TITLE: Antimicrobial Ointments for Patients Undergoing Hemodialysis: A Review of Evidence-Based Guidelines

DATE: 20 June 2013

CONTEXT AND POLICY ISSUES

Vascular access is an important concern in patients requiring hemodialysis.\textsuperscript{1,2} Centrally-inserted catheters are not the preferred access route when maintenance hemodialysis is required,\textsuperscript{1,3} mainly due to a high risk for bloodstream infections, hospitalizations and mortality.\textsuperscript{1,4} Despite these limitations, there are situations where autogenous vascular access is not possible and therefore, reliance on catheters for hemodialysis cannot be eliminated.\textsuperscript{1,2} Various measures to prevent catheter-related infections have been suggested, including adherence to sterile techniques, maintaining good personal hygiene, and paying proper attention to exit site care using antimicrobial or antiseptic agents.\textsuperscript{1,3-5} However, the effectiveness of these measures is not always clear, and they are not without risk. For example, the widespread prophylactic use of topical antibiotics, particularly mupirocin, may lead to an increased prevalence of drug-resistant micro-organisms.\textsuperscript{3,4,6,7} These ongoing concerns with regard to mupirocin microbial drug resistance have raised the question whether an antiseptic ointment, alternative antimicrobial ointments, or antiseptic-impregnated dressing products may be preferable alternatives.

This Rapid Response report aims to provide information on the clinical guidelines for the use of antimicrobial ointments versus antiseptic ointments or impregnated dressings on button hole access sites, as well as arterial and central venous lines, in order to avoid bloodstream infections and microbial drug resistance in patients undergoing hemodialysis. This will inform decision-making regarding the review of policies and procedures with regard to hemodialysis access site care in a participating jurisdictional hemodialysis program.

RESEARCH QUESTIONS

1. What are the evidence-based guidelines for the use of antimicrobial ointments (mupirocin) for button holes access sites?

2. What are the evidence-based guidelines for the use of antimicrobial ointments (mupirocin) for arterial venous lines?

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3. What are the evidence-based guidelines for the use of antimicrobial ointments (mupirocin) for central venous lines?

**KEY FINDINGS**

There was no evidence in the literature searched regarding the use of antimicrobial ointments for button holes access sites or arterial venous lines. Four publications evaluated antimicrobial ointments in hemodialysis patients using central venous lines. Findings suggested mupirocin, povidone-iodine and Polysporin ointments, as well as chlorhexidine-impregnated dressings, may be useful to prevent catheter-related infections; however, various inconsistencies were noted, as some authors concluded there was insufficient data to support their routine use. No conclusion could be drawn on the impact of mupirocin ointment on microbial drug resistance. Therefore, the overall absence of satisfactory high-quality evidence cautions the interpretation of the findings.

**METHODS**

**Literature Search Strategy**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2013, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and May 15, 2013.

**Selection Criteria and Methods**

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

**Table 1: Selection Criteria**

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients undergoing hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Antimicrobial ointments of mupirocin for:</td>
</tr>
<tr>
<td></td>
<td>• Button holes access sites</td>
</tr>
<tr>
<td></td>
<td>• Arterial venous lines</td>
</tr>
<tr>
<td></td>
<td>• Central venous lines</td>
</tr>
<tr>
<td>Comparator</td>
<td>Antiseptic ointments</td>
</tr>
<tr>
<td></td>
<td>Antiseptic impregnated dressings</td>
</tr>
<tr>
<td></td>
<td>Povidone iodine ointments</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Bloodstream infections</td>
</tr>
<tr>
<td></td>
<td>MRSA infections</td>
</tr>
<tr>
<td></td>
<td>Multi drug resistant organisms</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health Technology Assessment / Systematic reviews / Meta-analysis Guidelines</td>
</tr>
</tbody>
</table>

MRSA = Methicillin-resistant Staphylococcus aureus
Exclusion Criteria

Articles were excluded if they did not meet the selection criteria, if they were published prior to January 2008, or if they were duplicate publications. Health technology assessments, meta-analyses, systematic reviews and guidelines were excluded if there was incomplete reporting of methods or if they were superseded by a more recent or rigorous publication.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. We elected to assess the quality of included systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.8 For included guidelines, the assessment tool selected was the AGREE II instrument.9

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 89 citations were identified in the literature search. Following screening of titles and abstracts, 85 citations were excluded and four potentially relevant reports from the electronic search were retrieved for full-text review. In addition, five potentially relevant publications were retrieved from the grey literature search. Of these nine potentially relevant articles, five publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report: one systematic review1 and three guidelines.6,7,10 Appendix 1 describes the PRISMA flowchart of the study selection.

