

Dialysis

A Meta-analysis of Hemodialysis Catheter Locking Solutions in the Prevention of Catheter-Related Infection

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Background: Catheter-related infection (CRI) is associated with increased all-cause mortality and morbidity in hemodialysis patients and may be reduced by using antimicrobial lock solutions (ALSs).

Study Design: We performed a meta-analysis of studies identified from a search conducted in February 2007 of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, databases of ongoing trials, major renal journals, and reference lists of relevant reports.

Setting & Population: Patients receiving acute or long-term hemodialysis through a tunneled or nontunneled central venous catheter.

Selection Criteria for Studies: We included all prospective randomized studies that compared ALS with heparin.

Intervention: Administration of antibiotic and/or antimicrobial catheter locking solution.

Outcome Measures: Primary outcome was CRI rate in patients using ALSs compared with those using heparin alone. We also examined effects of ALS use on mortality, adverse events, and catheter thrombosis.

Results: 7 studies were identified with a total of 624 patients and 819 catheters (448 tunneled, 371 nontunneled). CRI was 7.72 (95% confidence interval, 5.11 to 10.33) times less likely when using ALS. There were no consistent suggestions of adverse outcomes with ALS use; in particular, rates of catheter thrombosis did not increase. There was no evidence of antibiotic resistance developing during a maximum follow-up of 12 months.

Limitations: The major limitation of this review is the relatively short duration of follow-up of the included studies, which does not allow complete reassurance regarding the development of antibiotic resistance. Lack of direct comparisons means that determination of the most efficient ALS is not possible.

Conclusions: This review confirms that antibiotic locking solutions reduce the frequency of CRI without significant side effects.

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INDEX WORDS: Hemodialysis; antimicrobial locking; antibiotic locking; catheter-related infection/bacteremia.

Editorial, p. 165

Sepsis is the second most common cause of death in hemodialysis (HD) patients after cardiovascular disease.¹ In large part, this is caused by catheter-related infection (CRI).² CRI constitutes a substantial component of hospital-acquired infections, and hospital admissions for vascular access infection have doubled in the last decade.^{3,4} Therefore, CRI results not only in substantial patient morbidity, but also in consumption of resources,^{5,6} and is associated with increased all-cause and infection-related mortality.⁶⁻⁸ In addition, repeated use of antibiotic treatment was associated with the selection of such resistant organisms as methicillin-resistant *Staphylococcus*

aureus,⁹ with methicillin-resistant *S aureus* rates directly proportional to rates of catheter sepsis.¹⁰

Despite international recommendations that a native arteriovenous fistula is the gold-standard

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vascular access for HD, venous catheter use is widespread.^{1,11} As many as 60% of new HD patients in the United States rely on tunneled catheters for the initiation of HD therapy, and a large proportion of these patients are still using tunneled catheters after 60 days.^{2,12} Fistula failure, arteriopathy, late recognition of end-stage renal disease, difficulty in access placement, and resource limitations ensure the continued use of catheters.

CRI results from migration of skin organisms along the catheter into the bloodstream or contamination and colonization of catheter lumens.⁹ All indwelling vascular catheters develop a biofilm on internal and external surfaces. Subsequent colonization of this biofilm occurs in a high percentage of catheters and precedes peripheral bacteremia and septic symptoms.¹³ Even in the absence of overt bacteremia, bacterial colonization of catheters may induce a chronic inflammatory state shown to have multiple adverse effects, including resistance to erythropoietin.¹⁴ Use of cuffed tunneled catheters instead of uncuffed catheters has not translated to significant decreases in catheter-related bacteremia or resultant infective endocarditis in this population.¹⁵

It is self-evident that the optimal intervention for reducing CRI is to reduce the number of HD patients dependent on central venous catheters. However, it is inevitable that there will always be a proportion of patients who require catheters and who will remain susceptible to CRI. Techniques introduced to reduce CRI include catheter design, use of antimicrobial impregnated catheters, use of cuffed tunneled catheters, local topical treatments, nasal carriage eradication, and use of antimicrobial lock solutions (ALSs).

We performed a systematic review of the literature to assess the efficacy of ALSs in decreasing CRI rates. We also sought to examine their effect on rates of catheter thrombosis, mortality, and genesis of other side-effects. Cost-benefit analyses were not the focus of this review.

