure under investigation, were the groups selected from similar populations?	Unclear.	This is a historical cohort. It is possible that there were changes during the four year time period of the study that could have affected either the treatment patients received or the baseline characteristics of the patients within that time period. However, in describing the setting, including clinical practice recommendations and types of catheters and ports no obvious change likely to affect the selection of populations is noted.

Aside from the exposure, were the groups treated the same?	Unclear.	As noted in the previous criteria, though patients were reportedly treated the same we cannot be sure about changes in clinical practices and staff that occurred between the control and intervention periods. Over this time period changes in staff and clinical policies and practices could have exposed patients to different quality of treatment. Even with the same staff, catheter techniques may change over time. There is a different bacterial profile between the study time periods, with six strains present in period one (2003-2005) that are not present in period two (2005-2007), and five strains present in period two that are not present in period one. The presence of different bacterial species may influence the effectiveness of the catheter lock solution, and hence the results of this study.
Was exposure measured in a standard, valid and reliable way?	Yes.	Exposure to the lock solution was according to unit protocol within the two time periods. Each CVAD was counted separately and incidence density was measured using inpatient CVAD utilisation days (p104).
Were outcome assessors blind to the exposure?	Not reported.	This is not reported however, given that this is a historical cohort study and practice changed for the entire unit, it is unlikely that assessors of infection (ie fever) were blinded. As one of the data analysts also designed the study protocol it is unlikely that the analysis was performed in a blinded manner.
Were all outcomes measured in a standard, valid and reliable way?	Yes.	For all patients with fever (defined as >38.5^{o}C for at least 4 hours or >39^{o}C) two blood cultures were collected prior to administration of antibiotics. These were tested according to routine microbiology procedures (p104).
Were outcomes assessed objectively and independently?	Yes.	Presence of fever was necessary for blood cultures to be performed. Fever was defined as >38.5^{o}C for at least 4 hours or >39^{o}C. Outcome of blood cultures was assessed by standard laboratory methods (p104).
Is the paper free of selective outcome reporting?	Not reported.	In the absence of a published protocol we cannot be sure of the originally proposed aims and/or outcome measures of this project.
Were the outcomes measured appropriate?	Yes.	
Was there sufficient duration of follow-up?	Partial.	Outcomes were measured while catheters were in use in the oncology unit. There is no mention of follow up on discharge. It is possible that an infection developing on discharge day may not be detected before discharge (eg if a patient develops an undetected infection the day before discharge, is then discharged, but has a detectable infection later).
Was the study sufficiently powered to detect any differences between the groups?	Partial.	No sample size calculation is presented. The study shows a significant difference between the two groups in CoNS and MRSE infections. However, while no difference is reported in other types of blood stream infections we cannot be sure if the study is powered to detect such differences.
If statistical analysis was undertaken, was this appropriate?	Yes.	Data was checked for normality and appropriate statistical methods were used.
Were the groups similar at baseline with regards to key prognostic variables?	No.	The two groups are different in regards to several key prognostic variables (see Table 1). The intervention group had a higher proportion of male patients (67% vs 57%). The age range between the two groups is also different with the intervention group having a lower median age and a wider interquartile range (IQR). Though the setting was the paediatric oncology unit, both intervention and control groups had patients up to 35 years of age (however the upper limit of the IQR was 14.7 years for the control group and 16.1 years for the intervention group). The distribution of malignancies was different between the two groups and there were more Broviac and less Port catheters in the intervention group.

What percentage of the individuals recruited into each arm of the study were lost to follow-up?	0% exposed; 0% control/ comparison.	No patients were lost to follow up.
What percentage of the individuals were not included in the analysis?	0% exposed 0% control/ comparison.	All patients are included in the analysis.
Other		
What is the overall risk of bias?	Moderate.	A historical cohort study provides lower level evidence than either a prospective cohort study or a RCT because changes other than the intervention may be introduced between the control and intervention periods. The outcomes of this study are not clearly stated which also makes it difficult to assess it follow up was an appropriate length. The study has partially specified inclusion/exclusion criteria. It is unclear if the groups are selected from similar populations. It is not reported if outcome assessors were blind to the exposure nor can we be sure the paper is free of selective outcome reporting. No power calculation was reported. There is also some dissimilarity of groups at baseline.

Results

The main outcomes are presented in Table 2 of the paper (p105), reproduced below:

Item	Group 1 (Heparin)	Group 2 (Taurolock™)	P value
No of BSI events	30	25	
No (%) of patients with at least one BSI	24 (27)	21 (24)	0.74
No (%) of BSI with CoNS or MRSE	14 (47)	3 (11)	0.004
	CoNS: 4 (13)	CoNS: 3 (11)	
	MRSE: 10 (33)	MRSE: 0 (0)	
Incidence density* for all BSI events (95% CI)	4.93 (3.33 – 7.04)	3.82 (2.52 – 5.56)	0.35
Incidence density calculated with the number of specific isolates			
BSI with CoNS/MRSE	2.30 (1.26 – 3.86)	0.45 (0.09 – 1.31)	0.004
BSI other gram positive	0.66 (0.18 – 1.68)	1.19 (0.52 – 2.35)	0.32

BSI E.Coli	0.66 (0.18 – 1.68)	1.49 (0.72 – 2.74)	0.15
BSI all Gram negative	1.97 (1.02 – 3.44)	2.24 (1.25 – 3.69)	0.74

* The incidence density refers to the number if events per 1000 inpatient CVAD utilisation days.