The study designs evaluated in this Rapid Response report consisted of systematic reviews and guidelines. However, several references found in the literature search with out-of-scope designs may provide additional and relevant information, such as non-systematic reviews and non-randomized studies. These additional references of potential interest are listed in Appendix 2.

A. Guidelines for the use of antimicrobial ointments for button holes access sites

No publications providing evidence-based recommendations regarding the use of antimicrobial ointments, such as mupirocin, for button holes access sites met the inclusion criteria and could be included in this review.

B. Guidelines for the use of antimicrobial ointments for arterial venous lines

No publications providing evidence-based recommendations regarding the use of antimicrobial ointments, such as mupirocin, for arterial venous lines met the inclusion criteria and could be included in this review.

C. Guidelines for the use of antimicrobial ointments for central venous lines

Summary of Study Characteristics

The four publications included in this report provided evidence-based recommendations on the use of antimicrobial ointments, such as mupirocin, for central venous lines.
The population of interest in the included systematic review\(^1\) consisted of patients requiring hemodialysis and using a central venous catheter as vascular access. Interventions evaluated included mupirocin, povidone-iodine and Polysporin ointments and relevant outcomes related to infection and microbial drug resistance. Details on study characteristics figure in Table 2.

### Table 2: Summary of Systematic Reviews

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Key inclusion criteria</th>
<th>Relevant Interventions, N studies</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| McCann 2010\(^1\) | Patients with end-stage kidney disease requiring hemodialysis and using a central venous catheter as vascular access. | • Topical antimicrobial vs no antimicrobial N=5 studies (379 patients)  
    • Topical mupirocin ointment vs no ointment N=3 studies (217 patients)  
    • Topical povidone-iodine ointment vs no ointment N=1 study (129 patients)  
    • Topical Polysporin Triple ointment vs placebo N=1 study (162 patients) | Primary outcomes  
    • Infectious complications  
    • Patient mortality  
    • Catheter survival rate  
Secondary outcomes  
    • Time to infection  
    • Hospitalization  
    • Patient morbidity  
    • Quality of life |

Three guidelines were included in this Rapid Response report\(^6,7,10\). All of them provided recommendations on the use of mupirocin, povidone-iodine and Polysporin ointments, as well as chlorhexidine-impregnated antiseptic dressings, to prevent infections in hemodialysis patients using a central venous catheter. One guideline was Canadian\(^10\), one was American\(^7\), and one was Australian\(^6\). Details regarding the characteristics of these guidelines figure in Table 3.
Table 3: Summary of Guidelines

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Objectives</th>
<th>Patient population</th>
<th>Interventions</th>
</tr>
</thead>
</table>
| Association for Professionals in Infection Control and Epidemiology, 2010⁷   | “To provide evidence-based guidance for the prevention of healthcare-associated infections in all hemodialysis settings.” (pp. 11) | Patients requiring hemodialysis and using a central venous catheter as vascular access. | - Povidone-iodine antiseptic ointment  
- Triple antibiotic ointment  
- Mupirocin ointment  
- Chlorhexidine-impregnated antiseptic dressing |
| Australian National Health and Medical Research Council, 2010⁶                | “To provide a coordinated approach to the prevention and management of healthcare-associated infections.” (pp. 7) | Patients requiring hemodialysis and using a central venous catheter as vascular access. | - Povidone-iodine antiseptic ointment  
- Polysporin antibiotic ointment  
- Mupirocin ointment  
- Chlorhexidine-impregnated sponge dressing |
| British-Columbia Renal Agency, 2008¹⁰                                        | “This guideline provides recommendations for prevention […] of vascular access related infections.” (pp. 1) | Patients requiring hemodialysis and using a central venous catheter as vascular access. | - Povidone-iodine antiseptic ointment  
- Polysporin Triple antibiotic ointment  
- Mupirocin ointment  
- Chlorhexidine sponge antiseptic dressing |

Note: Only sections of the guidelines relevant to the Rapid Response research questions are presented.