METHODS

Criteria for Considering Studies for This Review

Types of Studies

All prospective randomized controlled studies that tested 1 or more ALSs were included in this analysis (see fig 1). We included only studies using catheter-locking solutions, excluding those that examined antimicrobial impregnated tub-

ing or exit-site cleaning solutions alone. Only trials using heparin lock solution as control were included. Studies that assessed either tunneled or nontunneled catheters were permitted. Other acceptable catheter variables included duration in situ, position site, and catheter brand. We excluded studies in which catheters were not used solely for HD. We included trials written in English and investigated both published and unpublished studies.

Types of Participants

Adult men and women (age > 18 years) receiving HD through a central venous catheter were eligible. This included patients with acute renal failure and those with chronic end-stage renal disease, both incident and prevalent.

Primary Outcome Measure

This was defined as rate of CRI per 1,000 catheter-days in patients using ALSs versus heparin-only groups.

Secondary Outcome Measures

These included rates of catheter dysfunction, bleeding, mortality, and effects on hemoglobin level. In addition, adverse events between the ALS and heparin groups were compared.

Search Strategy for Identification of Studies

The following search terms were used as medical subject headings and key words when searching electronic databases: end stage renal disease, end stage renal failure, end stage kidney failure, h(a)emodialysis, catheter related bacter-(a)emia, catheter related sepsis, catheter related infection, antibiotic lock(ing) solution, antimicrobial lock(ing) solution, tunnel(1)ed cuffed HD catheters, untunnel(1)ed/nontunnel(1)ed HD catheters, mortality, prospective, randomized(s)ed trial, and heparin lock.

Electronic Searches

We examined the following databases: Cochrane Central Register of Controlled Trials, MEDLINE 1966 to 2005, EMBASE (up to 2005), and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

We also searched the contents of 4 major renal journals (*Journal of American Society of Nephrology*, *American Journal of Kidney Diseases*, *Kidney International*, and *Nephrology, Dialysis, and Transplantation*).

We searched the following databases of ongoing trials: National Research Register (United Kingdom; www.update-software.com), ClinicalTrials.gov (www.clinicaltrials.gov), Current Controlled Trials (www.controlled-trials.com), and European Clinical Trials Database (www.eudract.emea.eu.int).

Manual Searches

We searched reference lists from all relevant review articles and also reference lists from all studies obtained in full text.

All appropriate records were downloaded into a database (EndNote, version 9.0, Carlsbad, CA) and titles were loaded

into the Review Manager program (RevMan 4.2.9; Cochrane Collaboration).

Methods of the Review

Trial Selection

One author assessed all titles and abstracts identified in the search. Full-text articles then were retrieved and independently assessed by 2 authors for selection in the review.

Quality Assessment of Trials

Two reviewers independently assessed the method quality of trials selected. Differences were resolved by discussion.

Particular attention was given to the following aspects of study design: randomization; demographics of each study arm; catheter type and make; definition for CRI and criteria used for diagnosis; techniques of catheter insertion, including operator ability and use of radiographic guidance; and catheter insertion site.

In addition, each study was assessed for possible confounding factors, particularly those that might predispose to CRI, recent infection, and fallible diagnostic criteria for CRI.

Data Extraction and Analysis

Data were extracted by using predefined criteria and were summarized statistically only if of sufficient quality and presented in compatible formats. Results are expressed as rate ratios and compared by using generic inverse variance. Overall results were calculated by using a random-effects model.¹⁶ We dealt with zero counts according to Cochrane guidelines, replacing zero with 0.5 to avoid division by zero. Because all zero counts were in treatment groups, this approach is conservative and would tend to underestimate differences between study and control arms.

RESULTS

Description of Studies

Seven trials were identified from a search conducted in February 2007. All were published as full peer-reviewed journal articles and were randomized. All 7 were fully assessed and included in the final review.

