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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

# Coated and Uncoated Central Venous Catheters: A Review of Comparative Clinical Effectiveness and Safety


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**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

## Abbreviations

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| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CRBSI | Catheter-related bloodstream infection |
| CRD | Centre for Reviews and Dissemination |
| CSS-I-CVC | Chlorhexidine/silver sulfadiazine impregnated central venous catheter |
| CVC | Central venous catheters |
| ICU | Intensive care unit |
| MCR-I-CVC | Miconazole-rifampicin impregnated central venous catheter |
| MNR-I-CVC | Minocycline-rifampicin impregnated central venous catheter |
| RCT | randomized controlled trial |
| SIL-I-CVC | Silver impregnated central venous catheter |

## Context and Policy Issues

Central venous catheters (CVC) are commonly used in the hospital setting, especially in critical care units.[1] There are many reasons for the use of CVCs; however, they may introduce the risk of bloodstream infection.[1] CVCs may be uncoated or coated with the coated type believed to reduce catheter-related bloodstream infections (CRBSI). There are various types of coatings, including antibacterial, antimicrobial and antiseptic. However, patients may be allergic to such coatings, and this may limit the use of coated CVCs.[1]

Recently, a new type of coated CVC has become available in Canada, which is manufactured by Kimal Proactive and it contains a polyHexaMethylene biguanide coating. There is evidence from European hospitals that suggests a benefit of CVCs with this type of coating — though, the benefit has not been demonstrated clinically.[2] Therefore, it is important to compare the clinical effectiveness and safety of CVCs with this new coating versus other available CVCs — including uncoated CVCs. This comparison will provide context and allow decision makers to make an informed decision with regard to what may be the most appropriate type of CVC for patients. In addition, this information may elucidate whether there is a benefit to the use of coated CVCs as compared to uncoated CVCs.

The Canadian Agency for Drugs and Technologies in Health (CADTH) previously published a summary of abstracts report on the clinical effectiveness and safety of coated central venous catheters in adult patients.[3] A total of four systematic reviews, one meta-analysis, two randomized controlled trials and two non-randomized studies were identified in the previous search.[3] This report will include an updated search and will also provide more details comparing coated versus non-coated central venous catheters. Of note, the inclusion criteria were narrower in the current report as compared to the previous report; therefore, certain studies from the previous report were rendered ineligible.

The objective of this review is to assess the comparative clinical effectiveness, as well as harms and safety, between coated CVCs and uncoated CVCs for critically ill adult patients.

## Research Questions

1. What is the comparative clinical effectiveness of coated versus non-coated central venous catheters to prevent infection in adult patients?

2. What is the safety of coated central venous catheters in adult patients?

## Key Findings

Four systematic reviews with meta-analyses and three primary studies comparing coated central venous catheters and non-coated central venous catheters were identified by this review. The evidence compared various coatings such as chlorhexidine/silver sulfadiazine, silver, minocycline-rifampicin, and micozonazole-rifampicin; however, no evidence was identified describing polyHexaMethylene biguanide coated central venous catheters.

The systematic reviews were generally characterized by a low risk of bias. Three of the systematic reviews reported a statistically significant lower risk of catheter-related bloodstream infection with antimicrobial and antibiotic coated central venous catheters compared to non-coated central venous catheters. The fourth systematic review reported the findings of a meta-analysis indicating there was no difference in catheter-related bloodstream infections for silver coated central venous catheters compared to non-coated central venous catheters. Adverse events were captured in two of the systematic reviews and both concluded there was no statistical difference between the antimicrobial and antibiotic coated central venous catheters compared with non-coated central venous catheters. Three non-randomized, comparative primary studies were identified from a single center in Spain reporting a statistically significant lower rate of catheter-related bloodstream infections with chlorhexidine/silver sulfadiazine coated catheters compared to non-coated central venous catheters for subclavian venous access, internal jugular venous access, and femoral venous access.

Most of the studies included in this review point to a lower risk of catheter-related bloodstream infection with the use of antimicrobial or antibiotic coated central venous catheters compared to non-coated central venous catheters with no difference in adverse events. Additional research is needed to assess the clinical effectiveness and safety of polyHexaMethylene coated central venous catheters.

## Methods

### Literature Search Methods

This report makes use of a literature search developed for a previous CADTH report. The original literature search was conducted in August 2018 on key resources including PubMed, the Cochrane Library, 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 retrieval by study type. Where possible, retrieval was limited to the human population. The initial search was also limited to English-language documents published between January 1, 2013 and August 23, 2018. For the current report, database searches were rerun on December 10, 2018 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since August 2018.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

## Table 1: Selection Criteria

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| Population | Adult patients who require central venous catheters |
| Intervention | Coated central venous catheters (antibacterial, antimicrobial, antiseptic) including: Teleflex (chlorhexidine) and Cook (antibiotic), Kimal ProActive (polyHexaMethylene Biguanide coating) |
| Comparator | Q1: Non-coated central venous catheters<br>Q2: Non-coated central venous catheters or no comparator |
| Outcomes | Clinical effectiveness, prevention or reduction of infections, harms, safety |
| Study Designs | HTA/systematic reviews/meta-analyses; RCTs; non-randomized studies |

CVCs = central venous catheters; RCTs = randomized controlled trials

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Abstracts for conferences were also excluded.

### Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 tool,[4] and non-randomized studies were critically appraised using the Downs and Black checklist.[5] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 284 citations were identified in the literature search. Following screening of titles and abstracts, 253 citations were excluded and 31 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 28 publications were excluded for various reasons, whereas seven publications met the inclusion criteria and were included in this report. These comprised four systematic reviews and three non-randomized studies. Appendix 1 presents the PRISMA[6] flowchart of the study selection.

### Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

#### *Study Design*

Four systematic reviews were identified[7-10]; two of which compared the use of antimicrobial impregnated central venous catheters (CVC) and non-impregnated CVCs [7,8]; one compared chlorhexidine/silver sulfadiazine impregnated CVCs (CSS-I-CVC) and minocycline-rifampicin impregnated CVCs (MNR-I-CVC) to standard CVCs,[9] and; one compared silver-impregnated CVCs (SIL-I-CVC) and non-impregnated CVCs.[10] The systematic review comparing antimicrobial impregnated CVCs to standard CVCs was published in 2018 with a search that identified sources to July 2017, and included 33

randomized controlled trials (RCTs) reporting data for a total of 10,464 patients and synthesized the studies using both a meta-analysis and network meta-analysis.[7] Another systematic review comparing antimicrobial CVCs with standard CVCs was published in 2017 with a search that was conducted up to August 2016 and included 60 RCTs, reporting on a total of 17,255 catheters, which were combined into both a meta-analysis and network meta-analysis.[8] Lai et. al. published a Cochrane systematic review in 2016 with a search was conducted up until March 2015 and included 57 RCTs reporting data for a total of 16,784 catheters.[9] The systematic review that compared SIL-I-CVCs with uncoated CVCs was published in 2014 with a search that identified sources to April 2014 and included 12 studies; 11 of which were RCTs, reporting data for a total of 2,854 patients.[10]

Three relevant primary studies were identified from the literature search with one of them published in 2015 and the other two in 2014. All three studies compared the use of CSS-I-CVCs and standard CVCs without impregnation;[11-13] two were retrospective cohort studies[11,12] while the third was a prospective, cohort study.[13]

### *Country of Origin*

Authors of two of the systematic reviews were from China[7,10] while authors of the other two systematic reviews were from Malaysia.[8,9] All three of the primary studies were conducted in Spain.[11-13]

### *Patient Population*

In the systematic review by Wang et. al., patients needing a CVC were included.[7] Another systematic review included adult patients in the inpatient hospital setting who needed CVC, but excluded studies if the CVC was for hemodialysis.[8] The Cochrane systematic review included adult patients over 18 years of age who needed CVCs and were in the intensive care unit (ICU), oncology units and patients receiving long-term total parenteral nutrition.[9] Another systematic review included patients who needed CVC.[10]

All three of the primary studies included adult patients in the ICU; one included patients with CVCs at subclavian sites;[11] one included patients who received CVCs in the internal jugular vein,[13] and; another included patients with CVCs at femoral sites.[12]

### *Interventions and Comparators*

Two systematic reviews compared central lines with antimicrobial impregnation versus non-coated CVCs[7,8]; one included MNR-I-CVCs, CSS-I-CVCs, silver impregnated CVCs, miconazole-rifampicin impregnated CVC (MCR-I-CVC), and uncoated CVCs,[8] while the other considered chlorhexidine/silver sulfadiazine, Oligon Vantex silver or silver, 5-fluorouracil, vancomycin, benzalkonium chloride, teicoplanin, miconazole/rifampicin, minocycline, and minocycline/rifampin.[7] Lai et. al. compared various coatings including CSS-I-CVCs, MNR-I-CVCs, heparin CVCs, silver CVCs, platinum and carbon CVCs with non-impregnated CVCs.[9] The fourth systematic review compared silver-impregnated CVCs with non-impregnated CVCs.[10]

All three primary studies compared the use of CSS-I-CVCs versus standard CVCs without impregnation.[11-13]

### *Outcomes*

The primary outcome for the systematic review conducted by Wang et al. was rate of catheter-related bloodstream infection (CRBSI) per 1000 catheter-days.[7] One systematic

review reported three primary outcomes including clinically diagnosed sepsis, CRBSI rate (CRBSI per 1000 catheter-days), and all-cause mortality.[8] Secondary outcomes for this systematic review included number of participants with catheter-related local infections, mortality from CRBSI, adverse events, or premature catheter removal.[8] The primary outcomes for the Cochrane review included number of participants clinically diagnosed with sepsis, number of participants with CRBSI, and all-cause mortality, while the secondary outcomes included a composite outcome of the number of participants with catheter-related local infections, a composite outcome including number of participants or catheters with skin or site colonization, mortality from CRBSI, adverse events, catheter failure or premature catheter removal, use of systemic antibiotics, length of hospital stay, and quality of life.[9] Chen et al. included risk of CRBSI as outcomes.[10]

The eligible outcomes for all three primary studies were CRBSI rate.[11-13]

## Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

### *Systematic Reviews*

All of the systematic reviews were designed using *a priori* methods, included some elements of a comprehensive literature search, duplicate study selection and data extraction.[7-10] The Cochrane review included grey literature as a part of the search[9] while it is unclear whether the other systematic reviews included grey literature in their search methods.[7,8,10] All systematic reviews provided a list of included studies;[7-10] however, while the Cochrane review conducted by Lai et al. included a list of excluded studies,[9] the others did not.[7,8,10] All studies described the characteristics of the included trials.[7-10] Three of the systematic reviews assessed and provided details of the scientific quality and appropriately incorporated this while formulating the conclusion.[7-9] One systematic review did not appear to evaluate the scientific quality; therefore, it was unclear if this was accounted for when formulating the conclusion.[10] All systematic reviews combined the findings appropriately using summary statistics, assessed the likelihood of publication bias, and declared conflict of interest.[7-10]

