

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.^{1,2} Centrally-inserted catheters are not the preferred access route when maintenance hemodialysis is required,^{1,3} mainly due to a high risk for bloodstream infections, hospitalizations and mortality.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.^{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.^{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.^{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

Population	Patients undergoing hemodialysis
Intervention	Antimicrobial ointments of mupirocin for: <ul style="list-style-type: none"> • Button holes access sites • Arterial venous lines • Central venous lines
Comparator	Antiseptic ointments Antiseptic impregnated dressings Povidone iodine ointments
Outcomes	Bloodstream infections MRSA infections Multi drug resistant organisms Recommendations
Study Designs	Health Technology Assessment / Systematic reviews / Meta-analysis Guidelines

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 review¹ 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

Author, year	Key inclusion criteria	Relevant Interventions, N studies	Outcomes
McCann 2010 ¹	Patients with end-stage kidney disease requiring hemodialysis and using a central venous catheter as vascular access.	<ul style="list-style-type: none"> • 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) 	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Infectious complications • Patient mortality • Catheter survival rate <p>Secondary outcomes</p> <ul style="list-style-type: none"> • 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

Author, year	Objectives	Patient population	Interventions
Association for Professionals in Infection Control and Epidemiology, 2010 ⁷	“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.	<ul style="list-style-type: none"> • Povidone-iodine antiseptic ointment • Triple antibiotic ointment • Mupirocin ointment • Chlorhexidine-impregnated antiseptic dressing
Australian National Health and Medical Research Council, 2010 ⁶	“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.	<ul style="list-style-type: none"> • Povidone-iodine antiseptic ointment • Polysporin antibiotic ointment • Mupirocin ointment • Chlorhexidine-impregnated sponge dressing
British-Columbia Renal Agency, 2008 ¹⁰	“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.	<ul style="list-style-type: none"> • 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 2010¹ 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-Columbia 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 review¹ and three guidelines.^{6,7,10} 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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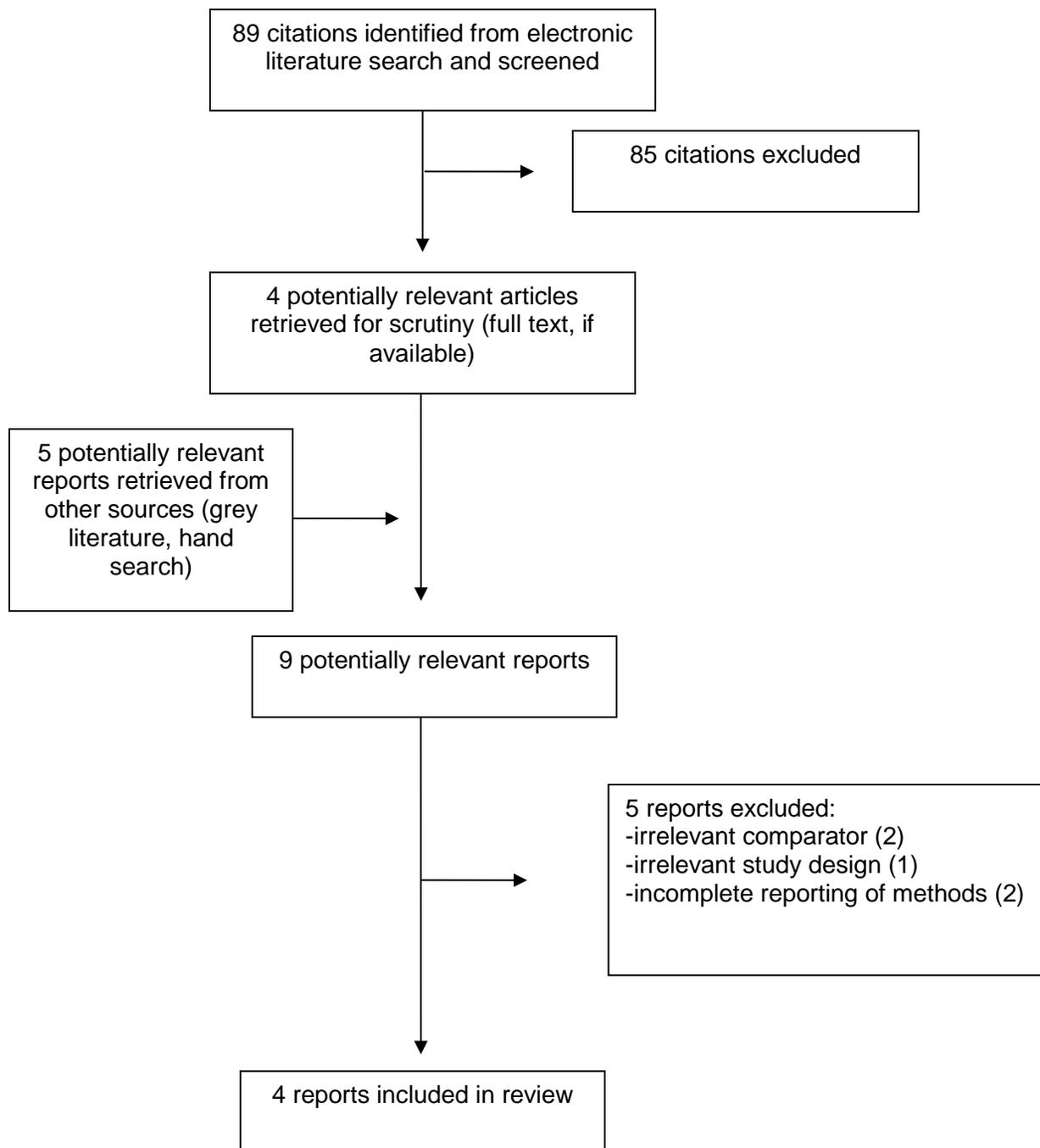
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9. AGREE: advancing the science of practice guidelines [Internet]. London (UK): The AGREE Research Trust. 2010 [cited 2013 May 22]. Available from: <http://www.agreetrust.org/>
10. Prevention, treatment, & monitoring of VA related infection in HD patients (approved March 13, 2008): vascular access guideline [Internet]. Vancouver: BC Renal Agency; 2008. [cited 2013 May 28]. Available from: <http://www.bcrenalagency.ca/NR/rdonlyres/AC0BB28B-00A9-41A6-BD76-55F441559B03/59104/VAInfectionsFullGuidelineFINALMarch1320091.pdf>

