Evaluating the Incidence of Sepsis Post–Central Catheter Removal When Using Prophylactic Vancomycin in the Neonatal Intensive Care Unit

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OBJECTIVE With no consensus, the practice of using prophylactic antibiotics prior to central venous catheter (CVC) removal in NICU patients remains controversial. The objective of this study was to compare the incidence of sepsis post–CVC removal in those who received a dose of vancomycin prophylactically with those who did not.

METHODS This single-center, retrospective chart review included NICU patients who had CVCs removed. Patients were excluded if they had a confirmed or suspected infection at the time of CVC removal or if the indwelling CVC was removed prior to 30 days from insertion. Primary outcome was the occurrence of a sepsis evaluation within 72 hours from CVC removal. Secondary outcomes included the development of acute kidney injury, source and identification of positive cultures, time to onset of suspected or confirmed sepsis, and the appropriate administration of intravenous vancomycin.

RESULTS Eighty-two CVC removals received prophylactic vancomycin (P-VAN), and 22 CVCs did not receive prophylactic vancomycin (NP-VAN) prior to CVC removal. There were no significant differences in patient demographics between groups and median duration of indwelling CVC. Two clinical sepsis evaluations occurred in the P-VAN group compared with none in the NP-VAN group. Of all the P-VAN CVC removals, 45 (55%) received vancomycin appropriately. There were no statistical differences in all evaluated secondary outcomes.

CONCLUSIONS Vancomycin administered prophylactically prior to CVC removal did not reduce the number of subsequent clinical sepsis evaluations or infections in NICU patients.

ABBREVIATIONS CDC, Centers for Disease Control and Prevention; CLABSI, central line–associated bloodstream infection; CoNS, coagulase-negative staphylococci; CVC, central venous catheter; NICU, neonatal intensive care unit; NP-VAN, no prophylactic vancomycin; PICC, peripherally inserted central catheter; P-VAN, prophylactic vancomycin

KEYWORDS antibiotics; central catheter; neonatal intensive care unit; neonate; prophylactic; sepsis; vancomycin

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Introduction

Patients in the NICU often have central venous catheters (CVCs), such as peripherally inserted central catheters (PICCs), placed for long-term intravenous therapy. Such CVCs can lead to bloodstream infection, thrombus, infusion extravasation, phlebitis, and distal edema.¹ The incidence of neonatal central line–associated bloodstream infections (CLABSIs) is 5.3 per 1000 catheter-days in PICCs, with risk factors including low birth weight, prematurity, increased length of NICU stay prior to CVC insertion, and prolonged duration of an indwelling CVC.^{1–3} Despite improvements in CVC care, patients remain at risk for a bloodstream infection while the catheter remains in place and even upon removal. The peak occurrence of infections following

CVC removal occurs within 72 hours, often involving coagulase-negative staphylococci (CoNS).⁴

The majority (80%) of culture-positive CLABSIs are due to Gram-positive organisms, with CoNS being the most common.^{5–7} Thus, prophylactic vancomycin (P-VAN) is sometimes given to neonates prior to CVC removal to reduce the risk of CoNS infection. However, the benefits of this practice are not clear as other organisms associated with CLABSIs include *Staphylococcus aureus*, *Enterobacter*, *Klebsiella*, and *Escherichia coli*. The presence of these bacteria in the bloodstream is a potential source of late-onset neonatal sepsis and is associated with high rates of morbidity and mortality and increased length of stay, as well as increased health care costs.^{2,3}

The use of antibiotics administered prophylactically to reduce the rate of clinical sepsis after CVC removal

Table 1. Baseline Patient Demographics (n = 104)

	P-VAN (n = 82)	NP-VAN (n = 22)	p value
Birth weight, median (IQR), g	960 (705–1770)	1700 (823–2554)	0.17
Birth weight class, n (%)			
Extremely low birth weight (<1000 g)	43 (52)	7 (32)	0.1
Very low birth weight (1000–1499 g)	8 (10)	3 (14)	0.7
Low birth weight (1500–2499 g)	19 (23)	6 (27)	0.78
Normal birth weight (≥2500 g)	12 (15)	6 (27)	0.2
Gestational age, median (IQR), wk	28 (25–34)	31 (26–36)	0.17
Sex, male, n (%)	46 (56)	12 (55)	1.0
Hispanic, n (%)	26 (32)	5 (23)	0.27
Concurrent antibiotics, n (%)*	10 (12)	4 (18)	0.49
Central catheter type, n (%)			
PICC	76 (93)	18 (82)	0.21
Broviac	2 (2)	1 (4)	0.51
Other	4 (5)	3 (14)	0.16
Patients with >1 central catheter†, n (%)	14 (17)	3 (14)	0.72
Postnatal age†, median (IQR), days	47 (38–63)	44 (37–85)	0.98
Duration of indwelling central catheter, median (IQR), days	36 (32–45)	37 (35–47)	0.49
Indication for central catheter removal: no longer needed, n (%)	48 (59)	15 (68)	0.11