A total of 624 patients and 819 catheters (448 tunneled, 371 nontunneled) were included in the analysis. Three studies were multicenter^{11,17,18} and 4 were single center.^{14,19-21} Three studies were double blinded,^{17,18,21} whereas the other 4 were only single blinded.^{11,14,19,20} Four studies included solely tunneled catheters,^{11,14,18,21} 1 study included solely nontunneled catheters,²⁰ and 2 included a mixture of both tunneled and nontunneled catheters.^{17,19} Most studies did not standardize catheter type or position site, and only 2 studies specified a single catheter make,^{14,20} whereas the remaining 5 studies either used a variety of catheter makes or did not

specify.^{11,17-19,21} All except 1 study recruited a mix of incident and prevalent patients (Kim et al²⁰ studied only incident patients), and Saxena et al²¹ included only patients with diabetes. Characteristics of individual studies are listed in Table 1.

Six studies used heparin, 5,000 U/mL, as the control group, and the study by Kim et al²⁰ used 1,000 U/mL. Antibiotics tested include gentamicin,^{11,14,18} cefotaxime,²¹ minocycline,¹¹ and ceftazolin/gentamicin combination.²⁰ Nonantibiotic solutions tested included taurolidine¹⁹ and high-concentration (30%) citrate.¹⁷ One study tested more than 1 ALS.¹¹ All studies monitored routine variables, including catheter flow, dialysis adequacy, bleeding and thrombosis rates, morbidity, and mortality.

Outcome Measures

CRI Rates

CRI rates were significantly lower with the use of ALSs in all 7 studies. When all studies were pooled, the CRI rate with ALS was 7.72 (95% confidence interval, 5.1 to 10.3) times less compared with heparin locks. Using absolute risk reduction for each study, this translates to a number needed to treat of 3 to prevent 1 CRI/100 catheter-days. Overall results and those of individual studies are listed in Table 2. CRI rates in heparin groups were similar across all studies (range, 2.1 to 4.1/1,000 catheter-days), and decreases in CRI rates achieved by using the different ALSs were of similar magnitude.

Gentamicin was shown to be an effective ALS at high and low concentrations (rate ratio, 11.8; 95% confidence interval, 8.4 to 15.3), as shown in Table 2 and Fig 2. However, gentamicin at high concentrations (40 mg/mL) resulted in significant systemic exposure, with median predialysis serum gentamicin levels of 2.8 mg/L (range, 0.6 to 3.5 mg/L),¹⁸ whereas lower concentrations of gentamicin did not produce serum levels greater than 0.2 mg/L.¹⁴ The lowest effective concentration tested was 4 mg/mL in combination with 3.13% citrate.¹¹

Additional Outcomes

Two studies reported significantly lower rates of mortality caused by CRI in patients using ALSs.^{17,21} Weijmer et al¹⁷ observed 5 CRI

Table 1. Summary of the 7 Included ALS Randomized Controlled Trials

	Betjes et al, ¹⁹ 2004	Dogra 2002 ¹⁸	Nori et al, ¹¹ 2006
Recruitment	Single teaching hospital renal unit (The Netherlands)	2 tertiary renal units (Australia)	3 tertiary renal units (United States)
Blinding	Not stated	Double blinded, good allocation concealment	Not blinded (precluded by color of ALS)
ALS used	Taurolidine, 1.35%, + citrate, 4%, v heparin, 5,000 U/mL	Gentamicin, 40 mg/mL, + citrate, 3.13%, v heparin, 5,000 U/mL	Gentamicin, 4 mg/mL (in citrate 3.13%) v heparin, 5,000 IU, minocycline, 3 mg/mL (in EDTA) v heparin, 5,000 U/mL
Randomization	Computer-generated randomization	Block randomization by pharmacists	Block randomization, open label
Mean age (y)	50.3, control group; 58.3, ALS group	59.3, control group; 55.7, ALS group	59, control group; 58, minocycline group; 58, gentamicin group
Men (%)	61.5, control group; 56.8, ALS group	47, control group; 45, ALS group	50, control group; 55, minocycline group; 62, gentamicin group
Duration of follow-up (catheter-days)	1,885, control group; 1,519, ALS group	2,643, control group; 3,280, ALS group	1,734, control group; 2,002, minocycline group; 2,453, gentamicin group
Dropouts	4	4	0
Catheter type	76 catheters; 18 tunneled, 58 untunneled	112 tunneled	61 tunneled; all vintages included
Catheter make	All varieties	All varieties	Not documented
Dressing used	Transparent, oxygen permeable	Transparent, oxygen permeable	Not stated
Nasal mupirocin use?	Yes	Yes	Not stated
Definition of CRI/CRB	CDC criteria	CDC criteria	Non-CDC criteria
Technique of catheter insertion	Aseptic insertion by experienced nephrologists using radiographic guidance	Insertion by experienced radiologists, image guided	Not documented
Catheter Site	All sites including femoral	Not stated	All internal jugular
Outcomes	Effective at reducing CRI	Effective at reducing CRI; serum gentamicin levels increased; fewer exit site infections	Effective at reducing CRI; improved catheter patency with ALS
Adverse events	Nil	4 Patients in study arm reported nonspecific dizziness	Nil

