Treatment of dialysis catheter infection

Date written: May 2012
Author: George Chin

GUIDELINES

No recommendations possible based on Level I or II evidence

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

- Catheter removal should be the first consideration in treatment of catheter-related infection (CRI).
- After catheters have been removed, either delayed placement of new catheters or replacement of catheters over guide-wire exchange is possible depending on clinical presentations.
- Catheter salvage combined with catheter antibiotic lock and systemic antibiotics might be considered in those with limited alternative vascular access options.
- A multidisciplinary approach following suggested guideline recommendations can reduce recurrent CRI.

IMPLEMENTATION AND AUDIT

1. Documenting and monitoring the incidence and prevalence of CRI in each dialysis unit.
2. An audit of patients with infective complications as a result of catheter mismanagement should be conducted.
3. Further evaluation of the use of combined systemic and intraluminal antibiotics as a means of catheter salvage might be allowed in a more defined “low risk” population.

BACKGROUND

There were over 10,000 patients receiving dialysis, either haemodialysis or peritoneal dialysis, in 2010 in Australia[1]. Haemodialysis accounted for over 75% as the dialysis modality. While arteriovenous 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% 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%.

In the Australian dialysis population, infection accounted for 11% of mortality, the third most common cause of death following dialysis withdrawal (37%) and cardiac disease (34%)[3]. Of the 11% (n = 166), approximately 25% was secondary to bacterial sepsicaemia. The widespread use of vascular catheters is an important cause of the high infective complications seen in the haemodialysis population.

Catheter-related infection (CRI) has an enormous adverse impact, not only at 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].
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 bacteraemia 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, without changing the catheter, has been evaluated in the literature.

The objective of this guideline is to examine various strategies in the treatment of CRI.

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 bacteraemia and bloodstream infection. The search was carried out in Medline (1950 – January, Week 3 2008 and Nov 2010). An update of the 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: 20 April 2012

WHAT IS THE EVIDENCE?

Most studies examining the treatment strategies of CRI are non-randomised prospective observational in nature. Catheter removal is often regarded as the preferred strategy in treatment of CRI if patients remain unstable after 48-72 hours of different catheter salvage strategies. The following section examines the evidence in supporting the suggestions for clinical care in managing CRI

Catheter removal

Marr et al. enrolled 102 patients with dual-lumen tunnelled catheters over a 9-month study period [5]. Forty one (40%) patients developed 62 episodes of bacteraemia, translating into an incidence of CRI of 3.9 per 1000 catheter-days. Catheter salvage was attempted in 38 episodes. Treatment failure developed in 68% of the cases. Treatment failure was defined as either clinical signs of sepsis, tunnel infection, persistent fevers over 72 hours, or bacteraemia during antibiotics treatment. Only six catheters (16%) were in-situ at the end of the three-month follow-up period. 22% of the 41 patients with bacteraemia developed complications, these included osteomyelitis (n = 6), septic arthritis (n = 1), infective endocarditis (n = 4), and 2 deaths. These complications did not differ between those who had the catheters removed immediately or those who had attempted salvage.

Saad et al. studied 101 chronic haemodialysis patients with tunnelled catheters[6] who were prospectively monitored over a 24-month period. There were 86 episodes of CRI in 52 patients, giving an incidence of 5.5 per 1000 catheter days. Immediate removal of the catheters occurred in five cases (5.8%). Further eight catheters were removed for non-infective reasons. Of the remaining 73 episodes, attempted salvage was only successful in 36.7% treated with antibiotics alone, compared to 81.4% who had both antibiotics and catheter exchange. There were three cases of infective endocarditis.