Summary of Critical Appraisal

The critical appraisal of the included systematic review and guidelines is summarized in Appendix 3. Overall, the systematic review was conducted with robust methodology. Analyses of the clinical benefits of antibiotic ointments were performed as a class, but also for each individual agent.

All the guidelines were clear in their overall objectives and the populations for whom the guidance was intended. However, methods used to identify and select the evidence for inclusion, as well as to develop recommendations, were not consistently described in the publications. Although guidelines were evidence-based, recommendations often relied on expert consensus, due to a lack of high quality evidence; nevertheless, most of the relevant recommendations were specific and clearly stated. The guidelines were intended for use in various specific geographical regions, which may have an impact on their application to local clinical practice.

Summary of Findings

**Bloodstream infections and microbial drug resistance**

The key findings of the included systematic review are summarized in Appendix 4. Results from McCann 2010⁷ suggested that topical antimicrobial ointments as a class were superior to placebo in reducing exit site infections and catheter-related bacteremia caused by any type of pathogens.
Similar statistically significant results were obtained when mupirocin, povidone-iodine and Polysporin ointments were individually compared to placebo. The systematic review showed that the use of mupirocin ointment was associated with a relative risk reduction of 83% in the occurrence of bacteremia compared to placebo (RR = 0.17; 95% CI 0.07, 0.43). An analysis of infections caused specifically by S. aureus suggested that the use of topical mupirocin ointment led to a similar statistically significant reduction in the occurrence of both exit site infections and catheter-related bacteremia compared to placebo. Despite these results, the authors suggested careful use of this agent depending on local prevalence of antibiotic resistance. Corresponding relative risk (RR) reductions of 90% and 60% were obtained for povidone-iodine (RR = 0.10; 95% Confidence Interval [CI] 0.01, 0.72) and Polysporin ointments (RR = 0.40; 95% CI 0.19, 0.86). However, the authors concluded that the evidence was insufficient to recommend the routine use of these agents.

Guideline recommendations

Appendix 5 summarizes the key recommendations of the included guidelines for the interventions of interest to prevent catheter-related infections in patients requiring hemodialysis. Various inconsistencies are noted in the recommendations for topical antimicrobial ointments and antiseptic impregnated dressings across guidelines. The use of mupirocin ointment is supported with strong evidence by the Australian National Health and Medical Research Council 2010 guideline;6 whereas the Association for Professionals in Infection Control and Epidemiology 2010 guideline7 suggests restricting its use out of concerns for microbial drug resistance, a recommendation likely based on expert opinion. Povidone-iodine and Polysporin ointments, as well as chlorhexidine impregnated dressings, figure as useful options to prevent catheter-related infections in two guidelines;6,7 only the British-Colombia Renal Agency 2008 Guideline10 suggests restricting their use, as well as the use of mupirocin ointment, to special circumstances only.

Limitations

No evidence pertaining to the use of antimicrobial ointments for button holes access sites or arterial venous lines could be included in this review.

Four publications were identified that evaluated the topical use of antimicrobial ointments in hemodialysis patients using central venous lines. The included systematic review was conducted with robust methodology, but the overall evidence included was insufficient to allow the authors to draw definite conclusions on the use of these agents.

The three included guidelines provided limited reporting of methods used to identify and select the evidence for inclusion. This precluded adequate judgment regarding the completeness of the information considered relevant for guideline development. In addition, various inconsistencies were noted in the recommendations for topical antimicrobial ointments and antiseptic impregnated dressings across guidelines. Recommendations often relied on expert consensus, due to a lack of high quality evidence. Therefore, the limited body of evidence and the absence of data from high-quality primary studies caution the interpretation of the findings.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There was no evidence in the literature searched pertaining to antimicrobial ointments for button holes access sites or arterial venous lines. However, four publications were identified that
evaluated the use of antimicrobial ointments in patients requiring hemodialysis and using central venous lines as vascular access: one systematic review and three guidelines. Findings suggested that topical mupirocin, povidone-iodine and Polysporin ointments, as well as chlorhexidine-impregnated dressings, may be useful to prevent catheter-related infections in this population; however, inconsistencies across the findings were noted. Indeed, some authors concluded that the evidence currently available from primary studies was insufficient in terms of quantity and quality to support the routine use of these agents in hemodialysis patients. In addition, the scarcity of data regarding the impact of mupirocin ointment on microbial drug resistance precluded any conclusion on this outcome. As a result, the limited body of evidence and the absence of data from high-quality primary studies should caution the interpretation of the findings with regard to hemodialysis access site care in hemodialysis programs.

