Clinical Investigation

Appropriate Use of Vancomycin in NICU Despite Free-for-All Policy

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OBJECTIVES: Because of increases in antimicrobial resistance, the use of vancomycin in late-onset sepsis has come under scrutiny. The primary outcome of this study was to determine if vancomycin for the treatment of late-onset sepsis in the neonatal intensive care unit (NICU) was being discontinued within 72 hours according to the existing protocol. Secondary outcomes included the appropriateness of therapeutic drug monitoring associated with vancomycin, and renal dysfunction associated with the use of vancomycin in the NICU outside of the 72-hour policy.

METHODS: A retrospective chart review was completed for patients in the NICU who received vancomycin for the treatment of late-onset sepsis between the dates of January 1, 2014, and July 1, 2014.

RESULTS: There were 125 vancomycin treatment courses, of which 97 were included. Appropriate use of vancomycin, per policy, occurred in a total of 87 of 97 courses (89.6%). Therapeutic drug monitoring was evaluated by the number of appropriate troughs, determined using renal function and previous trough concentrations. There was not a statistically significant difference in the number of inappropriate troughs drawn between those that were continued on vancomycin appropriately (n = 17 courses; 4 of 44 inappropriate troughs) versus inappropriately (n = 10 courses; 1 of 22 inappropriate troughs; p = 0.66), despite the large number of troughs drawn. Adverse renal outcomes were not statistically significant in patients continued inappropriately on vancomycin (p = 1.0).

CONCLUSIONS: Vancomycin use in the NICU for late-onset sepsis is appropriate per the existing antibiotic policy. Therapeutic drug monitoring could be improved, and adverse renal outcomes due to inappropriate continuation of vancomycin are rare.

INDEX TERMS: antibiotics, late-onset sepsis, newborn intensive care units, serum concentrations, therapeutic drug monitoring, vancomycin

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INTRODUCTION

Sepsis in the neonate is diagnosed based on non-specific signs and symptoms, such as apnea, tachycardia, and shortness of breath, and can be potentially life threatening. Because of the mortality associated with neonatal sepsis, it is often imperative to begin empiric antibiotic treatment before there is a confirmed infection. In the United States, the mortality rate associated with neonatal sepsis is approximately 16 per 100,000 live births.[1] Sepsis in the neonatal intensive care unit (NICU) presents as either early or late onset, and both forms have increased in prevalence because of the increased survival of very low birth weight (VLBW) neonates, defined as weighing less than 1500 g at birth; the evolution of invasive treatments; and longer stays in the NICU.[2] The approximate prevalence of confirmed early-onset sepsis—that which occurs within the first 72 hours of life—is between 0.5% and 1% of all neonates.[3] However, late-onset sepsis—that which occurs after the first 72 hours of life—has a prevalence closer to 25% of VLBW neonates.[3]

Drug therapy for each form of neonatal sepsis is driven by the likely bacterial organisms and differs between the two. Late-onset sepsis is typically associated with organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, extended-spectrum beta-lactamase–producing organisms, and, most commonly, coagulase-negative *Staphylococcus* species (CONS).[4] The prevalence

of CONS-related sepsis in the NICU is reported to be 48.3% in some studies.[2] Another study found it to be the cause of approximately 55% to 58% of hospital-acquired bacteremias in VLBW neonates.[4] Because of this organism's prevalence, vancomycin used in conjunction with gentamicin has become one of the drugs of choice in late-onset sepsis. This along with the increasing incidence of methicillin-resistant staphylococcal infections, has in turn led to an increased use of vancomycin.[3]

Because of increases in antimicrobial resistance, the use of vancomycin in late-onset sepsis has come under scrutiny. Vancomycin also has its own set of risks to sensitive neonates, including renal insufficiency.[2,5] There are associated costs with vancomycin due to added monitoring involving labs for renal function and therapeutic drug concentrations. Of note, there is no consensus about the frequency, goals, and applicability of therapeutic drug monitoring in the neonatal population in the literature.[5] The most concerning reason against the use of vancomycin is that the reported rate of microbiologically evaluable infections is only 1 to 2 cases per 1000 live births.[5] This means confirmed bacterial infection with a known organism is rarely found in these patients, yet empiric antibiotic choices often leave these patients with a full treatment course in what is termed *culture-negative sepsis*.

The practice of treating with vancomycin empirically at this level 4 NICU is only allowed for 72 hours, before infectious disease (ID) is required to approve further use of the drug to complete a treatment course. This practice has been in place since 2005 and is currently being reconsidered by the ID team because of concerns about overall antimicrobial resistance. The hospital policy does not include dosing or monitoring recommendations. The new proposal, if implemented, would limit empiric use to 24 hours before requiring ID approval. Before implementation, assessment of the current policy was needed. Therefore, the primary outcome of this study was to determine whether vancomycin for the treatment of late-onset sepsis in the NICU was being discontinued according to the existing policy. Secondary outcomes included the appropriateness of therapeutic drug monitoring practices associated with vancomycin, and renal dysfunction associated with the use of vancomycin in the NICU outside of the 72-hour policy.