### *Primary Studies*

The three primary studies were conducted by the same research group; therefore, all three shared a similar methodology and approach.[11-13] The studies were non-randomized, resulting in the potential of introducing systematic bias and confounding factors that may either underestimate or overestimate the magnitude of harm and reducing the certainty of the outcome, as two were retrospective cohort studies[11,12] and one was a prospective cohort study.[13] The authors did not provide any information on the funding of the study nor declare conflict of interest.[13] Without funding information, it is unclear if there is funding bias, which may potentially lead to results that support the interest of the funders. All three studies clearly described the objectives of the study; though, the methods were unclear, making it difficult to determine if data collection was conducted appropriately.[11-13] All three studies were single-center studies conducted in Spain and may therefore not be reflective of the Canadian healthcare system.[11-13] For the outcome of CRBSI, the diagnosis was made by an expert panel that was blinded to the catheter type, minimizing bias that may influence the results for all three studies.[11-13] Although these are not randomized studies, the baseline characteristics of the two groups reported were apparently similar, increasing confidence in the studies' validity.[11-13] Each of the studies focused on specific access sites,

including subclavian veins,[11] internal jugular veins,[13] and femoral veins, providing evidence for all three types of CVC access for decision making.[12] Statistical analyses were appropriate for all three of these studies and the results were described clearly in the text, as well as presented in tables.[11-13]

## Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

*What is the comparative clinical effectiveness of coated versus non-coated central venous catheters to prevent infection in adult patients?*

Three systematic reviews reported that antimicrobial coated CVCs had a lower rate of CRBSI compared with uncoated CVCs.[7-9] The systematic review by Wang et al. conducted a meta-analysis of 23 studies out of 33 included RCTs included, and reported that antimicrobial-impregnated CVCs had as lower rate of CRBSI per 1000 catheter-days compared to standard CVCs (relative risk [RR] 0.70, 95% CI 0.53 to 0.91, $P = 0.008$).[7] In addition, the results of a network meta-analysis of 25 RCTs was reported indicating that both antimicrobial-impregnated CVCs and CSS-I-CVCs had a lower rate of CRBSIs per 1000 catheter-days compared to standard CVCs with an odds ratio (OR) of 0.64 (95% CI 0.40 to 0.96) and OR 0.53 (95% CI 0.25 to 0.95), respectively.[7] Silver catheters were reported to have no statistical difference with regard to the rate of CRBSI per 1000 catheter-days compared with standard CVCs, with an OR 0.77 (95% CI 0.46 to 1.27).[7] The authors concluded that antimicrobial CVCs have the greatest potential of reducing CRBSIs with CSS-I-CVCs ranking second and uncoated CVCs ranking third.[7]

In another systematic review, a meta-analysis of CRBSI rate using 50 out of 60 included RCTs, resulted in the investigators concluding that MNR-I-CVCs were the most effective in the prevention of CRBSI as compared to CSS-I-CVCs, silver impregnated CVCs, and uncoated CVCs.[8] Specifically, MNR-I-CVCs were associated with a lower rate of CRBSI when compared with CSS-I-CVCs, with a RR 0.38 (95% CI 0.21 to 0.71), and when compared with uncoated CVCs, generating a RR of 0.29 (95% CI 0.16 to 0.52).[8] Silver coated CVCs were also associated with a lower rate of CRBSI versus uncoated CVCs (RR 0.57, 95% CI 0.38 to 0.96).[8] Additionally, eighteen studies were included in a network meta-analysis for CRBSI incidence per 1000 catheter-days, indicating that MNR-I-CVC was associated with fewer CRBSI per 1000 catheter days compared to CSS-I-CVCs and uncoated CVCs with a RR of 0.28 (95% CI 0.08 to 0.87) and RR 0.28 (95% CI 0.11 to 0.74) respectively.[8] For all-cause mortality, ten studies of the 50 studies were included in the network meta-analysis, demonstrating no difference between silver-impregnated CVCs, CSS-I-CVCs and uncoated CVCs.[8] When compared to silver-impregnated CVCs, all-cause mortality not significantly different from either uncoated CVCs and CSS-I-CVCs i.e., 0.90 (95% CI 0.70 to 1.15) and 1.36 (95% CI 0.72 to 2.58), respectively.[8] The risk ratio comparing CSS-I-CVCs to uncoated CVCs for all-cause mortality was reported to be 0.87 (95% CI 0.71 to 1.07).[8] 13 studies were included for catheter-related local infections where MCR-I-CVCs reduced the rate of catheter-related local infection compared to both CSS-I-CVCs (RR 0.26, 95% CI 0.09 to 0.70) and uncoated CVCs (RR 0.25, 95% CI 0.01 to 0.64).[8] In this systematic review, no differences were found between the different types of CVCs for CRBSI mortality.[8]

The Cochrane review included 12 of 57 RCTs in a meta-analysis which reported on clinically diagnosed sepsis and found no statistically significant differences between impregnated CVCs and uncoated CVCs based on moderate-quality evidence (RR 1.0, 95%

CI 0.88 to 1.13).[9] A meta-analysis of 42 of 57 included RCTs, considered to comprise high-quality evidence, reported a statistically significant reduction in CRBSI for coated CVCs as compared to uncoated CVCs (RR 0.62, 95% CI 0.52 to 0.74).[9] A meta-analysis of ten of 57 included RCTs of high-quality evidence did not report a statistical difference between coated and uncoated CVCs for the outcome of all-cause mortality.[9] No statistically significant difference between coated and uncoated CVCs was found with regards to catheter-related local infection based on meta-analysis of 12 of 57 included RCTs of moderate-quality evidence.[9] CRBSI-related mortality was reported to not be statistically significantly different between coated and uncoated CVCs based on a meta-analysis of five of 57 included RCTs.[9] This systematic review also did not find a statistically significant difference between coated and uncoated CVCs for number of catheters removed prematurely, systemic antibiotic use, and length of ICU stay.[9] The review did not identify any studies that reported on the outcome of quality of life.[9]

Chen et. al. performed a meta-analysis on nine of 12 included studies comparing silver impregnated CVCs with uncoated CVCs and found no statistically significant difference for risk of CRBSI (OR 0.72, 95% CI 0.48 to 1.10).[10]

