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Challenges of Vancomycin Dosing and Therapeutic Monitoring in Neonates

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Late-onset sepsis in neonates can lead to significant morbidity and mortality, especially in preterm infants. Vancomycin is commonly prescribed for the treatment of Gram-positive organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci, and ampicillin-resistant *Enterococcus* species in adult and pediatric patients. Currently, there is no consensus on optimal dosing and monitoring of vancomycin in neonates. Different vancomycin dosing regimens exist for neonates, but with many of these regimens, obtaining therapeutic trough concentrations can be difficult. In 2011, the Infectious Diseases Society of America recommended vancomycin trough concentrations of 15 to 20 mg/L or an AUC/MIC ratio of ≥400 for severe invasive diseases (e.g., MRSA) in adult and pediatric patients. Owing to recent reports of increased risk of nephrotoxicity associated with vancomycin trough concentrations of 15 to 20 mg/L and AUC/MIC of ≥400, a revised consensus guideline, recently published in 2020, no longer recommends monitoring vancomycin trough concentrations in adult patients. The guideline recommends an AUC/MIC of 400 to 600, which has been found to achieve clinical efficacy while reducing nephrotoxicity. However, these recommendations were derived solely from adult literature, as there are limited clinical outcomes data in pediatric and neonatal patients. Furthermore, owing to the variation of vancomycin pharmacokinetic parameters among the neonatal population, these recommendations for achieving vancomycin AUC/MIC of 400 to 600 in neonates require further investigation. This review will discuss the challenges of achieving optimal vancomycin dosing and monitoring in neonatal patients.

ABBREVIATIONS AKI, acute kidney injury; AUC, area under the curve; AUC/MIC, area under curve to minimum inhibitory concentration; BMD, broth microdilution; CoNS, coagulase-negative staphylococci; GA, gestational age; IDSA, Infectious Diseases Society of America; LOS, late-onset sepsis; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; NICU, neonatal intensive care unit; PD, pharmacodynamic; PK, pharmacokinetic; PMA, postmenstrual age; PNA, postnatal age; VIN, vancomycin-induced nephrotoxicity

KEYWORDS area under the curve; dosing; minimum inhibitory concentration; neonate; pharmacodynamic; pharmacokinetic; vancomycin

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Late-onset sepsis (LOS) in neonates can lead to significant morbidity and mortality, with a mortality rate of approximately 15% in very-low-birth-weight infants (infants with birth weight <1500 g).[1] Late-onset sepsis generally occurs 3 to 7 days after birth following exposure to pathogens in the NICU.[2] The most common pathogens are coagulase-negative staphylococci (CoNS), predominantly methicillin-resistant *Staphylococcus epidermidis* (MRSE); other pathogens include *Staphylococcus aureus,* Enterobacteriaceae, and *Candida* species. Risk factors for LOS include use of invasive devices, such as mechanical ventilation, intravascular catheters and/or other indwelling catheters, and prolonged duration of parenteral nutrition.[3,4]

Empiric therapy for LOS should be guided by the presence of risk factors for commensal organisms (including previously isolated pathogens) and the local antibiotic resistance data at the individual unit or institution. Vancomycin is commonly prescribed for the treatment of Gram-positive organisms, particularly methicillin-resistant *S aureus* (MRSA), CoNS, and ampicillin-resistant *Enterococcus* species in adult and pediatric/neonatal patients. MRSA is considered to be vancomycin susceptible at a MIC of ≤2 mg/L, although susceptible MICs for CoNS are ≤4 mg/L.[5]

Empiric Vancomycin Dosing

Variations in Vancomycin Pharmacokinetics in Neonates. Currently, there is no consensus on optimal dosing and monitoring of vancomycin in neonates. Vancomycin dosing regimens are mainly based on neonatal age (postmenstrual age [PMA] and postnatal age [PNA]), body weight, and serum creatinine. Different vancomycin dosing regimens exist for neonates, but with many of these regimens, obtaining therapeutic trough concentrations may be difficult. This may be due