METHODS

Patient Population

The study was a retrospective chart review of any patient at this level 4 NICU located in the children's hospital within an adult teaching hospital. The NICU has 48 beds and currently does not have a clinical pharmacist present. NICU patients who received vancomycin for late-onset sepsis between January 1, 2014, and July 1, 2014, were included in the study. Patients were identified by performing a search through electronic medical records looking for vancomycin charges, which are recorded when doses are dispensed. Patients with more than one treatment course of vancomycin separated by 48 hours or more were counted as separate occurrences. Patients were included if they were in the NICU and had at least one course of vancomycin (greater than or equal to 24 hours). Patients were excluded if vancomycin was being used for any indication other than late-onset sepsis, or the if course was completed or started somewhere other than this NICU. The Institutional Review Board approved this study.

Data Collection

Data collected included baseline patient demographics (sex, day of life, weight, and corrected gestational age) as well as laboratory neonatal sepsis markers at baseline and 24-hour increments during the first 72 hours of the vancomycin course (white blood cell [WBC] count, temperature, platelets, and C-reactive protein [CRP]). Baseline renal function (serum creatinine [SCr] and urine output [UOP]) was collected at 24-hour intervals during the first 72 hours of the vancomycin course in addition to at the end of the course. Empiric vancomycin dosing, total number of vancomycin troughs, culture speciation and susceptibilities, length of therapy, and ID participation were also documented.

Definitions

Appropriate continuation of vancomycin was defined as continuation with ID approval (provided by ID team member 24 hours a day, 7 days a week) as well as discontinuation prior to 72 hours. Inappropriate continuation was

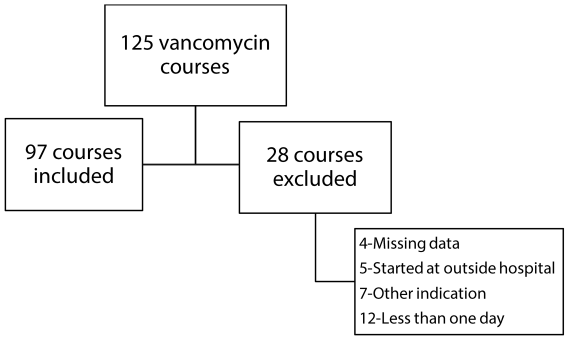

Figure. Distribution of data according to inclusion and exclusion criteria.

defined as continuation after 72 hours without ID approval. Appropriate troughs were defined as a concentration between 10 and 20 mg/L; a trough following a supratherapeutic (>20 mg/L) or subtherapeutic (<10 mg/L) trough, 5 or more days after the last therapeutic concentration; or an acute kidney injury. Acute kidney injury was defined based on clinical experience as an increase in serum creatinine of 50% above baseline and/or decrease in urine output to less than 1 mL/kg/hr.

Data Analysis

Statistical analysis was performed using Microsoft Excel (Redmond, WA) for descriptive statistics. The χ^2 and Wilcoxon-Mann-Whitney *U* tests were used for determining statistical significance, which was established as a p value ≤0.05.

RESULTS

There were 125 vancomycin courses within the selected date range, of which 97 were included and 28 excluded (reasons for exclusion can be found in the Figure). Appropriate continuation of vancomycin occurred in 89.8% of the treatment courses (87 of 97 courses), which included continuation per policy as well as discontinuation prior to 72 hours. Inappropriate continuation occurred in 10.3% of the treatment courses (10 of 97 courses; Table 1), and length of therapy for these courses averaged about 6 days. Infectious disease was seen in 4 of the 10 courses in this group by 96 hours, which when added to the 87 in the appropriate group would give a 93.8% (91 of 97) compliance rate. Only 17 of a total 97 courses were continued on vancomycin with ID approval after 72 hours, meaning 72% (70 of 97) were discontinued prior to 72 hours when cultures returned.

Table 1. Primary Outcome

	No. (%), n = 97
Continued appropriately (with infectious disease oversight)	17 (17.5)
Discontinued ≤72 hr	70 (72.2)
Continued inappropriately (without infectious disease oversight)	10 (10.3)

There were no statistically significant differences between the demographics of the two groups, appropriate continuation vs. inappropriate. There were more males in both groups (60% vs. 90%, appropriate vs. inappropriate, respectively; p = 0.06), and most were preterm infants (<37 weeks' gestational age; 90.8% vs. 80%, appropriate vs. inappropriate, respectively; p = 0.27), with a median day of life of about 40 days (41 vs. 42, appropriate vs. inappropriate, respectively; p = 0.17). About 22% in the appropriate use group were VLBW, compared with none in the inappropriate use group, and the median weight in both groups was about 2000 g (1930 vs. 2000 g, appropriate vs. inappropriate, respectively; p = 0.51; Table 2).