Catheter replacement

A prospective observational study involving 827 catheters in 387 patients over a 2-year period was conducted by Beathard et al [7]. Patients with CRI were divided into those with mild and severe symptoms. The latter group was characterised by a combination of symptoms including rigors, high fevers, hypotension, nausea, vomiting or altered sensorium. Those with mild symptoms were further subdivided into those with normal exit site and tunnel, and those with exit site or tunnel infection. Three different strategies were deployed. Those with mild symptoms, in the absence of exit site or tunnel
infection, had their catheters exchanged over a guide-wire using the same subcutaneous tunnels (Group 1). Those with evidence of exit or tunnel infection had catheter exchange over a guide-wire with creation of a new tunnel (Group 2). Those with severe symptoms had their catheters removed with delayed replacement (Group 3). Vancomycin and either gentamicin or cefazolin were given until cultures and sensitivities were available to guide specific therapy. A total of 123 episodes of CRI were observed in 95 patients. Of these, 49 (Group 1) were treated by catheter exchange over guide-wire without creation of new tunnel, 28 (Group 2) were treated with creation of new tunnel, and 37 (Group 3) had catheter removal with delayed replacement. A mean of 3.4 days was the duration between old catheter removal and new catheter insertion in the Delay group. Cures were comparable between all three groups: 69.4% vs 50% vs 73% and these were not statistically significant. This study suggests that catheter management may be determined depending on the severity of clinical presentations. However, this study lacked a control group (antibiotics only without catheter exchange), though the authors considered this approach as inappropriate based on previous study indicating high failure rate of this strategy.

**Catheter salvage**

Use of antibiotic lock solutions (ALS) in conjunction with systemic antibiotics was assessed in a prospective observational study conducted by Krishnasasmi and colleagues [8]. Sixty two episodes of CRI were recorded in this study. All patients received empirical Vancomycin (loading dose of 20mg/kg, followed by a maintenance dose of 500mg over the next eight dialysis sessions) and Gentamicin (loading dose of 1.5mg/kg followed by 1mg/kg not exceeding 100mg). Antibiotics were changed according to subsequent culture results and sensitivities. ALS consisted of Vancomycin (2.5mg/L), Cefazolin (5mg/ml), Vancomycin + Gentamicin (1mg/ml) and Cefazolin + Gentamicin, all of which were compatible with Heparin (2500units/ml). A total of 64.5% achieved protocol success, defined as resolution of symptoms in 48 hours and negative surveillance cultures one week after antibiotics completion. Of the 20 cases of treatment failure, nine grew Candida. Five of the nine patients had an initial Enterococcal bacteraemia. The likelihood of subsequent Candida infection was 42% if the initial pathogen was Enterococcus, compared with 8% for other pathogens. A comparison was made to a historic group where cases were treated with catheter replacement. Both groups had similar infection-free catheter survival. Two cases of bacteraemia due to Staphylococcus aureus did not respond to the ALS protocol.

The same group extended the previous study to examine the likelihood of achieving a cure based on the type of microbial pathogen [9]. Patients with Enterococcal bacteraemia were excluded because of the increased risk of developing candidaemia based on observation from the previous study. Cure was defined as negative blood culture and any clinical manifestations of metastatic infection up to 150 days after the initial bacteraemic episode. A total of 88 patients were initiated with Vancomycin-Ceftazidime ALS together with systemic therapy of the same antibiotics. Of the 47 episodes of CRI (exclusion of 21 cases because of indeterminate outcome), cure was attained in 70%. When the success rate was stratified according to the type of microorganisms, ALS and systemic antibiotics had a success rate of 87% for Gram-negative infections, 75% for Staphylococcus epidermidis and 40% for Staphylococcus aureus. Four out of six patients with polymicrobial CRI were treated successfully with the study protocol. There were three serious complications in those who completed the ALS protocol: septic shock, empyema and infected superior vena cava thrombus.

Peterson and colleagues assessed the management of vancomycin-sensitive enterococcus CRI using vancomycin ALS combined with systemic vancomycin [10]. Sixty four enterococcal CRI were treated with vancomycin ALS and 3 weeks of systemic vancomycin. Antibiotic levels were not measured. Treatment failure was defined as persistent fever of 48 hours duration or recurrent enterococcal bacteraemia within 90 days. Treatment success was observed in 39 patients (61%). There were four serious complications in the treatment failure group (one infective endocarditis and three osteomyelitis), compared with none in the other group. There was no reported increased incidence of candidaemia.

A prospective interventional study involving 67 dialysis patients examining the role of intraluminal lock of vancomycin in addition to systemic antibiotics suggested a statistical significant reduction in the rate of catheter removal[11]. Only one out of 28 patients (3%) in the group using intraluminal and systemic antibiotics, compared to 22 out of 39 cases (56%) using systemic antibiotic alone, had the dialysis
catheter removed. The two groups, however, received different systemic antibiotic regimes, raising concerns about validity of the comparison.