All three primary studies found a lower proportion of CRBSIs with CSS-I-CVCs compared to standard catheters for subclavian vein access (1.4% vs. 0%, $P = 0.03$),[11] internal jugular vein access (2.0% vs. 0%, $P = 0.03$),[13] and femoral vein access (7.4% vs. 0%, $P = 0.02$).[12] CSS-I-CVCs also reduced the number of CRBSIs per 1000 catheter-days compared with standard catheters for subclavian vein access (2.12 vs. 0, $P = 0.02$),[11] internal jugular vein access (5.04 vs. 0, $p < 0.001$),[13] and femoral vein access (8.61 vs. 0, $P < 0.001$).[12]

*What is the safety of coated central venous catheters in adult patients?*

Two systematic reviews reported on safety outcomes.[8,9] Chong et al. reported no statistically significant difference between adverse events in antimicrobial-impregnated coatings, other coatings and uncoated CVCs.[8] Another systematic review reported no statistically significant difference in adverse events — including thrombosis, thrombophlebitis, bleeding and the composite outcome of bleeding, pain, erythema, or tenderness — based on a meta-analysis of 10 of 57 included RCTs comparing coated and uncoated CVCs, and incorporating high-quality evidence, (RR 1.09, 95% CI 0.94 to 1.27).[9]

## Limitations

The systematic reviews included in this review generally demonstrated a low risk of bias[7-10]. Nonetheless, three did not report the use of grey literature, and therefore may have missed relevant studies; especially considering one of the types of CVC coatings is newer.[7,8,10]. For one of the systematic reviews, it was unclear whether the quality of included studies was assessed; this increases uncertainty in the review's findings.[10]

The eligible primary studies identified were all conducted in a single hospital in Spain and may not necessarily be generalizable to the Canadian healthcare context.[11-13] While all three of these studies were comparative, the patients were not randomized to the study groups; therefore, this may introduce bias, potentially underestimating or overestimating the effects of the CVCs under study.[11-13]

No studies were identified for the polyHexaMethylene biguanide coated CVCs. Therefore, it not possible to describe its effectiveness compared with other types of coated CVCs and uncoated CVCs.

## Conclusions and Implications for Decision or Policy Making

Four systematic reviews and three primary studies were identified from the literature to address the research questions posed in this report. Notably, no studies were identified describing polyHexaMethylene biguanide coated CVCs.

A previous CADTH report provided a summary of the abstracts on a similar topic;[3] however, the current report asked a more stringent research question. As well, it updated and identified studies that were not included in the previous report.[3] The previous report identified mixed outcomes for CRBSI when comparing coated and uncoated CVCs; however, in addition to CVCs, it also included peripherally inserted central catheters and other types of CVCs that were out of scope for the current report.[3] The current report specifically focused on CVCs and the impact of coatings on clinical effectiveness and found the identified evidence demonstrated a reduction in CRBSI with coated CVCs.

Overall, the available evidence indicates there is a reduction in CRBSIs associated with antimicrobial coated CVCs, including CSS-I-CVCs, MNR-I-CVCs, and MCR-I-CVCs, compared to uncoated CVCs. However, the evidence does not indicate any significant differences between all-cause mortality and CRBSI-related mortality. Some of the identified studies reported no difference for adverse events between coated and uncoated CVCs, but adverse events were not reported in many of the studies, making it difficult to compare the safety between the CVCs. The lack of high-quality evidence describing severe adverse events, such as severe allergic reactions and death, is an important limitation as it concerns informing decisions regarding as to which type of CVCs should be made available in hospital settings. Consequently, uncertainty remains in determining which type of coating for CVCs is optimal. In addition, further research on the use of polyHexaMethylene biguanide coated CVCs versus other types of coating CVCs and uncoated CVCs will further help to inform decisions necessitating an understanding of their clinical effectiveness.

