JPPT | Single Center Retrospective Study

Retrospective Evaluation of Empiric Vancomycin Therapy for Infectious Workups in Relation to Methicillin-Resistant *Staphylococcus aureus* (MRSA) Risk Factors in the Neonatal Intensive Care Unit

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OBJECTIVES This study evaluated empiric antibiotic prescribing patterns in relation to methicillin-resistant *Staphylococcus aureus* (MRSA) risk factors in infants with potential late-onset sepsis (LOS). Secondarily, this study evaluated rates of escalation and de-escalation from initial antibiotic choice in patients who received at least 5 days of therapy.

METHODS This was a retrospective study of infants admitted to the neonatal intensive care unit (NICU) from December 1, 2022, to May 31, 2023. Infants at least 3 days old who received antibiotics for an infectious workup were included. The prevalence of risk factors for MRSA, including low birth weight, prematurity, outborn status, length of stay, parenteral nutrition, presence of indwelling lines, and history of MRSA-positive blood culture or colonization, was compared between patients who received vancomycin empirically or an alternative agent.

RESULTS A total of 143 blood cultures were obtained from 95 patients who received antibiotics for an infectious workup during the study period. Group 1 received vancomycin and included 51 (36%) blood cultures. Group 2 received an alternative agent and included 92 (64%) blood cultures. Patients in group 1 had higher rates of every MRSA risk factor included in this study, except for patients who were outborn. Group 1 also averaged a higher total number of MRSA risk factors per patient than group 2 (4.88 vs 2.53; $p < 0.001$).

CONCLUSION This institution uses MRSA risk factors to determine empiric antimicrobial therapy in suspected LOS. Further studies are needed to determine the relationship between the studied risk factors and incidence of MRSA infection.

ABBREVIATIONS AKI, acute kidney injury; CoNS, coagulase-negative staphylococci species; LOS, late-onset sepsis; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NICU, neonatal intensive care unit

KEYWORDS antibacterial agents; infant; newborn; infant; very low birth weight; methicillin-resistant *Staphylococcus aureus*; sepsis; vancomycin

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Introduction

Sepsis is one of the most common complications associated with neonatal intensive care, especially in premature and very low birth weight infants.[1,2] In the neonatal period, sepsis can be categorized as early-onset sepsis or late-onset sepsis (LOS). Generally, LOS is defined as sepsis occurring after the first 72 hours of life.[3,4] With a global incidence of approximately 2800 per 100,000 live births, and a mortality rate of nearly 17.6%, sepsis is one of the leading causes of morbidity and mortality in hospitalized neonates.[5]

The causative organisms in LOS are often coagulase-negative staphylococci species (CoNS), as well as *Staphylococcus aureus*.[6,7] There is a high rate of resistance among CoNS to beta-lactam antibiotics, making vancomycin the agent of choice in suspected LOS.[8,9] However, the risks associated with vancomycin use, namely toxicity and rising rates of resistance mechanisms, demonstrate the need for antimicrobial stewardship programs in intensive care settings.[10] A review of studies in antimicrobial stewardship found that these programs can reduce the use of broad-spectrum antibiotics, as well as the incidence of health care–associated infections.[11] Several neonatal intensive care units (NICUs) have successfully reduced the use of vancomycin in the setting of neonatal

sepsis with no significant differences in morbidity and mortality.[12–14]

The American Academy of Pediatrics (AAP) has published guidance on how to approach antibiotic treatment of LOS; administration of antibiotics should occur as quickly as possible once concern for sepsis is established, but there are several accepted approaches in choosing an empiric agent.[15] The 2024–2027 Report of the Committee on Infectious Diseases, otherwise known as the Red Book from AAP, currently recommends vancomycin as an empiric drug of choice for *S aureus* infections with unknown susceptibility.[16] Many infants receive vancomycin as empiric therapy owing to a history of colonization and/or the presence of risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) as reported in the literature. These risk factors include, but are not limited to, indwelling foreign bodies such as central venous catheters or endotracheal tubes, parenteral nutrition, history of colonization, gestational age, birth weight, and place of birth (inborn vs outborn).[1,2,17–21] The purpose of this retrospective chart review is to compare the use of vancomycin with alternative Gram-positive agents in patients admitted to the NICU who are ≥3 days of age, based on the number of MRSA risk factors present. Secondarily, this study aims to compare rates of escalation and de-escalation in patients who receive at least 5 days or more of antimicrobial therapy. Finally, we present an algorithm based on the data in this study to aid clinicians in choosing empiric antimicrobial therapy for suspected LOS as well as de-escalating at an appropriate time to reduce exposure to vancomycin and antibiotics in general.