Though this study shows a significantly lower number and incidence density of CoNS or MRSE blood stream infections in the intervention group, there is no difference in number or incidence density for all blood stream infections.
Figure 1 of the paper shows the distribution of bacterial isolates identified (p106). An increase in E.coli isolates is found in the taurolidine/citrate group, though this is not statistically significant, and it is unclear if the study is powered to detect such a difference.

Author's Conclusions

The authors conclude that "This 48 months prospective cohort study from a paediatric oncology unit showed that the use of Taurolidine 1.35%/Sodium Citrate 4% (TauroLock^{TM}) as standard lock solution in long-term CVADs significantly reduced the incidence density of CVAD-associated infections due to CoNS or MRSE. The described reduction of infectious events reveals an insistent argument to perform a prospectively randomized, double-blinded, multicenter study including a sufficient number of cancer patients with long term CVAD" (p108).

Our comments/summary

This historical cohort study has a moderate risk of bias.
As suggested by the authors, an adequately powered RCT would provide more conclusive evidence about the effectiveness of a taurolidine/citrate lock solution for preventing catheter-related blood stream infections in paediatric oncology patients (p107). Though this study shows a significant decrease in CoNS and MRSE in the intervention group it does not show a reduction in overall numbers of or incidence density of all blood stream infections. It is possible that the different time periods (2003-2005 versus 2005-2007) that these two treatments were applied may have influenced the outcomes. Firstly, as shown in Figure 1 (p106) there are different and unique strains of bacterial species present for each time period. The control period (2003-2005) had seven strains that were not present in the intervention period (2005-2007). The intervention period had five strains that were not present previously. Since the treatments were not given during the same time period, it is possible that other factors in addition to the change in catheter-lock solution may have changed the presence of bacterial species in this unit. This could be changes in infection control procedures (eg hand washing), changes in staff members and their respective catheter care techniques, or changes in other hospital policies that could influence infection control (with the same staff, and with changing staff). We could also hypothesise that the presence of different bacterial species may influence the effectiveness of the catheter lock solution, and hence the results of this study.

Appendix 2 – Guidelines & Internet Search Strategy

Identification of Clinical Practice Guidelines

Guidelines are generally published as electronic 'stand alone' documents on the internet rather than as papers in peer reviewed journals. The search to identify guidelines is therefore quite different to searches usually undertaken for systematic reviews of primary research in the health literature. Methods to identify guidelines include identification of relevant websites followed by searches within them, direct searches of the internet and searches within the electronic health databases.

Unlike systematic reviews of the primary research literature which usually involve a single clinical question, a guideline is a compilation of systematic reviews arising from numerous clinical questions. These reviews may be grouped within the guideline into sections or chapters based on patient characteristics, health care settings, domains of clinical care or other categories related to the particular condition or patient population. Due to this complexity and comprehensiveness, the information contained in a particular section or chapter may be found in more than one type of guideline. For example, information on catheter locking could be found within a guideline about haemodialysis catheter use, or trisodium citrate may be mentioned in a section on catheter line infection prevention within a guideline about infection control.

Internet searches to identify relevant websites

The reviewers were aware of websites of guideline clearinghouses, guideline developers, centres of evidence-based practice and Australian government health services and websites of specific relevance (eg Cancer Care Ontario) known to contain evidence-based resources. Additional websites of specific relevance (eg ICUs) were sought via an internet search using the Google 'Advanced Search' function with the following search string:

- (ICU OR "intensive care unit" OR ITU OR "intensive therapy unit" OR "intensive care" OR "intensive therapy" OR "critical care" OR "coronary care" OR intensivist OR anaesthe OR anesthesiol OR anesthe) AND (professional OR association OR organisation OR organization OR college OR society OR academy OR peak).

The 16 generic websites known by the review team (nine guideline services, two Australian government websites, one centre of evidence-based practice, four professional organisations and four cancer related websites) as well as the three additional intensive care related websites were searched for relevant guidelines.

Details of websites searched are below.

Website searches to identify relevant guidelines

Websites were searched using lists of guidelines, publications or other resources identified on the website and scanned for relevant documents mentioning catheter infections and/or sodium citrate. In some cases, where an internal search engine was available, websites were searched using the following search terms:

- catheter AND infection;
- "sodium citrate";
- "trisodium citrate".

The searches are outlined in below.

Internet searches to identify relevant guidelines

An internet search strategy was conducted using the Google 'Advanced Search' function. The search string was limited to documents in English and was used to identify guidelines for prevention of catheter-related infections in ICUs using sodium citrate. The search string used was:

- (catheter) AND (sodium citrate) AND (evidence OR guideline OR systematic).