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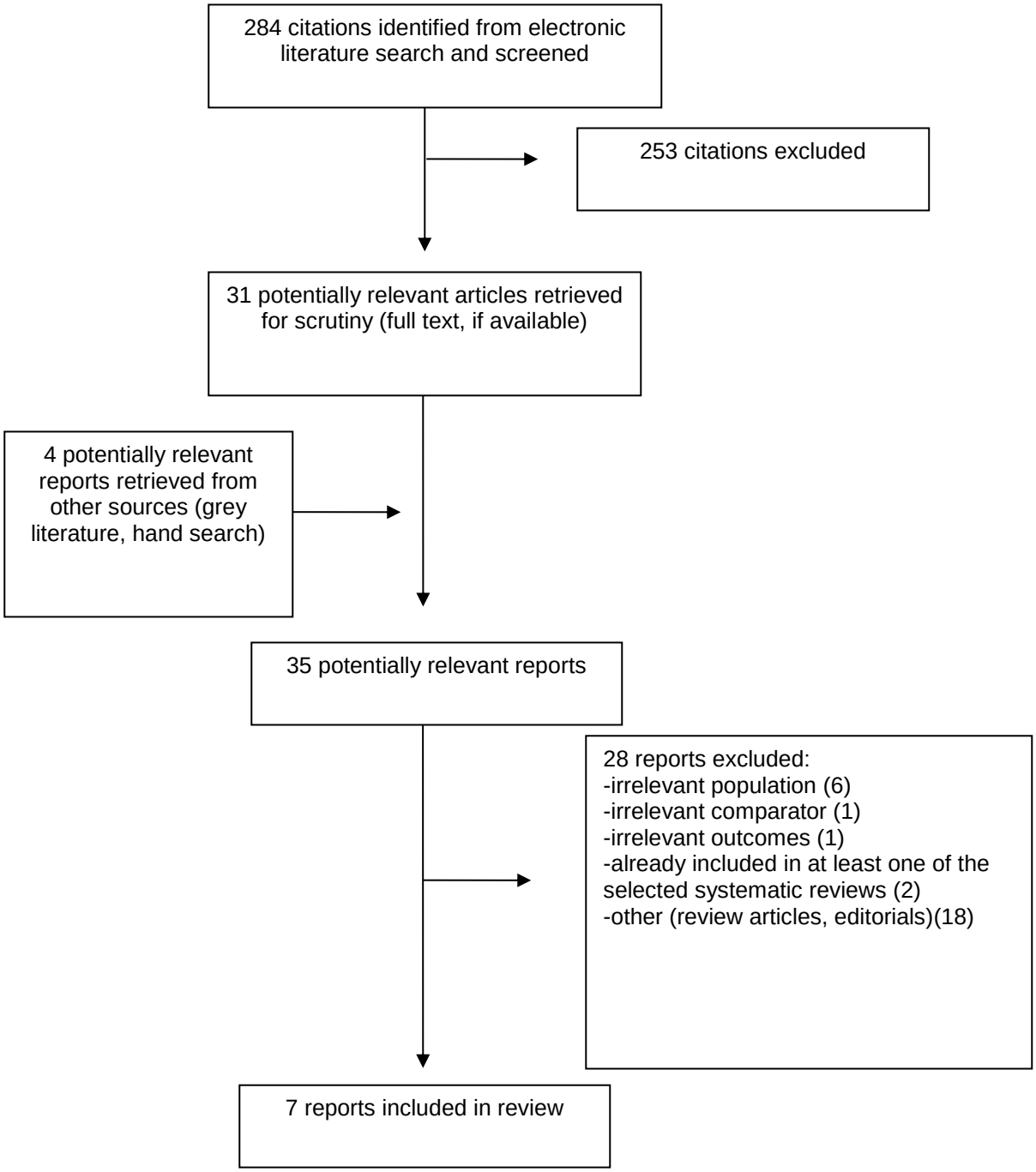
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| Wang 2018<br><br>China[7] | Systematic review and network meta-analysis of RCTs up to July 2017<br><br>33 RCTs for a total of 10,464 patients | Mostly adult patients needing a CVC | Central line bundle with antimicrobial interventions including chlorhexidine/silver sulfadiazine, Oligon Vantex silver or silver, and other antibiotics (5-fluorouracil, vancomycin, benzalkonium chloride, teicoplanin, miconazole/rifampicin, minocycline, and minocycline/rifampin or antimicrobial CVCs<br><br>Standard non-impregnated CVC | Primary outcome: Rate of CRBSI per 1000 catheter-days |
| Chong 2017<br><br>Malaysia[8] | Systematic review and network meta-analysis of RCTs up to August 2016<br><br>60 RCTs and included a total 17,255 catheters | Inpatient hospital setting in adult patients needed CVC; excluded CVCs for hemodialysis<br><br>A mix of patients from ICUs, general medical or surgical units, trauma and those receiving total parenteral nutrition | Antimicrobial-impregnated CVCs<br><br>Non-impregnated CVCs<br><br>Catheters with another impregnation | Primary outcome: clinically diagnosed sepsis, CRBSI rate (CRBSI per 1000 catheter-days), all-cause mortality<br><br>Secondary outcomes: composite outcome including number of participants with catheter-related local infections, mortality from CRBSI, adverse events, premature catheter removal |
| Lai 2016<br><br>Malaysia[9] | Cochrane systematic review and meta-analysis of RCTs up to March 2015<br><br>57 RCTs including 16,784 catheters | Patients needing CVCs, most were over the age of 18 including patients who were in ICU, oncology units, and patients receiving long-term total parenteral nutrition | Chlorhexidine/silver sulfadiazine impregnated CVCs<br><br>Minocycline-rifampin/rifampicin CVCs<br><br>Non-impregnated CVCs<br><br>Heparin and silver, platinum and carbon impregnated CVC | Primary outcome: number of participants clinically diagnosed with sepsis; number of participants with CRBSI; all-cause mortality<br><br>Secondary outcome: number of participants with catheter-related local infections; a composite outcome of |

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | | Standard CVCs | including number of participants or catheters with skin or site colonization; mortality from CRBSI; adverse events; catheter failure or premature catheter removal; use of systemic antibiotics; length of hospital stay; cost of care; quality of life |
| Chen 2014<br><br>China[10] | Systematic review and meta-analysis of RCTs and/or comparative prospective studies<br><br>Search up to April 2014<br><br>12 studies (11 RCTs) for a total of 2854 patients | Patients needing CVC | Silver-impregnated CVC<br><br>Standard non-impregnated CVC | CVC-associated bloodstream infection |

CRBSI = catheter-related bloodstream infections; CVC = central venous catheter; ICU = intensive care unit; RCT = randomized controlled trial

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| Lorente 2015<br><br>Spain[11] | Retrospective cohort study | ICU patients who received one or more subclavian venous catheters | Chlorhexidine and silver sulfadiazine coated CVC<br><br>Standard CVC without impregnation | CRBSI |
| Lorente 2014<br><br>Spain[13] | Prospective cohort study | ICU patients who received one or more internal jugular venous catheters | Chlorhexidine and silver sulfadiazine coated CVC<br><br>Standard CVC without impregnation | CRBSI |
| Lorente 2014<br><br>Spain[12] | Retrospective cohort study | ICU patients who received one or more femoral venous catheters | Chlorhexidine and silver sulfadiazine coated CVC<br><br>Standard CVC without impregnation | CRBSI, |

CRBSI = catheter-related bloodstream infection; CVC = central venous catheter; ICU = intensive care unit

# Appendix 3: Critical Appraisal of Included Studies

## Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[4]

| AMSTAR Item | | Wang et. al. 2018[7] | Chong et. al. 2017[8] | Lai et. al. 2016[9] | Chen et. al. 2014[10] |
|---|---|---|---|---|---|
| Was an a priori design provided? | | + | + | + | + |
| Was there duplicate study selection and data extraction? | Selection | + | + | + | + |
| | Extraction | + | + | + | + |
| Was a comprehensive literature search performed? | | + | + | + | + |
| Was the status of publication (i.e. grey literature) used as an inclusion criteria? | | - | - | + | - |
| Was a list of studies (included and excluded) provided? | Included | + | + | + | + |
| | Excluded | - | - | + | - |
| Were the characteristics of the included studies provided? | | + | + | + | + |
| Was the scientific quality of the included studies assessed and documented? | | + | + | + | - |
| Was the scientific quality of included studies used appropriately in formulating conclusion? | | + | + | + | ? |
| Were the methods used to combine the findings of studies appropriate? | | + | + | + | + |
| Was the likelihood of publication bias assessed? | | + | + | + | + |
| Was conflict of interest included? | | + | + | + | + |

