Epidemiological Evaluation of Blood Culture Patterns among Neonates Receiving Vancomycin

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Abstract The objective of this study was to assess the frequency of blood culture (BC) collection among neonates who received vancomycin. Demographic, clinical, microbiologic, and pharmacy data were collected for 1275 neonates (postnatal age 0–27 days) who received vancomycin at an Intermountain Healthcare facility between 1/2006 and 9/2011. Neonates treated with vancomycin had a BC collected 94 % ($n = 1198$) of the time, of which 37 % ($n = 448$) grew one or more bacterial organisms (BC positive). Of these, 1 % ($n = 5$) grew methicillin-resistant *Staphylococcus aureus* (MRSA), 71 % ($n = 320$) grew coagulase-negative Staphylococci (CoNS), 9 % ($n = 40$) grew methicillin-sensitive *Staphylococcus aureus* (MSSA), and 22 % ($n = 97$) grew other bacterial species (total exceeds 100 % due to co-detection). In patients with negative BC or no BC, vancomycin therapy was extended beyond 72 h 52 % of the time. The median duration of vancomycin therapy for patients with a negative BC was 4 (IQR: 2–10) days. BCs were frequently obtained among neonates who received vancomycin. Vancomycin therapy beyond the conventional ‘empiric’ treatment window of 48–72 h was common without isolation of resistant gram-positive bacteria.

Keywords Infectious diseases · Neonatology · Pharmacology · Microbiology

Abbreviations

MRSA Methicillin-resistant *Staphylococcus aureus*
CoNS Coagulase-negative *Staphylococcus*
MSSA Methicillin-sensitive *Staphylococcus aureus*

Introduction

Vancomycin is a narrow-spectrum glycopeptide antibiotic that is typically reserved for the prophylaxis and treatment of selective infections by resistant gram-positive bacteria. Its empiric use in neonates is widespread and can be life-saving [1]. A reported surge in methicillin-resistant *Staphylococcus aureus* (MRSA) has led to a resurgence of vancomycin use [2]. However, vancomycin use is fast outpacing the incidence of MRSA infections [3, 4]. This has occurred in the broader context of increasing concern for the emergence of vancomycin-resistant bacteria and adverse events [5–8]. Due to these risks, several institutions have adopted stringent protocols for its use [9, 10]. Furthermore, several professional societies, including the Infectious Disease Society of America and the European Society for Microbiology and Infectious Diseases emphasize the importance of collecting blood cultures (BC) to guide the use of vancomycin [11].

BC remains the current gold standard for the diagnosis of bacteremia [12, 13] and is recommended to serve as the basis for the transition from empiric treatment to continued course of therapy and may be used to guide rational antibiotic selection [14]. Nonetheless, BC is limited by its low sensitivity and the time required to grow fastidious organisms. The amount of time for the results to become available is variable (typically 24–72 h), depending on

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several factors, including the type of microorganism, and early- versus late-onset sepsis. [15]. Additionally, pathogen identification from positive BC may require additional testing, adding further time and expense [16]. Obtaining cultures from neonates is particularly challenging because blood collection volumes and prenatal antibiotic therapy for the mother affect the sensitivity and reliability of the BC, respectively [17]. While false negative results are of concern, antibiotic treatment can be initiated based on false-positive BC, which has been reported to be in the range of 0.6–6 % and can arise from contamination of the culture with bacterial strains from normal skin flora (common in heel prick specimens), or from introduction by iatrogenic means [18, 19]. Although the risk of contamination can be minimized by obtaining multiple cultures from different sites at different times, this is often impractical or impossible for neonates.

Neonatologists must balance and integrate clinical signs, assay results, and microbiologic information to support the use of antibiotic therapy and avoid risks associated with a delay in treatment. Biomarker tests, such as C-reactive protein (CRP) levels, white blood cell (WBC) counts, and band neutrophil (BN) counts, are an example of indicators commonly used to evaluate possible sepsis in neonates [20]. However, evaluation of possible neonatal septicemia by clinical signs such as pallor, apnea, poor feeding tolerance, or increased mechanical ventilatory support, even in conjunction with standard blood biomarker tests, is highly subjective and notoriously non-specific for diagnosing neonatal sepsis [21]. Adding further complication, some neonates may have received antibiotics prior to the collection of the BC, which makes interpretation of a negative BC challenging [19].