There were also no statistically significant differences between the laboratory sepsis markers taken at the beginning of the antibiotic course between the two groups. The median baseline temperature was 37.2°C in both groups, with a median WBC count of 13.5 and a median CRP concentration of 2.1 vs. 2.5 mg/L (appropriate vs. inappropriate, respectively). In the appropriate continuation group, 15% were thrombocytopenic (platelets <50 10^3/μL) at baseline vs. 25% in the inappropriate group (p = 0.37; Table 2).

Patients' renal function markers were fairly similar at baseline (median SCr, 0.37 vs. 0.34 mg/dL, appropriate vs. inappropriate, respectively; p = 0.76; and median UOP was 3.3 mL/kg/hr in both groups, p = 0.76) and at completion of therapy. Only 1 patient developed an acute kidney injury (SCr, 1.91 mg/dL), and he was in the appropriately continued group (p = 1.0). His UOP was 3.4 mL/kg/hr at that time. His vancomycin concentrations during his treatment course were maintained within a therapeutic range of 15 to 20 mg/L, and he grew *Klebsiella* and *Enterococcus* in

Table 2. Demographics

	Appropriate, n = 87	Inappropriate, n = 10	p Value
Female, n (%)	35 (40.2)	1 (10)	0.06
Full-term, n (%)	8 (9.2)	2 (20)	0.27
Day of life, days, median (IQR)	41 (18-71)	42 (19-71)	0.17
VLBW, n (%)	19 (21.8)	0 (0)	0.20
Weight, g, median (IQR)	1930 (1140-2230)	2000 (1200-3200)	0.51
Baseline temperature, °C, median (IQR)	37.2 (37-37.5)	37.2 (36.9-37.6)	0.28
Baseline WBC count, 10^3/mcL, median (IQR)	13.5 (8-21.2); n = 84	13.5 (7.4-19.2); n = 8	0.65
Baseline CRP, mg/L, median (IQR)	2.1 (1-5.4); n = 79	2.5 (1.2-5.8); n = 8	0.29
Baseline thrombocytopenia, n (%)	13 (15)	2 (25); n = 8	0.37

CRP, C-reactive protein; IQR, interquartile range; VLBW, very low birth weight; WBC, white blood cell

his urine. He was treated with vancomycin and cefotaxime, which was then switched to triple therapy with vancomycin, meropenem, and gentamicin, finally finishing on ampicillin/sulbactam after susceptibilities returned. There were a total of 41 positive cultures (blood, sputum, or urine): 39 in the appropriate treatment group and 2 in the inappropriate treatment group. Of those, 16 were positive blood cultures. There were 4 CONS, 3 *Enterobacter*, 3 methicillin-sensitive *Staphylococcus aureus* (MSSA), 3 *Serratia*, 1 *Escherichia coli*, 1 methicillin-resistant *Staphylococcus aureus* (MRSA), and 1 *Enterococcus*. All were in the appropriate treatment group except for 1 CONS, which was marked inappropriate because ID did not consult until after 72 hours.

In total, 197 troughs were drawn (175 vs. 22, appropriate vs. inappropriate, respectively), of which 93.4% were deemed appropriate in both groups (163 of 175 vs. 21 of 22, appropriate vs. inappropriate, respectively; p = 1.0). All patients had at least one trough concentration drawn. There was not a statistically significant difference in the number of inappropriate troughs drawn between those that were continued on vancomycin appropriately (n = 17 courses; 4 of 44 inappropriate troughs) versus inappropriately continued (n = 10 courses; 1 of 22 inappropriate troughs; p = 0.66). There were 70 patients who received vancomycin for 72 hours or less. In this group, there were a total of 109 troughs, of which 102 were deemed appropriate. The median empiric vancomycin dose was 15 mg/kg per dose in both groups, and about 30% of the time in both groups vancomycin was inappropriately empirically dosed per Neofax (Table 3).[6]

DISCUSSION

The policy at this level 4 NICU of 72 hours empirical use of vancomycin in the setting of late-onset sepsis was followed 89.8% (87 of 97) of the time in this study. These results show good compliance with the policy as well as a strong discontinuation rate associated with negative cultures, despite limited education on this policy to medical residents. Residents are educated on all hospital policies at the beginning of their training in year one. The average length of therapy for those continued with ID approval was about 10 days, which is considered to be a normal treatment course for late-onset sepsis.