(Continued)

deaths in 143 patients in the heparin group compared with none in the ALS group ($P = 0.005$). Mortality rates in the study by Saxena et al²¹ were much greater overall, with 11 of 49 patients dying in the heparin group compared

with 5 of 49 patients in the ALS group ($P = 0.023$).

Catheter function was similar between the ALS and heparin groups in 3 studies^{14,17,19} and not reported in 1 study.²⁰ In the remaining 3 stud-

Table 1 (Cont'd). Summary of the 7 Included ALS Randomized Controlled Trials

Kim et al, ²⁰ 2006	McIntyre et al, ¹⁴ 2004	Saxena et al, ²¹ 2006	Weijmer et al, ¹⁷ 2005
Single teaching hospital renal unit (S Korea)	Single teaching hospital renal unit (United Kingdom)	Single teaching hospital renal unit (Saudi Arabia)	10 tertiary and secondary renal units (The Netherlands, Belgium)
Double blinded	Single blinded	Diabetics only Double blinded	Double blinded, good allocation concealment
Cefazolin, 10 mg/mL, + gentamicin, 5 mg/mL, + heparin v heparin, 1,000 U/mL	Gentamicin, 5 mg/mL, + heparin v heparin, 5,000 U/mL	Cefotaxime, 10 mg/mL, + heparin, 5,000 U/mL, v heparin, 5,000 U/mL	Trisodium citrate, 30%, v heparin, 5,000 U/mL
Block randomization	Block randomization, sealed envelopes	Randomized, sequential sealed envelopes	Randomized
56.2, control group; 53.7, ALS group	57.8, control group; 63.6, ALS group	57.5, control group; 59.7, ALS group	61.3, control group; 61.6, ALS group
47, control group; 55, ALS group	72, control group; 56, ALS group	55.3, control group; 59.2, ALS group	61, control group; 56, ALS group
Stated only as mean number/patient; longest follow-up in any patient, 61	2,470, control group; 3,252, ALS group	Total follow-up for control and ALS groups combined, 39,785	8,116, control group; 8,431, ALS group
None stated	None stated	5	31
120 untunneled	50 new tunneled	109 tunneled	298 catheters; 98 tunneled, 193 untunneled
Mahurkar dual lumen	Kimal KSC split ash	Quinton perm-cath	All varieties
Not stated	Transparent, O ₂ permeable	Not stated	Dry gauze dressings
Yes	Not used	Not stated	Only for those with documented nasal <i>S aureus</i> carriage
Non-CDC criteria	CDC criteria	Not documented	CDC criteria
By radiologists with US fluoroscopic guidance	Fluoroscopic insertion by experienced nephrologist	Insertion by vascular surgeons, confirmed by CXR	Aseptic insertion by experienced operator
All right internal jugular	Subclavian or internal jugular	Subclavian or internal jugular	All sites including femoral
Effective at reducing CRI	Effective at reducing CRI; higher mean Hb and lower mean ESA dose with ALS	Effective at reducing CRI Reduction in CRI related mortality with ALS Improved catheter patency with ALS	Effective at reducing CRI Reduction in CRI related mortality with ALS Fewer exit site infections
Nil	Nil	Nil	In heparin grp, increased rates of bleeding immediately post catheter insertion and of major bleeds

Abbreviations: ALS, antibiotic locking solution; CRI, catheter-related infection; CRB, catheter-related bacteremia; CDC, Centers for Disease Control and Prevention; CXR, chest X-ray; US, ultrasound; Hb, hemoglobin; ESA, erythropoiesis-stimulating agent.

ies, catheter malfunction or use of thrombolytics was less in the ALS groups,^{11,18,21} although in the study by Dogra et al,¹⁸ this trend did not reach statistical significance. McIntyre et al¹⁴ reported

decreased mean hemoglobin levels and greater mean erythropoietin doses in the heparin group.