Tejwani and Parry [12] conducted a retrospective review over a 10 year period of patients with catheter related bacteraemia where catheter salvage was attempted in combination with an antimicrobial lock solution. The review included 83 episodes in haemodialysis patients. Treatment failure was defined as positive surveillance blood cultures, documented catheter removal and/or exchange during the course of treatment as a result of infection, or recurrence of bacteraemia with the same organism within 14 days of ending the antimicrobial lock treatment. Successful treatment was achieved in 61 episodes (73.5%) with a mean antimicrobial lock treatment time of 13.4 days. Success was independent of age or sex and most dependent on the infecting organism and availability of an appropriate antimicrobial agent.

**Multidisciplinary care**

Morkrzcki *et al.* reported CRI management based on a collaborative team model in a multicentre interventional controlled trial [13]. The intervention arm consisted of an infection manager who made treatment recommendation based on DOQI guidelines and literature-based recommendations, though treating nephrologists made final treatment decisions. Salvage of tunnelled catheters was not recommended, and catheters removal was suggested if patients were unstable over 36 hours. The study consisted of seven satellite haemodialysis units. Study duration was 2 years. Of the 166 CRI, 111 episodes were randomised to the interventional group (INT), and 55 to the usual care group (UC). There was significantly lower recurrent CRI in INT (OR 0.25, 95% CI: 0.09-0.84, P = 0.015). While infective complications were similar in both groups, there was no septic death in INT, compared to 6% in UC. In a multivariate analysis, INT was associated with 73% lower risk of recurrent bacteraemia or septic death (OR 0.27, 95% CI: 0.09-0.75 P < 0.02).

**SUMMARY OF EVIDENCE**

Despite the best effort to salvage tunnelled catheter in the events of CRI, treatment failure remains unacceptably high. The use of systemic antibiotics without catheter exchange results in high failure rate of close to 70%. While combining systemic antibiotics with ALS seemingly leads to 50% improvement (compared with systemic antibiotics alone), failure rate still reaches up to 35%. Potential complications are often serious and life-threatening. However, in patients where no other vascular access sites are possible, combined systemic and intra-luminal antibiotics could be considered.

Preferred strategy of CRI treatment remains catheter removal in conjunction with systemic antibiotics. However, infection severity would determine if catheter replacement should be delayed by inserting a temporary catheter, or whether it is replaced over a guide-wire exchange.

As CRI in haemodialysis patients are often due to coagulase-negative Staphylococcus or *S.aureus*, empiric antimicrobial regime involving Vancomycin has been recommended. This should be used in conjunction with gram-negative rods coverage based on local antibiotic-prescribing pattern [14].

In uncomplicated CRI, a three-week course of systemic antibiotic has been used in trial setting [7] and suggested in guideline recommendation [14]. Management of the complicated cases of CRI, including assessment of metastatic infection, choice and duration of antibiotics, should be collaborated with microbiologists and/or infectious disease physicians.

**WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcome Quality Initiatives (2006):** In the absence of a tunnel infection, catheter exit-site infections can be treated with topical and/or oral antibiotics. In patients who are bacteraemic but became afebrile and stable within 48 hours, catheter salvage can be considered using combined interdialytic antibiotic lock solution and 3 weeks of parental antibiotics. Follow-up blood culture one week after completion of antibiotics is recommended. In those patients with limited catheter sites, the
same regime can be used if subsequent follow-up blood cultures indicated reinfection with the same organism [14].

**UK Renal Association (2010):** Venous catheters should be removed in all haemodialysis patients with catheter-related bacteraemia, unless no alternative vascular access is feasible [15].

**Canadian Society of Nephrology (2006):** Treat central venous catheter-related bacteremia with systemic antibiotics and catheter exchange over a wire. Treat catheter tunnel infections without bacteremia with parenteral antibiotics and appropriate local measures. Catheter removal is indicated if the infection fails to respond to 2 wk of therapy [16].