to the changes in pharmacokinetic (PK) parameters, such as volume of distribution and clearance within the neonatal population, and variations in dosing regimens published in common references. Vancomycin protein binding also needs to be considered when determining optimal dosing in neonates. The fraction of vancomycin that remains unbound is higher in neonates than in children and adults owing to lower levels of mature proteins in neonates.[6] Smits et al[6] reported that the total vancomycin concentration and albumin levels were the most important covariates of unbound vancomycin concentrations, based on multiple regression analysis. Future PK and pharmacodynamic (PD) analyses should consider protein binding when evaluating vancomycin dosing and determining vancomycin PD targets for neonates. Based on these findings, a lower AUC/MIC ratio may be adequate for the treatment of Gram-positive pathogens in neonates owing to higher drug concentrations secondary to lower protein levels and drug protein binding.

Evaluation of Vancomycin Dosing in Neonates. The vancomycin dosing regimen recommended in Neofax[7] is based on a combination of PMA and PNA. The American Academy of Pediatrics' *Red Book*[8] uses serum creatinine, which can fluctuate within the first 5 to 7 days of life, as a covariate for vancomycin dosing in all neonates.[8,9] Lexicomp[10] provides 2 vancomycin dosing regimens for neonates: renal function–based dosing (using serum creatinine and gestational age [GA]) and weight-directed dosing (using body weight and PNA). In a population PK vancomycin study of preterm and term neonates, Bhongsatiern et al[11] reported that body weight, creatinine clearance, and PMA all significantly influenced vancomycin clearance. However, body weight was found to be the most significant covariate on vancomycin volume of distribution.[11] Kato et al[12] reported that 95% of very-low-birth-weight infants achieved AUC/MIC ≥400 (MIC ≤1 mg/L) with vancomycin 12.5 mg/kg/dose every 8 hours, and 70.5% of infants achieved vancomycin trough concentration of 10 to 20 mg/L with vancomycin 10 mg/kg/dose every 8 hours (Table).[12]

Dao et al[13] performed model-based simulations to evaluate and compare 20 different vancomycin guidelines in achieving vancomycin target attainment. Target attainment meant AUC/MIC ratio of 400 to 700 and trough concentration of 10 to 20 mg/L, on days 1 and 7. The median proportion of patients on day 1 with an AUC/MIC ≥400 was 42% (IQR, 28%–69%); with trough concentrations of 10 to 20 mg/L, it was 32% (IQR, 24%–45%). The proportion of patients achieving target attainment after 7 days of vancomycin exposure increased to 48% (IQR, 43%–52%) for AUC/MIC ≥400 and 38% (IQR, 32%–41%) for trough concentrations of 10 to 20 mg/L. The dosing regimens from Neofax (high dose)[7] and Lexicomp (high dose)[10] were 2 of the best regimens for achieving targeted AUC/MIC after 7 days of vancomycin.[13] High dose is defined as using the higher end of the dosing range (Supplemental Table).

A recent study conducted by Frymoyer et al[14] evaluated the utility of a PK model–based dosing approach, known as the Neo-Vanco, and compared it to commonly used vancomycin recommendations (Neofax, Red Book, and Lexicomp) in 492 neonates with a median GA of 32 weeks and PMA of 36 weeks. Neo-Vanco is a utility tool designed to individualize vancomycin dosing in neonates. The tool is based on a population PK model developed by Frymoyer et al[15] with external validation described by Stockmann et al[16] that included neonatal population PK (weight, PMA, and serum creatinine). The authors reported a significantly higher percentage of infants achieving an AUC/MIC ratio of >400 with Neo-Vanco (94%) than with Neofax (23%), Red Book (49%), and Lexicomp (55%) ($p < 0.0001$). The overall rates of neonates predicted to have high vancomycin trough concentrations > 20 mg/L was low in all 4 dosing strategies and were similar between Neo-Vanco, Red Book, and Lexicomp (2.8% vs 2.6% vs 4.1%, respectively). However, this rate was significantly higher with Neo-Vanco than with Neofax (2.8% vs 1%, $p = 0.03$). The proportion of infants with predicted subtherapeutic vancomycin trough concentrations < 5 mg/L was significantly lower with Neo-Vanco (1%) than with Neofax (18%), Red Book (23%), and Lexicomp (19%), ($p < 0.0001$) (Table).[14] Neo-Vanco is a user-friendly cloud-based Web tool (http://neovanco.insight-rx.com/neo-vanco) that is widely used, tested, and embedded in several electronic health records (e.g., Epic Systems, Madison, WI). Based on the study result, Neo-Vanco may be used for empiric vancomycin dosing in both term and preterm infants. Neo-Vanco is intended for use only in neonates with PMA < 52 weeks with no major congenital heart disease (including those receiving extracorporeal membrane oxygenation) or congenital kidney disease (including those receiving renal replacement therapy).