Exit-site infections were reported in all except 2 studies.^{11,20} Of the remaining 5 studies, 2

Table 2. CRI Rates Provided by Each Randomized Controlled Trial and Overall Effects for Gentamicin Studies and All Studies Combined

	CRI Rate in Heparin Group (episodes/1,000 catheter-days)	CRI Rate in ALS Group (episodes/1,000 catheter-days)	Rate Ratio \pm SE	95% Confidence Interval	Weight (%)
Dogra et al, ¹⁸ 2002 (gentamicin/citrate)	4.2	0.3	14.0 \pm 1.46	11.1-16.9	11.7
McIntyre et al, ¹⁴ 2004 (gentamicin/heparin)	4.0	0.3	13.3 \pm 1.05	11.3-15.4	12.6
Nori et al, ¹¹ 2006 (gentamicin/citrate)	4.0	0	8.0 \pm 1.46	5.1-10.1	11.7
Overall effect for gentamicin			11.8 (favors ALS)	8.4-15.3	
Weijmer et al, ¹⁷ 2005 (trisodium citrate)	4.1	1.1	3.73 \pm 0.38	3.0-4.5	13.5
Betjes et al, ¹⁹ 2004 (taurolidine/citrate)	2.1	0	4.2 \pm 1.5	1.26-7.14	11.6
Nori et al, ¹¹ 2006 (minocycline/EDTA)	4.0	0.4	10.0 \pm 1.07	7.9-12.1	12.6
Kim et al, ²⁰ 2006 (cefazolin/gent/heparin)	3.12	0.44	7.1 \pm 1.07	5.0-9.2	12.6
Saxena et al, ²¹ 2006 (cefotaxime/heparin)	3.68	1.56	2.36 \pm 0.22	1.9-2.8	13.6
Overall effect, all studies			7.72 (favors ALS)	5.1-10.3	

Note: Weight refers to that allocated in the overall meta-analysis.

Abbreviations: CRI, catheter-related infection; ALS, antibiotic locking solutions; gent, gentamicin.

reported fewer exit-site infections in the ALS arms,^{17,18} 2 reported no difference between the ALS and heparin groups,^{19,21} and McIntyre et al¹⁴ observed no exit-site infection during the study.

Few adverse events were observed across the studies listed in Table 1. Interestingly, Weijmer et al¹⁷ found a greater rate of bleeding complications using heparin locks compared with trisodium citrate both immediately after catheter insertion and during follow-up. The investigators suggested

that this was caused by leakage of heparin from the catheter, leading to systemic exposure and prolonged bleeding times, although coagulation measurements were not stated. Dogra et al¹⁸ reported nonspecific dizziness in 4 of 42 patients in the study arm using high-concentration gentamicin plus citrate in the context of a significant increase in serum gentamicin levels. In 3 patients, symptoms resolved spontaneously or on termination of the study, but the fourth patient continued to experience intermittent symptoms. No adverse events

