Prevention of tunnelled dialysis catheter infection

Date written: May 2012
Author: George Chin

GUIDELINES

a. We recommend application of either topical agents or intraluminal lock solutions for the reduction of exit-site infection and catheter-related bacteraemia. Options of topical agents include mupirocin 2% ointment and polysporin. Intraluminal lock agents include both antibiotic based and non-antibiotic-based solutions. Ideal antibiotics and optimal doses are yet to be defined. (Level 1 evidence)

SUGGESTIONS FOR CLINICAL CARE
(Suggestions are based on Level III and IV evidence)

- Basic care of catheter management should be reinforced in every dialysis unit. An aseptic protocol has been shown to reduce catheter-related infection (CRI).
- Choice of topical agents and/or intraluminal lock solutions should be unit-based, with consideration given to the availability, safety, and costs of the agents used.
- There are no studies to-date comparing the efficacy of topical agents versus intraluminal lock solutions, or the use of both topical agents and intraluminal antimicrobial lock solutions together in reduction of CRI. There is thus insufficient evidence to recommend one over the other.
- The potential emergence of antimicrobial resistance remains a concern. Use of either strategy should be considered in patients who rely on long-term tunnelled-catheter, have previous infective complications and/or have prosthetic devices.

IMPLEMENTATION AND AUDIT

1. Documenting and monitoring the incidence and prevalence of CRI in each dialysis unit.
2. Implement policy regarding the use of either topical or intraluminal antimicrobial agents based on individual dialysis unit

BACKGROUND

There were over 10,000 patients receiving dialysis, either haemodialysis (HD) or peritoneal dialysis (PD), in 2010 in Australia[1]. Over 75% of patients on dialysis were on HD. While an arterio-venous fistula (AVF) remains the gold standard as vascular access, it is not always possible to have AVF ready by the time dialysis is initiated. Indeed, vascular catheter, both tunnelled and non-tunnelled, was the means of vascular access in 61% of the incident patients in Australia and 75% of patients in New Zealand in 2010[2] . This figure has changed little in the last five years. The prevalence of catheter use has been around 14%, i.e. one in seven prevalent dialysis patients.

Catheter-related infection (CRI) is defined by either exit-site infection, or the presence of the same microorganism cultured from the catheter tip and from peripheral and central blood cultures. In clinical practice, CRI is often diagnosed after exclusion of infection of other sources[3]. Catheter-related infection has an enormous adverse impact, not only at the individual level of increased morbidity and mortality, but also financial implications with the costs of hospital admissions, antibiotics
use and catheter change. Cost-per-infective-episode has been estimated to be between US$3703 to US$29000 in the United States from non-tunnel catheters in intensive care units [4].

In the Australian dialysis population, infection accounted for 11% of mortality, the third most common cause of death following dialysis withdrawal (35%) and cardiac disease (43%) [5]. Of the 11% (n = 148), approximately 25% was secondary to bacterial septicemia. Similarly, 17% of mortality was attributed to infection in the New Zealand dialysis population. The widespread use of vascular catheters is an important cause of the high infective complications seen in the haemodialysis population.

With the high incidence of catheter use in incident haemodialysis patients, it is imperative to develop strategies to prevent and treat CRI. There have been studies examining the application of topical agents to the exit site to prevent both local and systemic infections. Intense interests have been concentrating on the use of antimicrobial lock solutions to reduce CRI in recent years. Once bacteremia has occurred, catheter removal, with or without delay in insertion of a new vascular catheter, is often indicated. Alternative therapy such as combining systemic antibiotics and antimicrobial lock solutions (ALS), without changing the catheter, has been evaluated in the literature.

The objective of this guideline is to examine various strategies in prevention of CRI in dialysis patients with tunnelled catheters in-situ. This guideline does not assess preventive measures in those with non-tunnelled dialysis catheters.

**SEARCH STRATEGY**

**Database searched:** MeSH terms and text words for renal replacement therapy, haemodialysis, haemofiltration, haemodiafiltration and renal dialysis were combined with MeSH terms and text words for tunnel, cuff, indwelling and vascular catheter and combined with MeSH terms and text words for bacteremia and bloodstream infection. The search was carried out in Medline (1950 – January, Week 3 2008 and Nov 2010). An updated search was carried out in Medline (2010 – April 2012) using the same MeSH terms and text words.

