Antibiotic Use at Planned Central Line Removal in Reducing Neonatal Post-Catheter Removal Sepsis: A Systematic Review and Meta-analysis

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Abstract

**Background:** Post-catheter removal sepsis (PCRS) is a severe complication of indwelling central venous catheters (CVCs) in neonates, which is postulated to be secondary to the disruption of biofilms formed along catheter tips upon CVCs removal. It remains controversial whether antibiotic use upon CVCs removal will help to prevent this situation. We aimed to evaluate the protective effect of antibiotic administration at the time of CVCs removal in preventing PCRS in neonates.

**Methods:** The systematic review was performed based on a registered protocol (CRD42022359677). We searched through PubMed, EMBASE and Cochrane databases, as well as reference lists of review articles (September 2022) for studies comparing the use of antibiotics versus no use within 12 hours of CVCs removal. Selection of studies and data extraction were performed independently by two researchers. Risk of bias was assessed using the modified Newcastle-Ottawa Scale or Cochrane risk-of-bias tool according to the study design. Results of quantitative analyses were presented as mean differences (MD) or odds ratio (OR). Subgroup and univariate meta-regression analyses were performed to identify heterogeneity.

**Results:** The review included 470 central lines in the antibiotic group and 658 lines in the control group from five studies. Antibiotic use within 12 hours of CVCs removal did not significantly reduce the incidence of PCRS (OR=0.35, 95% CI: 0.08 to 1.53), but was associated with a lower incidence of post-catheter removal blood stream infection (OR=0.31, 95% CI: 0.11 to 0.86). Dosage of vancomycin and world region were major sources of interstudy heterogeneity.

**Conclusion:** Antibiotic administration in neonates upon CVCs removal does not significantly reduce the incidence of PCRS but offers less post-catheter removal blood stream infection. Whether this will be converted to better clinical outcomes lacks evidential support. Further randomized controlled studies with longer follow-up are needed.

**Introduction**

Central venous catheters (CVCs) are commonly used in the neonatal intensive care unit (NICU), contributing to better survival outcomes in critically ill newborn infants. Post-catheter removal sepsis (PCRS) is an important complication of CVCs, predominantly caused by late-onset central line-associated blood stream infection (CLABSI) which is defined as a primary blood stream infection developing within 48 hours after CVCs removal in the absence of other known infection sites. It is hypothesized that a biofilm forms along the inserted catheter, which is disrupted and washed into blood stream at the removal of CVCs, leading to bacteremia. CLABSI is correlated with increased morbidity and mortality, additional antibiotic use and prolonged hospitalization. Fortunately, implementation of central-line bundles and prophylactic systemic antibiotics use during catheterization may help to reduce the incidence of late-onset CLABSI. However, continuous antibiotic exposure during infancy is challenged by the selection of antibiotic-resistant organisms and gut microbiome dysbiosis, and thus prophylactic antibiotics use is not recommended. Hence, concurrent antibiotics given at the time of CVCs removal might be an alternative strategy. Inconsistent results have been reported in several interventional or observational studies, which underscores the need to perform a systematic review and meta-analysis to quantitatively evaluate whether antibiotics administration at the time of CVCs removal prevents late-onset sepsis in neonates.

**Materials And Methods**

We performed the systematic review based on a protocol with the registration number CRD42022359677 and complied with the Preferred Reporting terms for Systematic Review and Meta-Analysis (PRISMA) statement. Reporting items were detailed in the PRISMA checklist (Supplementary Material 1).

The purpose of this review was to evaluate whether antibiotics administration within 12 hours of planned CVCs removal can reduce the incidence of post-catheter removal sepsis in neonates.

**Literature search**

We searched through PubMed, EMBASE and Cochrane databases. The search strategy in PubMed was: (central AND (catheter OR line)) AND (removal OR remove OR removing) AND (infection OR sepsis OR bacteremia) AND (infant OR neonate OR neonatus OR neonatal OR newborn) AND (antibiotic OR prevention OR prevent OR preventing OR prophylaxis OR prophylactic). The search strategy was adapted for EMBASE and Cochrane databases. We also searched references of review articles for relevant studies. The last search update was September 2022.

**Selection of studies**

Studies were selected according to the PICOS (patients/participants, intervention, comparison, outcome, study type) approach. Inclusion criteria were:

Patients/participants: neonates aged ≤ 28 days admitted in NICU, undergoing planned removal of CVCs.

Intervention: antibiotics use within 12 hours of planned CVCs removal.

Comparison: no antibiotics use within 12 hours of planned CVCs removal.

