

# Antibiotic-Impregnated Central Venous Catheters for the Prevention of Catheter-Related Bloodstream Infection in Children: A Meta-Analysis

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## ABSTRACT

**Background:** Use of central venous catheters (CVCs) ensure stable access in critically ill patients but is associated with increased infection rates. CVCs with antimicrobials has been recommended for infection reduction in adults. A review of antibiotic-impregnated CVCs' usefulness in children is needed.

**Objectives:** To determine the effectiveness of antibiotic-impregnated CVCs in reducing infection in children

**Search Methods:** Extensive search of MEDLINE, Cochrane Database of Systematic Reviews and Cochrane Register of Controlled Trials, Clinicaltrials.gov, Google scholar was done for trials published until June 2016. Reference lists from retrieved journals were checked for relevant articles.

**Selection Criteria:** RCTs evaluating antibiotic-impregnated compared with standard CVCs for reducing infection in children.

**Data Collection and Analysis:** Two authors assessed trial quality and extracted data. Statistical analysis was done using Review Manager with fixed or random effects model. Outcomes: bloodstream infection, hypersensitivity, thrombosis, mortality, site infection, length of ICU and hospital stay. Dichotomous data were presented as risk ratios (RR), continuous data as mean differences with 95% confidence intervals (CIs).

**Main Results:** Two low quality trials (n=1773) were analyzed showing nonsignificant reduction of bloodstream infection in the antibiotic-impregnated group compared to standard catheters (RR 0.49; 95% CI 0.23-1.02, I<sup>2</sup>=0%) with no increased risk of thrombosis (RR 1.04 95% CI 0.84-1.28, I<sup>2</sup>=0%). No statistical difference was seen in the duration of ICU and hospital stay.

**Authors' Conclusions:** There is no evidence that antibiotic-impregnated CVCs reduced bacteremia in children, increased the risk for thrombosis, or improved ICU and hospital stay. More RCTs are needed to determine benefits of antibiotic-impregnated CVCs.

## Keywords

Antibiotic-impregnated catheter, infection, children.

## Background

### Description of the condition

Central venous catheters have long been used in the hospital and outpatient settings, however, they may introduce catheter-related

bloodstream infections (CRBSIs) which may be detrimental especially to immunocompromised hosts. The gold standard for the diagnosis is the combination of a positive blood culture and a similar pathogen isolated from the catheter [1].

In general, CRBSI from central venous catheters is approximated at 10%, with a mortality rate of up to 25%, significantly increasing

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hospital stay and treatment costs [1]. A study by Smith in 2008 reviewed data from 36 pediatric intensive care units and presented a pooled mean of 5.3 CRBSIs per 1000 catheter-days and a median of 3.6 CRBSIs per 1000 catheter days. Most infections were caused by gram positive bacteria [2], but gram negative bacilli accounts for 19-21% [3].

### Description of the intervention

CVCs eventually evolved to include catheters impregnated with antiseptics (i.e. chlorhexidine, silver sulfadiazine), or antibiotics, such as minocycline and rifampin. Antibiotic-impregnated CVCs have several advantages compared with antiseptic coated CVCs. Antiseptic impregnated catheters are coated on the external surface only, whereas antibiotic-impregnated catheters are coated both externally and internally thereby reducing intraluminal and subsequent hematogenous sources of colonization. In vitro, the half-life of minocycline-rifampin is 25 days in contrast to chlorhexidine-silver sulfadiazine with a shorter half-life of 3 days [4].

### How the intervention might work

Antibiotics used in catheters include minocycline and rifampin. Minocycline is a tetracycline derivative that binds with the 30s ribosomal subunit, while rifampin is a semisynthetic derivative of rifamycin which inhibits bacterial RNA synthesis by blocking RNA transcription [4]. Minocycline and rifampin impregnated CVCs may reduce bacterial colonization; reduce micro-organism adhesion and survival, thus inhibiting intraluminal or extra-luminal biofilm formation [5].

### Why it is important to do this review

Catheter-related bloodstream infections increase morbidity and mortality rates, and treatment costs. Most studies that support its recommendation are trials or reviews primarily of adults [6]. Because of this scarcity of trials in children, efficacy and safety concerns remain an issue [7].

A review on the available studies will help assess the efficacy and safety of the intervention, for possible formulation of guidelines or recommendations on the use of CVCs.

### Objectives

The aim of this review is to determine whether antibiotic-impregnated CVCs are effective in reducing CRBSI through a meta-analysis of relevant trials. The study further aims to identify mortality rates, adverse effects, complications of utilizing antibiotic-impregnated catheters and effect on hospital/ICU stay in pediatric patients.

### Methods

#### Types of studies

All published and unpublished randomized controlled trials.