Materials and Methods

This was a retrospective study conducted at a 92-bed, Level IV NICU in Cincinnati, OH. Blood cultures obtained from patients admitted to the NICU between December 1, 2022, and May 31, 2023, were screened for inclusion. Patients were included if they were at least 3 days of age at time of culture and received vancomycin or an alternative Gram-positive–covering agent during the study period. Patients who received antibiotics preoperatively or for a reason other than a sepsis workup were excluded. Repeated cultures from the same patient were required to be at least 2 weeks apart—indicating a new infectious workup—to be included. Patients were analyzed in 2 groups: group 1 received vancomycin empirically and group 2 received an alternative Gram-positive agent (e.g., ampicillin, nafcillin, cefepime) empirically.

As shown in Figure 1, all patients in this institution's NICU undergo weekly screening for *Staphylococcus* colonization, using nasal swabs. According to this institution's most recent data, the rate of methicillin resistance in *S aureus* cultures was approximately 25%. Patients who test positive for methicillin-sensitive *Staphylococcus aureus* (MSSA) or MRSA receive 5 days of topical nasal mupirocin plus monthly treatment if they have a central line, external ventricular drain, or open wound. These patients also receive nasal mupirocin for 3 days prior to any surgery. In this unit, nafcillin is typically recommended over vancomycin for empiric Gram-positive coverage for LOS in infants without a history of MRSA colonization or MRSA infection.

Data Collection. Baseline characteristics including gestational age, postnatal age at time of blood culture, dosing weight, and birth weight were collected and analyzed. The primary endpoint of this study was the number of MRSA risk factors present in the vancomycin group (group 1) compared with the alternative group (group 2). A literature review was performed to determine which risk factors have been previously described. A collection of some of the most commonly studied risk factors were included for use; the final risk factors included in this study were low birth weight (defined as birth weight less than 2.5 kg), prematurity (defined as gestational age below 37 weeks), outborn status, length of stay over 10 days at time of culture, parenteral nutrition, presence of a central line, presence of an endotracheal tube, presence of an alternative indwelling line (Foley, chest tube, or external ventricular drains), history of a MRSA-positive blood culture, and history of MRSA colonization.[1,2,6,7,17–26] Secondary endpoints were the rates of escalation to vancomycin in group 2 and de-escalation to alternative agents in group 1 for patients who received at least 5 days of antimicrobial therapy.

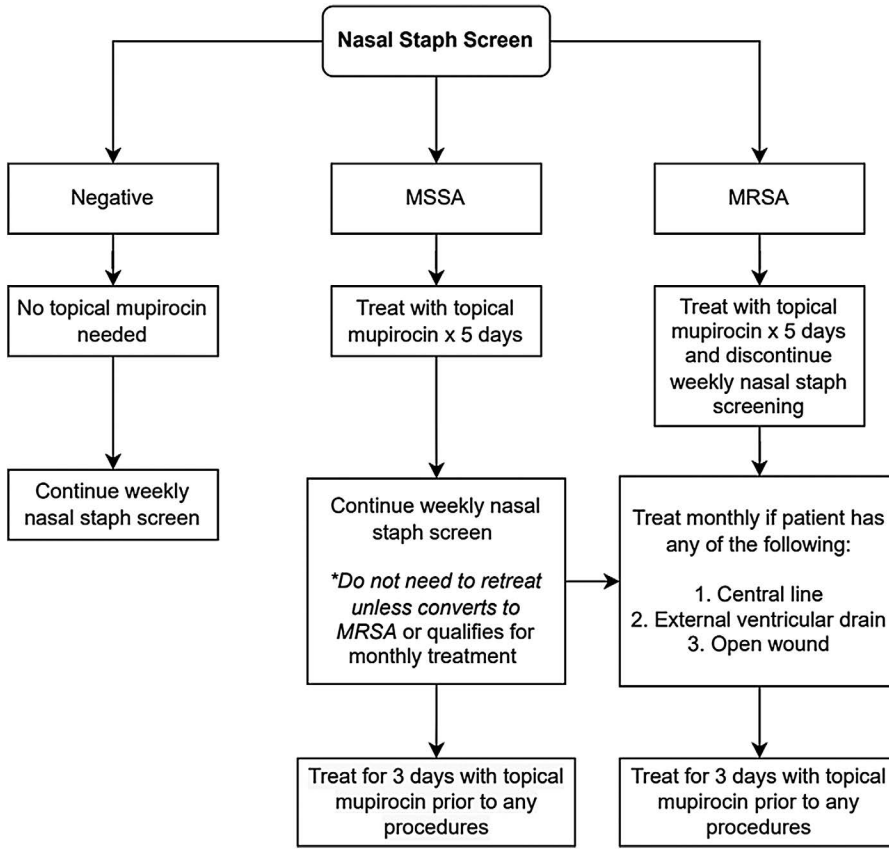
Statistical Analysis. Analysis of the 2 groups was performed with GraphPad QuickCalcs 2024 (Dotmetrics, Boston, MA). All categorical variables were analyzed by using chi-square tests and were reported as number (%). Continuous variables were assessed by using independent samples *t* test and were reported as means ± SD. Medians and IQRs were assessed via Mann-Whitney *U* tests, based on the distribution of the data. A p value <0.05 was considered statistically significant.