**Date of initial search:** 25 January 2008
**Date of update search:** 30 April 2012

**WHAT IS THE EVIDENCE?**

Pathogenesis of CRI is thought to relate to the migration of bacteria from the exit site along the extraluminal surface of the catheter. Infection can also be acquired via contamination of the catheter hub by dialysis staff. The micro-organisms then colonise and form a biofilm along the catheter. Biofilms may develop as early as 24 hours after catheter placement. It forms a barrier protecting the bacteria from systemic antibiotics, but may also enhance the degradation of antibiotics due to retention of enzymes such as B-lactamases [6]. Coagulase-negative staphylococci, Staphylococcus aureus and Gram-negative bacilli are among the most common pathogens that cause CRI.

There are many randomised-controlled trials (RCT) in the recent literature examining the use of antimicrobial agents to prevent CRI. The two most commonly used strategies are: 1) the application of topical agents to exit site, and 2) the use of intra-luminal solutions. The choice of topical or intra-luminal agents could have anti-microbial properties without being classified as antibiotics, such as Medihoney and trisodium citrate.

Five meta-analyses assessing a total of 32 randomised control trials are summarised here. Two included both topical and ALS agents, whereas the remaining three examined studies only concerning ALS (Tables 1a). The primary outcome is reduction of CRI: exit-site infection, catheter removal, mortality and adverse events including antibiotic resistance were other outcome measures examined. It is important to emphasize that there are no studies to-date comparing between topical therapy and intra-luminal antimicrobial lock solutions or the combination, and thus no conclusion can be reached concerning the superiority of either strategy.
**Topical agents**

Concerning the use of topical exit site anti-microbial agents, James et al. examined five studies: mupirocin ointment 2% (n = 3), polysporin triple-antibiotic ointment (n = 1) and medihoney (n = 1) [7]. The last trial of medihoney was not included in the meta-analysis because it did not have a control arm [8]. However, the author found almost identical efficacy between medihoney and mupirocin ointment 2% in prevention of CRI, 0.97 episodes per 1000 catheter-days in the medihoney group versus 0.85 episodes per 1000 catheter-days in the mupirocin group. There were no exit-site infections in either arm during the entire study period. The use of both mupirocin and polysporin triple-antibiotic ointment was associated with a significant reduction in the rates of CRI, rate ratio RR 0.22 (95%CI: 0.12-0.40); staphylococcal aureus bacteraemia, RR 0.14 (95%CI: 0.06-0.30); and exit-site infection. RR 0.17 (95%CI: 0.08-0.38). Catheter removal, assessed in three trials, was reduced by 64%; RR 0.36 (95%CI: 0.26-0.52). Hospitalisation for infection, assessed in two trials, was reduced by 76%; RR 0.24 (95%CI: 0.12-0.47). Mortality was reported in only one trial using polysporin triple antibiotic, with reduction in mortality of 78%; RR 0.22 (95%CI: 0.07-0.74). No mupirocin-resistant strains were isolated.

Six studies examining topical agents were included in a systemic review [9] where the application of exit-site antimicrobial agents reduced the rate of CRI: RR 0.21 (95%CI: 0.12-0.36, P<0.00001), and of exit-site infection; RR 0.22 (95%CI: 0.10-0.47, P<0.0001). Risk of catheter loss was reduced; RR 0.54 (95%CI: 0.29-0.99).

**Intraluminal lock solutions**

Regarding intraluminal lock solutions, pooled results from eleven trials in the paper by James et al. showed a significant reduction of CRI with prophylactic ALS; RR 0.32 (95%CI: 0.22-0.47) [7]. Five trials were reported as blinded. When stratified by the antibiotics type, results remained significant for gentamicin, minocycline, cefotaxime, combined vancomycin and gentamicin, but not for taurolidine and combined cefazoline/gentamicin. Staphylococcal aureus bacteraemia (n = 5) and exit-site infection (n = 4) were not reduced by the use of ALS. Catheter removal rate (n = 5) was reduced by 63%; RR 0.37 (95%CI: 0.23-0.59). Three trials reported mortality. There was a trend towards a reduction in the ALS arm. Antimicrobial resistance was monitored in the trial using cefotaxime ALS and no resistant strain was reported.