#### Types of participants

Patients aged less than 18 years old who needed or were expected to need central venous catheters: preterm infants, patients undergoing

elective surgery, patients admitted at intensive care units.

#### Types of interventions

The intervention is antibiotic-impregnated central venous catheters compared to the control or standard central venous catheters.

#### Types of outcome measures

**Primary outcomes:** The primary outcome is the reduction in bloodstream infection between the two treatment groups.

**Secondary outcomes:** Secondary outcomes include adverse events such as hypersensitivity reactions, venous thrombosis, local site infection, hospital or ICU stay, and mortality rates.

#### Search methods for identification of studies

**Electronic searches:** Several search engines were used to screen for relevant trials and reviews with no language or year restrictions. PubMed was used to scan the National Library of Medicine by utilizing Medical SubHeading (MeSH) terms. Cochrane Clinical Trials Registry and ClinicalTrial.gov were searched for reviews or meta-analyses and ongoing clinical trials.

Free-text search was done to exhaust all relevant articles, and references of significant studies were scanned as well for pertinent pieces. Retrieval of related local studies was attempted from Health Research and Development Information Network (HERDIN) and pimedicus.upm.edu.ph.

#### Data collection and analysis

**Selection of studies:** All abstracts were read independently by two reviewers and full articles of abstracts meeting the inclusion criteria or were 'uncertain' were retrieved. Communication with the original authors was done if needed. The retrieved articles were assessed for eligibility and appraised independently by two reviewers. Issues were resolved by consulting a third party.

**Data extraction and management:** Review Manager Version 5.3 (RevMan) software was used for entry of data extracted by 2 review authors. Any discrepancy was resolved by discussion or consultation of a third-party if needed. Any relevant information that was unclear warranted contacting of the authors of the studies for clarification.

**Assessment of risk of bias in included studies:** Each included study was independently assessed by two reviewers using the criteria outlined in the Cochrane handbook for Systematic Reviews of Intervention [8].

**Measures of treatment effect:** Dichotomous data were reported as risk ratio with 95% confidence interval, and continuous data as mean differences if arithmetic means and standard deviations were available.

**Unit of analysis issues:** All included studies were randomized with no issues of unit analysis such as participants undergoing more than one intervention and multiple observations for the same

outcome.

Dealing with missing data: Analysis of stated outcomes was done on an intention to treat basis. Any missing data was retrieved through contacting primary authors of the study and sensitivity analysis was planned where worst and base case scenarios were reported if feasible.

Assessment of heterogeneity: We assessed heterogeneity by inspecting the forest plots to detect overlapping 95% CI. To test for heterogeneity, Chi-squared test was used and I<sup>2</sup> computed to quantify degree of inconsistency. I<sup>2</sup> of 30%-60% may represent moderate heterogeneity, 50%-90% substantial heterogeneity, and 75%-100% as considerable heterogeneity [8].

Assessment of reporting biases: Funnel plots to determine reporting bias could not be done because there were only two trials included.

### Data synthesis

Statistical analyses were conducted using the Review Manager Software (RevMan 5.3). Dichotomous data were combined using the Mantel-Haenszel method and continuous data reported as mean differences were analyzed using the inverse variance approach. Depending on the degree of heterogeneity of the data, we performed either a fixed-effects model or a random-effects model (Der Simonian and Laird model).

### Subgroup analysis and investigation of heterogeneity

We were not able to do subgroup analysis as planned using different age groups (0-2 months (including preterms), 2 months-2 years, 2 – 10 years, more than 10 years); severity of underlying disease; site of venous catheter insertion; type of catheter inserted and type of antibiotic used because there were only two trials included in the meta-analysis.

### Sensitivity analysis

Sensitivity analysis was planned in case there are more than 10 trials to determine the effect of trial quality by excluding studies with inadequate randomization, questionable allocation concealment and significant loss to follow-up.

## Results

### Results of the search

Various methods were used to search for catheter-related infection and antibiotic-impregnated central venous catheter/arterial catheter/PICC lines. Results from MEDLINE yielded 6 articles, only 2 identified to have met the eligibility criteria. Further search in Clinicaltrials.gov yielded 8 studies, 4 immediately excluded because they involved ventricular catheters. Of the 4 remaining articles, 2 were already included, 1 was a completed study on the use of CVC, however, on adults. The last article focused on the comparison of an antibiotic impregnated PICC catheter vs a regular one - but the article was not available and the current status of the study was unknown [9]. Further search was done to retrieve the unpublished article however was unsuccessful. Primary author was contacted for trial update and possible retrieval of available

results or paper. (Appendix A)

Free-text search on Google scholar was done which additionally yielded an ongoing unblinded trial on preventing infection using antimicrobial-impregnated PICC line in preterm neonates (PREVail Study), started last December 2014 and expected to run until August 2017 [10]. Details of the study are summarized in Appendix C.