APPENDIX 1: Selection of Included Studies



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

Worth LJ, McLaws ML. Is it possible to achieve a target of zero central line associated bloodstream infections? *Curr Opin Infect Dis.* 2012 Dec;25(6):650-7.

Ramanathan V, Darouiche RO. Prevention and management of hemodialysis catheter infections. *Expert Rev Anti Infect Ther.* 2012 Dec;10(12):1447-55.

Boyce JM. Prevention of central line-associated bloodstream infections in hemodialysis patients. *Infect Control Hosp Epidemiol.* 2012 Sep;33(9):936-44.

Betjes MG. Prevention of catheter-related bloodstream infection in patients on hemodialysis. *Nat Rev Nephrol.* 2011 May;7(5):257-65.

Lok CE, Mokrzycki MH. Prevention and management of catheter-related infection in hemodialysis patients. *Kidney Int.* 2011 Mar;79(6):587-98.

Stefanidis CJ. Preventing catheter-related infections in children undergoing hemodialysis. *Expert Rev Anti Infect Ther.* 2010 Nov;8(11):1239-49.

Barracough KA, Hawley CM, Playford EG, Johnson DW. Prevention of access-related infection in dialysis. *Expert Rev Anti Infect Ther.* 2009 Dec;7(10):1185-200.

Wilcox TA. Catheter-related bloodstream infections. *Semin Intervent Radiol* [Internet]. 2009 Jun [cited 2013 May 22];26(2):139-43. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036424>

Beathard GA, Urbanes A. Infection associated with tunneled hemodialysis catheters. *Semin Dial.* 2008 Nov;21(6):528-38.

Non-Randomized Studies

Battistella M, Bhola C, Lok CE. Long-term follow-up of the Hemodialysis Infection Prevention with Polysporin Ointment (HIPPO) Study: a quality improvement report. *Am J Kidney Dis.* 2011 Mar;57(3):432-41.