The overall objective of this study was to assess vancomycin use in conjunction with blood culture results in a neonatal population. Specifically, this study sought to evaluate the proportion of neonates who had blood cultures obtained and determine the duration of vancomycin use among patients with varying blood culture results.

Materials and Methods

Study Design and Patients

Neonates (0–27 days postnatal age at the time of admission) hospitalized at a Utah Intermountain Healthcare facility (IHC) who were administered two or more doses of vancomycin, initiated at the discretion of the attending neonatologist, from January 1, 2006 to September 30, 2011 were evaluated in this study. IHC is comprised of 22 hospitals within the Intermountain West region, including the quaternary-care Primary Children's Hospital (PCH). A

waiver of informed consent was granted for the retrospective data collected. This research was reviewed and approved by the University of Utah and PCH Institutional Review Boards, which conform to the provisions set forth by the Declaration of Helsinki in 1995 (as revised in Tokyo in 2004).

Data, including admission, discharge and treatment dates, length of stay, vancomycin concentration and dosage, co-medications, laboratory and culture results, hospital discharge codes (ICD9 codes), length, weight, Apgar score, multiple births, ventilator/CPAP utilization, surgical procedures, and gestational age were extracted in addition to cultures including blood, cerebrospinal fluid, wounds, abscesses, urine, blood, and body fluids from an Enterprise Data Warehouse (EDW). An automated continuous agitation system (Bactec 9240; Becton–Dickinson Microbiology Systems, Franklin Lakes, NJ) was used for culture of collected blood specimens. Standard microbiological procedures were used for BC evaluation including antibiotic susceptibility testing via minimum inhibitory concentration (MIC) testing, in accordance with Clinical and Laboratory Standards Institute guidelines [22].

For this study neonatal patients were stratified by blood culture (BC) status into three main categories: (1) no BC available; (2) positive BC(s) with the presence of bacterial growth in one or more specimens; or (3) negative BC(s) where there was an absence of bacterial growth in all specimens collected. For all positive BC results the type and susceptibility of the organism to vancomycin were recorded. Patients with positive BC were further classified based on the colonizing organism (i.e., MRSA (methicillin-resistant *Staphylococcus aureus*), coagulase-negative Staphylococci (CoNS), methicillin-sensitive *Staphylococcus aureus* (MSSA), or 'other' bacterial strain). Pre- and full-term were defined as <37 and ≥37 weeks gestational age, respectively.

The number of vancomycin doses was included in this study along with the duration of vancomycin use, which was estimated by calculating the difference in the time period between the first and last dose. Since blood culture reports are available within 72 h for >99 % of cases [23], this time point was used to differentiate between empiric (≤72 h) and prolonged (i.e., >72 h treatment and/or 10 doses) vancomycin use.

Statistical Analysis

Demographic and clinical factors of the neonatal population were characterized with the use of descriptive statistics. Fisher's exact test, ANOVA, t test, or Dixon test for outliers were performed, as appropriate using R (version 2.15.1) or Prism 6 (GraphPad, San Diego, CA).

Table 1 Demographic and clinical characteristics of neonates who received vancomycin for the treatment of presumed sepsis

Characteristic	Number (%) (<i>n</i> = 1,275)
Birthweight, g	
Mean $\pm$ SD	1840 $\pm$ 1088 (<i>n</i> = 1206)
Range	380–5104
Sex	
Male	757 (59 %)
Female	518 (41 %)
Gestational age, wks	
Mean $\pm$ SD	31.4 $\pm$ 5.5 (<i>n</i> = 1,167)
Range	21 – 41
Postmenstrual age, wks	
Mean $\pm$ SD	32.0 $\pm$ 5.7 (<i>n</i> = 1,167)
Range	22 – 44
Postnatal age, dys	
Mean $\pm$ SD	2.7 $\pm$ 6.1
Range	0 – 27
Race/ethnicity	
Non-Hispanic White	939 (74 %)
Hispanic	176 (14 %)
Black	23 (2 %)
Hawaiian/Pacific Islander	33 (3 %)
Asian	15 (1 %)
American Indian/Alaskan Native	13 (1 %)
Other	16 (1 %)
Not reported	60 (5 %)
Apgar score at 1 min	
Mean $\pm$ SD	5.7 $\pm$ 2.5 (<i>n</i> = 981)
Range	1 – 9
Apgar score at 5 min	
Mean $\pm$ SD	7.6 $\pm$ 1.8 (<i>n</i> = 983)
Range	1 – 10
Respiratory support	
Mechanical ventilation	795 (62 %)
Continuous positive airway pressure	287 (23 %)