### Included studies

2 studies were included, one of which recruited 1485 children below 16 years old, and the other enrolled 326 below the age of 18. Details of the studies are summarized in Appendix B.

The study by Cox [7] included patients less than 18 years of age who underwent cardiovascular surgery from October 2006 to March 2010 at Riley Hospital for Children in Indianapolis. These patients required placement of a double lumen central venous catheter, either minocycline/rifampin impregnated or the conventional one, under full sterile conditions in an operating room. Post-operative care for these patients was done in the pediatric intensive care unit and the Heart Center step down unit managed by pediatric cardiologists. Exclusion criteria for this study were: 1) drug allergy to minocycline, tetracycline, or rifampin; 2) ventricular assist device therapy; 3) ECMO therapy; 4) cardiac transplant; 5) active infection; and 6) delayed closure of sternum. 326 patients were eligible but only 288 were deemed evaluable and included in the analysis. Reasons for further exclusion after allocation included: open chest (10), ECMO (5), inability to place catheter (16), catheter inadvertently inserted in the wrong vessel (3), pre-existing infection (1), no assent obtained (1), biopatch dressing instead of standard dressing (1), and study catheter placed and removed in the operating room (1). 11.6% or 38 patients who were randomized were not included in the analysis and the author was contacted for retrieval of additional data. Although some patients were not analyzed due to presence of exclusion criteria, the reason for exclusion of the other patients was unclear. Due to unaccounted data, the 38 excluded patients' group allocation could not be ascertained. Results showed that the number of infections and catheter complications were the same for each group. There was no statistical significance in the rates of catheter-related bloodstream infections in both groups.

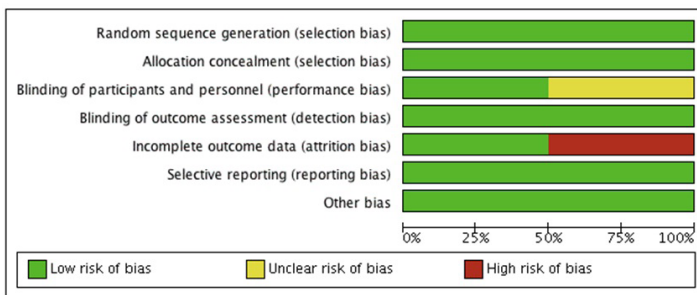
The CATCH trial [6] involved a larger population with 1485 recruited to the study. Children below 16 years old admitted in 14 English pediatric intensive care units expected to need central venous catheterization for more than 3 days were included between December 2010 and November 2012. Polyurethane central venous catheters were used, either double or triple lumen. Concentrations of the antibiotics were reported (by Cook Medical Incorporated) as 503 ug/cm minocycline and 480 ug/cm rifampicin. Pediatric Index of Mortality was extracted at admission from their PICANet Database. Scores from the pediatric index of mortality were similar for all treatment groups. The standard venous catheter was used in 502 children, antibiotic-impregnated catheters in 486 and heparin impregnated catheters in the remaining 497. Bloodstream

infection was similar for the standard and heparinized catheters (4% and 3% respectively) compared to 1% in the antibiotic-impregnated treatment group. In this meta-analysis, only data for minocycline/rifampicin vs. standard catheter were analyzed.

Incidences of bloodstream infections were reported as primary outcomes in both studies. Determination of secondary outcomes differed in the two studies. Cox enumerated hospital stay and ICU days, as well as venous thrombosis, catheter occlusion, antibiotic days, and other catheter-related complications (not specified) [7]. Gilbert focused on mortality, thrombosis, median time to catheter removal and number of bloodstream infections per 1000 days as the secondary outcomes [6]. Information and results on local site infection and hypersensitivity reactions were not included in either of the studies.

### Risk of bias in included studies

Figure 1 shows the summary of risk of bias of the two studies included in this meta-analysis. Both studies were assessed to have low risk of bias.



**Figure 1:** Summary of Risk of Bias of the Included Studies.

**Random sequence generation (selection bias):** The randomization procedure in the two trials was adequately performed. The CATCH trial used computer generated randomization sequences while Cox assigned a random identification number for the study catheters [7].

**Allocation concealment (selection bias):** Gilbert had low risk for selection bias as evidenced by allocation to clinician through the use of pressure-sealed, sequentially numbered, opaque envelopes [6]. Cox on the other hand utilized central allocation by an external source (Cook Critical Care) who packed the catheters in identical trays then assigned a random identification number, hence also having a low risk for selection bias [7].

**Blinding (performance bias and detection bias):** The CATCH trial used computer generated randomization sequences while Cox assigned a random identification number for the study catheters [7].