Results

Baseline Characteristics and Primary Outcome. Table 1 compares the baseline characteristics across the 2 groups. Patients in group 1 had a lower gestational age (29.58 vs 33.17 weeks; $p < 0.001$) and birth weight (1.32 vs 2.13 kg; $p < 0.001$) than those in group 2 at baseline. Group 1 patients also had a higher postnatal age than group 2 (58 vs 23 days; $p < 0.001$). Dosing weight was not significantly different between the 2 groups. A total of 143 blood cultures from 95 patients were included in the final analysis; 30 patients had at least 2 cultures included, and 11 patients had 3 or more cultures included.

Table 2 details the rates of each MRSA risk factor between the groups. Patients who started on vancomycin had higher rates of every MRSA risk factor included in this study, except outborn status. The most common

Figure 1. NICU *Staphylococcus* screening flowsheet.



NICU, neonatal intensive care unit*; MRSA, methicillin-resistant* Staphylococcus aureus*; MSSA, methicillin-sensitive* Staphylococcus aureus*; staph, Staphylococcus aureus*

Table 1. Baseline Characteristics

	Group 1: Vancomycin (n = 51)	Group 2: Alternatives (n = 92)	p value
Gestational age, mean ± SD, wk	29.58 ± 5.15	33.17 ± 6.13	<0.001
Postnatal age, median (IQR), days	58 (24–126)	23 (7–61)	<0.001
Dosing weight, mean ± SD, kg	2.74 ± 1.65	2.83 ± 1.29	0.728
Birth weight, mean ± SD, kg	1.32 ± 1.00	2.13 ± 1.14	<0.001

risk factors in the vancomycin group were low birth weight (80.4% vs 58.7%; p = 0.009), prematurity (84.3% vs 63.0%; p = 0.008), and length of stay over 10 days (80.4% vs 41.3%; p < 0.001). Overall, the total number of MRSA risk factors per patient was higher in group 1 than group 2 (4.88 vs 2.53; p < 0.001).

Secondary Outcome. A total of 19 patients in group 1 and 31 patients in group 2 continued antibiotic therapy for at least 5 days. Of these, 8 patients in each group either escalated or de-escalated from their empiric agent of choice. Figure 2 describes the distribution of MRSA risk factors present in these patients. Patients who de-escalated from vancomycin had an average of 5.7 (SD, ±1.7) MRSA risk factors, and patients who escalated to vancomycin had an average of 2.9 (SD, ±1.9) risk factors. Additionally, only 9 of the 143 cultures (6%) grew organisms; most were CoNS, with 2 cultures positive for MRSA.