**European Renal Best Practice Guidelines (2010):**
Systemic antibiotic treatment should be always administered as part of therapy of catheter infection. Catheter removal is the first therapeutic option in case of severe complications and metastatic infections, and tunnel infection with fever. Catheter removal should be balanced against the risk of reinsertion, or if an alternative insertion site is not available. Guide-wire exchange of catheter could be employed, preferably 3 days after appropriate and effective antibiotics treatment. Catheter salvage consisting of systemic antibiotics and antibiotic locks could be an option if guide-wire exchange is impossible. Blood culture should be rechecked one week after completion of antibiotic if a catheter is not removed.[17]

**International Guidelines: Infectious Disease Society of America (2009):** Infected catheters should always be removed for infection due to Staphylococcal aureus, Pseudomonas species or Candida species. A temporary catheter should be inserted into another anatomical site. If no alternative sites are available, then exchange the infected catheter over a guide-wire. Replacement of a long-term catheter can be performed once negative blood cultures are obtained. For infection due to other pathogens (e.g. coagulase-negative staphylococci or gram-negative bacilli other than Pseudomonas species), empirical intravenous antibiotics can be initiated without immediate catheter removal. If symptoms persist or if there is evidence of metastatic infection, catheter should be removed. Those in whom catheter removal is not indicated, an antibiotic lock can be used after each dialysis session for 10-14days. A 4-6 week course of antibiotics should be administered if there is persistent bacteraemia or fungaemia (>72hours), patients with endocarditis or supplicative thrombophlebitis. A 6-8 weeks course is recommended for patients with osteomyelitis [18].

**SUGGESTIONS FOR FUTURE RESEARCH**

- Long-term follow-up and documentation of antimicrobial resistance, infective complications, morbidity and mortality in patients treated with catheter salvage therapy.

- Optimal timing in delayed catheter insertion, whether this be based on clinical evidence of defervesce or microbiological clearance from negative blood cultures.