Legend: + = Yes, - = No, ? = Unclear

## Table 5: Strengths and Limitations of Clinical Studies using Downs and Black[5]

| Strengths | Limitations |
|---|---|
| Lorente, 2015[11] | |
| • Clear description of the objectives of the study.<br>• Diagnosis of CRBSI was made by expert panel who was blinded by catheter type.<br>• Specifically compared CVC subclavian venous access.<br>• Baseline characteristics of both groups seemed similar.<br>• Statistical analyses appears to be appropriate for the study. | • Retrospective comparative study.<br>• The exact methods of the retrospective study was unclear.<br>• Non-randomized study can introduce bias.<br>• Single center study from Spain and cost information may not be reflective of Canadian healthcare system.<br>• No adverse events nor safety outcomes were reported. |

| Strengths | Limitations |
|---|---|
| • Results were clearly described and also presented in a table.<br>• Authors' conclusion was correct based on the study results. | • No information on funding of the study was provided.<br>• Authors did not declare of conflict of interest information. |
| Lorente, 2014[13] | |
| • Clear description of the objectives of the study.<br>• Diagnosis of CRBSI was made by expert panel who was blinded by catheter type.<br>• Specifically compared CVC Internal jugular venous access.<br>• Baseline characteristics of both groups seemed similar.<br>• Statistical analyses appears to be appropriate for the study.<br>• Results were clearly described and also presented in a table.<br>• Authors' conclusion was correct based on the study results. | • Non-randomized study may introduce bias.<br>• Exact methods of prospective observational study was unclear.<br>• Single center study from Spain and cost information may not be reflective of Canadian healthcare system.<br>• No adverse events nor safety outcomes were reported.<br>• No information on funding of the study was provided.<br>• Authors did not declare of conflict of interest information. |
| Lorente, 2014[12] | |
| • Clear description of the objectives of the study.<br>• Diagnosis of CRBSI was made by expert panel who was blinded by catheter type.<br>• Specifically compared CVC femoral access.<br>• Baseline characteristics of both groups seemed similar.<br>• Statistical analyses appears to be appropriate for the study.<br>• Results were clearly described and also presented in a table.<br>• Authors' conclusion was correct based on the study results. | • Retrospective comparative study.<br>• The exact methods of the retrospective study was unclear.<br>• Non-randomized study can introduce bias.<br>• Single center study from Spain and cost information may not be reflective of Canadian healthcare system.<br>• No adverse events nor safety outcomes were reported.<br>• No information on funding of the study was provided.<br>• Authors did not declare of conflict of interest information. |

CRBSI = catheter-related bloodstream infection; CVC = central venous catheters

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 6: Summary of Findings for Included Systematic Reviews and Meta-Analyses

| Main Study Findings | Authors' Conclusion |
|---|---|
| Wang, 2018[7] | |
| • Meta-analysis of 23 studies: lower rate of CRBSIs per 1000 catheter-days with the use of antimicrobial-impregnated and standard CVCs (RR 0.70, 95% CI 0.53 to 0.91, *P* = 0.008).<br>• Network meta-analysis of 25 RCTs:<br>  • both antimicrobial and chlorhexidine/silver sulfadiazine catheters reduced the rate of CRBSIs per 1000 catheter-days compared to standard CVCs<br>  • Antimicrobial CVCs vs. standard CVCs: OR 0.64 (95% CI 0.40 to 0.96)<br>  • Chlorhexidine/silver sulfadiazine CVCs vs. standard CVCs: OR 0.53 (95% CI 0.25 to 0.95)<br>  • No statistical difference between Oligon Vantex silver or silver catheters and standard CVCs: OR 0.77 (95% CI 0.46 to 1.27)<br>• Antimicrobial CVCs have the greatest potential of reducing the incidence of CRBSIs per 1000 catheter-days, chlorhexidine/silver sulfadiazine ranked second and conventional standard catheters ranked third. | *"In conclusion, our results demonstrate that antimicrobial-impregnated CVCs were more effective than standard non-impregnated CVCs in decreasing the rate of CRBSIs per 1000 catheter-days and catheter colonization with the application of bundles. Moreover, the capacities of catheters impregnated with chlorhexidine/silver sulfadiazine and other antibiotic catheters (5-fluorouracil, vancomycin, benzalkonium chloride, teicoplanin, miconazole/rifampicin, minocycline, and minocycline/rifampin) are superior to those of traditional catheters in preventing CRBSIs and catheter colonization when applied with bundles. Despite their demonstrated efficacy, we could not determine whether other antibiotic catheters are superior to chlorhexidine/ silver sulfadiazine-impregnated catheters. Compared to silver ion-impregnated CVCs, chlorhexidine/silver sulfadiazine antiseptic catheters reduce microbial colonization but do not reduce CRBSIs."* p. 9-10[7] |
| Chong, 2017[8] | |
| • 50 studies reported on the outcome of CRBSI:<br>  • MNR-I-CVCs were associated with a lower CRBSI rate compared to CSS-I-CVC (RR 0.38, 95% CI 0.21 to 0.71)<br>  • MNR-I-CVCs were associated with a lower CRBSI rate compared to standard CVCs (RR 0.29, 95% CI 0.16 to 0.52)<br>  • Silver impregnated CVCs were associated with a lower CRBSI rate compared to standard CVCs (RR 0.57, 95% CI 0.38 to 0.86)<br>  • MNR-I-CVC was the most effective CVC in the prevention of CRBSI<br>• 18 studies reported CRBSI per 1000 catheter days and were included in the network meta-analysis<br>  • MNR-I-CVC is associated with less CRBSI per 1000 catheter days compared to CSS-I-CVC (RR 0.28, 95% CI 0.08 to 0.87)<br>  • MNR-I-CVC is associated with less CRBSI per 1000 catheter days compared to standard CVC (RR 0.28, 95% CI 0.11 to 0.74)<br>• 10 studies was available for the network meta-analysis for the outcome of all-cause mortality and showed there was no difference between silver impregnated CVC, CSS-I-CVC, and standard CVC<br>• 13 studies were included for the outcome of catheter-related local infections:<br>  • MCR-impregnated CVCs significantly reduced the rate of catheter-related local infection compared with CSS-I-CVC (RR 0.26, 95% CI 0.09 to 0.70)<br>  • MCR-impregnated CVCs significantly reduced the rate of catheter-related local infection compared with standard CVC | *"In summary, this review provided robust evidence supporting MNR-I-CVC as potentially the most effective strategy for the prevention of CRBSI. In view of the scanty evidence related to clinically important outcomes, its overall benefit remains uncertain, and caution is needed in the overall clinical decision making and guideline development. Surveillance for antibiotic resistance attributed to the routine use of MNR-I-CVC should be emphasized in future trials."* p. S138[8] |