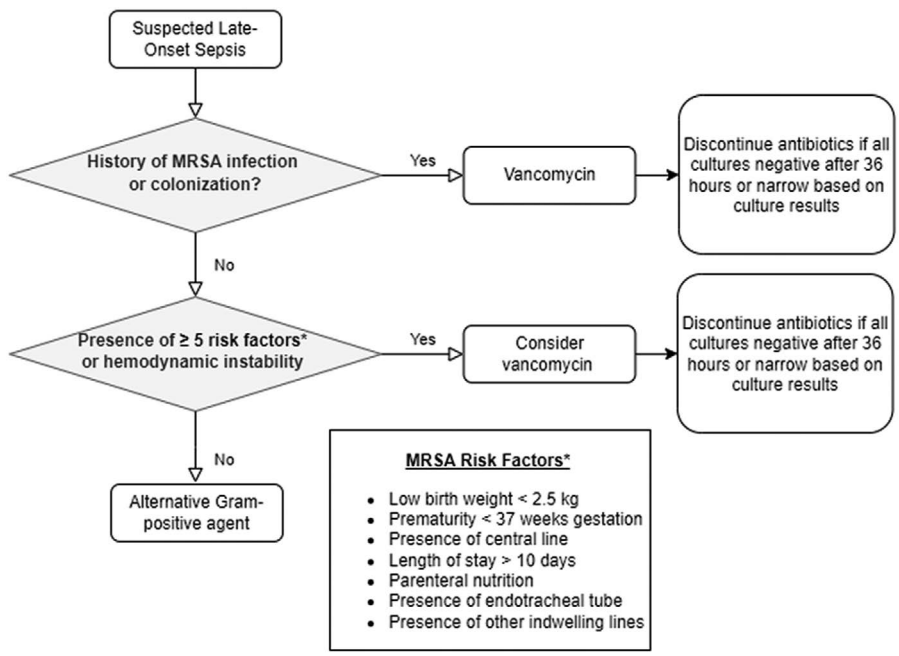
For patients in group 1 who received at least 5 days of therapy, 11 patients did not de-escalate from vancomycin. Only 4 patients had cultures requiring vancomycin; this included 2 resistant *Staphylococcus epidermidis* bacteremias, 1 MRSA respiratory culture, and 1 MRSA wound culture. The latter 2 patients had blood cultures during their respective workups, which qualified them for inclusion, but ended up being

Table 2. MRSA Risk Factors

	Group 1: Vancomycin (n = 51)	Group 2: Alternatives (n = 92)	p value
Low birth weight <2.5 kg, n (%)	41 (80.4)	54 (58.7)	0.009
Prematurity <37 weeks' GA, n (%)	43 (84.3)	58 (63.0)	0.008
Outborn, n (%)	49 (96.1)	88 (95.6)	0.903
Central line, n (%)	39 (76.5)	32 (34.8)	<0.001
Endotracheal tube, n (%)	30 (58.8)	16 (17.4)	<0.001
Length of stay >10 days, n (%)	41 (80.4)	38 (41.3)	<0.001
Parenteral nutrition, n (%)	27 (52.9)	23 (25.0)	<0.001
Other indwelling lines (Foley, chest tube, or external ventricular drains), n (%)	10 (19.6)	7 (7.6)	0.034
History of MRSA-positive blood culture, n (%)	3 (5.9)	0 (0)	0.019
History of MRSA colonization, n (%)	13 (25.5)	1 (1.1)	<0.001
Total number of MRSA risk factors, mean ± SD	**4.88 ± 1.8**	**2.53 ± 1.8**	**<0.001**

GA, gestational age; MRSA, methicillin-resistant Staphylococcus aureus

Figure 2. Proposed Algorithm for selecting Vancomycin as Empiric Antimicrobial Therapy in Infants with Suspected Late-Onset Sepsis



MRSA, methicillin-resistant Staphylococcus aureus

negative. Therefore, 7 patients had the opportunity to de-escalate to a narrower agent. For patients in group 2 who received at least 5 days of therapy, only 3 of the 8 patients who escalated to vancomycin had cultures requiring escalation. All of the positive cultures in group 2 were blood cultures that grew

CoNS, and the blood cultures requiring escalation were all resistant *S epidermidis* species.

Discussion

The results of this study helped to identify patterns of vancomycin prescribing for the indication of LOS in our NICU. Patients who were started on vancomycin were appropriately found to have more MRSA risk factors than those who were started on alternative Gram-positive–covering antibiotics. Empiric vancomycin was prescribed more in patients who a had low birth weight, prematurity, a central line, endotracheal tube, other indwelling lines, longer durations of hospitalization, parenteral nutrition, history of positive MRSA blood culture, and history of positive MRSA nares colonization. Outborn status was not found to be a statistically significant risk factor, likely owing to the few number of patients who were born at this institution during our study period. A meta-analysis on the incidence of MRSA colonization found that colonization was more prevalent in outborn than inborn patients.[1] Outborn status, specifically in relation to MRSA risk factors, has not been studied in patients with LOS, as more data exist in patients who develop sepsis within 3 days of birth.[1,27] This study also found a relatively low rate of de-escalation from vancomycin in patients who had negative cultures; this may be because this study was not able to capture the full clinical picture at the time of blood culture, which may have had more influence on the selection of antimicrobial agent and duration than patient-specific risk factors.