In the study by Cox, although the color of the catheter was unique and visible to the inserting physician, it was not documented and was not visible after placement [7]. In effect, the clinical and infection control teams assessing the outcomes were blinded to the study arm into which each patient had been assigned. Similarly,

in the CATCH Trial [6], the clinician inserting the catheter was not blinded to the allocation because of the colors of the catheters, but because they looked identical after placement, allocation was concealed from the parents, patients, and clinical team.

**Incomplete outcome data (attrition bias):** In the study by Cox, 326 patients were enrolled but 288 were deemed evaluable because of further exclusion done as mentioned above [7]. The treatment allocation of the patients excluded from analysis was not reported and the proportion of patients whose outcomes were not accounted for was substantial (>10%) relative to those who developed bacteremia.

The CATCH Trial had outcome data analyzed according to the intention-to-treat principle. 5% did not receive a central venous catheter since insertion was attempted but unsuccessful or not attempted at all (no longer needing a central venous catheter, e.g. died).

**Selective reporting (reporting bias):** Primary and secondary outcomes were reviewed and analyzed in both studies. Incidences of bloodstream infections were identified as primary outcomes and are reported in both studies. However, reporting of secondary outcomes was variable in the two studies. Cox [7], reported the primary outcome as incidence of catheter-associated bloodstream infection determined by hospital infection control specialists according to accepted National Healthcare Safety Network. Other pre-specified outcomes reported were complications (pneumothorax, thrombosis, etc.), and infections with identified source other than the CVC. Hospital stay and ICU days, as well as antibiotic days were eventually included as part of the reported outcomes. Gilbert [6], defined their primary outcome as presence of bloodstream infection and median time to first bloodstream infection. Secondary outcomes focused on mortality, thrombosis, median time to catheter removal and number of bloodstream infections per 1000 days as the secondary outcomes, with post hoc analyses providing results on median ICU and hospital stay. Information and results on hypersensitivity reactions were not included in either of the studies and neither of the determined local site infection as well.

### Effects of interventions

#### Presence of bloodstream infection in patients given antibiotic-impregnated central venous catheter vs. standard catheter

The included studies by Cox [7] and Gilbert [6], were used to combine data from the primary outcome of bloodstream infections. The pooled data showed that there was no significant difference between the antibiotic-impregnated catheter and the standard catheter. Although there was a trend for benefit in those who used the antibiotic-impregnated CVCs, the results were not significant since the upper limit of the 95% CI crossed the value of 1 (RR 0.49, 95% CI 0.23 - 1.02) and the overall effect was not significant with a z-score of 1.83 (p value of 0.06). Test for heterogeneity yielded homogenous results with a Chi2 of 0.92, p = 0.34, and I2 of 0%. Results were similar when random effects analysis was used (Figure 2).

**Development of venous thrombosis in antibiotic-impregnated central venous catheter vs. standard catheter**

Both studies reported on thrombosis. Figure 3 shows a risk ratio of 1.03 [95% CI 0.83 - 1.28], hence there is no statistical significance in the development of thrombosis between antibiotic-impregnated central venous catheter vs. the standard catheter. Results were homogenous with a Chi<sup>2</sup> of 0.92, p = 0.34, and I<sup>2</sup> = 0%. Test of overall effect was not statistically significant with p value of 0.75.

**Mortality rates of antibiotic-impregnated central venous catheter vs. standard catheter**

Only the study by Gilbert reported on the mortality rates, defined as death within the first 30 days after randomization [6]. Rates were similar in both intervention arms, with 8% (n=42 for standard catheter, n=39 for antibiotic-impregnated). Mortality was not part of the outcomes measured in Cox [7].

**Mean ICU and hospital stay between antibiotic-impregnated catheter and standard**

Duration of ICU and hospital stay was both reported in the studies by Cox [7] and Gilbert [6]. Assuming normal distribution,

the combined data on ICU stay from the two studies yielded a mean difference of 0.17, with a 95% confidence interval [-1.50, 1.83] showing no statistical difference between the antibiotic-impregnated treatment group and the standard catheter group (Figure 4). The data however is heterogeneous with an I<sup>2</sup> of 94%. Data was initially done with fixed effects model but changed to random effects due to high heterogeneity. Subgroup analysis to determine the possible cause of heterogeneity was not done because only 2 studies were available for comparison.

Similarly, pooled data on the duration of hospital stay (Figure 5), showed 0 mean difference with a 95% confidence interval [-0.76,0.76], and overall effect of 0. There was no statistical difference, with a p value of 1.00 between using antibiotic-impregnated CVCs and standard catheters. Results were homogenous with a Chi<sup>2</sup> and I<sup>2</sup> of 0.