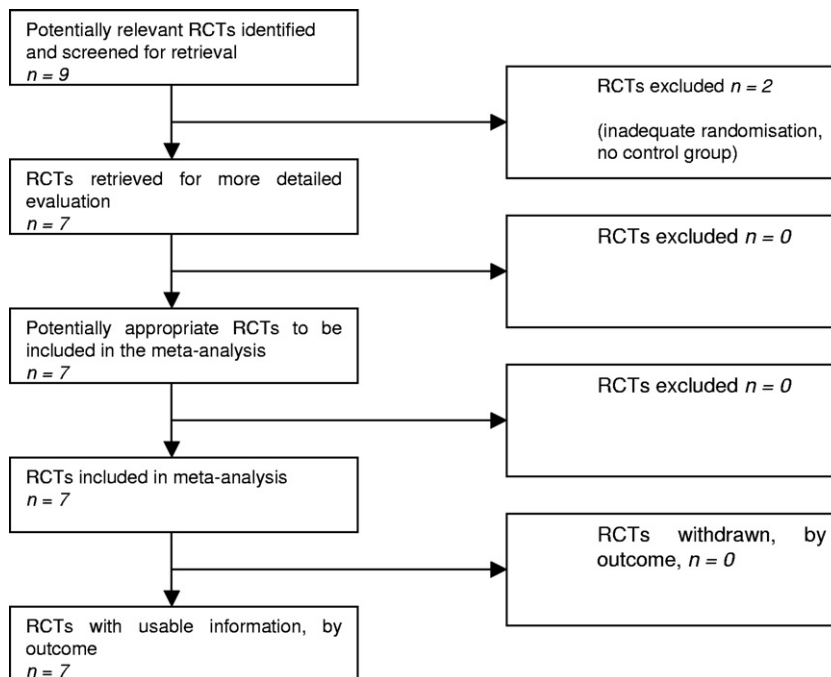


Figure 1. The Quality of Reporting of Meta-analyses (QUOROM) flow diagram summarizes study selection. Abbreviation: RCT, randomized controlled trial.

Review: Comparison of dialysis catheter lock solutions in the prevention of catheter related bacteraemia
 Comparison: 02 CRI
 Outcome: 01 CRI rate

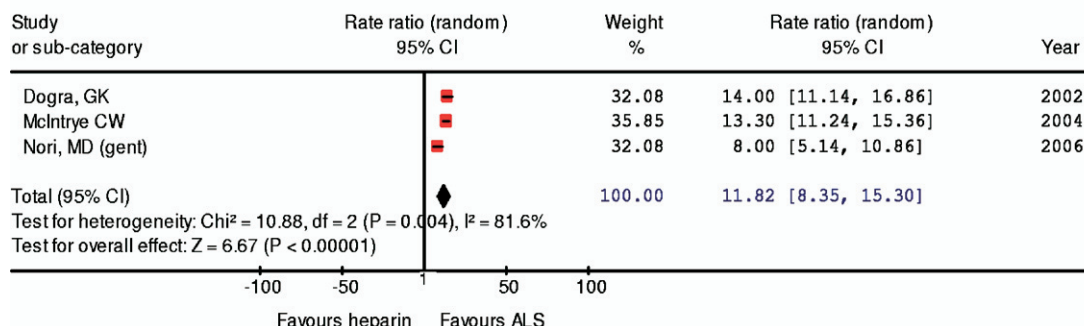


Figure 2. Meta-analysis graph of gentamicin-containing locking solutions in the prevention of catheter-related infection (CRI). Results expressed as rate ratio at 95% confidence interval (CI). Test for heterogeneity refers to statistical heterogeneity. This reflects differences in effect size produced by the different studies and whether observed variability is greater than expected by chance. This measure does not assess method heterogeneity, which is addressed in the text of the review. Abbreviation: ALS, antimicrobial lock solution; gent, gentamicin.

were observed with lower concentrations of gentamicin,^{11,14,20} although formal audiology testing was not performed in any study.

DISCUSSION

This meta-analysis of randomized controlled trials supports the effectiveness of ALSs as a successful strategy to decrease the incidence of CRI in HD patients. All ALSs studied were effective in this way, and the overall number needed to treat to prevent 1 CRI was small.

Gentamicin was the most commonly tested antimicrobial agent. Two studies mixed gentamicin with citrate because of concerns regarding insolubility with heparin. However, evidence suggests that lower concentration gentamicin solutions are soluble with heparin and adequate to inhibit local bacterial growth. This was shown by both McIntyre et al¹⁴ and Kim et al.²⁰ Dogra et al¹⁸ used high-concentration gentamicin (40 mg/mL) that resulted in systemic exposure of gentamicin, possibly causing dizziness in a small number of patients. However, gentamicin was tested at much lower concentrations by Nori et al¹¹ (4 mg/mL) and McIntyre et al¹⁴ (5 mg/mL) without increased serum gentamicin levels, but with similar efficacy to the 10-fold greater concentration. No adverse effects (especially ototoxicity) were shown during use of low-concentration gentamicin use. Therefore, low-dose gentamicin appears safe, although monitoring

serum gentamicin levels when introducing a policy of ALSs may be prudent. Alternatively, Saxena et al²¹ showed that cefotaxime was an effective substitute. Although the magnitude of effect for cefotaxime was the least for all studies (shown by the smallest rate ratio), this may be explained because only patients with diabetes were included.