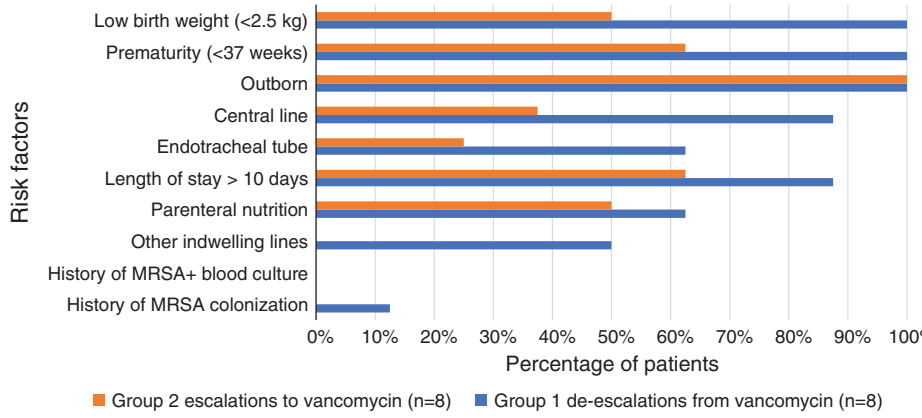
This study evaluated multiple risk factors for MRSA, based on previous findings in the literature. Our results are generally consistent with the findings of other studies that evaluated MRSA risk factors in the neonatal population. Balamohan and colleagues[21] found MRSA colonization to be a risk factor for infection when adjusted for length of stay and gestational age, and a case-control study by El Manouni El Hassani and colleagues[23] found that parenteral nutrition for more than 10 days was associated with higher odds of developing LOS irrespective of an identified pathogen. Additionally, similar to this study's findings, Stoll and colleagues[25] found that rates of LOS were inversely related to birth weight and gestational age and positively correlated with length of hospital stay and duration of intravascular access. Though our study did not evaluate duration of intravascular access, significantly more patients with central lines were initiated on vancomycin empirically. Finally, prematurity was the most prevalent risk factor in patients who were started on vancomycin. Many studies have found a strong correlation between lower gestational age at birth and risk of infection, while others have found links between lower gestational age and the development of comorbidities such as bronchopulmonary dysplasia, cognitive deficits, and necrotizing enterocolitis.[7,24,28,29]

Antimicrobial stewardship is an important tool to use in the NICU setting, and several practices have been established to help promote stewardship principles. For example, nares swabs can be helpful in determining colonization status in suspected and confirmed MRSA infections. One hospital found that educating providers on the use of nasal screening to guide vancomycin de-escalation resulted in both an increase in the use of nasal swabs and a decrease in vancomycin use per 1000 patient-days.[30] In a pharmacist-led nasal MRSA screening for adult intensive care patients, Diep and colleagues[31] saw a decrease in the average duration of vancomycin and number of vancomycin concentrations drawn. Other data have shown that nasal *S aureus* surveillance can help detect and prevent infection in high-risk neonates.[32,33]

Decolonization using topical agents such as mupirocin may also prove to be an important tactic in reducing exposure to MRSA and developing infection. Kotloff and colleagues[34] conducted a study on the safety and efficacy of topical mupirocin at multiple body sites (including intranasally) in eligible NICU patients, and found that most patients achieved decolonization within 3 days of completion of therapy. Another retrospective cohort study completed by Pierce and colleagues[35] found that among MRSA-colonized neonates, the hazard ratio for developing a Gram-positive infection was 64% lower in patients who received topical mupirocin than in those who did not. This institution's *Staphylococcus* screening policy, as illustrated in Figure 1, has helped to identify patients who are at higher risk of developing a MRSA infection. This study demonstrated that history of positive MRSA blood culture, as well as colonization, is used at our institution to determine empiric therapy.

The risk of nephrotoxicity related to vancomycin use is also an important factor to consider when choosing empiric therapy. The AWAKEN study by Jetton and colleagues,[36] which included patients at this institution, found an overall acute kidney injury (AKI) prevalence of about 29.9% in NICU patients, which increased to 47.9% in patients between 22 and 29 weeks' gestational age. This study also found that patients with AKI had a mortality odds ratio of 4.6 and an increase in the average length of stay by 8.8 days, compared with patients who did not have AKI. Several other studies have found that acute kidney injury in neonates is associated with higher rates of morbidity and mortality, and the risk is greater in patients with sepsis, prematurity, and very low birth weight.[37,38] Because nephrotoxic drug exposure may be considered a modifiable risk factor for AKI, institutions who use programs such as Baby NINJA may be more inclined to choose agents based on risk of nephrotoxicity.[39,40] Indicators of neonatal renal function in this study were not evaluated at time of review, which may have affected providers' decision-making. However, our study emphasizes the need for using stewardship strategies in the management of antimicrobial therapy

Figure 3. MRSA Risk Factors in Patients who Received ≥ 5 Days of Antibiotic Therapy and Broadened or Narrowed from Empiric Choice



MRSA, methicillin-resistant Staphylococcus aureus

in LOS. Considering risk factors such as gestational age and birth weight can potentially help mitigate risk of acute kidney injury in these patients. Additionally, increasing monitoring of renal function and vancomycin levels may be sufficient when considering initiation of vancomycin where there is a clear benefit.