- Cost-effectiveness in a multi-disciplinary approach using a nurse-led model

**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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheter removal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Marr et al (1997) [5] | 102 | Prospective cohort. Multi-centre, US | Haemodialysis patients with tunnelled cuffed catheters. Treatment: Long and short course antibiotics. | 9 months | - 23 (23%) patients were immunocompromised.  
- 41 (40%) developed 62 episodes of bacteraemia, with salvage attempted in 38 patients.  
- Risk factors for catheter related bacteraemia – previous history of bacteraemia and being immunocompromised.  
- 12 (32%) catheters were successfully salvaged with 6 still in place at 3 months.  
- Complications associated with bacteraemia were similar between those whose catheters were removed and those where salvage was attempted. |
| Saad et al (1999) [6] | 101 | Prospective cohort. Single centre, US | Haemodialysis patients with tunnelled catheters. Treatment: Antibiotics leaving catheter in place or antibiotics with catheter exchange. | 24 months | - Mean unassisted and assisted catheter survival was 50 and 104 days respectively.  
- 52 patients (51%) patients developed 86 episodes of bacteraemia.  
- Catheter salvage attempted for 73 episodes.  
- Success rate for antibiotics was 37% compared to 81% for catheter exchange. |
| **Catheter replacement** | | | | | |
| Beathard (1999) [7] | 114 | Prospective cohort. Single centre, US. | Haemodialysis patients with tunnelled catheters divided into patients with mild and severe symptoms of bacteraemia with positive blood cultures. Treatments as follows:  
1. Catheter exchange over a guidewire only (patients with mild symptoms and no exit site or tunnel infection).  
2. Catheter exchange over a guidewire and creation of a new tunnel and exit site (patients with mild symptoms and exit site or tunnel infection).  
3. Catheter removal and delayed replacement (patients with severe symptoms). All received antibiotics for 3 weeks. | 2 year study period | - Catheter related bacteraemia in 67 (19%) of the 352 new catheter insertions and in 56 (11.7%) of the 475 catheter replacements.  
- Cure rates were 69.4%, 50% and 73% for groups 1, 2 and 3 respectively (P=0.10).  
- There was no control group i.e. antibiotics without catheter exchange. |
<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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catheter salvage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Krishnasami et al (2002) [8] | 62    | Prospective cohort. Single centre, US. | Haemodialysis patients with tunneled catheters. All patients with positive blood cultures treated with vancomycin and gentamicin. Catheters removed from patients with severe symptoms. Compared 5 antibiotic-heparin lock solutions: vancomycin/gentamicin; vancomycin; gentamycin; cefazolin; cefazolin/gentamycin.                                                                 | 6 month study period. | • A total of 98 episodes of catheter related bacteraemia were confirmed over 6 months with 36 (37%) excluded due to catheter removal or loss of follow up.  
• Overall success rate with the use of antibiotic lock solutions was 64.5%.  
• Comparison with non-concurrent control patients of similar, age and gender distribution and proportion with diabetes, showed similar infection free survival curves. The median infection free catheter survival was 70 days for antibiotic lock solution patients and 71 days for patients treated with catheter replacement (P=0.57). |
| Poole et al (2004) [9] | 68    | Prospective cohort. Single centre, US. | Haemodialysis patients with tunneled catheters. Positive blood cultures treated with empiric therapy (vancomycin and ceftazidime) and antibiotic-heparin lock solutions.                                                                 | 6 month study period. | • A total of 83 episodes of catheter related bacteraemia were confirmed over 6 months with 15 (18%) excluded.  
• Overall success rate with the use of antibiotic lock solutions was 70%.  
• Success rate was 87% for gram-negative infections, 75% for *S.epidermis* and 40% for *S.aureus* (P=0.04).  
• Comparison with historical controls (routine catheter replacement) which had similar age, gender and diabetes profiles, indicated significantly higher 45 day infection free survival of 75% for the antibiotic lock solution treated patients compared to 65% for the controls (P=0.02). |
| Peterson et al (2009) [10] | 64    | Retrospective review. Single centre US. | Haemodialysis patients with tunneled catheters and confirmed catheter related bacteraemia. Standard protocol on all patients: empiric vancomycin and ceftazidime treatment (3 weeks), and vancomycin-heparin lock solution. Catheter removal in the event of treatment failure.                                                                 | 3 year review period. | • Treatment success defined as resolution of fever and no recurrence within 90 days.  
• Overall success was achieved in 39 (61%) patients.  
• Serious complications was 0% in patients successfully treated and 16% (P=0.01) in those with treatment failure.  
• Patient survival at 6 months was similar 94% (successful) vs 92% (failed) P=0.5. |
| Tejwani and Parry (2011) [12] | 83    | Retrospective review. Single centre, US. | Patients with tunneled catheters and confirmed catheter related bacteraemia. Intervetion: Attempted catheter salvage using antibiotic lock solution.                                                                                                                                                                                                 | 10 year review period. | • Attempted salvage in combination with antibiotic lock solution was undertaken for 83 episodes in 80 renal disease patients.  
• Overall success was achieved in 61 (73.5%) instances.  
• Successfully treated episodes had a mean treatment time of 13.4 days and a median of 9 days. There was no clear threshold duration that predicted successful lock therapy. |
| **Multidisciplinary care** |       |                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |           |                                                                                                                                                                                                                                                                                                                                                                                                           |
| Mokrzycki et al (2006) [13] | 223   | RCT; multicentre, US. | Haemodialysis patients with tunneled catheters with confirmed initial catheter related bacteraemia.                                                                 | 2 year study period with a 6 month | • Randomisation was on a unit basis and not case by case.  
• Primary outcome: recurrent bacteraemia with the same organism within 90 days of initial catheter related infection. |
Table 2. Methodological quality of randomised trials

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>Method of allocation concealment *</th>
<th>Method of allocation concealment (participants)</th>
<th>Method of allocation concealment (investigators)</th>
<th>Method of allocation concealment (outcome assessors)</th>
<th>Blinding</th>
<th>Intention-to-treat analysis †</th>
<th>Loss to follow up (%)</th>
<th>Comments ‡</th>
</tr>
</thead>
</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 patients with events/ number of patients exposed)</th>
<th>Control group (number of patients with events/ number of patients not exposed)</th>
<th>Relative risk (RR) [95% CI]</th>
<th>Risk difference (RD) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mokrzycki et al (2006) [13]</td>
<td>Recurrent bacteraemia (&lt;90 days)</td>
<td>6/108</td>
<td>9/51</td>
<td>0.31 (0.12, 0.84)</td>
<td>-0.12 (-0.23, -0.01)</td>
</tr>
<tr>
<td>Mokrzycki et al (2006) [13]</td>
<td>Infectious complications</td>
<td>4/111</td>
<td>2/55</td>
<td>0.99 (0.19, 5.25)</td>
<td>-0.00 (-0.06, 0.06)</td>
</tr>
</tbody>
</table>