Rabindranath et al. examined a total of 29 trials, including the use of peri-operative systemic antibiotics (n = 1), topical antimicrobial application (n = 6), anti-microbial coating of the catheter or catheter cuff (n = 3), and luminal antimicrobial lock (n = 19) [9]. Eleven trials were blinded, though one of these only involved blinding of the patients. There were a total of 2886 patients with 3005 catheters. Use of ALS significantly reduced both the rates of CRI and exit-site infection; RR 0.33 (95%CI: 0.24-0.45, P<0.00001) and 0.67, (95%CI: 0.47-0.96, P=0.03), respectively. Risk of catheter loss was reduced; RR 0.61 (95%CI: 0.45-0.83). Neither anti-microbial coating of the catheter of catheter-cuff, nor peri-operative systemic antibiotics resulted in any significant reduction of CRI or exit-site infection.

Yahav et al. assessed 16 randomised controlled trials involving both antibiotic (n = 11) and non-antibiotic (n = 5) solutions [10]. Eleven trials concerned antibiotic lock solutions and five assessed non-antibiotic based solutions. Of the eleven studies, the antibiotics included gentamicin (n = 3), gentamicin and citrate (n=3), gentamicin and vancomycin (n = 1), gentamicin and cefazolin (n = 1), cefotaxime (n = 2), and minocycline with EDTA (n = 2). Heparin was used as the control arm in all trials. All, but two, assessed tunneled catheters. Both incident and prevalent dialysis catheters were included in this meta-analysis. All examined CRI as the primary end-point, and seven also reported all-cause mortality. Of the 16 trials, six were double-blind studies.

Of the eleven trials examining antibiotic lock solutions, both CRI per patient, RR 0.44 (95%CI: 0.38-0.50, P<0.00001) and per catheter-day, RR 0.37 (95%CI: 0.30-0.47, P<0.0001) were significantly lower in the ALS arm. Exit-site infections were reduced, but did not reach statistical significance. Catheter removal rates were significantly reduced: both per patient-day, RR 0.35 (95%CI: 0.23-0.55) and per catheter-day, RR 0.34 (95%CI: 0.21-0.55). Catheter thrombosis rates were also lower with intervention RR 0.48 (95%CI: 0.32-0.72). ALS using gentamicin alone (n = 6) was not inferior to those that used antibiotics combination. Both regimes reduced gram-negative and gram-positive micro-organisms, including Staphylococcus aureus CRI. Five assessed adverse events, three of which reported none.
Two studies using gentamicin and citrate reported one case of rash resulting in discontinuation, and four cases of dizziness of whom all were assigned to the gentamicin arm.

Similar results were observed in the five trials involving non-antibiotic lock solutions. Four used citrate solution alone (concentration varied between 4% and 46.7%) and one used combined citrate 4% and taurolidine 1.35%. Rates of CRI were significantly reduced compared to heparin: both per patient, RR 0.46 (95%CI: 0.29-0.71, P=0.0005) and per catheter-day, RR 0.48 (95%CI: 0.30-0.76, P=0.002). Two trials that did not use nasal mupirocin and topical iodine/chlorhexidine did not reach statistical significance RR 0.90 (95%CI: 0.48-1.69). Exit site infections were significantly reduced by lock solutions: both per patient-day, RR 0.58 (95%CI: 0.40-0.84) and per catheter-day RR 0.60 (95%CI: 0.40-0.90). Catheter removal rates were also significantly lower, but no difference was found with regards to catheter thrombosis.