Determining the need for broad-spectrum antibiotics can vary across institutions, based on policies and local antibiograms, but there is strong evidence to support the use of protocols to promote stewardship. At one hospital, Chiu and colleagues[41] developed a NICU vancomycin use guideline for their institution that does not allow vancomycin initiation until the condition of the infant receiving an alternative agent, such as nafcillin or oxacillin, clinically deteriorates after 48 hours of sterile cultures, or the cultures grow MRSA or CoNS. This guideline reduced both the number of infants exposed to vancomycin as well as the use of vancomycin per 1000 patient-days.[41,42] At the time of data collection, this institution's NICU did not have a guideline for the use of vancomycin. Therefore, the data in this study have been used to create a NICU vancomycin algorithm that may be helpful to institutions that do not currently have the means to guide antibiotic choices through established policies or protocols.

As shown in Figure 3, the proposed algorithm is based on our finding that patients who were started on vancomycin had 4.88 risk factors for MRSA on average. MRSA colonization and culture history are well described in the literature as being highly correlated to MRSA infection, and patients with either of these risk factors should receive vancomycin empirically. According to the proposed algorithm, vancomycin can be considered in patients with 5 or more of the risk factors listed in our study. Although hemodynamic instability was not recorded in our patients, it is included in the algorithm to account for patients who may not have enough risk factors but have a higher acuity. This addition is also supported by the AAP Red Book guidance on invasive staphylococcal infections, which recommends vancomycin empirically for life-threatening *S aureus* infections with unknown susceptibility.[16] Finally, our algorithm recommends narrowing based on cultures and susceptibilities, as well as discontinuing antibiotics after 36 hours of negative culture findings. While we did not capture time to discontinuation, other studies have used between 24 and 48 hours to rule out the need for antibiotics.[43–46]

When applied to this study's patients, the algorithm highlights the need for reduction in both the initial exposure and duration of therapy for vancomycin, especially considering the low incidence of MRSA (1%) found during the study timeframe. In group 1 patients, 33 of 51 workups (65%) would have resulted in initiation of vancomycin when using the algorithm without accounting for hemodynamic instability. Of the patients in group 1 who received vancomycin for at least 5 days, 6 of the 11 patients (55%) would have been initiated on vancomycin according to our algorithm, and only the 4 patients with positive culture findings would have received vancomycin for the full treatment course.

Our study was limited by being conducted at a single center, which may influence factors such as local resistance patterns or provider prescribing preferences. Owing to the retrospective nature of this study, it was difficult to capture patient acuity at the time of infectious workup, which would have been valuable information when determining appropriateness of antibiotic choice. Infectious markers such as white blood cell count, C-reactive protein, and procalcitonin were also not evaluated in this study, which may be useful

in determining empiric antibiotic choice and length of therapy according to previous findings.[26,39,47]

Limitations also exist for the proposed vancomycin use algorithm. While we recommend that all institutions use an algorithm or protocol to conserve the use of vancomycin for patients with LOS, local antibiograms should be used to evaluate rates of MSSA/MRSA incidence and guide therapy. This algorithm should be used only as a guideline, as medical treatment of LOS should occur through shared decision-making with the care team and the patient's family.

Conclusions

Many risk factors for MRSA infection are present in infants started on vancomycin empirically at our institution, and these risk factors are used to determine empiric antibiotic regimens in LOS at this institution. Using a history of MRSA infection or colonization, as well as MRSA risk factors, is important in choosing an empiric antimicrobial agent. This institution had opportunities to avoid vancomycin as well as reduce the length of vancomycin exposure according to the proposed algorithm, largely owing to the lack of patients with positive culture results and incidence of MRSA, and future efforts will be focused on narrowing therapy 36 hours after cultures are obtained. Further studies are needed to determine the true nature of the relationship between the studied risk factors and the incidence of MRSA infection to optimize empiric antibiotic choices.