Antibiotic usage has fallen under scrutiny thanks to the efforts of antimicrobial stewards in many institutions recently, as well as a push from the Centers for Disease Control and Prevention (CDC). In 2009, Patel and colleagues examined the NICU and its adherence to the CDC's 12-Step Campaign to Prevent Antimicrobial Resistance, and found that the inappropriate use of antimicrobials in the NICU was associated with the decision to continue them in the setting of negative cultures 32% of the time.[7] The results of the SCOUT (Surveillance and Correction of Unnecessary Antibiotic Therapy) study determined culture-negative sepsis to be a large reason

Table 3. Secondary Outcomes

	Appropriate, n = 87	Inappropriate, n = 10	p Value
Baseline SCr, mg/dL, median (IQR)	0.37 (0.26-0.51); n = 60	0.34 (0.25-0.5); n = 8	0.76
Baseline UOP, mL/kg/hr, median (IQR)	3.3 (2.6-4)	3.3 (2.6-4.1)	0.76
SCr at 72 hr, mg/dL, median (IQR)	0.345 (0.288-0.443); n = 26	0.425 (0.198-0.518); n = 6	0.90
UOP at 72 hr, mL/kg/hr, median (IQR)	3.7 (2.8-4.7); n = 38	3.9 (2.7-5.4); n = 10	0.81
SCr at course completion, mg/dL, median (IQR)	0.33 (0.25-0.44); n = 62	0.35 (0.273-0.51); n = 6	0.67
UOP at course completion, mL/kg/hr, median (IQR)	3.7 (3-4.5); n = 87	4.5 (3.53-5.53); n = 10	0.16
Culture speciation (blood, sputum, urine), n (%)	39 (45)	2 (20)	0.12
Empiric dosing, mg/kg per dose, median (IQR)	15 (13-15)	15 (11-15)	0.47
Inappropriate empiric dosing per Neofax, n (%)	28 (32)	3 (30)	0.60

IQR, interquartile range; Scr, serum creatinine; UOP, urine output

for the inappropriate continuation of antibiotic therapy, often 7 days or longer.[8] Another study by Ericson and colleagues[9] in 2015 strongly argued toward a new emphasis on the appropriate discontinuation of antibiotics in the NICU because of an increased risk of adverse effects as well as a lack of benefit for empiric vancomycin versus delayed start of vancomycin for the treatment of CONS bloodstream infections. The study showed an effective use of a restricted antibiotic policy to help prevent the inappropriate continuation of such drugs as vancomycin in the setting of late-onset sepsis in the NICU. The results from this current study also support that an effective restricted antibiotic policy has the ability to decrease inappropriate vancomycin use when executed effectively and followed without a clinical pharmacist in the unit. However, there were concerns about dosing and monitoring practices in the unit, which would benefit greatly from the addition of a pharmacist to the NICU team.

Therapeutic drug monitoring practices were shown in this study to be appropriate 93.4% of the time. A total of 72% of the repeat concentrations were the result of subtherapeutic previous concentrations. The initial subtherapeutic concentrations could be due to incorrect empiric regimens. In each group the empiric regimen was incorrect about 30% of the time, with changes needed to dosing and/or the interval based on Neofax.[6] Every time, the choice was a more conservative empiric dose than what is recommended. However, the empiric regimens in Neofax may not be ideal because that still leaves 42% of patients with subtherapeutic concentrations on a correct empiric regimen. In addition, there were 109 troughs drawn in the 70 patients who received vancomycin for 72 hours or less. Despite 102 of these troughs being labeled as appropriate, one could argue about whether concentrations should be drawn at all until therapy duration is determined. Empiric dosing and monitoring for vancomycin in the neonate could be improved greatly if there were reeducation of the medical staff in addition to the addition of standard dosing and monitoring guidelines to the policy. Clearly, this demonstrates the need for clinical pharmacy services in the NICU.

There were no adverse renal outcomes that could be directly linked to either inappropriate or appropriate continuation of vancomycin in this study.

Limitations for this study include the retrospective and non-randomized design, which makes it difficult to establish cause and effect regarding the secondary objectives and which relies on the accuracy of historical records. Also, the data were not entirely electronically entered; some of the values were found on scanned, hand-written documents, which increase the chance for error. In addition, definitions of "appropriate" and "inappropriate" in all cases were a combination

of definitions currently found in the primary literature because there is no current widely accepted definition.

This level 4 NICU appropriately discontinues vancomycin or continues its use with the oversight of ID about 90% of the time. Dosing and therapeutic drug monitoring practices need to improve, and no adverse renal outcomes were seen when vancomycin was continued outside of the policy. The success of appropriate discontinuation of vancomycin with this policy is a step in the right direction in moving toward a stronger degree of antimicrobial stewardship in the NICU.

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Abbreviations CDC, Centers for Disease Control and Prevention; CONS, coagulase-negative *Staphylococcus*; CRP, C-reactive protein; NICU, neonatal intensive care unit; SCr, serum creatinine; UOP, urine output; VLBW, very low birth weight; WBC, white blood cell count

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