Results

Demographics

The demographics of neonates included in this study are outlined in Table 1. The number of neonates admitted to the hospital with only one encounter (a single clinical episode) was 1225 (96 %). Multiple encounters occurred for 50 patients (4 %) with the maximum number of encounters being three. For those neonates with a recorded birth weight (*n* = 1206), the mean (SD) was 1840 (1088) grams. For those neonates with recorded gestational age (91 %), there were 858 (67 %) neonates born pre-term

(<37 weeks gestation), while 309 (24 %) were born full-term ($\geq$ 37 weeks gestation); altogether the mean (SD) gestational age was 31.4 (5.5) weeks.

Blood Culture

Of 1,275 unique neonates, 94 % (*n* = 1,198) had a BC performed. Of those with recorded BC results, 37 % (*n* = 448) had cultures with evidence of bacterial growth (positive BC), while 63 % (*n* = 751) had cultures with no bacterial growth (negative BC) (Fig. 1). There were 31 additional patients with a culture from a source other than a BC who were treated with vancomycin. Twelve of the cultures were from cerebrospinal fluid with no bacterial growth, three from pericardial fluid with one positive for micrococcus species, five were urine collections, one with fungal growth, and 11 were external or wound sources with either no growth or colonization with normal non-resistant skin flora. Of the patients with positive BC, only 1 % (*n* = 5) grew MRSA, 71 % (*n* = 320) grew CoNS, 9 % (*n* = 40) grew MSSA, and 22 % (*n* = 97) grew other bacterial strains (co-detection of some patients results in >100 %).

Vancomycin treatment

For patient encounters where vancomycin was administered beyond 72 h (53 %, *n* = 427) or for ten or more doses (50 %, *n* = 322), roughly half (53 %, *n* = 427) had negative BC (Table 2). The median interquartile range (IQR) treatment duration for neonates receiving ten or more doses was 11.5 (7–32) days as compared to 2 (1–3) days for those receiving less than ten doses (*p* < 0.0001). The number of vancomycin doses administered and the duration of therapy were significantly associated with the culture outcome. Positive BC result(s) were strongly associated with receiving ten or more doses (odds ratio (OR) = 2.6 (95 % confidence interval (CI), 2.1–3.4, *p* < 0.0001)) and treatment beyond 72 h (OR = 2.5 (CI, 1.9–3.2, *p* < 0.0001)).

Gender and gestational age (i.e., pre-term versus term) were not factors influencing BC collection practices or BC results (Table 2). Only when considering cultures from all sources was prematurity significantly associated with culture positivity (*p* = 0.02). Patients receiving vancomycin without BC collection (7 %, *n* = 92) were less likely to receive 10 or more doses than those with BC (OR = 3.2 (CI, 2.0–5.3, *p* < 0.0001)). They were also less likely to receive 72 h or more of vancomycin therapy (OR = 4.0 (CI, 2.5–6.4, *p* < 0.0001)).

Overall, neonates with at least one positive BC had a greater number of vancomycin doses with a median (IQR) of 15 (7–28) compared to those with negative BC with a median of 7 (4–14) doses (*p* < 0.001). As expected, this matched the trend for duration of vancomycin therapy with

Fig. 1 Classification of unique neonatal patients by blood culture status

Table 2 Blood culture and vancomycin dosing profiles for patient encounters in conjunction with biomarkers commonly used in the evaluation of neonatal sepsis