Article Information

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References

1. Zervou FN, Zacharioudakis IM, Ziakas PD, Mylonakis E. MRSA colonization and risk of infection in the neonatal and pediatric ICU: a meta-analysis. *Pediatrics*. 2014;133(4):e1015-23.
2. Carey AJ, Duchon J, Della-Latta P, Saiman L. The epidemiology of methicillin-susceptible and methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit, 2000-2007. *J Perinatol*. 2010;30(2):135–139.
3. Singh M, Alsaleem M, Gray CP. Neonatal sepsis. In: *StatPearls*. Stat Pearls Publishing; 2023.
4. Wynn JL. Defining neonatal sepsis. *Curr Opin Pediatr*. 2016;28(2):135–140.
5. Fleischmann C, Reichert F, Cassini A, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. *Arch Dis Child*. 2021;106(8):745–752.
6. Berlak N, Shany E, Ben-Shimol S, et al. Late onset sepsis: comparison between coagulase-negative staphylococci and other bacteria in the neonatal intensive care unit. *Infect Dis (Lond)*. 2018;50(10):764–770.
7. Flannery DD, Edwards EM, Coggins SA, et al. Late-onset sepsis among very preterm infants. *Pediatrics*. 2022;150(6), 1–9.
8. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis*. 2011;52(3):e18–55.
9. Wang J, Zhang H, Yan J, Zhang T. Literature review on the distribution characteristics and antimicrobial resistance of bacterial pathogens in neonatal sepsis. *J Matern Fetal Neonatal Med*. 2022;35(5):861–870.
10. Gkentzi D, Dimitriou G. Antimicrobial stewardship in the neonatal intensive care unit: an update. *Curr Pediatr Rev*. 2019;15(1):47–52.
11. Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, et al. Role of antimicrobial stewardship programmes in children: a systematic review. *J Hosp Infect*. 2018;99(2):117–123.
12. Lamba V, D'Souza S, Carafa C, et al. Standardizing the approach to late onset sepsis in neonates through antimicrobial stewardship: a quality improvement initiative. *J Perinatol*. 2020;40(9):1433–1440.
13. Magers J, Prusakov P, Speaks S, et al. Safety and efficacy of nafcillin for empiric therapy of late-onset sepsis in the NICU. *Pediatrics*. 2022;149(5), 1–10.
14. Romanelli RM, Anchieta LM, Bueno ESAC, et al. Empirical antimicrobial therapy for late-onset sepsis in a neonatal unit with high prevalence of coagulase-negative Staphylococcus. *J Pediatr (Rio J)*. 2016;92(5):472–478.
15. Coggins SA, Glaser K. Updates in late-onset sepsis: risk assessment, therapy, and outcomes. *Neoreviews*. 2022;23(11):738–755.
16. Committee on Infectious Diseases, Kimberlin DW, Barnett ED, et al. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. American Academy of Pediatrics; 2021.
17. Washam M, Woltmann J, Haberman B, et al. Risk factors for methicillin-resistant Staphylococcus aureus