Searches

Search 1: Searches within relevant websites that are known to contain guidelines.

Search 2: Search for relevant websites for ICU related peak bodies using Google that contain evidence-based guidelines.

Search 3: Search for relevant guidelines for Trisodium Citrate in Catheter use using Google.

Search 1: Searches within relevant websites that are known to contain Guidelines		
Guideline Services		
National Health and Medical Research Council (NHMRC)	www.nhmrc.gov.au	Searched by guidelines; health: scrolled entire list.
National Institute for Health and Clinical Excellence UK (NICE)	www.nice.org.uk	Searched by advanced search option: catheter = 43 results.
New Zealand Guideline Group (NZGG)	www.nzgg.org.nz	Searched by publications: Guidelines and Reports - scrolled entire list. Searched by Evidence for Practice; scrolled entire list.
Scottish Intercollegiate Guidelines Network (SIGN)	www.sign.ac.uk	Searched by: Guidelines: scrolled entire list.
Joanna Briggs Institute	www.joannabriggs.edu.au	Searched by: Members Area: Systematic Reviews & Best Practice Information – scrolled lists.
Guidelines International Network	www.g-i-n.net	Searched by: International Guideline Library (members only) Searched by keyword: catheter.
Guidelines Advisory Committee	www.gacguidelines.ca	Searched by: List all topics and summaries – scrolled entire list.
National Guideline Clearinghouse US (NGC) (1) **searched on 18/12/2008 – 127 Results total** (2) **searched on 18/12/2008 – 2 Results total** (3) **searched on 18/12/2008 – 0 Results total**	www.guidelines.gov	Searched by: catheter AND infection. Searched by: “sodium citrate”. Searched by: “trisodium citrate”.
TRIP Database (1) **searched on 18/12/2008 – 911 Results total** (43 – North America, 48 – Europe, 4 – Other) (2) **searched on 18/12/2008 – 247 Results total** (13 – North America, 14 – Europe, 2 – Other) (3) **searched on 18/12/2008 – 4 Results total** (0 – North America, 0 – Europe, 0 – Other)	www.tripdatabase.com	Searched by: catheter AND infection – limited by guidelines. Searched by: “sodium citrate” – limited by guidelines. Searched by: “trisodium citrate” – limited by guidelines.
Australian Government Website containing Guidelines		
Australian Government Department of Health and Ageing	www.health.gov.au	Searched by: Health Professionals – Treatments & Techniques – Guidelines – None relevant.
NSW Health	www.health.nsw.gov.au	Searched by: Publications & Resources – Policy Directives and Guidelines – None relevant.

EB Websites		
WA Centre for Evidence Based Nursing and Midwifery	http://wacebnm.curtin.edu.au	Searched by: Resources – 'Reports, Guidelines and Article' – None relevant.
Other relevant Cancer Websites		
Cancer Care Alliance	http://www.cancercarealliance.nhs.uk	Searched by: Clinical Guidelines – scrolled lists – none relevant.
Cancer Care Ontario	http://www.cancercare.on.ca	Searched by: CCO toolbox.
National Breast Cancer Centre	http://www.nbcc.org.au	Searched by: catheter AND infection, sodium citrate – none relevant.
The Cancer Council Australia	http://www.cancer.org.au	Searched by: Clinical Practice Guidelines – searched lists – none relevant.
Other relevant Websites		
Intensive Care Society	http://www.ics.ac.uk/	Searched by: Standards and Guidelines – Clinical Standards – none relevant.
American Association of Critical Care Nurses	www.aacn.org	Searched by: Clinical Practice – Evidence-based resources – Protocols for Practice – scrolled list – none relevant (can only purchase from this site no free resources).
The Association of Anaesthetists of Great Britain and Ireland	http://www.aagbi.org/	Searched by: Publications – Guidelines – scrolled list – none relevant.

Search 2: Identification of relevant websites for ICU related peak bodies using Google that contain evidence-based guidelines	
Find web pages that have **all these words**	(ICU OR "intensive care unit" OR ITU OR "intensive therapy unit" OR "intensive care" OR "intensive therapy" OR "critical care" OR "coronary care" OR intensavist OR anaesthe OR anesthesiol OR anesthe) AND (professional OR association OR organisation OR organization OR college OR society OR academy OR peak)
Find web pages that have this **exact wording or phrase**	
Find web pages that have **one or more of these words**	
Don't show pages that have **any of these unwanted words**	
Language	English
Results 24/12/2008 completed search	9,720,000
Google Edits at	489

Search 3: Identification of relevant guidelines for Trisodium Citrate in Catheter use using Google	
Find web pages that have **all these words**	(catheter) AND (sodium citrate) AND (evidence OR guideline OR systematic)
Find web pages that have this **exact wording or phrase**	
Find web pages that have **one or more of these words**	
Don't show pages that have **any of these unwanted words**	
Language	English
Results 22/12/2008 completed search	39,900
Google Edits at	311