There were two additional meta-analyses published in 2008, both of which involved similar trials, examining the efficacy of intra-luminal lock solutions in the reduction of CRI. Labriola et al reported a significant reduction of CRI with RR 0.32, (95%CI: 0.10-0.42) [11]. There were 829 patients with a total of 882 catheters. Subgroup analyses demonstrated a higher efficacy of gentamicin-containing ALS. There was no significant effect of the proportion of diabetic patients, maximum duration of follow-up, biochemical markers including mean albumin and ferritin levels, proportion of tunnel catheter, and use of intranasal mupirocin on the overall relative risk between patients on heparin and those on ALS. Catheter malfunction was not examined in this meta-analysis as most studies lacked detailed information concerning this outcome. The second meta-analysis, involving seven studies with a total of 624 patients and 819 catheters, was conducted by Jaffer et al [12]. CRI was 7.72, (95%CI: 5.11-10.33) times less likely to occur in the ALS arm. The number needed to treat was three to prevent one CRI per 100 catheter days. Two studies demonstrated survival benefits, although one had high overall mortality in the heparin group. Catheter malfunction was less in the ALS group in three studies, similar in three studies and not reported in one. It was therefore not possible to draw any conclusion regarding the superiority of ALS in maintaining patency of catheters. Similarly exit site infections were either reduced (n = 2) or no different (n = 2) in those received ALS.

**Other strategies**

The application of a chlorhexidine impregnated dressing (Biopatch) at the exit site of tunnelled catheters was examined by Onder et al [13]. The study population was 70 paediatric chronic haemodialysis patients. The Biopatch group was compared with a historic group where the exit sites were cleansed with betadine in conjunction with transparent dressing coverage. The application of biopatch was associated with a significant reduction in exit site infection, though this had no effect on the incidence of CRI or catheter survival time. A cross-over interventional trial examining the use of biopatch showed no reduction in the incidence of CRI in 121 haemodialysis patients using tunnelled catheters [14]. The authors speculated that the catheter hub, rather than the exit site, may be involved in the pathogenesis of CRI.

Power et al. conducted a randomised control trial in a single-centre using high concentration sodium citrate (46.7%) versus 5% heparin to examine the effects on CRI and exit-site infection [15]. Both of these primary outcomes did not differ between the two groups. Use of urokinase lock, a secondary endpoint, was significantly more common in the citrate group. There was greater incidence of adverse events in the citrate group, leading to it being curtailed.

Minocycline, an antibiotic that is not usually used to treat serious infection, was trialled as an antimicrobial lock solution in a study by Campos et al. [16]. A randomised controlled trial comparing minocycline-EDTA with conventional unfractionated heparin for prevention of CRI in 204 incident dialysis catheters, both cuffed (27.8%) and non-cuffed. CRI was significantly lower in the minocycline-EDTA group (1.1 per 1000 catheter-days, P=0.005), as opposed to the heparin group (4.3 per 1000 catheter-days). No difference was seen in catheter removal for dysfunction.
SUMMARY OF EVIDENCE

There is convincing evidence to support the use of either topical agents or ALS, to reduce the incidence of catheter related infection. There are, however, a number of unresolved issues and concerns regarding each method.

Firstly, it is unclear if either topical agents or intraluminal lock solutions offer superior outcome as there has been no direct comparison between these two modalities. It is also uncertain if a single specific antibiotic agent or combination is more efficacious than another. The meta-analysis by James et al [7] suggested similar efficacy for gentamicin, minocycline, cefotaxime, combined vancomycin and gentamicin, but not for taurolidine and combined cefazoline/gentamicin. Use of combined topical antibiotics and ALS cannot be recommended because of the extremely low rates of CRI achieved by either method. It is unlikely that the addition of either method will translate into clinical significant outcome.

Secondly, the emergence of antimicrobial resistance remains a major and serious concern. Mupirocin resistance was not observed in the two trials conducted by Johnson et al. but the follow-up periods were relatively short. [8, 17] This potential public health hazard has been highlighted by a study from New Zealand. Abbas et al. examined the use of heparin-gentamicin ALS on the incidence of CRI, hospitalisation, catheter removal, and the patterns of bacterial resistance [18]. While ALS use resulted in reduction in both CRI, as suggested by other studies, there was a trend towards increased gentamicin resistant coagulase-negative staphylococci isolates. More recently, Landry et al. reported their experience after four years of gentamicin/heparin lock in 1410 chronic haemodialysis patients [19]. There were a total of 24 cases of gentamicin resistant CRI, resulting in four deaths, two cases of septic shock requiring admission to the intensive care unit and four cases of infective endocarditis. Coagulase-negative staphylococcus was the most common bacteria isolated, accounting for 54% of all gentamicin-resistant isolates. This was followed by 7 cases (29%) of Enterococcus faecalis. These findings are of both clinical and public health concerns, because of the potential risk of multi-resistant microorganisms.