Therapeutic Monitoring

Challenges of the Application of Adult Guidelines to Pediatric and Neonatal Patients. Monitoring of vancomycin is important to avoid bacterial resistance and drug toxicity, particularly vancomycin-induced nephrotoxicity (VIN). Bacterial killing of *S aureus* for vancomycin is best predicted by the AUC-time curve over 24 hours divided by the MIC of the organism.[17,18] Adult literature has demonstrated that when the MIC is ≤1 mg/L, achieving an AUC/MIC of ≥400 results in superior clinical and bacteriologic response in patients with *S aureus* infections.[19] In 2011, the Infectious Diseases Society of America (IDSA) published the first set of guidelines with a recommendation of vancomycin dosing of 15 mg/kg/dose every 6 hours in children with serious or invasive disease (e.g., bacteremia, infective endocarditis, osteomyelitis, meningitis, or pneumonia).[20] The guidelines also state that the efficacy and safety of trough concentrations of 15 to 20 mg/L

Table. Clinical Studies of Vancomycin Dosing and Monitoring in Neonates

Reference	Study Objectives	Patient Population	Results
Vancomycin Dosing: Correlation Between Dosing and Trough Concentrations and AUC/MIC			
Bhongsatiern[11]	Develop population PK model for vancomycin and determine probability of attaining target AUC/MIC ≥400 by using conventional dosing regimens	152 preterm and term neonates (n = 152) with median GA 27 (IQR, 24–33) wk Vancomycin serum concentrations (n = 528)	PK changes: body weight, CrCL, PMA all significantly influenced vancomycin clearance; body weight was the most significant covariate on vancomycin Vd Target AUC/MIC ≥400 (MIC ≤1) • 64.6% (15–29 mg/kg/day) • 57.1% (≥60 mg/kg/day) • 54.5% (30–44 mg/kg/day) • 50% (<15 mg/kg/day) • 22.7% (45–59 mg/kg/day)
Kato[12]	Develop optimal vancomycin dosing regimen by using population parameters and assess relationship between target vancomycin trough concentration 10–20 mg/L and AUC/MIC ≥400	10 VLBW infants ≤ 1500 g with mean GA 26.8 ± 3.0 wk and BW 780 ± 17 g	Target AUC/MIC ≥ 400 (MIC ≤1) • 95% vancomycin (12.5 mg/kg/dose q 8 hr) • 93.6% (17.5 mg/kg/dose q 8 hr) • 86.7% (10 mg/kg/dose q 8 hr) • 70% (7.5 mg/kg/dose q 8 hr) • 56.8% (10 mg/kg/dose q 12 hr) Target vancomycin trough concentration, 10–20 mg/L • 70.5% (10 mg/kg/dose q 8 hr) • 61% (12.5 mg/kg/dose q 12 hr) • 58.9% (12.5 mg/kg/dose q 8 hr) • 57.4% (10 mg/kg/dose q 12 hr) • 56.9% (7.5 mg/kg/dose q 8 hr)
Dao[13]	Perform model-based simulations to evaluate and compare the performance of 20 current vancomycin dosing guidelines to target attainment (AUC/MIC of 400–700 and vancomycin trough concentrations 10–20 mg/L) on days 1 and 7*	Evaluated 20 different vancomycin dosing guidelines in neonates (n = 405); preterm (n = 331), term neonates (n = 740) with 1831 vancomycin serum concentrations	Early vancomycin exposure on day 1 • Median proportion with AUC/MIC 400–700 was 42% (IQR, 28%–69%); 1% (IQR, 0%–3%) for AUC/MIC >700; 52% (IQR, 29%–71%) for <400 • Median proportion with trough 10–20 mg/L was 32% (IQR, 24%–45%); 9% (IQR, 5%–20%) for <5 mg/L; 12% (IQR, 1%–27%) for >20 mg/L Early vancomycin exposure on day 7 • Median proportion with AUC/MIC 400–700 was 48% (IQR, 43%–52%); 20% (8%–25%) for >700; 32% (IQR, 19%–43%) • Median proportion with trough 10–20 mg/L was 38% (IQR, 32%–41%) Optimal exposure in 94% of infants on day 1 • Janssen and NICU-CH7 (15 mg/kg/dose q 8 hr for all neonates) were the best Optimal exposure in 73% of infants on day 7 • NICU-CH6 (Hi-Dose)†, Neofax (Hi-Dose)†, Lexicomp (Hi-Dose)†, and NNF7 were the best

