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No Survival Benefit with Empirical Vancomycin Therapy for Coagulase-negative Staphylococcal Bloodstream Infections in Infants

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Abstract

Background—Coagulase-negative *Staphylococcus* (CoNS) is the most common cause of bloodstream infections (BSI) in hospitalized infants. CoNS BSI is most reliably treated with vancomycin; however, concerns about side effects and promoting resistance often delay empirical vancomycin therapy until culture results become available.

Methods—All infants with CoNS BSI discharged from 348 neonatal intensive care units managed by the Pediatrix Medical Group from 1997–2012 were identified. Empirical vancomycin therapy was defined as vancomycin exposure on the day of the first positive blood culture. Delayed vancomycin therapy was defined as vancomycin exposure 1–3 days after the first positive blood culture. We used multivariable logistic regression with random effects for site to evaluate the association between the use of empirical vancomycin therapy vs. delayed vancomycin therapy and 30-day mortality, controlling for gestational age, small-for-gestational age status, postnatal age on the day of the first positive culture, oxygen requirement, ventilator support, and inotropic support on the day the first positive culture was obtained.

Results—Of the 4364 infants with CoNS BSI, 2848 (65%) were treated with empirical vancomycin. The median postnatal age at first positive culture was 14 days (interquartile range: 9, 21). Unadjusted 30-day mortality was similar for infants treated with empirical vancomycin and infants treated with delayed vancomycin therapy (166/2848 [6%] vs. 69/1516 [4%]; p=0.08). There was no significant difference in 30-day mortality on multivariable analysis (odds ratio: 1.14 [0.84, 1.56]). The median duration of bacteremia was 1 day longer for infants with delayed vancomycin therapy (4 days [interquartile range 2, 6] vs. 3 days [2, 5]; p<0.0001).

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Conclusions—The median duration of bacteremia was 1 day longer in infants with CoNS BSI who received delayed vancomycin therapy. Despite this finding, empirical vancomycin therapy for CoNS BSI was not associated with improved mortality.

Keywords

late-onset sepsis; NICU

Coagulase-negative staphylococci (CoNS) are the most common cause of late-onset bloodstream infections (BSI) in hospitalized infants, accounting for 48% of infections.[1–3] CoNS BSI has been shown to increase the incidence of intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, cerebral palsy, and neurodevelopmental impairment.[4–6] These long-term complications are associated with increased hospital length of stay and increased costs.[7,8]

To avoid these complications, infants with suspected infection often receive empirical antibiotic therapy while awaiting culture results. Agents used for empirical antibiotic therapy vary by institution, postnatal age, and clinical symptoms but frequently include vancomycin due to the high risk of CoNS infection.[9–11]

Vancomycin is used for treatment of infections caused by CoNS and other gram-positive organisms, which are frequently resistant to beta-lactam antibiotics.[10] However, use of empirical vancomycin is associated with increased incidence of infections caused by resistant organisms such as vancomycin-resistant *Enterococcus* and highly resistant enteric gram-negative bacteria.[12,13] Moreover, the impact of empirical vancomycin therapy on the outcome of infants with CoNS infections is unknown.

In the current study, we used a large, nationally representative database to evaluate whether empirical vancomycin therapy improves outcomes for infants with CoNS BSI.

METHODS

We identified all infants diagnosed with CoNS BSI in the first 120 days of life discharged from 348 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group between 1997 and 2012. Data were obtained from an administrative database that prospectively captures information from notes generated by clinicians on all infants cared for by the Pediatrix Medical Group. Data are extracted, de-identified, and stored in the Pediatrix Clinical Data Warehouse.[14] Information stored for infants on a daily basis includes maternal history, demographics, medications, laboratory results, microbiology results, diagnoses, and procedures. We excluded infants with major congenital anomalies.

Definitions

We included the first episode of CoNS bacteremia in each infant who met the following criteria: 2 positive blood cultures within 4 days, 3 positive cultures within 7 days, or 4 within 10 days.[15] All positive CoNS cultures obtained within 21 days of each other were considered as single infectious episodes. Duration of bacteremia was defined as the time from the first to the last positive CoNS culture within a single episode. Inotropic support

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was defined as exposure to dopamine, dobutamine, epinephrine, norepinephrine, or milrinone on the day the first positive culture was obtained. Mechanical ventilation was defined as exposure to any invasive mechanical ventilation on the day the first positive culture was obtained. Oxygen supplementation was defined as the administration of any fraction of inspired oxygen >21% on the day the first positive culture was obtained. Small-for-gestational-age status was defined as previously described.[16] Vancomycin exposure on the day the first positive CoNS culture was obtained was considered empirical therapy. Delayed vancomycin therapy was defined as vancomycin exposure 1–3 days after the first positive blood culture. Infants who were never given vancomycin or who were started on vancomycin >4 days after the positive culture were excluded. However, we did include these infants in a sensitivity analysis.