Factor	Neonatal encounters	Blood culture			Sepsis biomarkers		
		Negative	Positive	None	BN ^a	WBC ^b	CRP ^c
Gender, <i>n</i> (%)	<i>N</i> = 1,334						
Male	791 (59)	464 (59)	273 (35)	54 (7)	645 (82)	702 (89)	74 (9)
Female	543 (41)	314 (58)	191 (35)	38 (7)	453 (83)	483 (89)	61 (11)
Gestational age, <i>n</i> (%)	<i>N</i> = 1,225						
Pre-term (<37 weeks)	910 (74)	545 (60)	338 (37)	27 (3)	760 (84)	799 (88)	91 (10)
Term (≥37 weeks)	315 (26)	173 (55)	100 (32)	42 (13)	252 (80)	286 (91)	33 (10)
Vancomycin therapy, <i>n</i> (%)	<i>N</i> = 1,334						
<10 doses	688 (52)	456 (66)	162 (24)	70 (10)	523 (76)	588 (85)	60 (9)
≥10 doses	646 (48)	322 (50)	302 (47)	22 (3)	575 (89)	597 (92)	75 (12)
<72 h	531 (40)	351 (66)	115 (22)	65 (12)	395 (36)	452 (38)	43 (32)
≥72 h	803 (60)	427 (53)	349 (43)	27 (3)	703 (64)	733 (62)	92 (68)
Doses of vancomycin	<i>N</i> = 1,334						
Median	9	8	15	5	11	10	12
IQR ^d	5–19	4–15	7–28	3–9	5–21	5–20	6–22
Duration of vancomycin (days)	<i>N</i> = 1,334						
Median	5.7	4	9	2	6	6	7
IQR ^d	2–13.5	2–10	3–30	1–3	2–16	2–15	3–23

^a BN count Band neutrophil

^b WBC count White blood cell

^c CRP C-reactive protein

^d IQR Interquartile range

neonates with positive BC treated for a median of 9 (3–30) days while those with negative BC were treated for a median of 4 (2–10) days ($p < 0.001$). Only 1 % of patients had ten or more doses administered in 72 h or less.

CoNS and MRSA detection in BC were each significantly associated with an increased number of doses

compared to those with negative ($P < 0.0001$), no BC ($P < 0.0001$), other species ($P < 0.0001$), and MSSA ($P < 0.01$) (Fig. 2a). Evaluation by the duration of therapy revealed similar findings, but significant differences existed in the treatment duration between neonates without BC and those with either ‘other species’ or ‘negative BC’ (Fig. 2b).

Fig. 2 Level of neonatal vancomycin therapy and corresponding BC organism detection. **a** General categorization of blood culture status by number of vancomycin doses administered. Red line indicates 10 doses. **b** Duration of therapy by blood culture status. **c** Relative % of neonates administered 10 or more doses of vancomycin according to

BC status. **c** Number of vancomycin doses administered within the context of non-*S. aureus* or CoNS species identified in the BC analysis. One-way ANOVA performed with Tukey post-test; * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$

However, a single patient with MRSA received 284 doses of vancomycin in an encounter spanning 260 days, which were spent almost exclusively in the NICU. If this patient's dosing data is excluded as an outlier ($p = 0.0044$), the level of dosing or treatment duration was similar to the other categories with the exception of 'No BC' ($p < 0.05$, $p < 0.01$, respectively). Proportionally, patients with vancomycin susceptible organisms were more likely to receive ten or more doses of vancomycin (Fig. 2c). Nonetheless, there were cases where vancomycin was continued even

when there was microbiologic confirmation that vancomycin would be an ineffective agent (i.e., culture of exclusively fungal or gram-negative species) (Fig. 2d, middle and right plots; Table 3).

Other Indicators Used to Assess Sepsis

CRP, WBC, and BN counts were assessed in 10 % ($n = 135$), 89 % ($n = 1,185$), and 82 % ($n = 1,098$), of neonate encounters for which vancomycin was

Table 3 Blood culture results and vancomycin prescribing patterns among septic neonates

Organism	Blood culture + N = 448	Vancomycin dosing	
		≥10 doses	Median (IQR)
MRSA ^a	5 (1 %)	5 (100 %)	45 (15–171) ^c
MSSA ^b	40 (8 %)	20 (50 %)	9 (5–20)
CoNS ^c	320 (69 %)	256 (80 %)	19 (11–33)
Other ^d	N = 97	N = 40	8 (4–19)
Gram-positive	48 (11 %)	22 (46 %)	9 (5–17)
Gram-negative	42 (9 %)	15 (36 %)	8 (4–24)
Fungal	7 (2 %)	3 (43 %)	7 (5–16)