**Hypersensitivity reactions from antibiotic-impregnated catheters vs. standard**

Neither of the researches included hypersensitivity reactions as part of their outcome.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio
Cox 2013	3	146	3	142	14.7%	0.97 [0.20, 4.74]
Gilbert 2016	7	486	18	502	85.3%	0.40 [0.17, 0.95]
<b>Total (95% CI)</b>		<b>632</b>		<b>644</b>	<b>100.0%</b>	<b>0.49 [0.23, 1.02]</b>
Total events: 10 (Experimental), 21 (Control)						
Heterogeneity: Chi <sup>2</sup> = 0.92, df = 1 (P = 0.34); I <sup>2</sup> = 0%						
Test for overall effect: Z = 1.90 (P = 0.06)						

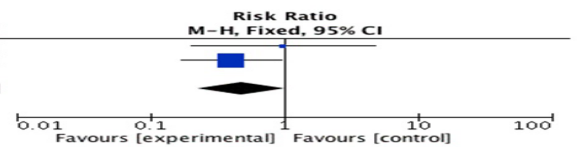


Figure 2: Forest Plot on the Comparison Between Antibiotic-impregnated and Standard Venous Catheters on the Reduction of Bloodstream Infection.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference
Cox 2013	3	1.48	146	2	2.22	142	51.1%	1.00 [0.56, 1.44]
Gilbert 2016	4.4	5.26	486	5.1	5.33	502	48.9%	-0.70 [-1.36, -0.04]
<b>Total (95% CI)</b>			<b>632</b>			<b>644</b>	<b>100.0%</b>	<b>0.17 [-1.50, 1.83]</b>
Heterogeneity: Tau <sup>2</sup> = 1.36; Chi <sup>2</sup> = 17.71, df = 1 (P < 0.0001); I <sup>2</sup> = 94%								
Test for overall effect: Z = 0.20 (P = 0.84)								

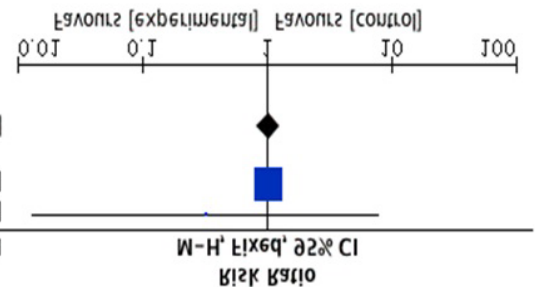


Figure 3: Forest Plot Comparison on the Development of Venous Thrombosis in Antibiotic-impregnated vs. Standard Catheter.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference
Cox 2013	6	3.7	146	6	3.7	142	78.4%	0.00 [-0.85, 0.85]
Gilbert 2016	12	11.85	486	12	14.22	502	21.6%	0.00 [-1.63, 1.63]
<b>Total (95% CI)</b>			<b>632</b>			<b>644</b>	<b>100.0%</b>	<b>0.00 [-0.76, 0.76]</b>
Heterogeneity: Chi <sup>2</sup> = 0.00, df = 1 (P = 1.00); I <sup>2</sup> = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								

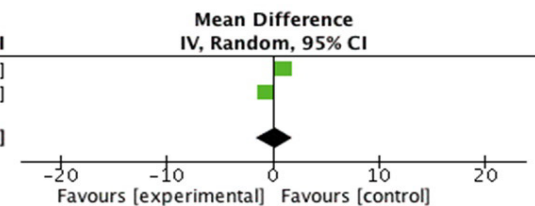


Figure 4: Forest Plot Comparison on Duration of ICU Stay between Antibiotic-impregnated CVC and Standard CVC.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference
Cox 2013	6	3.7	146	6	3.7	142	78.4%	0.00 [-0.85, 0.85]
Gilbert 2016	12	11.85	486	12	14.22	502	21.6%	0.00 [-1.63, 1.63]
<b>Total (95% CI)</b>			<b>632</b>			<b>644</b>	<b>100.0%</b>	<b>0.00 [-0.76, 0.76]</b>
Heterogeneity: Chi <sup>2</sup> = 0.00, df = 1 (P = 1.00); I <sup>2</sup> = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								

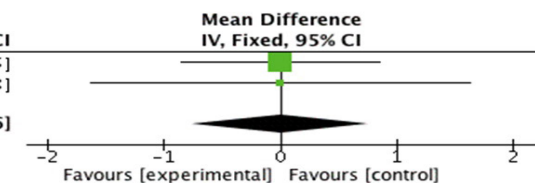


Figure 5: Forest Plot Comparison on Duration of Hospital Stay between Antibiotic-impregnated CVC and Standard CVC.