To describe empirical vancomycin use by NICU size, we divided NICUs into tertiles based on mean number of discharges per year over the entire study period. The mean number of annual discharges was <122 for small NICUs, 122–291 for medium-sized NICUs, and >291 for large NICUs. The proportion of infants treated with empirical vancomycin annually was determined.

Statistical Analysis

The primary outcome of our study was mortality within 30 days of the first positive CoNS culture. Secondary outcomes were mortality within 7 days from the first positive CoNS culture, mortality prior to hospital discharge, length of hospital stay, and duration of bacteremia. Summary statistics were used to describe all study variables, and chi-square tests of association or Wilcoxon rank sum tests were used to compare the distribution between infants who did or did not receive empirical vancomycin. All predictors significantly associated with the primary outcome were included in the full model. A hierarchical backwards variable selection (significance level for removal = 0.25) was used to select the most parsimonious model. Testing for interactions between empirical vancomycin therapy and all relevant covariates included in the final model was performed. We used the Hausman specification test to evaluate the correlation between a NICU-specific effect and the included covariates. Given that the test failed to reject the null hypothesis for each outcome modelled, we opted to use mixed models with random effects for site for our primary analysis. The following main effects were included in the final model as covariates: gestational age, small-for-gestational age status, postnatal age on the day of first positive culture, oxygen requirement, ventilator support, and inotropic support on the day the first positive culture was obtained. Statistical significance was set at $p<0.05$. Statistical analyses were performed using Stata 12 (College Station, TX). This study was approved by the Duke University Institutional Review Board.

RESULTS

Infant Characteristics

We identified 4364 (0.5%) infants with CoNS BSI out of a total of 887,910 infants. Over half of all infants were treated with empirical vancomycin (2848/4364, 65%) (Table 1). Of the 1516 (35%) infants who received delayed vancomycin therapy, 1016/1516 (67%) were

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started on vancomycin after 1 day, 292/1516 (19%) after 2 days, 96/1516 (6%) after 3 days, and 34/1516 (2%) after 4 days from the day of the first positive culture. Among infants receiving delayed treatment, vancomycin was started at a median of 1 day (interquartile range 1, 2) following collection of the first positive blood culture. The most common antibiotics used empirically in the delayed vancomycin therapy group were ampicillin, oxacillin, and gentamicin.

The difference in median postnatal age at the time of the first positive blood culture for CoNS in infants treated with empirical vancomycin versus infants with CoNS sepsis who received delayed vancomycin was statistically significant: 14 days (10, 22) vs. 13 days (9, 21), respectively, p<0.001. Gestational age at birth and birth weight were similar between empirical vancomycin and delayed vancomycin groups: 27 weeks (25, 29) vs. 27 weeks (25, 29), p=0.21, and 860 g (673, 1130) vs. 865 g (685, 1145), p=0.18, respectively. The majority of infants in both groups were very-low-birth-weight with 2583/2848 (91%) infants who received empirical vancomycin and 1341/1514 (88%) who received delayed vancomycin therapy weighing <1500 g at birth.

Outcomes

On multivariable analysis, the odds of mortality at 30 days were not different between the infants who received delayed vancomycin therapy vs. those who received empirical vancomycin therapy (odds ratio [OR]: 1.14 [95% confidence interval {CI}: 0.84, 1.56]) (Table 2). Odds of mortality at 7 days and at hospital discharge were not significantly different in infants treated with delayed vs. empirical vancomycin (OR: 1.10 [0.67, 1.82] and OR: 1.06 [0.81, 1.39], respectively) (Table 2). A sensitivity analysis that included infants with CoNS BSI who received vancomycin 5 or more days after the culture was obtained and those who never received vancomycin resulted in similar odds of mortality at 30 days (OR: 0.96 [0.62, 1.49]), at 7 days (OR: 0.83 [0.35, 1.96]), and at hospital discharge (OR: 0.92 [0.63, 1.35]). The median duration of bacteremia was 1 day less for infants receiving empirical therapy (3 days [2, 5]) compared with those receiving delayed vancomycin therapy (4 days [2, 6]; p<0.0001). The median duration of vancomycin therapy was 2 days longer for infants receiving empirical vancomycin therapy (15 days [11, 22]) compared with those receiving delayed vancomycin therapy (13 days [11, 19]; p<0.0001). Median length of stay was similar for infants in both groups: 78 days (52, 106) for empirical vancomycin vs.77 days (50, 106) for delayed vancomycin, p=0.35.