Trisodium citrate was used as an ALS because of its known inherent anticoagulant and antimicrobial properties. However, as a known chelating agent that acts on calcium and magnesium, it carries the potential risk of cardiac arrhythmia if there is leakage and entry into the systemic circulation, as occurred in 2000 when a patient died of cardiac arrest after inadvertent systemic instillation of 46.7% citrate.²² However, Weijmer et al¹⁷ used high-concentration citrate ALS (30%), and no serious adverse symptoms were reported during administration in 12,624 locks. Despite this, warnings from the Food and Drug Administration are likely to prove a major obstacle to high-concentration citrate locks gaining widespread use in the United States.

Although none of the included studies reported the development of antibiotic resistance, this remains a major concern for many regarding the use of ALSs. This remains an unresolved issue in view of the relatively short duration of these studies. In this respect, high-concentration citrate locks may have an advantage because they will not generate antibiotic resistance. How-

ever, Taal et al²³ subsequently reported no problems with resistance in more than a year since the unit-wide introduction of ALSs, and similar (R.J.F., M.W.T., C.W.M., unpublished, May 2007) findings during a 2-year period of follow-up are discussed by Nori et al.¹¹ In addition, the potential for the development of resistance has to be weighed against the fact that if ALS use decreases CRI, the reduced administration of vancomycin may help ease the antibiotic pressure leading to vancomycin resistance.

Morbidity and mortality did not increase with the use of ALSs. Two studies showed that ALS use led to decreased CRI-related mortality rates.^{17,21} In addition, ALS use did not correlate with a decrease in premature catheter removals for flow-related problems or thrombosis, with 3 studies reporting improvements in catheter patency. The mechanisms underlying this improved patency are not clear, although possibilities include ALS reducing the formation of biofilm and thrombus per se or that use of citrate as opposed to heparin has an improved local anticoagulant effect. This may occur, although Weijmer et al¹⁷ showed that use of 30% citrate locks was associated with less systemic bleeding complications compared with heparin.

A formal cost-effectiveness analysis was not the emphasis of any of the included studies or of this review. However, cost is likely to be an important factor for clinicians when deciding whether to use a strategy of ALS. Only 3 studies discussed cost; Nori et al¹¹ and McIntyre et al¹⁴ reported similar costs for low-concentration gentamicin of \$32/mo and £100/y, respectively. However, minocycline (now no longer available for intravenous use in many areas) was 4 times more expensive. Weijmar et al¹⁷ stated that 30% citrate was less expensive than heparin when prepared from base (without stating costs), but in many countries, pre-prepared citrate locks are significantly more expensive than heparin. However, the cost of the ALS needs to be balanced against potentially large savings made in terms of treating fewer CRIs, decreased hospital admissions, and fewer catheter exchanges. At present, low-concentration gentamicin-heparin locks appear to be the least expensive. The very low number needed to treat would also suggest that ALS as an overall therapeutic strategy is cost-effective.

This review has limitations. The major one is the relatively short duration of follow-up of the included studies (maximum follow up, 1 year), which does not allow complete reassurance regarding the development of antibiotic resistance. In addition, the ALS tested was different in every study, and only 1 trial compared more than 1 ALS.¹¹ Therefore, it is not possible to say which ALS at which concentration is most effective, although a higher concentration of antibiotics will have more systemic leakage, thereby increasing the chances of adverse effects and the development of antibiotic resistance. There was a degree of method variation between studies: catheter insertion technique, catheter site, type of dressing, and use of topical antibiotics all varied among studies, and only 3 studies documented appropriate use of CDC criteria to diagnose CRI.^{14,18,19} This further hampers possible comparisons between different ALSs.

In conclusion, this review shows that ALS decreases rates of CRI without causing significant adverse effects, in particular, without increasing rates of catheter thrombosis. This has the potential to positively impact on patient mortality and overall costs of treatment. There were no reports of the development of antibiotic resistance, although this question will only be answered definitively after longer periods of follow-up.

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