NP-VAN, no prophylactic vancomycin; PICC, peripherally inserted central catheter; P-VAN, prophylactic vancomycin

* Within 24 hr of removal.

† At time of central catheter removal.

in NICU patients remains controversial.^{4,5,8-10} A 2018 Cochrane Review¹¹ concluded that there was inadequate evidence for giving cefazolin at the time of removal of a central line to prevent complications in newborn infants. While antimicrobial prophylaxis may decrease the incidence of subsequent infections, it also carries the risk of selecting for antimicrobial-resistant organisms, abnormal gastrointestinal biome, and increased health care costs.^{2,3,12-15} Thus, we compared the incidence of clinical sepsis evaluations and documented infections in NICU patients following removal of CVCs that had been indwelling for at least 30 days to evaluate the benefit of administering vancomycin prophylactically prior to CVC removal at our institution.

Materials and Methods

A single-center, retrospective cohort study was conducted at the Inova Children's Hospital, which has a 108-bed Level IV tertiary referral NICU. Patients were identified via the Medical Data Systems (Fairfax Neonatal Associates, Falls Church, VA), with further clinical points of interest obtained via manual chart review of the electronic medical record. Patients were included in the study if they were admitted to the NICU and had

at least one central venous line, including both PICC and CVC, removed between December 1, 2012, and October 31, 2019. Patients were excluded if they had a confirmed or suspected infection at the time of CVC removal or if the indwelling CVC was removed within 30 days of insertion.

Baseline patient demographics included birth weight, birth weight class, gestational age, sex, ethnicity, concurrent use of antibiotics within 24 hours of CVC removal, type of CVC, number of CVCs at time of CVC removal, postnatal age at time of removal, duration of indwelling CVC, and indication for CVC removal.

The primary outcome was the occurrence of sepsis evaluations within 72 hours following CVC removal. A sepsis evaluation was defined as the initiation of antibiotics within 72 hours of CVC removal and the collection of at least one of the following: complete blood count and differential, C-reactive protein, or a specimen culture (blood, urine, tracheal aspirate, and/or cerebrospinal fluid). Secondary outcomes included acute kidney injury within 48 hours after vancomycin administration, source and identification of positive cultures, time to onset of suspected or confirmed sepsis, and the appropriate administration of prophylactic vancomycin

Table 2. Baseline Patient Demographics in Matched Cohort (n = 30)

Demographics	P-VAN (n = 15)	NP-VAN (n = 15)	p value
Birth weight, median (IQR), g	1030 (635–2535)	1030 (725–2523)	0.98
Birth weight class, n (%)			
Extremely low birth weight (<1000 g)	7 (47)	7 (47)	1.0
Very low birth weight (1000–1499 g)	1 (7)	1 (7)	1.0
Low birth weight (1500–2499 g)	3 (20)	3 (20)	1.0
Normal birth weight (≥2500 g)	4 (27)	4 (27)	1.0
Gestational age, median (IQR), wk	31 (25–36)	31 (26–36)	0.84
Sex, male, n (%)	9 (60)	9 (60)	1.0
Hispanic, n (%)	3 (20)	3 (20)	1.0
Concurrent antibiotics*, n (%)	1 (7)	3 (20)	0.67
Central catheter type, n (%)			
PICC	15 (100)	13 (87)	0.48
Broviac	0	0	—
Other	0	2 (13)	0.48
Patients with >1 central catheter†, n (%)	4 (27)	3 (20)	1.0
Postnatal age†, median (IQR), days	53 (40–64)	41 (37–56)	0.42
Duration of indwelling central catheter, median (IQR), days	39 (33–46)	36 (34–43)	0.63
Indication for central catheter removal: no longer needed, median (IQR)	8 (53)	10 (67)	0.71

NP-VAN, no prophylactic vancomycin; PICC, peripherally inserted central catheter; P-VAN, prophylactic vancomycin

* Within 24 hr of removal.