Variation by NICU and Discharge Year

Empirical vancomycin use for CoNS BSI varied greatly by NICU site. At sites with >10 episodes of CoNS BSI, use of empirical vancomycin ranged from 8–100% (Figure 1). Small NICUs (570/822 [69%]) used empirical vancomycin for treatment of CoNS sepsis more often than medium-sized (895/1406 [64%]) or large NICUs (1383/2136 [65%]) (p=0.02). The year of discharge did not significantly affect the use of empirical vancomycin (Figure 2). In 1998, 41/74 (55%) of CoNS sepsis episodes were treated with empirical vancomycin. In 2012, 119/189 (63%) received empirical vancomycin (p=0.05).

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DISCUSSION

Vancomycin is often necessary for treatment of CoNS due to frequent resistance to beta-lactam antibiotics.[10,11] However, vancomycin exposure is associated with renal dysfunction, hearing loss, and other side effects.[17–19] Additionally, widespread use of vancomycin is associated with vancomycin-resistant *Enterococcus*, invasive *Candida* infections, and more frequent colonization with resistant gram-negative rods.[12,20,21] As much as 32% of vancomycin use in the NICU is inappropriate, largely due to continuation in the setting of negative cultures.[22] Vancomycin is commonly used in the NICU and is the third most commonly used drug in infants <32 weeks gestation.[23] Limiting unnecessary vancomycin use is a priority.[13] For infants in this nationally representative cohort, the use of empirical vancomycin did not improve mortality following an episode of CoNS BSI. The duration of bacteremia was 1 day longer for infants receiving delayed vancomycin therapy.

A prior study evaluating outcomes following sepsis comparing adequate empirical antibiotic therapy to inadequate therapy found that adequate empirical therapy significantly increased the number of infants who survived, from 12/33 (36%) to 7/12 (75%) (OR=5.3 [1.2, 23.2]).[24] However, this study considered all organisms, including gram-negative rods, together, and vancomycin was part of the standard empirical protocol for all infants >7 days of age. CoNS sepsis occurred in 43% of infants included in the study. Our study evaluated CoNS BSI separately and sought to determine if adequate empirical therapy affects mortality and hospital length of stay for this disease in particular. Empirical vancomycin did not improve mortality or hospital length of stay for our cohort.

Our findings are consistent with other studies of outcomes following CoNS BSI. A multicenter study found that mortality is not increased following gram-positive infections, including CoNS.[25] One center retrospectively evaluated infant outcomes following CoNS BSI after changing their standard empirical antibiotic regimen for late-onset sepsis from vancomycin and cefotaxime to oxacillin and gentamicin.[26] They found no difference in the incidence of death at 48 hours, with 1 death per 141 sepsis cases when vancomycin was used empirically and 1 death per 136 sepsis cases when oxacillin was used empirically. The duration of bacteremia was also the same between the 2 periods.

Another study, conducted in the era of increased methicillin-resistant *Staphylococcus aureus* (MRSA) colonization and disease, demonstrated that vancomycin use could be significantly restricted in the NICU without increasing mortality or morbidity.[27] The incidence of late-onset sepsis was 2.15 per 1000 infant-days prior to vancomycin restriction and 2.65 per 1000 infant-days after the protocol was implemented. The number of deaths due to late-onset sepsis decreased with vancomycin restriction (8.1% to 5.8%). These investigators used an algorithm for vancomycin use that waited until CoNS susceptibility results were available prior to starting vancomycin. Our current study supports this practice.

We expected the year of discharge to be associated with increasing empirical vancomycin use. With the incidence of community-acquired MRSA increasing since the 1990s, some centers moved to include vancomycin therapy as part of their standard antibiotic protocol for late-onset sepsis.[9] We observed a trend toward increased use of empirical vancomycin for

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infants with CoNS BSI over the 16-year study period but this did not reach statistical significance. As annual use was analyzed in aggregate, this may not reflect increases in use at individual centers or in communities with higher burdens of MRSA disease.