Quality Assessment							Summary of Findings		
Number of studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Overall Overall Quality of evidence	Number of patients		Effect
							Intervention	Control	RR (95% CI)
<b>Outcome: Catheter-associated bloodstream infection</b>									
2	RCT	Serious <sup>1</sup>	Not serious <sup>2</sup>	Not serious <sup>3</sup>	Serious <sup>4</sup>	⊕⊕⊕⊕ Low quality	10	21	0.49 (0.23-1.02)
<b>Outcome: Development of Venous Thrombosis</b>									
2	RCT	Serious <sup>1</sup>	Not serious <sup>2</sup>	Not serious <sup>3</sup>	Serious <sup>4</sup>	⊕⊕⊕⊕ Low quality	126	125	1.03 (0.83-1.28)
							Mean Difference (95% Ci)		
<b>Outcome: Duration of ICU Stay</b>									
2	RCT	Serious <sup>1</sup>	Not serious <sup>2</sup>	Not serious <sup>3</sup>	Serious <sup>4</sup>	⊕⊕⊕⊕ Low quality	0.17 (-1.50-1.83)		
<b>Outcome: Duration of Hospital Stay</b>									
2	RCT	Serious <sup>1</sup>	Not serious <sup>2</sup>	Not serious <sup>3</sup>	Serious <sup>4</sup>	⊕⊕⊕⊕ Low quality	0 (-0.76-0.76)		

**Table 1:** Summary of GRADE Quality of Evidence.

<sup>1</sup>Downgraded by 1 because there was no ITT analysis in the trial by Cox (2013) and because of variable and incomplete reporting of outcomes in both studies.

<sup>2</sup>No serious inconsistency: There was no statistical heterogeneity (I squared is 0% and p value for heterogeneity is greater than 0.10). The effect sizes in the trials are compatible with no significant differences between the antibiotic-impregnated CVCs and standard CVCs.

<sup>3</sup>No serious indirectness: The trials were conducted in children less than 18 years old admitted in pediatric intensive care units.

<sup>4</sup>Downgraded by 1 for imprecision: There were only 2 trials and number of events were small resulting in a pooled estimate with a 95% confidence interval ranging from benefit to no effect for catheter-associated infection and an estimate ranging from benefit to increased harm for development of venous thrombosis in those who used the antibiotic impregnated CVC.

### GRADE Quality of Evidence

The quality of evidence was downgraded for overall risk of bias because in the study of Cox [7], not all patients randomized were included in the analysis and because of incomplete and variable reporting of outcomes. Since the 95% confidence interval included both benefit and no effect for catheter-associated bacteremia and both benefit and possible increased risk for thrombosis with the use of antibiotic-impregnated CVCs, the quality of evidence was downgraded by one for imprecision.

## Discussion

### Summary of main results

Pooled data and calculated relative risk from both included studies failed to show statistical significance in the reduction of bloodstream infection in children in intensive care units. Comparison of reported results from the studies of Cox [7] and Gilbert [6] was homogenous based on test for heterogeneity.

From secondary outcomes, only data on reported thrombosis and duration of ICU and hospital stay were pooled and were also not statistically significant for both treatment arms. No data was available for hypersensitivity reactions and local sites infections, and only Gilbert [6] presented results on mortality.

Upon separate review of the studies, Gilbert [6], relayed that antibiotic impregnation of venous catheters reduced the risk of infection by 57% compared to standard catheters, with an absolute

risk reduction of 2.15%, meaning 47 children would need to be treated with antibiotic-impregnated central venous catheters to prevent 1 case of bloodstream infection. In contrast, in the study by Cox [7], the number of infections on each treatment group was the same (3 each), hence there was no statistical difference between the two groups. Furthermore, all identified infections from the study by Cox [7], were found in patients not more than 2 years old, 3 cases in the internal jugular, 2 in the femoral location, and 1 in the subclavian vein.

### Overall completeness and applicability of evidence

Both studies included participants of the pediatric population and were representative of patients less than 18 years of age admitted primarily at an intensive care unit. However, generalizability to other populations with different population characteristics, admitted in other locations or in different settings is unknown.

### Quality of the evidence

We used the GRADE approach in assessing the quality of evidence. Both studies of Cox [7] and Gilbert [6] (CATCH Trial) were adequately designed randomized controlled trials. However, there was risk of bias due to lack of ITT analysis in the trial of Cox and variable and incomplete reporting of outcomes in the two studies. Although results were consistent, there was imprecision since the upper value of the 95% confidence interval crossed the value of 1, implying that the use of antibiotic-impregnated CVC may not reduce blood stream infections compared with the standard CVC.

This imprecision could be due to the low event rates and the small number of trials and sample size. The overall low quality of evidence suggests that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

#### Potential biases in the review process

A comprehensive search was done to identify eligible studies to be included in this review and there were no language restrictions. Both authors independently reviewed articles and extracted data from the included studies, after following criteria for their inclusion. Disagreements were resolved through discussion or solicitation from a third party.