Lastly, potential toxicities of antibiotics need consideration. Inadvertent administration of 46.7% citrate resulting in one case of fatality from cardiac arrhythmia led to the disapproval of this agent as a catheter lock solution by the FDA in 2000 [20]. Detectable gentamicin levels have been reported in the study by Dogra et al. [21]. In the same study, four patients, all of whom were assigned to the active arm, reported dizziness, though there was no formal audiometry performed. Other studies using lower doses of gentamicin did not report any clinical issues with ototoxicity or systemic exposure with undetectable gentamicin levels. Similarly, use of biopatch has been associated with severe contact dermatitis [14].

Use of these antimicrobial agents is effective in reducing the incidence of CRI and exit-site infection. While there are a number of drawbacks, such strategies should be considered in a subset of patients such as those with prosthetic devices or those running out of vascular access options. Such decision should be individualised, with a risk-to-benefit assessment. Basic care of catheter management by the nursing staff should be reinforced in every dialysis unit. An aseptic protocol has been shown to reduce CRI.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcome Quality Initiatives: No recommendation.

UK Renal Association: (2011) Vascular catheters should be used as the last resort as the longer-term vascular access. Aseptic technique is mandatory in handling the catheters. Exit site should be cleaned with chlorhexidine 2% solution. Suggestion is also made to use antimicrobial or antibiotic lock solution to reduce catheter-related infection [22].

Canadian Society of Nephrology: (2006) IV. Infection Prevention in the Vascular Access: Instruct all staff and patients on infection control measures. Change catheter exit site dressings at each haemodialysis treatment. Use dry gauze dressings and povidone iodine, mupirocin, or polysporin triple ointment at the catheter exit site [23].
European Renal Best Practice Guidelines (2010): Aseptic handling of catheter is essential. Use of antimicrobial locks is advocated to reduce the rate of CRI. However, its use should be balanced against the potential risks of spillover of the locking solution, and associated risks. The catheter site should be covered by a dressing as long as the catheter remains in place. Application of antibiotic ointment at the exit site should be considered after catheter placement until the insertion site has healed but should be discontinued after healing. Development of mupirocin resistance with long-term exit-site and nasal application should be taken into account as an effect counterbalancing the potential benefits on infectious complications.[24]

International Guidelines: Centers for Disease Control and Prevention (2011):
Use povidone iodine antiseptic ointment or bacitracin/gramicidin/polymyxin B ointment at the haemodialysis catheter exit site after catheter insertion and at the end of each dialysis session only if this ointment does not interact with the material of the haemodialysis catheter per manufacturer’s recommendation.
Use prophylactic antimicrobial lock solution in patients with long term catheters who have a history of multiple CRI despite optimal maximal adherence to aseptic technique.[25]

SUGGESTIONS FOR FUTURE RESEARCH
1. Direct comparison between topical agents and intraluminal lock solutions will provide knowledge regarding if one strategy is more efficacious than the other in preventing CRI.
2. Long-term follow-up and documentation of antimicrobial resistance in patients using either strategy is essential.
3. Exploration and assessment of non-antibiotic based agents, either topical or intraluminal, might be the ideal method in prevention of infective complications of dialysis catheters.