colonization in the neonatal intensive care unit: a systematic review and meta-analysis. *Am J Infect Control*. 2017;45(12):1388–1393.
18. Sakaki H, Nishioka M, Kanda K, Takahashi Y. An investigation of the risk factors for infection with methicillin-resistant Staphylococcus aureus among patients in a neonatal intensive care unit. *Am J Infect Control*. 2009;37(7):580–586.
19. Nelson MU, Gallagher PG. Methicillin-resistant Staphylococcus aureus in the neonatal intensive care unit. *Semin Perinatol*. 2012;36(6):424–430.
20. Huang YC, Chou YH, Su LH, et al. Methicillin-resistant Staphylococcus aureus colonization and its association with infection among infants hospitalized in neonatal intensive care units. *Pediatrics*. 2006;118(2):469–474.
21. Balamohan A, Beachy J, Kohn N, Rubin LG. Risk factors for nosocomial methicillin resistant Staphylococcus aureus (MRSA) colonization in a neonatal intensive care unit: a case-control study. *Am J Infect Control*. 2021;49(11): 1408–1413.
22. Nurjadi D, Eichel VM, Tabatabai P, et al. Surveillance for colonization, transmission, and infection with methicillin-susceptible Staphylococcus aureus in a neonatal intensive care unit. *JAMA Netw Open*. 2021;4(9):e2124938.
23. El Manouni El Hassani S, Berkhout DJC, Niemarkt HJ, et al. Risk factors for late-onset sepsis in preterm infants: a multicenter case-control study. *Neonatology*. 2019;116(1):42–51.
24. Klinger G, Bromiker R, Zaslavsky-Paltiel I, et al. Late-onset sepsis in very low birth weight infants. *Pediatrics*. 2023;152(5); 1–10.
25. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics*. 2002;110(2 pt 1):285–291.
26. Tang YH, Jeng MJ, Wang HH, et al. Risk factors and predictive markers for early and late-onset neonatal bacteremic sepsis in preterm and term infants. *J Chin Med Assoc*. 2022;85(4):507–513.
27. Jiang S, Hong L, Gai J, et al. Early-onset sepsis among preterm neonates in China, 2015 to 2018. *Pediatr Infect Dis J*. 2019;38(12):1236–1241.
28. Twilhaar ES, Wade RM, de Kieviet JF, et al. Cognitive outcomes of children born extremely or very preterm since the 1990s and associated risk factors: a meta-analysis and meta-regression. *JAMA Pediatr*. 2018;172(4):361–367.
29. Platt MJ. Outcomes in preterm infants. *Public Health*. 2014;128(5):399–403.
30. Gentges J, El-Kouri N, Rahman T, et al. Use of nares swab to de-escalate vancomycin for patients with suspected methicillin-resistant Staphylococcus aureus. *Antimicrob Steward Healthc Epidemiol*. 2023;3(1):e167.
31. Diep C, Meng L, Pourali S, et al. Effect of rapid methicillin-resistant Staphylococcus aureus nasal polymerase chain reaction screening on vancomycin use in the intensive care unit. *Am J Health Syst Pharm*. 2021;78(24):2236–2244.
32. Symons E, VanWanzeele D, McCulloh R. Methicillin-resistant Staphylococcus aureus surveillance testing: more than meets the nare. *Hosp Pediatr*. 14 (2):e113–e115.2024;
33. Khamash DF, Mongodin EF, White JR, et al. The association between the developing nasal microbiota of hospitalized neonates and Staphylococcus aureus colonization. *Open Forum Infect Dis*. 2019;6(4):ofz062.
34. Kotloff KL, Shirley DT, Creech CB, et al. Mupirocin for Staphylococcus aureus decolonization of infants in neonatal intensive care units. *Pediatrics*. 2019;143(1); 1–11.
35. Pierce R, Bryant K, Elward A, et al. Bacterial infections in neonates following mupirocin-based MRSA decolonization: a multicenter cohort study. *Infect Control Hosp Epidemiol*. 2017;38(8):930–936.
36. Jetton JG, Boohaker LJ, Sethi SK, et al. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *Lancet Child Adolesc Health*. 2017;1(3):184–194.
37. Starr MC, Charlton JR, Guillet R, et al. Advances in neonatal acute kidney injury. *Pediatrics*. 2021;148(5), 1–14.
38. Hanna MH, Askenazi DJ, Selewski DT. Drug-induced acute kidney injury in neonates. *Curr Opin Pediatr*. 2016;28(2):180–187.
39. Stoops C, Stone S, Evans E, et al. Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action): reduction of nephrotoxic medication-associated acute kidney injury in the neonatal intensive care unit. *J Pediatr*. 2019;215:223–228 e6.
40. Stone SB, Bisaccia E, Zakhary MS, et al. Implementation strategies for Baby NINJA (Nephrotoxic Injury Negated by Just-in-Time Action) to prevent neonatal medication-induced kidney injury. *J Pediatr Pharmacol Ther*. 2023;28(4):287–296.
41. Chiu CH, Michelow IC, Cronin J, et al. Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. *Pediatr Infect Dis J*. 2011;30(4):273–278.
42. Cantey JB, Patel SJ. Antimicrobial stewardship in the NICU. *Infect Dis Clin North Am*. 2014;28(2):247–261.
43. Pantoja A, Sveum S, Frost S, et al. New strategies to reduce unnecessary antibiotic use in the NICU: a quality improvement initiative. *Pediatr Qual Saf*. 2023;8(3):e659.
44. Bauer SC, Kaeppler C, Soung P, et al. Using electronic health record tools to decrease antibiotic exposure in infant sepsis evaluation. *Hosp Pediatr*. 2021;11(9):936–943.
45. Cantey JB, Wozniak PS, Pruszynski JE, Sanchez PJ. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. *Lancet Infect Dis*. 2016;16(10):1178–1184.
46. Ur Rehman Durrani N, Rochow N, Alghamdi J, et al. Minimum duration of antibiotic treatment based on blood culture in rule out neonatal sepsis. *Pediatr Infect Dis J*. 2019;38(5):528–532.
47. Kurul S, Simons SHP, Ramakers CRB, et al. Association of inflammatory biomarkers with subsequent clinical course in suspected late onset sepsis in preterm neonates. *Crit Care*. 2021;25(1):12.