#### Agreements and disagreements with other studies or reviews

A systematic review of 34 randomized controlled trials in adults [11] showed that antibiotic-impregnated catheters using minocycline-rifampicin reduced rates of catheter-related infections. The use of minocycline-rifampicin CVCs was recommended to be considered when baseline incidence of catheter-related bloodstream infections is above an institution's goal despite appropriate measures to prevent infection. However, in these cases, there must be monitoring of microbial sensitivity to the agents used in these CVCs, as well as document any adverse events. Currently, there are no published reviews available on the use of antibiotic-impregnated central venous catheters in children.

#### Author's Conclusions

##### Implications for practice

The review failed to establish statistical significance on the use of antibiotic-impregnated venous catheters for patients admitted in intensive care units needing central lines to reduce bloodstream infection. Its use cannot be recommended at this time and more trials are needed to reinforce the evidence. Decision of its use at present will depend on the physician's clinical judgment after careful consideration of the costs and benefits.

##### Implications for research

More high quality trials on the use of antibiotic impregnation for central venous catheters may be suggested, with similar large

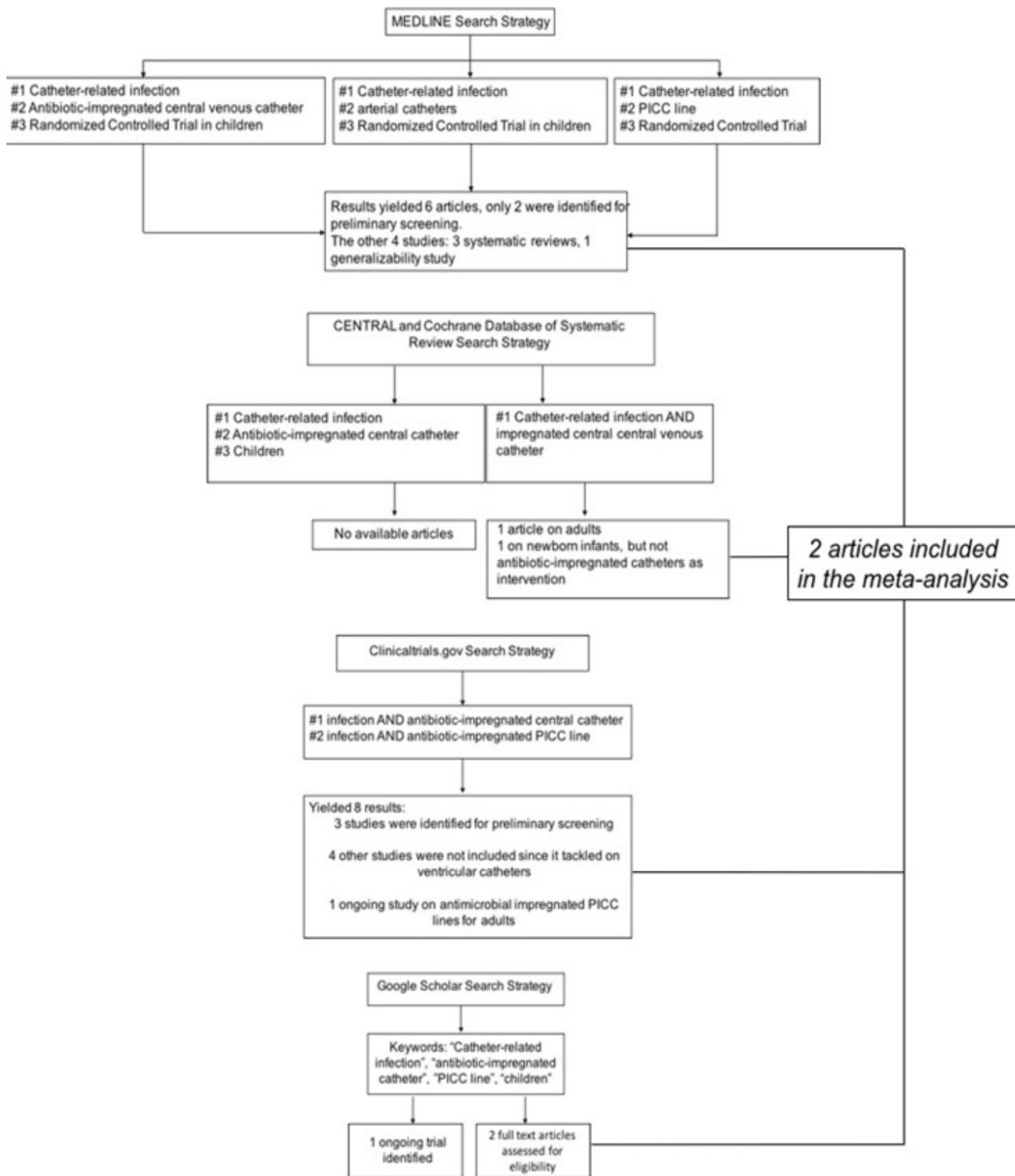
populations, focusing on the pediatric population and including mortality and hypersensitivity reactions in the outcomes.