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REFERENCES


APPENDIX 1: Selection of Included Studies

89 citations identified from electronic literature search and screened

⇒ 85 citations excluded

⇒ 4 potentially relevant articles retrieved for scrutiny (full text, if available)

⇒ 5 potentially relevant reports retrieved from other sources (grey literature, hand search)

⇒ 9 potentially relevant reports

⇒ 5 reports excluded:
  - irrelevant comparator (2)
  - irrelevant study design (1)
  - incomplete reporting of methods (2)

⇒ 4 reports included in review
APPENDIX 2: Other References Pertaining to Excluded Study Designs

The study designs evaluated in this Rapid Response report consisted of systematic reviews and guidelines. However, several references were found in the literature search with out-of-scope designs that might still be of interest. These references, although not included in the report as per the pre-specified protocol, are listed here in appendix.

Non-Systematic Reviews


Non-Randomized Studies


## APPENDIX 3: Summary of Critical Appraisal of Included Studies

### Systematic Reviews

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| McCann 2010<sup>7</sup> | • Comprehensive literature search of multiple databases based on pre-defined criteria.  
• Duplicate study selection and data extraction performed; appropriate description of statistical methods used to combine findings.  
• Appropriate reporting of individual study characteristics.  
• Scientific quality of included studies assessed using the quality checklist developed for the Cochrane Renal Group and appropriately reported; quality of evidence used in formulating conclusions.  
• Conflicts of interest stated. | • Publication bias not assessed. |

### Guidelines

| Association for Professionals in Infection Control and Epidemiology, 2010<sup>7</sup> | • Scope / purpose of the guidelines and target users clearly described.  
• References provided, with explicit link between the recommendations and supporting evidence.  
• Guideline reviewed externally prior to publishing.  
• The recommendations are clear, specific and unambiguous.  
• Competing interest of development group members disclosed. | • Unclear whether guideline development group includes individuals from all the relevant professional groups, although specialists in the field were consulted.  
• Unclear whether patients’ views and preferences were sought.  
• Methods used to search for and select the relevant evidence are not described.  
• Relevant recommendations are based on expert consensus, due to lack of high quality evidence. |
| Australian National Health and Medical Research Council, 2010<sup>6</sup> | • Scope / purpose of the guidelines and target users clearly described.  
• Guideline development methods explicitly defined.  
• References provided for the recommendations, which are based on previous infection control guidelines and systematic reviews.  
• The recommendations are clear, specific and unambiguous. | • Guideline development group includes individuals from relevant professional groups, but not in the field of renal disease or hemodialysis.  
• Unclear whether patients’ views and preferences were sought, despite stakeholder consultations.  
• Unclear whether the guideline was reviewed externally prior to publishing.  
• Competing interest of development group members undisclosed. |
| British-Colombia Renal Agency, 2008<sup>10</sup> | • Scope / purpose of the guidelines and target users clearly described.  
• Guideline development group was described as a vascular access working group of multidisciplinary care providers.  
• Guideline reviewed externally prior to publishing.  
• References provided. | • Unclear whether patients’ views and preferences were sought.  
• Methods used to search for and select the relevant evidence are not described.  
• Link between the relevant recommendations and supporting evidence not always explicit.  
• Relevant recommendations are based on expert consensus; no quality of evidence or grading system reported.  
• Competing interest of development group members undisclosed. |
### APPENDIX 4: Summary of Findings – Systematic Review