| Main Study Findings | Authors' Conclusion |
|---|---|
| (RR 0.25, 95% CI 0.01 to 0.64)<br>• No significant differences were seen between the types of CVCs for the outcomes of mortality from CRBSI and adverse events | |
| Lai, 2016[9] | |
| • Clinically diagnosed sepsis (12 studies): no difference between impregnated CVCs and standard CVCs (RR 1.0, 95% CI 0.88 to 1.13) based on moderate quality evidence<br>• CRBSI (42 studies): significant reduction for the impregnated group of CVCs compared to standard CVCs (RR 0.62, 95% CI 0.52 to 0.74) based on high quality evidence<br>• All-cause mortality (10 studies): no difference between impregnated CVCs and standard CVCs (RR 0.92, 95% CI 0.80 to 1.07) based on high quality evidence<br>• Catheter-related local infection (12 studies): no difference between impregnated CVCs and standard CVCs based on moderate quality evidence.<br>• CRBSI-related mortality (5 studies): no difference between the impregnated CVC group and standard CVC group<br>• Adverse events: no differences between impregnated CVC and standard CVC for thrombosis/thrombophlebitis, bleeding, and composite of bleeding, pain, erythema or tenderness.<br>• No difference between the two groups (impregnated and standard CVCs) for number of catheters removed prematurely, systemic antibiotic use, length of ICU stay, cost.<br>• No studies compared quality of life. | *"While there is high-quality evidence for the benefits of antimicrobial-impregnated central venous catheters (CVCs) in reducing catheter-related blood stream infections (CRBSIs) and moderate quality evidence for reducing catheter colonization, there is also a high-quality, but smaller body of evidence that shows no significant benefit of these catheters in reducing mortality, and moderate-quality evidence shows no difference in clinically diagnosed sepsis. Therefore, there remains uncertainty about the value of these modified catheters in improving overall patient mortality and morbidity. Furthermore, this review shows that there were significant benefits with impregnated CVCs for catheter-related outcomes, such as catheter colonization, in trials conducted in intensive care units (ICUs) only. Currently, while the overall body of evidence still allows recommendations in favour of their use in practice, there should be great caution in recommending the use of antimicrobial-impregnated CVCs across all settings without incorporating the current uncertainties on their overall benefits."* p. 31[9] |
| Chen, 2014[10] | |
| • Nine studies were available reporting on the risk of CRBSI and showed no statistically significant differences between silver impregnated CVCs compared to standard CVCs: OR 0.72, 95% CI 0.48 to 1.10 (*P* = 0.12) | *"In conclusion, silver-impregnated CVCs are not associated with lower rates of catheter bacterial colonization and do not reduce the incidence of CRBSI as compared to standard CVCs. Other options, such as rifampin–minocycline or chlorhexidine–silver sulfadiazine impregnated/coated catheters may be considered to reduce the rate of CRBSI."* p.285[10] |

CI = confidence interval; CRBSI = catheter-related bloodstream infection; CSS-I-CVC = chlorhexidine/silver sulfadiazine impregnated central venous catheter; CVC = central venous catheter; MCR-I-CVC = miconazole-rifampicin impregnated central venous catheter; MNR-I-CVC = minocycline-rifampicin impregnated central venous catheter; RCT = randomized controlled study; SIL-I-CVC = silver impregnated central venous catheter

## Table 7: Summary of Findings for Included Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| Lorente, 2015[11] | |
| • 7 (1.4%) CRBSIs in 518 patients with standard catheters vs. 0 (0%) CRBSI in 353 patients with chlorhexidine/silver sulfadiazine impregnated catheters (*P* = 0.03)<br>• 2.12 CRBSIs per 1000 catheter-days in patients with standard catheters vs. 0 CRBSI per 1000 catheter-days in patients with chlorhexidine/silver sulfadiazine impregnated catheters (*P* = 0.02) | *"The use of CHSS-impregnated catheters is an efficient measure to prevent catheter-related bloodstream infection in patients with subclavian venous access."* p. 713[11] |

| Main Study Findings | Authors' Conclusion |
|---|---|
| Lorente, 2014[13] | |
| • 8 (2.0%) CRBSIs in 391 patients with standard catheters vs. 0 (0%) CRBSI in 245 patients with chlorhexidine/silver sulfadiazine impregnated catheters (*P* = 0.03)<br>• 5.04 CRBSIs per 1000 catheter-days in patients with standard catheters vs. 0 CRBSI per 1000 catheter-days in patients with chlorhexidine/silver sulfadiazine impregnated catheters (*P* < 0.001) | *"In conclusion, the use of CHSS-impregnated catheters reduces the incidence of CRBSI and immediate CVC-related costs in the internal jugular venous access."* p. 323[13] |
| Lorente, 2014[12] | |
| • 14 (7.4%) CRBSIs in 190 patients with standard catheters vs. 0 (0%) CRBSI in 64 patients with chlorhexidine/silver sulfadiazine impregnated catheters (*P* = 0.02)<br>• 8.61 CRBSI per 1000 catheter-days in patients with standard catheters vs. 0 CRBSI per 1000 catheter-days in patients with chlorhexidine/silver sulfadiazine impregnated catheters (*P* < 0.001) | *"CHSS-impregnated catheters for femoral venous access reduce the risk of CRBSI and save costs."* p. 1132[12] |