Balancing the opposing goals of providing the narrowest antimicrobial coverage possible while potentially treating the yet-unknown infecting organism is difficult. Use of broad-spectrum antibiotics for empirical therapy in the NICU has been linked to adverse outcomes and increased mortality.[28–30] Increased incidence of resistant organisms is also a known consequence of routine broad-spectrum antibiotic use.[31] However, inadequate early antibiotic coverage may increase mortality and sequelae from certain pathogens. For example, late-onset sepsis caused by *Pseudomonas* species or *Candida* species significantly increases the odds of death (OR: 14 and OR: 6, respectively).[32] Many empirical antimicrobial regimens lack significant coverage for these organisms, which may contribute to this increased mortality. In the case of *Candida*, empirical antifungal therapy reduces the risk of death and neurodevelopmental impairment (OR: 0.27).[33]

The current study demonstrates that empirical therapy for CoNS BSI does not significantly improve mortality. This large sample size allowed us to control for important cofounders. We were limited in our ability to assess for long-term complications such as neurodevelopmental impairment, which is associated with CoNS BSI in premature infants. Another limitation is the lack of dosing information; it is possible that different doses of vancomycin could affect mortality. Additionally, the absence of vancomycin therapy was used as a surrogate for inappropriate antibiotic therapy for CoNS due to frequent resistance to beta-lactam antibiotics. However, this resistance pattern is not universal, and this assumption may lead to an underestimation of the difference between the 2 groups. Lack of sensitivity data prevented us from making a direct comparison of appropriate to inappropriate therapy.

Conclusion

Empirical vancomycin therapy does not improve short-term mortality or reduce hospital length of stay following CoNS BSI. This finding can inform decision-making for clinicians seeking to strike a balance between the risks of vancomycin exposure and potential complications of delayed therapy for this common pathogen. Empirical use of vancomycin should be limited to cases when MRSA is suspected. In most cases, culture and sensitivity data should guide use.

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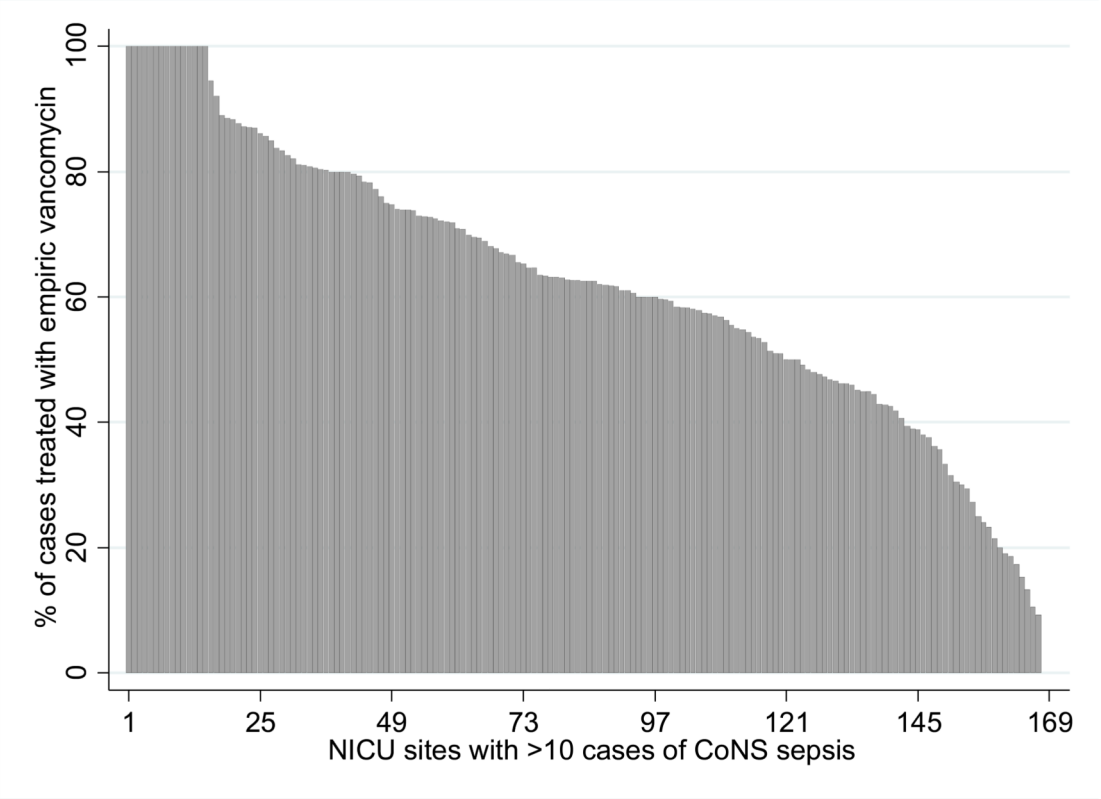

FIGURE 1.