Primary outcomes: PCRS which is defined based on a sepsis workup including two or more of the following: complete blood count with differential, C-reactive protein, blood/urine/cerebrospinal fluid culture, or antibiotics given for more than 48 hours within 72 hours of catheter removal, including both culture-positive and culture-negative sepsis.
Secondary outcomes: (1) late-onset blood stream infection which is defined as clinical or laboratory signs of infection plus a positive blood culture; (2) CLABSIs which is defined as clinical or laboratory signs of infection plus a positive blood culture developing within 48 hours after CVCs removal in the absence of other known infection sites; (3) neonatal mortality.

Studies: retrospective or prospective human studies.

Exclusion criteria included: (1) noncomparative studies; (2) prophylactic antibiotics use for the duration of the CVCs; (3) therapeutic antibiotics use for known or suspected catheter-related bloodstream infections; (4) insufficient data for quantitative analyses; (5) grey literature lacking details or peer review. We set no restriction on language, publication type or date. Study selection was conducted by two researchers (RYJ and ZYTH) independently, with disagreements resolved through discussion with a senior investigator (SYF).

Data extraction

We extracted the following data: (1) study information: publication (article title, authors, year, journal title), study design (patient inclusion and exclusion criteria, grouping, sample size of each) and bias control; (2) baseline characteristics: gestational age, sex, birth weight, races and country or region; (3) CVCs management: type, duration of insertion and indications for removal. (4) antibiotic use: type, dosage, frequency, start and end time. (5) outcomes: incidence of PCRS, late-onset blood stream infection and CLABSIs after catheter removal, neonatal mortality. Data extraction was conducted by two researchers (RYJ and ZYTH) independently, with disagreements resolved through discussion with a senior investigator (SYF).

Risk of bias assessment

Risk of bias for randomized clinical trial (RCT) studies was assessed using the Cochrane risk-of-bias tool based on seven domains: sequence generation, allocation concealment, binding of participants and personnel, binding of outcome assessment, incomplete outcome data, selective reporting and other bias (Supplementary Material 2). For observational studies, risk of bias was assessed using a modified Newcastle-Ottawa Scale (NOS) with the intention of best evaluating our phenomenon of interest (Supplementary Material 2). Assessment was performed based on three domains: selection, comparability and exposure, with a maximum score of 10. A total score of 5 or less, 6–7 and 8 or more was considered low, moderate and high quality, respectively. Risk of bias assessment was conducted by two researchers (RYJ and ZYTH) independently, with disagreements resolved through discussion with a senior investigator (SYF).

Statistical analysis

Basic characteristics of enrolled studies were firstly tabulated. Variables reported by three or more studies were evaluated through quantitative analyses. For continuous data, the mean differences [MD] with 95% confidence intervals [CI] were calculated as the effect measurements. Data reported as the median with interquartile range were converted into the mean with standard deviation through a recommended formula. For binary data, the odds ratio (OR) and 95% CI were calculated as the effect measurements. Heterogeneity across studies were evaluated by Cochrane chi-square ($\chi^2$) and quantified with the $I^2$ statistics. $I^2$ values of 25, 50 and 75% represented low, moderate and high heterogeneity, respectively. For valuables with $I^2$ values $\leq 25\%$, the fixed-effect model will be used, otherwise, we used the random-effect model for data synthesis. We performed the following subgroup analyses to explore sources of heterogeneity: duration of catheter insertion, world region, type of study design and type, dosage and frequency of antibiotics use. Univariate meta-regression analyses were further performed to identify heterogeneity sources across studies. Multivariate meta-regression analyses were not performed due to limited number of studies. Publication bias was not evaluated as no more than ten studies were enrolled. All analyses were performed using Review Manager 5.3.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The electronic search yielded a total of 335 potentially relevant studies (Fig. 1). All records were imported into the Endnote with 37 duplicates removed. After reading the titles and abstracts, 288 irrelevant studies were further eliminated. Among the remaining 10 studies, four studies regarding routine prophylactic or therapeutic antibiotics use and one non-comparative study were excluded. Therefore, a total of five studies, including one RCT and four retrospective studies were ultimately enrolled in the quantitative analyses (Table 1).
# Table 1
Basic characteristics of included studies.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Country/Region</th>
<th>Antibiotic group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of CVCs</td>
<td>Male (%)</td>
<td>Gestational age (weeks)</td>
</tr>
<tr>
<td>Reynolds 2015</td>
<td>Retrospective</td>
<td>USA</td>
<td>48</td>
</tr>
<tr>
<td>Hemels 2011</td>
<td>RCT</td>
<td>Netherland</td>
<td>44</td>
</tr>
<tr>
<td>Teibel 2020</td>
<td>Retrospective</td>
<td>USA</td>
<td>107</td>
</tr>
<tr>
<td>Tran 2021</td>
<td>Retrospective</td>
<td>USA</td>
<td>14</td>
</tr>
<tr>
<td>Yan 2021</td>
<td>Retrospective</td>
<td>Taiwan</td>
<td>257</td>
</tr>
</tbody>
</table>

RCT = randomized clinical trial; CVCs = central venous catheters; hrs = hours; NA = not mentioned.