^a Methicillin-resistant *Staphylococcus aureus* (MRSA)^b Methicillin-sensitive *Staphylococcus aureus* (MSSA)^c Coagulase-negative staphylococci (CoNS)^d Species from positive blood cultures categorized as ‘other’ included: *Bacillus* spp., *C. albicans*, *C. freundii*, *E. coli*, *E. cloacae*, *E. faecalis*, group A streptococci, group B streptococci, *K. oxytoca*, *K. pneumoniae*, *Lactobacillus* spp., *P. aeruginosa*, *S. marcescens*, and *S. viridans*^e Median (interquartile range [IQR]) for ‘MRSA’ includes data from a single patient that was a significant outlier ($p = 0.0044$, Dixon test for outliers)

administered, respectively (Table 2). The assessment rate for these factors did not differ with gestational age, positive BC result, or gender. In more than half of patients (57 %) both BN were measured and BC were collected, 25 % of the time BN were measured without BC collection, and 6 % of the time BN were not measured and BC were not collected. Neonates administered ten or more doses of vancomycin were more likely to have WBC and BN assessed versus those who received fewer than ten doses ($p < 0.0001$ for both). Positive BC was significantly associated with neonates receiving more vancomycin doses including a stronger association than BN or WBC counts with number of doses ($p < 0.0001$) but not CRP. As a corollary, negative BC was associated with fewer doses of vancomycin as compared to BN ($p < 0.0001$), WBC ($p < 0.001$), and CRP ($p < 0.05$) measurement.

Discussion

BC are frequently collected for neonates who were prescribed vancomycin for the treatment of presumed sepsis. While BC was an important factor in the absolute duration of vancomycin therapy for this neonatal population, other factors are clearly being used to determine the duration of therapy. In this study, when a BC was collected a bacterial species was identified in 37 % of cases. More than half of the neonates with negative BC received vancomycin for more than 72 h.

‘Culture-negative’ sepsis is often cited as a reason for extending the duration of vancomycin therapy [24]. However, clinicians are faced with separating symptoms that mimic sepsis such as transient tachypnea of the newborn, pulmonary embolism, pneumonia, necrotizing enterocolitis, congestive heart failure, and congenital diaphragmatic hernia [25] from genuine infection. Additionally, it is possible that some risk factors for infection, like mechanical ventilation, prolonged pre-mature rupture of membranes, low Apgar scores, very low birth weight, and poor health status of the newborn may influence the decision to extend the course of vancomycin in light of negative culture results. Nevertheless, prolonged vancomycin can have adverse effects including an increase in the risk of developing necrotizing enterocolitis [24]. Therefore, while a negative BC result(s) strongly influences the decision to discontinue vancomycin it must also be balanced against the complex milieu of other sepsis indicators.

BCs are highly recommended for neonates with signs and symptoms of sepsis [26]. Taking more than one BC from different sites minimizes the probability of obtaining a false-negative, and ultimately, increases the reliability of the culture results. Yet, the optimal number of blood cultures and the ideal volume of blood needed to detect neonatal bacteremia are a matter of ongoing debate [27, 28]. Multiple BC collection is especially problematic in neonates and often only one culture is (or can be) obtained [29]. Efforts have been made to enforce the clinical use of BC. For instance, the Institute for Healthcare Improvement now recommends that provider reimbursement be conditional upon the collection of BC before antibiotics are administered [30, 31]. Even considering the constellation of problems with specimen collection mentioned above, the rate of BC collection was high (94 %). Yet, the decision to treat for >72 h was not consistent when the culture was negative. This suggests a more complex composite of clinical factors that may be used to guide the duration of vancomycin therapy.

The study’s findings should be considered in light of several limitations. Dosing records and/or microbiologic results from outside these hospitals were not available for review. However, all pharmacy and microbiologic data were available for births that occurred during this period at Intermountain facilities. Second, data regarding intrapartum antibiotic use were not available for review. Third, it is possible that alternative diagnostic tests may have influenced the decision to initiate or prescribe a continued course of vancomycin. Lastly, assessments of the clinical stability of individual patients could not be determined from these administrative data and no comment can be made as to the appropriateness of physician actions at the patient level. However, in aggregate, these data suggest that the decision to administer vancomycin for prolonged

durations in the absence of a positive blood culture may be a more common occurrence than was previously thought.

Conclusions

This study determined that neonatal vancomycin use was commonly accompanied by the collection of one or more blood cultures. Neonates with negative blood cultures had a shorter duration of therapy and received fewer vancomycin doses. However, many neonates without evidence of resistant gram-positive organisms received prolonged courses of vancomycin. This apparent dichotomy suggests that alternative factors may be influencing clinical decision making.

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Conflict of interest None.

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