Proportion of CoNS BSI cases treated with empirical vancomycin at NICU sites with >10 cases of CoNS sepsis.

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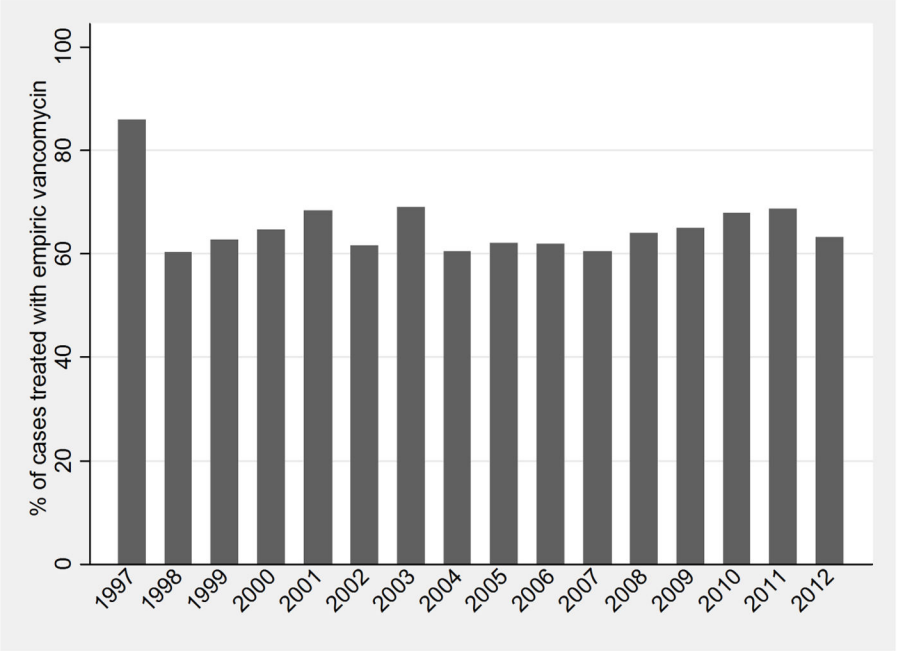

FIGURE 2.
Proportion of CoNS BSI cases treated with empirical vancomycin by year of discharge.

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TABLE 1

Demographics

	Delayed therapy N=1516 (%)	Empirical therapy N=2848 (%)
Gestational age, weeks		
<25	517 (34)	1028 (36)
26–28	590 (39)	1058 (37)
29–32	311 (20)	605 (21)
33–36	61 (4)	102 (4)
>37	37 (2)	52 (2)
Birth weight, g		
<1000	966 (64)	1842 (65)
1000–1499	375 (25)	741 (26)
1500–2499	129 (9)	205 (7)
2500–3499	33 (2)	39 (1)
>3500	11 (1)	21 (1)
Age at positive blood culture, days		
<7	286 (12)	90 (3)
7–14	969 (41)	1298 (44)
15–28	736 (31)	1071 (37)
>28	397 (17)	467(16)
Race/ethnicity		
White	667 (46)	1254 (46)
African-American	372 (25)	735 (27)
Hispanic	360 (24)	652 (24)
Other	67 (4)	107 (4)
Male	803 (53)	1534 (54)
Inborn	1185 (79)	2297 (82)
Cesarean section	1038 (69)	2006 (71)
Small for gestational age	276 (18)	547 (19)
Inotropic support on day of culture	121 (8)	302 (11)
Oxygen support on day of culture	1049 (69)	2058 (72)
Ventilator support on day of culture	733 (49)	1565 (55)

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TABLE 2

Mortality by Type

	Delayed therapy N=1516 (%)	Empirical therapy N=2848 (%)	Adjusted odds ratio (95% CI)*
Death within 30 days of 1st culture	69 (4)	166 (6)	1.14 (0.84, 1.56)
Death within 7 days of 1st culture	23 (2)	54 (2)	1.10 (0.67, 1.82)
Death before hospital discharge	100 (8)	236 (9)	1.06 (0.81, 1.39)

*Odds for empirical vancomycin therapy compared to delayed vancomycin therapy.

CI, confidence interval.

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