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Outcomes*</th>
<th>Bacteremia</th>
<th>S. aureus bacteremia</th>
<th>Exit site infections</th>
<th>S. aureus exit site infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCann 2010¹</td>
<td>Topical antimicrobial ointment compared to no ointment or placebo</td>
<td>RR = 0.26</td>
<td>No analysis reported</td>
<td>RR = 0.20</td>
<td>No analysis reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[95% CI 0.15, 0.46]</td>
<td>N = 5 studies, 508 patients</td>
<td>[95% CI 0.09, 0.45]</td>
<td>N = 4 studies, 346 patients</td>
</tr>
<tr>
<td></td>
<td>Topical mupirocin ointment compared to no ointment or placebo</td>
<td>RR = 0.17</td>
<td>N = 3 studies, 217 patients</td>
<td>RR = 0.13</td>
<td>N = 1 study, 136 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[95% CI 0.07, 0.43]</td>
<td>N = 3 studies, 217 patients</td>
<td>[95% CI 0.03, 0.54]</td>
<td>N = 1 study, 136 patients</td>
</tr>
<tr>
<td></td>
<td>Topical povidone-iodine ointment compared to no ointment or placebo</td>
<td>RR = 0.10</td>
<td>No analysis reported</td>
<td>RR = 0.26</td>
<td>No analysis reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[95% CI 0.01, 0.72]</td>
<td>N = 1 study, 129 patients</td>
<td>[95% CI 0.08, 0.88]</td>
<td>N = 1 study, 129 patients</td>
</tr>
<tr>
<td></td>
<td>Topical Polysporin ointment compared to no ointment or placebo</td>
<td>RR = 0.40</td>
<td>No analysis reported</td>
<td>No analysis reported</td>
<td>No analysis reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[95% CI 0.19, 0.86]</td>
<td>N = 1 study, 162 patients</td>
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</tr>
</tbody>
</table>

**Authors’ Conclusions**

“Our review indicates that mupirocin ointment is effective in reducing the risk of catheter-related bacteremia and CVC infections caused by S. aureus. No case of mupirocin resistance was reported and our review can therefore not conclude that mupirocin resistance is a real or proven threat. The clinical decision to use mupirocin ointment as a prophylactic agent in the prevention of CVC infections requires local knowledge of the prevalence of antibiotic sensitivity within that community. A lack of studies on the routine use of povidone-iodine ointment, polysporin ointment […] in hemodialysis patient population means that there is insufficient evidence to guide clinical practice. Clinical decisions on the use of these topical agents as part of a prophylactic strategy in the prevention of CVC infection need to be informed by larger high quality studies demonstrating evidence of effect.” (pp. 14)

CI = Confidence interval; CVC = Central venous catheter; RR = Relative risk.

* In a population of patients requiring hemodialysis and using a CVC as vascular access.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Summary of Recommendations</th>
</tr>
</thead>
</table>
| Association for Professionals in Infection Control and Epidemiology, 2010<sup>7</sup> | Measures recommended in the guideline:  
“Application of chlorhexidine impregnated insertion site dressing for hemodialysis central catheters. [...]”  
Application of povidone-iodine or triple antibiotic ointment for hemodialysis catheter exit site dressings after dialysis session.” (pp. 19)  
“Level of evidence supporting these measures is less than Category I Level.” (pp. 19)  
“Mupirocin use should be limited because of the risk of increasing incidence of S. aureus resistance. Additionally, mupirocin is not effective against Gram-negative organisms. Based on the published evidence related to infection risk reduction, the choice between povidone-iodine and triple antibiotic ointment (neomycin, polymyxin B, bacitracin) would seem equal and should be based on local preference.” (pp. 53) |
| Australian National Health and Medical Research Council, 2010<sup>6</sup> | “There is strong evidence (Grade B) that the use of chlorhexidine-impregnated sponges at the catheter insertion site significantly reduces intravascular device related bloodstream infection and device colonization rates compared to other types of dressings for peripheral arterial devices, short-term and long-term central venous devices. [...]”  
There is Grade B evidence that the use of an antimicrobial or antibiotic ointment (calcium mupirocin, or Polysporin) on long-term tunnelled central venous devices used for haemodialysis access significantly reduces intravascular device associated bloodstream infections and exit site infections.  
Povidone iodine antiseptic ointment or bacitracin/neomycin/polymyxin B ointment should only be used at the hemodialysis catheter exit site after catheter insertion and at the end of each dialysis session if this ointment does not interact with the material of the hemodialysis catheter [...]” (pp.143) |
| British-Colombia Renal Agency, 2008<sup>10</sup> | “No agreement yet on the use (or not) of chlorhexidine sponge dressings to reduce the incidence of infection.” (pp. 7)  
“Some studies support the application of a thin film of povidone-iodine, mupirocin, or Polysporin triple ointment at the exit site prior to putting on the dressing, particularly in Staphylococcus aureus carriers. [...] Despite the studies, the current consensus of the working group is that the use of prophylactic antibiotic/antimicrobial ointment is not recommended in most situations. Special circumstances may be appropriate such as their use in patients with long-term cuffed, tunneled catheters, a history of multiple S. aureus catheter-related infections, and very limited available access options.” (pp. 8) |