All enrolled studies were conducted in the health setting of NICU. Altogether, 470 central lines in the antibiotic group and 658 central lines in the control group were included. The commonly used antibiotic regimen was a single dose of vancomycin (10 or 15 mg/kg) given at 2 hours prior to CVCs removal. Other regimens included one dose of vancomycin plus cefazolin or two doses of cefazolin. There were no statistically significant differences between two groups in basic demographic characteristics including gestational age (Mean difference (MD)= -0.75 weeks, 95% confidence intervals (CI): -1.72 to 0.22, P = 0.13), male proportion (OR = 1.42, 95% CI: 0.91 to 2.22, P = 0.12) and birth weight (MD=-63.8 g, 95% CI: -232.6 to 105.0, P = 0.46). Also, the length of CVCs indwelling is comparable between two groups (MD = 1.61 days, 95% CI: -0.78 to 4.01, P = 0.19). (Table 2)

# Table 2
Comparison of clinical characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>#Antibiotic vs Control</th>
<th>I^2 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age MD (95% CI), weeks</td>
<td>-0.75 [ -1.72, 0.22]</td>
<td>36</td>
<td>0.13</td>
</tr>
<tr>
<td>Male proportion OR (95% CI)</td>
<td>1.42 [0.91, 2.22]</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Birth weight MD (95% CI), g</td>
<td>-63.8 [-232.6, 105.0]</td>
<td>32</td>
<td>0.46</td>
</tr>
<tr>
<td>CVCs indwelling time MD (95% CI), days</td>
<td>1.61 [0.78, 4.01]</td>
<td>22</td>
<td>0.19</td>
</tr>
</tbody>
</table>

MD = mean differences; OR = odds ratio; CI = confidence interval; # A positive MD or OR favors antibiotic group;

Incidence of PCRS

In total, 15 of 470 (3.2%) and 50 of 658 (7.6%) CVCs removal episodes had PCRS in the antibiotic group and control group, respectively. The random-effects meta-analysis demonstrated that antibiotics given within 12 hours of CVCs removal non-significantly reduced the incidence of PCRS (OR = 0.35, 95% CI: 0.08
to 1.53, P = 0.16, I² = 63%) (Fig. 2A).

Results of subgroup analyses and univariate meta-regression were detailed in Table 3. No significant subgroup difference was tested. Regarding antibiotic regimens, the vancomycin subgroup (OR = 0.63, 95% CI: 0.02 to 24.37) and the cefazolin subgroup (OR = 0.07, 95% CI: 0.00 to 1.22) showed non-significant protective effect, while the combination subgroup suggested a near equal incidence of PCRS (OR = 1.02, 95% CI: 0.42 to 2.47) with and without antibiotics use. In addition, the single-dose subgroup (OR = 0.56, 95% CI: 0.15 to 2.15) and two-doses (OR = 0.07, 95% CI: 0.00 to 1.22) subgroups both demonstrated non-significant protective effect. Similar results were reached in subgroup analyses according to types of study design and length of CVCs indwelling. In the Asian region and low-dose (10 mg/kg) vancomycin subgroups, a single-dose of vancomycin (10 mg/kg) given at 2 hours prior to CVCs removal significantly reduced the incidence of PCRS (OR = 0.12, 95% CI: 0.02 to 0.92), but such significant protective effect was not observed in the Western region subgroup (OR = 0.49, 95% CI: 0.10 to 2.47), and the high-dose (15 mg/kg) vancomycin subgroup (OR = 0.74, 95% CI: 0.02 to 39.78).