CONFLICT OF INTEREST
George Chin has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.
REFERENCES


## APPENDICES

### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design and setting</th>
<th>Participants and Interventions</th>
<th>Follow up</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Topical agents</strong></td>
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● Non-tunnelled catheters – 5 trials  
● Variable trial quality with limited reporting on loss to follow up, allocation concealment and blinding.  
● Limited reporting of adverse events.  
● Evidence of publication bias in the intraluminal trials.  
● No significant heterogeneity detected.  
● Short duration and small size of most trials limits generalisability. |
| Johnson et al (2005) [8] | 101 | RCT | Adult patients who had acute or chronic renal failure requiring haemodialysis via central venous catheter. Patients were randomised to either Medihoney or standard 2% calcium mupirocin ointment. All patients also had standard exit-site care and 10% povidone iodine disinfection. Single centre, Australia | 30 months | ● Catheter-related bacteraemia was similar in both groups: 0.97/1000 catheter-days for the medihoney group versus 0.85/1000 catheter-days for mupirocin, P=0.78  
● No exit-site infections were observed in any patient.  
● In this study, Medihoney is compared to another active treatment, no other control arm. |
| **Intraluminal lock solutions** |                    |                          |                                                                                                | NA        |          |
| Rabindranathan et al (2009) [9] | 29 trials, 2886 patients, 3005 catheters. | Meta-analysis of RCTs | Haemodialysis patients using central venous catheters. Interventions: peri-operative systemic antimicrobials; antimicrobial locks (AMLs); exist site antimicrobial application (ESAs), treatment of nasal *S. aureus* carriage before or after catheter insertion; antimicrobial coating of catheters or catheter components. Comparison: Head to head, placebo/control. | NA        | ● Tunnelled catheters – 17 trials  
● Non-tunnelled catheters – 9 trials  
● Tunnelled and non-tunnelled – 3 trials.  
● Insufficient evidence to draw conclusions relating to antimicrobial coatings.  
● Limited head to head comparisons of antimicrobial agents.  
● No significant heterogeneity between studies.  
● Studies of short duration (most <1 year) and relatively small patient numbers limiting conclusions in relation to development of drug-resistant organisms. |
● Non-tunnelled catheters – 2 trials  
● Tunnelled and non-tunnelled – 3 trials. |
<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study design and setting</th>
<th>Participants and Interventions</th>
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<th>Comments</th>
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● Publication bias indicated with possible under representation of small trials with non-significant or negative results. However, a large number of trials would be required to overall results.  
● Subgroup analyses indicate higher overall efficiency if the lock solution included gentamicin.  
● The limited follow up does not allow assessment of bacterial resistance. |
● Only 1 trial compared more than 1 lock solution, therefore not possible to say which solution or concentration is most effective.  
● Methodological variation across studies also limits ability to compare between solutions.  
● The limited follow up does not allow assessment of bacterial resistance. |
| Power et al (2009) [15] | 232 patients | RCT | Adult, long-term haemodialysis patients. Randomised to 46.7% sodium citrate or 5% heparin lock solution. Multicentre, UK. | 6 months | ● Catheter-related bacteraemia between the citrate and heparin groups did not differ: rate ratio 0.7/1000 catheter-day (95% CI: 0.40-1.2) and 0.7 (95% CI: 0.36-1.2), respectively (P=0.9).  
● Exit-site infections did not differ between the groups: 0.7/1000 catheter-days (95% CI: 0.36-1.2) for the citrate group and 0.5/1000 catheter-days (95% CI: 0.24-1.0) for the heparin group (P=0.5).  
● There was greater use of urokinase locks in the citrate group 8/1000 catheter-day (95% CI: 6.6-9.2) compared with 4.3/1000 catheter-days (95% CI: 3.4-5.4) in the heparin group, P<0.001.  
● 71/132 patients in the citrate group had side effects, P<0.001. |
| Campos et al (2011) [16] | 204 catheters | RCT | Adult haemodialysis patients requiring dialysis via central venous catheters (tunneled and non-tunneled) Multicentre, Brazil | 90 days | ● Catheter-related bacteraemia (CRB) incidence: 19 patients in the control group versus 5 in the intervention group (P=0.003), this corresponded with CRB rate of 4.3 per 1000 catheter-days and 1.1 per 1000 catheter-days (P=0.005), respectively  
● Tunnelled catheters with M-EDTA had lower rate of CRB (1.8 per
<table>
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<tr>
<th>Study ID</th>
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<tr>
<td></td>
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<td>Intervention: Minocycline with EDTA solution.  Comparison: unfractionated sodium heparin solution</td>
<td>1000 catheter-days) compared with tunnelled catheters in the comparator (4.8 per 1000 catheter-days), but this was non-significant (P=0.13)  ● Non-tunnelled catheters with M-EDTA had a significantly lower rate of CRB (0.7 per 1000 catheter-days) compared with the heparin non-tunnelled catheters (4.1 per 1000 catheter-days; P=0.01)  ● Catheter removal due to dysfunction: 20 in M-EDTA group (4.6 per 1000 catheter-days) versus 14 in heparin group (3.2 per 1000 catheter-days; P=0.31)  ● CRB-free survival was significantly higher in the M-EDTA group compared to the heparin group, hazard ratio = 0.32 (95% CI: 0.14-0.71, P=0.005)</td>
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### Table 1a. Summary of meta-analyses results for topical agents and intraluminal lock solutions.