Camins BC, Richmond AM, Dyer KL, Zimmerman HN, Coyne DW, Rothstein M, et al. A crossover intervention trial evaluating the efficacy of a chlorhexidine-impregnated sponge in reducing catheter-related bloodstream infections among patients undergoing hemodialysis. *Infect Control Hosp Epidemiol* [Internet]. 2010 Nov [cited 2013 May 22];31(11):1118-23. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3077924>

Nesrallah GE, Cuerden M, Wong JH, Pierratos A. Staphylococcus aureus bacteremia and buttonhole cannulation: long-term safety and efficacy of mupirocin prophylaxis. Clin J Am Soc Nephrol [Internet]. 2010 Jun [cited 2013 May 22];5(6):1047-53. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879300>

Onder AM, Chandar J, Billings A, Diaz R, Francoeur D, Abitbol C, et al. Chlorhexidine-based antiseptic solutions effectively reduce catheter-related bacteremia. Pediatr Nephrol. 2009 Sep;24(9):1741-7.

Onder AM, Chandar J, Coakley S, Francoeur D, Abitbol C, Zilleruelo G. Controlling exit site infections: does it decrease the incidence of catheter-related bacteremia in children on chronic hemodialysis? Hemodial Int. 2009 Jan;13(1):11-8.

APPENDIX 3: Summary of Critical Appraisal of Included Studies

Systematic Reviews		
Author, year	Strengths	Limitations
McCann 2010 ¹	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Publication bias not assessed.
Guidelines		
Association for Professionals in Infection Control and Epidemiology, 2010 ⁷	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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 ⁶	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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-Columbia Renal Agency, 2008 ¹⁰	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • 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

Author, year	Outcomes*			
	Bacteremia	<i>S. aureus</i> bacteremia	Exit site infections	<i>S. aureus</i> exit site infections
McCann 2010 ¹	Topical antimicrobial ointment compared to no ointment or placebo			
	RR = 0.26 [95% CI 0.15, 0.46] N = 5 studies, 508 patients	No analysis reported	RR = 0.20 [95% CI 0.09, 0.45] N = 4 studies, 346 patients	No analysis reported
	Topical mupirocin ointment compared to no ointment or placebo			
	RR = 0.17 [95% CI 0.07, 0.43] N = 3 studies, 217 patients	RR = 0.13 [95% CI 0.03, 0.54] N = 1 study, 136 patients	RR = 0.17 [95% CI 0.06, 0.48] N = 3 studies, 217 patients	RR = 0.18 [95% CI 0.06, 0.60] N = 1 study, 136 patients
	Topical povidone-iodine ointment compared to no ointment or placebo			
	RR = 0.10 [95% CI 0.01, 0.72] N = 1 study, 129 patients	No analysis reported	RR = 0.26 [95% CI 0.08, 0.88] N = 1 study, 129 patients	No analysis reported
	Topical Polysporin ointment compared to no ointment or placebo			
	RR = 0.40 [95% CI 0.19, 0.86] N = 1 study, 162 patients	No analysis reported	No analysis reported	No analysis reported
Authors' Conclusions				
<p>“Our review indicates that mupirocin ointment is effective in reducing the risk of catheter-related bacteremia and CVC infections caused by <i>S. aureus</i>. 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)</p>				
CI = Confidence interval; CVC = Central venous catheter; RR = Relative risk.				

* In a population of patients requiring hemodialysis and using a CVC as vascular access.

APPENDIX 5: Summary of Findings – Guideline Recommendations

Author, year	Summary of Recommendations
<p>Association for Professionals in Infection Control and Epidemiology, 2010⁷</p>	<p>Measures recommended in the guideline:</p> <p>“Application of chlorhexidine impregnated insertion site dressing for hemodialysis central catheters. [...]</p> <p>Application of povidone-iodine or triple antibiotic ointment for hemodialysis catheter exit site dressings after dialysis session.” (pp. 19)</p> <p>“Level of evidence supporting these measures is less than Category I Level.” (pp. 19)</p> <p>“Mupirocin use should be limited because of the risk of increasing incidence of <i>S. aureus</i> 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)</p>
<p>Australian National Health and Medical Research Council, 2010⁶</p>	<p>“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. [...]</p> <p>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.</p> <p>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)</p>
<p>British-Columbia Renal Agency, 2008¹⁰</p>	<p>“No agreement yet on the use (or not) of chlorhexidine sponge dressings to reduce the incidence of infection.” (pp. 7)</p> <p>“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 <i>Staphylococcus aureus</i> carriers. [...] Despite the studies, the current consensus of the working group is that the use of <i>prophylactic</i> 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 <i>S. aureus</i> catheter-related infections, and very limited available access options.” (pp. 8)</p>