CRBSI = catheter-related bloodstream infection; CVC = central venous catheter

# Appendix 5: Overlap between Included Systematic Reviews

## Table 8: Overlap in Primary Studies Across Included Systematic Reviews

| Primary Study Citation | Systematic Review Citation | | | |
|---|---|---|---|---|
| | Wang, 2018[7] | Chong, 2017[8] | Lai, 2016[9] | Chen, 2014[10] |
| Bennegard 1982 | | ✓ | ✓ | |
| Maki 1988 | | ✓ | ✓ | |
| Kamal 1991 | | ✓ | ✓ | |
| Babycos 1993 | | ✓ | ✓ | |
| Goldschmidt 1995 | | ✓ | ✓ | |
| Smith 1995 | | ✓ | ✓ | |
| Appelgren 1996 | | ✓ | | |
| Bach 1996 | | ✓ | ✓ | |
| Bach 1996 | ✓ | ✓ | ✓ | |
| Ciresi 1996 | | ✓ | ✓ | |
| Pemberton 1996 | | ✓ | ✓ | |
| Sheretz 1996 | | ✓ | ✓ | |
| Thornton 1996 | ✓ | | ✓ | |
| Van Heerden 1996 | | ✓ | ✓ | |
| George 1997 | | ✓ | ✓ | |
| Leon 1997 | ✓ | | ✓ | |
| Logghe 1997 | | ✓ | ✓ | |
| Maki 1997 | ✓ | ✓ | ✓ | |
| Raad 1997 | ✓ | ✓ | ✓ | |
| Tennenberg 1997 | ✓ | ✓ | ✓ | |
| Collin 1998 | ✓ | | | |
| Heard 1998 | | ✓ | ✓ | |
| Raad 1998 | | ✓ | ✓ | |
| Trerotola 1998 | | | | ✓ |
| Bach 1999 | ✓ | ✓ | ✓ | |
| Boswald 1999 | | ✓ | ✓ | ✓ |
| Collin 1999 | | ✓ | ✓ | |
| Darouiche 1999 | | ✓ | ✓ | |
| Hannam 1999 | | ✓ | ✓ | |
| Marik 1999 | | ✓ | ✓ | |
| Haeger 2001 | | ✓ | ✓ | |

| Primary Study Citation | Systematic Review Citation | | | |
|---|---|---|---|---|
| | Wang, 2018[7] | Chong, 2017[8] | Lai, 2016[9] | Chen, 2014[10] |
| **Jaeger 2001** | | | ✓ | |
| **van vliet 2001** | | ✓ | ✓ | |
| **Moss 2000** | ✓ | | ✓ | |
| **Sheng 2000** | ✓ | ✓ | ✓ | |
| **Harter 2002** | | ✓ | ✓ | |
| **Stoiser 2002** | | ✓ | ✓ | ✓ |
| **Theaker 2002** | ✓ | | ✓ | |
| **Bong 2003** | | ✓ | ✓ | ✓ |
| **Corral 2003** | ✓ | ✓ | ✓ | ✓ |
| **Ranucci 2003** | ✓ | ✓ | ✓ | |
| **Richards 2003** | ✓ | | | |
| **Bun-Christian 2004** | ✓ | ✓ | | |
| **Carrasco 2004** | ✓ | ✓ | ✓ | |
| **Leon 2004** | | ✓ | ✓ | |
| **Hanna 2004** | | ✓ | ✓ | |
| **Khare 2004** | ✓ | | | |
| **Yücel 2004** | ✓ | ✓ | ✓ | |
| **Darouiche 2005** | | ✓ | ✓ | |
| **Dünser 2005** | ✓ | ✓ | ✓ | ✓ |
| **Jaeger 2005** | ✓ | ✓ | ✓ | |
| **Kahveci 2005** | | ✓ | ✓ | |
| **Moretti 2005** | ✓ | ✓ | ✓ | |
| **Ostendorf 2005** | ✓ | ✓ | ✓ | |
| **Rupp 2005** | ✓ | ✓ | ✓ | |
| **Fraenkel 2006** | ✓ | ✓ | ✓ | |
| **Logghe 2006** | ✓ | | | |
| **Osma 2006** | ✓ | ✓ | ✓ | |
| **Abdelkefi 2007** | | ✓ | ✓ | |
| **Kalfon 2007** | ✓ | ✓ | ✓ | ✓ |
| **Camargo 2009** | ✓ | ✓ | ✓ | |
| **Hagau 2009** | | ✓ | | ✓ |
| **Hagaua 2009** | ✓ | | | |
| **Mer 2009** | | ✓ | ✓ | |
| **Walz 2010** | ✓ | ✓ | ✓ | |

| Primary Study Citation | Systematic Review Citation | | | |
|---|---|---|---|---|
| | Wang, 2018[7] | Chong, 2017[8] | Lai, 2016[9] | Chen, 2014[10] |
| **van Vliet 2011** | ✓ | | | |
| **Antonelli 2012** | ✓ | ✓ | ✓ | ✓ |
| **Arvaniti 2012** | | ✓ | ✓ | ✓ |
| **Rickard 2016** | ✓ | | | |
| **Storey 2016** | | ✓ | | |

Legend: ✓ = Included