† At time of central catheter removal.

followed by CVC removal within 90 minutes from the end of infusion. Acute kidney injury was defined as an increase in serum creatinine of more than 0.3 mg/dL within 48 hours and urine output less than 0.5 mL/kg/hr for 6 to 12 hours.¹⁶ Appropriate P-VAN systemic administration was defined as an intravenous dose of 15 mg/kg followed by CVC removal within 90 minutes from the end of infusion to removal. Our institution infuses vancomycin over the course of 60 minutes via Medfusion syringe pumps.

We compared the outcomes of interest in patients receiving P-VAN and non-prophylactic vancomycin (NP-VAN). Continuous variables were reported as the median and IQR and were compared using the Wilcoxon rank-sum test if they did not meet the normality assumption. For categorical variables, a Chi-squared test or the Fisher's exact test were used, as appropriate. All statistical tests were reported using 2-sided α , and statistical significance was determined by a p value of <0.05. Statistical analysis was performed using SPSS Statistics Base software, version 22.0 (IBM, Armonk, NY).

Results

A total of 637 CVCs were identified. We excluded 47

CVCs in patients who had a confirmed or suspected infection at the time of CVC removal; another 486 CVCs were excluded in patients who had an indwelling CVC duration of less than 30 days. Of the 104 qualifying CVCs, 82 of the patients received P-VAN and 22 did not (NP-VAN). In terms of unique patients, there were 75 in the P-VAN group and 22 in the NP-VAN group.

Baseline characteristics are shown in Table 1. Median gestational age, median birth weight, sex, and ethnicity were not statistically different between the P-VAN and NP-VAN groups. The median duration of the indwelling CVC and postnatal age at the time of catheter removal were not different for the 2 groups. Most of the CVCs within each group were PICCs (Table 1). Alternate types of CVCs included broviac, internal jugular, external jugular, and femoral catheters in the P-VAN vs NP-VAN groups. There was no difference in the frequency of PICCs or alternate CVCs between the P-VAN and NP-VAN groups. At the time of CVC removal, 14 of the P-VAN patients (17%) had at least 1 CVC, compared with 3 of the NP-VAN patients (14%) ($p = 0.72$).

Prophylactic vancomycin was administered appropriately in 45 patients (55%). Inappropriate administration, defined as an intravenous dose not equal to 15

Table 3. Clinical Sepsis Evaluations

	Patient 1	Patient 2	P-VAN (n = 82)
Birth weight, g	670	1040	960 (705–1770)*
Gestational age, wk	31	26	28 (25–34)*
Total no. of central catheters during hospitalization	4	3	2 (1–3)*
>1 central catheter†	No	No	14 (17)†
Concurrent antibiotics‡	No	No	10 (12)†
Postnatal age§, days	63	59	47 (38–63)*
Duration of indwelling central catheter, days	36	34	36 (32–45)*
Time between vancomycin infusion and central catheter removal, min	113	133	—
Indication for central catheter removal	Malposition	Not needed	—
Interval between central catheter removal and clinical sepsis evaluation, hr	52	64	—

P-VAN, prophylactic vancomycin

* Median (IQR).

† n (%).

‡ Within 24 hr of removal.

§ At time of central catheter removal.

mg/kg or catheter removal beyond 90 minutes from end of vancomycin infusion, occurred in 37 cases. Of the 82 CVC removal events in which vancomycin was administered, 77 (94%) received the recommended dose, and 47 (57%) received vancomycin within the recommended time duration relative to CVC removal. More specifically, 18 (22%) of CVC removals occurred within 30 minutes of the end of vancomycin infusion.

In further analysis of the clinical sepsis evaluations, a 1:1 matched cohort based on birth weight class, gestational age, sex, and ethnicity was performed in order to limit the effect of potential confounding variables (Table 2). Of the 104 CVCs analyzed, 30 CVC removals were included in the matched cohort analysis. The median gestational age, median birth weight, median duration of indwelling CVC, and postnatal age at the time of CVC removal were not significantly different for the P-VAN and NP-VAN groups. Two clinical sepsis evaluations, in 2 unique patients, occurred in the P-VAN group compared with no clinical sepsis evaluations in the NP-VAN group ($p = 1.0$). The average time to onset of clinical sepsis evaluation was 59.5 ± 10.6 hours because both types of patients had negative cultures. Acute kidney injury was not observed following vancomycin administration in any patient. Table 3 provides a comparison of the patients with clinical sepsis to those in the P-VAN group.