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>No. of studies</th>
<th>Topical agents</th>
<th>Intra-luminal lock solutions</th>
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<tr>
<td></td>
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<td>Rate ratio (95% CI)</td>
<td>Rate ratio (95% CI)</td>
<td>Catheter removal</td>
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<tr>
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<td>CRI</td>
<td>ESI</td>
<td>CRI</td>
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<td>James et al. 2008 [7]</td>
<td>16</td>
<td>0.22 (0.12-0.40)</td>
<td>0.17 (0.08-0.38)</td>
<td>0.32 (0.22-0.47)</td>
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<td>Rabindranath et al. 2009 [9]</td>
<td>29</td>
<td>0.21 (0.12-0.36)</td>
<td>0.22 (0.10-0.47)</td>
<td>0.33 (0.24-0.45)</td>
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<td>Yahav et al. 2008 [10]</td>
<td>16</td>
<td>NA</td>
<td>NA</td>
<td>ALS</td>
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<td></td>
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<td>0.37 (0.30-0.47)</td>
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<td></td>
<td>Non-ALS</td>
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<td></td>
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<td>0.48 (0.30-0.76)</td>
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<tr>
<td>Labriola et al. 2007 [11]</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>0.32 (0.10-0.42)</td>
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<tr>
<td>Jaffer et al. 2008 [12]</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>7.72 (5.1-10.3)</td>
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</tbody>
</table>

- * Pooled results showed that CRI rates with ALS was 7.72 times less compared with heparin locks
- CRI – catheter-related infection
- ESI – exit-site infection
- ALS – antimicrobial lock solution
- NA, not applicable
Table 2. Methodological quality of randomised trials

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Method of allocation concealment *</th>
<th>Blinding (participants)</th>
<th>Blinding (investigators)</th>
<th>Blinding (outcome assessors)</th>
<th>Intention-to-treat analysis †</th>
<th>Loss to follow up (%)</th>
<th>Comments ‡</th>
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<tbody>
<tr>
<td>Johnson et al (2005)[8]</td>
<td>Sequentially numbered opaque sealed envelopes, computer generated random number list</td>
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<td>Yes</td>
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<td>-</td>
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<td>Unknown</td>
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<td>Campos et al (2011)[16]</td>
<td>Sealed envelope</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Yes</td>
<td>0%</td>
<td>-</td>
</tr>
</tbody>
</table>

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.
† Choose between: yes; no; unclear.
‡ Quality score – “How successfully do you think the study minimised bias?” Choose between: very well (+); okay (Ø); poorly (–).

Table 3. Results for dichotomous outcomes

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Outcomes</th>
<th>Intervention group (number of events/ catheters)</th>
<th>Control group (number of events/ catheters)</th>
<th>Relative risk (RR) [95% CI]</th>
<th>Risk difference (RD) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campos et al (2011)[16]</td>
<td>Catheter related infections</td>
<td>5/92 (M-EDTA)</td>
<td>19/95 (Heparin)</td>
<td>0.27 [0.11, 0.70]</td>
<td>-0.15 [-0.24, -0.05]</td>
</tr>
</tbody>
</table>