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## Appendix

### Appendix A: Search Strategies.





<b>Methods</b>	Double-blinded randomized controlled trial
<b>Participants</b>	Patients <18 years of age who underwent cardiovascular surgery
<b>Interventions</b>	Antibiotic-impregnated central venous catheter (Minocycline/Rifampin) vs. conventional, non-impregnated catheters
<b>Outcomes</b>	catheter-associated bloodstream infection

**Appendix B:** Risk of Bias Table of Included Studies. Study of Cox et. Al (2003).

<b>Bias</b>	<b>Authors' judgment</b>	<b>Support for judgment</b>
Random sequence generation (selection bias)	Low risk	The randomization scheme consisted of blocks of six identical catheter trays stocked with the packed identical catheters (assigned with random identification number) in a random sequence
Allocation concealment (selection bias)	Low risk	The study utilized central allocation by an external source (Cook Critical Care) who packed the catheters in identical trays then assigned a random identification number
Blinding of participants and personnel (performance bias)	Low risk	Patients and clinical team were blinded to allocated intervention
Blinding of outcome assessment (detection bias)	Low risk	The clinical and infection control teams were blinded to study arm into which each patient had been assigned
Incomplete outcome data (attrition bias)	High risk	Total number of enrolled patients was 326 with 288 deemed evaluable (exclusions due to: open chest, ECMO, inability to place catheter, catheter inadvertently inserted in wrong vessel, pre-existing infection, no assent, biopatch instead of standard dressing, study catheter placed and removed in operating room)
Selective reporting (reporting bias)	Low risk	

Risk of bias table.

<b>Methods</b>	Three-group, double-blinded randomized controlled trial
<b>Participants</b>	Patients <16 years old admitted to pediatric intensive units
<b>Interventions</b>	Central venous catheter: 1) impregnated with antibiotics, 2) impregnated with heparin, 3) standard catheter
<b>Outcomes</b>	Bloodstream infection

Study of Gilbert et. Al (2016).

<b>Bias</b>	<b>Authors' judgment</b>	<b>Support for judgment</b>
Random sequence generation (selection bias)	Low risk	Randomization sequences were computer generated by an independent statistician
Allocation concealment (selection bias)	Low risk	The clinician or research nurse opened a pressure-sealed, sequentially numbered, opaque envelope containing the catheter allocation. Children were randomly assigned (1:1:1) at the bedside, or in operating room immediately before central venous insertion to receive CVC impregnated with antibiotics, heparin, or a standard one.
Blinding of participants and personnel (performance bias)	Low risk	The clinician responsible for inserting the central venous catheters was not masked to allocation (because of the different color of strips for antibiotic and heparin CVCs), but because these catheters looked identical while in situ, allocation was concealed from patients, their parents
Blinding of outcome assessment (detection bias)	Low risk	Participant inclusion in analysis and occurrence of outcome events were established before release of the randomization sequence for analysis and for data monitoring committee
Incomplete outcome data (attrition bias)	Low	Outcome data from the 1485 randomly assigned and consented participants were all analyzed according to the intention to treat principle
Selective reporting (reporting bias)	Low risk	

Risk of bias table.

<b>Methods</b>	Unblinded, two-arm randomized controlled trial
<b>Participants</b>	Preterm babies requiring a PICC
<b>Interventions</b>	1. Antimicrobial impregnated (with rifampicin and miconazole) peripherally inserted central venous catheters (AM-PICC). 2. Standard PICC (S-PICC)
<b>Outcomes</b>	Bloodstream infection

**Appendix C:** On-going Studies. PREVAIL study: Preventing infection using Antimicrobial Impregnated Long lines. December 2014-August 2017

<b>Methods</b>	Single blind, randomized controlled trial.
<b>Participants</b>	All patients ages 21 years or less admitted to the pediatric intensive care unit or general pediatric unit at DeVos Children's Hospital.
<b>Interventions</b>	An antibiotic coated CVC and non-coated CVC.
<b>Outcomes</b>	<b>Primary:</b> Reduction in catheter-associated blood stream infections. <b>Secondary:</b> Bacterial pathogens associated with antibiotic coated CVC BSI and compare these pathogens with those normally associated with non-antibiotic coated CVC.

**Appendix D:** Unpublished Studies. The Use of Antibiotic-coated Venous Catheters in the Critically Ill Child: Reducing the Rate of Bloodstream Related Infections. 2009.