### Table 3

<table>
<thead>
<tr>
<th>Groups</th>
<th>Subgroups</th>
<th>Studies (n)</th>
<th>OR [95% CI]</th>
<th>I² (%)</th>
<th>Heterogeneity across subgroups (%)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of antibiotics</td>
<td>Vancomycin</td>
<td>2</td>
<td>0.63 [0.02, 24.37]</td>
<td>74</td>
<td>36</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Cefazolin</td>
<td>1</td>
<td>1.02 [0.42, 2.47]</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Vancomycin plus cefazolin</td>
<td>1</td>
<td>0.07 [0.00, 1.22]</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Frequency of antibiotic administration</td>
<td>One dose</td>
<td>4</td>
<td>0.56 [0.15, 2.15]</td>
<td>52</td>
<td>42</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Two doses</td>
<td>1</td>
<td>0.07 [0.00, 1.22]</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Dosage of vancomycin</td>
<td>Low dose (10mg/kg)</td>
<td>1</td>
<td>0.12 [0.02, 0.92]</td>
<td>-</td>
<td>0</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>High dose (15mg/kg)</td>
<td>2</td>
<td>0.74 [0.02, 29.78]</td>
<td>67</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Length of catheter indwelling</td>
<td>Long length (&gt; 20 days)</td>
<td>2</td>
<td>0.69 [0.02, 21.80]</td>
<td>71</td>
<td>0</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Short length (&lt; 20 days)</td>
<td>2</td>
<td>0.36 [0.02, 5.50]</td>
<td>71</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Study design</td>
<td>Observational</td>
<td>4</td>
<td>0.56 [0.15, 2.15]</td>
<td>52</td>
<td>42</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>1</td>
<td>0.07 [0.00, 1.22]</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>World Region</td>
<td>Asian</td>
<td>1</td>
<td>0.12 [0.02, 0.92]</td>
<td>-</td>
<td>11</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>Western</td>
<td>4</td>
<td>0.49 [0.10, 2.47]</td>
<td>49</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

PCRS = post-catheter removal sepsis; OR = odds ratio; CI = confidence interval; RCT = randomized clinical trial # A positive OR favors antibiotic group; & Heterogeneity across subgroups; * P value of univariate meta-regression analyses which test for subgroup differences.

**Incidence of post-catheter removal blood stream infection**

In total, 4 of 408 (0.1%) and 15 of 481 (3.1%) CVCs removal episodes resulted in post-catheter removal blood stream infection, as was proven by blood culture, in the antibiotic group and control group, respectively. The fixed-effects meta-analysis demonstrated that antibiotics given within 12 hours of CVCs removal significantly reduced the incidence of post-catheter removal blood stream infection (OR = 0.31, 95% CI: 0.11 to 0.86, P = 0.03, I² = 0%) (Fig. 2B). Subgroup analysis was not performed due to limited number of relevant studies.

**Risk of bias assessment**

Risk of bias of retrospective studies were assessed by a modified NOS (Supplementary table 2). The total score of the four studies22–25 was 7, 8, 9, 7, respectively, indicating a moderate to low risk of bias. The risk of bias of the RCT21 was assessed by using the Cochrane risk-of-bias tool, which was detailed in supplementary Material 3. This study is an open RCT with no detailed randomization and allocation procedures reported. Also, the actual enrolled number of patients was fewer than the planned value. Therefore, we considered this RCT to be at high risk of bias.

**Publication bias**

Publication bias was not evaluated because of a lack of test power when ten or fewer studies are available15.

**Discussion**

Conflicting evidence surrounds the use of antibiotic at the time of CVCs removal to prevent late-onset sepsis. In this meta-analysis, we quantitatively evaluated the preventive effect of antibiotic administration within 12 hours of planned CVCs removal on late-onset sepsis based on five studies with a total of 1128 central lines. Results demonstrated that antibiotic use upon CVCs removal did not significantly alter PCRS rates (OR = 0.35, 95% CI: 0.08 to 1.53), but was correlated with a lower incidence of post-catheter removal blood stream infection (OR = 0.31, 95% CI: 0.11 to 0.86).

Our results suggested a non-significant protective effect of antibiotic use at the time of CVCs removal in reducing rates of PCRS, with a pooled rate of 3.2%. Similar results were also found in most subgroup analyses. However, the evidence is still inadequate to examine this clinical issue as prospective, high-quality studies regarding this issue are largely insufficient. More attention has been devoted to prophylactic antibiotic use where antibiotics were given during the
whole period of CVCs insertion or within 72 hours prior to CVCs removal. A large retrospective study demonstrated a protective effect (OR = 0.26, P < 0.001) of prophylactic antibiotics in preventing culture-negative sepsis. In the intervention group, PCRS was found in 17 of the 322 (5.3%) central lines that were free from infection before removal\(^26\). Inconsistently in an earlier RCT, infants were randomly assigned to receive amoxicillin prophylaxis or no antibiotic prior to CVCs removal\(^18\). PCRS was found in 3 of 75 (4.0%) lines and 8 of 73 (11.0%) lines in two groups (P = 0.107), indicating non-significant benefit brought by routine antibiotic prophylaxis. A Cochrane meta-analysis enrolling three RCTs further affirmed the effect of prophylactic antibiotics in reducing rates of PCRS (RR = 0.40, 95% CI: 0.20 to 0.78), with a pooled PCRS rate of 8.8%\(^6\). Though the absolute incidence of PCRS was comparable between antibiotic prophylaxis and antibiotics on CVCs removal, the superiority of one or another could not be determined due to a lack of comparative studies. However, there is no doubt that a single or two doses of antibiotics on CVCs removal could help to avoid antimicrobial resistance and microbiome dysbiosis brought by long-term antibiotic prophylaxis in neonates\(^7,27\).