Discussion

We compared the outcomes of neonates who re-

ceived vancomycin prophylactically to those who did not prior to CVC removal, inclusive of all CVCs and not just PICCs, in a contemporary setting. We did not observe a reduction in clinical sepsis evaluations with P-VAN administration prior to CVC removal. Less than 2% ($n = 2$) of the patients had clinical sepsis evaluations, and both patients received vancomycin prophylactically prior to CVC removal. The first patient was a 670-g male with a gestational age of 31 weeks. His CVC was indwelling for 36 days and was removed because of malpositioning. His postnatal age at CVC removal was 63 days. At the time of CVC removal, he had not received additional antibiotics within 24 hours. The second patient was a 1040-g male with a gestational age of 26 weeks. His CVC was indwelling for 34 days and was removed because the patient no longer needed CVC access. His postnatal age at CVC removal was 59 days. At the time of CVC removal, he had not received additional antibiotics within 24 hours.

In contrast, older studies^{4,8,9} have found a reduction in the incidence of sepsis with prophylactic antimicrobial administrations prior to CVC removal. In particular, Reynolds et al⁹ found a sixfold reduction in sepsis events in patients who received antibiotics at the time of CVC removal compared with those who did not receive prophylactic antibiotics ($p = 0.03$). However, the 2 cohorts differed in terms of gestational age, birth weight, and duration of the indwelling CVC prior to removal. Furthermore, 44% of the patients who received P-VAN prior to CVC removal had completed a course of gentamicin, ce-

fortaxime, or vancomycin within 12 hours of CVC removal; thus, the prophylactic antimicrobial agent could have actually been maintaining a steady-state therapeutic serum concentration.

Our findings were similar to those of a recent study⁵ comparing 137 neonates who received vancomycin prophylactically to 64 neonates who did not receive prophylactic vancomycin prior to CVC removal. Bhargava et al⁵ did not find a significant reduction in the rate of clinical sepsis evaluations ($p = 0.786$) after the administration of prophylactic vancomycin prior to PICC removal. Our study differs from that of Bhargava et al because we included patients with an indwelling CVC duration of at least 30 days, with the thought that this longer duration further increased the risk of an infection and therefore could better distinguish the potential benefits of P-VAN.

We also observed that when P-VAN was given, the dosing amount as well as the administration time relative to CVC removal varied. About 22% of CVC removals occurred with insufficient time for the vancomycin to reach a peak concentration prior to the CVC removal, thereby decreasing the potential therapeutic benefit. Such inconsistencies may have occurred because there was no codified guideline at our institution regarding P-VAN administration prior to CVC removal.

There were a number of limitations potentially affecting the results of this study. As a single-center study with a relatively small sample size, these results carry limited generalizability to other institutions and patient populations. Some of the CVCs removed in the NP-VAN group were the result of accidental dislodgement, with subsequent removal earlier than anticipated. Additionally, the retrospective design of this study carries the risk of information and selection bias. Finally, there were a number of non-pharmacologic infection control changes made to the protocols for CVC insertion and care that occurred between 2012 and 2019 at our institution. These non-pharmacologic changes included, but were not limited to, using a biopatch for infants greater than 2 months old, use of curocaps with IV hubs, expanded use of chlorhexidine gluconate as a skin preparation for skin punctures, and use of hats and masks for CVC tubing change. Such protocols were meant to minimize the risk of CVC infections and may have largely contributed to the significant reduction of CLABSIs at our facility, regardless of prophylactic antibiotic use.

Prior to any antibiotic prophylaxis use, in 2012, our NICU CLABSI rate was 0.4 per 1000 CVC days, when using the CDC's CLABSI definition. Using the same definition, our facility NICU rate consistently remained between 0.11 and 0.88 per 1000 CVC days between 2012 and 2019 even when vancomycin was used prior to CVC removal. The results of our study were brought forth to the NICU Infectious Disease Prevention Committee for review, and the final decision was made to discontinue P-VAN prior to CVC removals.

Conclusion

We did not observe a reduction in clinical sepsis evaluations or documented infections following a single 15 mg/kg dose of vancomycin administered prophylactically prior to CVC removal. The routine use of prophylactic vancomycin therapy prior to CVC removal in neonates did not reduce subsequent CLABSIs compared with use of non-pharmacologic interventions alone.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution. Given the retrospective nature of the study, informed consent was not required.

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