Although the antibiotic use upon CVCs removal did not exhibit a significant protective effect against PCRS, it was correlated a lower risk of post-catheter removal blood stream infection (culture-positive sepsis), as suggested by our analysis. The specific mechanisms underlying this is unclear. It might be explained that the infusion of antibiotic disrupts the catheter biofilm formed along the catheter tip, decreasing the load of bacteria showered into blood stream upon catheter removal and therefore preventing culture-positive sepsis\(^26\). Instead, a culture-positive sepsis could be caused by the inflammatory response to unculturable bacteremia. Though correlated with less blood stream infection, whether antibiotic use on CVCs removal will contribute to better clinical outcomes was not identified in our systematic review due to insufficient data reported. A recent large-scale meta-analysis indicated that despite similar mortality rate of sepsis shared by culture-positive and culture negative sepsis, patients with culture-positive sepsis had significantly longer hospitalization and mechanical ventilation duration\(^28\). A retrospective study based on the pediatric setting reported a significantly lower mortality rate and organ-dysfunction in the culture-negative group\(^29\). We thus speculate that antibiotic use on CVCs removal may bring clinical benefits by reducing the rate of culture-positive sepsis, which should be further examined with more relevant data reported.

To the best of our knowledge, this meta-analysis provides the most updated assessments of current evidence regarding the use of antibiotics at the time of CVCs removal in reducing late-onset sepsis. Despite this, several limitations exist. Enrolled studies are mostly retrospective and non-randomized, introducing potential bias to the analyses. Several critical clinical outcomes such as mortality rate, subsequent antibiotic and other treatments for PCRS, length of stay as well as long-term outcomes were not evaluated due to insufficient data reported. Also, there is a moderate to high interstudy heterogeneity for the primary outcome, even though sources of heterogeneity were partly identified by subgroup analyses. Therefore, with continuous publication of articles, the update of the meta-analysis is still warranted to improve the above deficiencies.

**Conclusions**

In conclusion, results of our review suggests that antibiotic administration in neonates within 12 hours of planned CVCs removal does not significantly reduce the incidence of PCRS but offers less post-catheter removal blood stream infection. However, whether this will be converted to clinical benefits lacks evidential support. These findings should be interpreted with caution due to limitations stated above. The update of meta-analysis is warranted with more randomized designed studies having a longer follow-up performed.

**Abbreviations**

PCRS=post-catheter removal sepsis; central venous catheters=CVCs; CLABSI=central line-associated blood stream infection; NICU=neonatal intensive care unit (NICU); RCT=randomized clinical trial; MD=mean differences; OR=odds ratio; CI=confidence intervals.

**Declarations**

**Ethics approval and consent to participate:** This study complied with the Declaration of Helsinki and the ethics approval was waived by the Ethics Committee of PUMCH.

**Consent for publication:** No applicable.

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**Financial disclosures:** None.

**Authors’ contributions:** Ruoyu Ji: initiation of study, study design, formal analysis, manuscript drafting and revision. Zhangyuting He: study design, study selection and data extraction, formal analysis, manuscript drafting. Jiawei Zhou: study selection and data extraction, formal analysis. Shiyuan Fang: study selection and data extraction, manuscript revision.

**Data availability statement:** The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

**Conflict of interest disclosures:** All authors have nothing to declare.
References


Figures

Figure 1
Study flow chart.
Figure 2

(A) Forrest plot of incidence of post-catheter removal sepsis (PCRS) for antibiotic use versus control. (B) Forrest plot of incidence of post-catheter removal bloodstream infection for antibiotic use versus control.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary1PRISMAchecklist.doc
- Supplementary2Riskofbiasassessment.docx
- Supplementary3Riskofbiasgraph.pdf