BW, birth weight; CoNS, coagulase-negative staphylococci; CrCL, creatinine clearance; GA, gestational age; IQR, interquartile range; MRSA, methicillin-resistant Staphylococcus aureus; PK, pharmacokinetic; PMA, postmenstrual age; Vd, volume of distribution; VLBW, very low birth weight

* See Supplemental Table for vancomycin dosing regimens.

† High dose is defined as using the higher end of the dosing range.

‡ Neofax 2011[7]; Neofax 2010.[25]

Table. Clinical Studies of Vancomycin Dosing and Monitoring in Neonates *(cont.)*

Reference	Study Objectives	Patient Population	Results
Vancomycin Dosing: Correlation Between Dosing and Trough Concentrations and AUC/MIC			
Frymoyer[14]	Compare expected vancomycin exposure concentrations (target AUC/MIC > 400, vancomycin trough concentrations >20 mg/L and <5 mg/L) in neonates by using a model-based dosing approach known as the Neo-Vanco–derived dosing strategy to the 3 commonly used dosing recommendations (Neofax, Red Book, Lexicomp)	Neonates (n = 492) with a median GA 32 wk and PMA 36 wk	Target AUC/MIC ≥ 400 (MIC 1) • Median vancomycin dose with Neo-Vanco (40 mg/kg/day) was significantly higher than with Neofax (29.6 mg/kg/day), Red Book (30 mg/kg/day), and Lexicomp (30.3 mg/kg/day), (p < 0.0001) • Achieving AUC/MIC > 400 was significantly higher with Neo-Vanco (94%) than with Neofax (23%), Red Book (49%), and Lexicomp (55%), (p < 0.001) Vancomycin trough concentrations • Median vancomycin trough concentrations were higher with Neo-Vanco (11.8 mg/kg/day) than with Neofax (7.5 mg/kg/day), Red Book (7.1 mg/kg/day), and Lexicomp (8.4 mg/kg/day), (p < 0.0001) Vancomycin trough concentration > 20 mg/L • No significant difference between Neo-Vanco (2.8%), Red Book (2.6%), and Lexicomp (4.1%) • Vancomycin trough concentration > 20 mg/L was significantly higher with Neo-Vanco (2.8%) than with Neofax (1%), (p = 0.03) Vancomycin trough concentration < 5 mg/L • Neo-Vanco had significantly less (1%) compared to Neofax (18%), Red Book (23%), and Lexicomp (19%), (p < 0.0001)
Vancomycin Monitoring: Correlation Between Trough Concentrations and AUC/MIC			
Frymoyer[15]	Determine the relationship between vancomycin trough concentration and target AUC/MIC >400 in neonates	Neonates (n = 233) with median GA 34 wk and PMA 39 wk, using vancomycin serum concentrations (n = 1702)	Vancomycin trough concentrations and AUC/MIC > 400 • Median AUC/MIC was 403 (range, 124–869) • AUC/MIC ranged up to 3-fold across neonatal population for a given trough concentration • >90% of neonates achieved AUC/MIC >400 with trough concentration of 10–11 mg/L Impact of PMA and serum creatinine on trough concentration and AUC/MIC >400 • Target trough concentrations that were predictive of >90% of neonates achieving AUC/MIC >400 ranged from 7–11 mg/L across PMA and serum creatinine (range, 0.4–1.6 mg/dL) • 20% had high vancomycin trough concentrations (20 mg/L) and 40% had low vancomycin trough concentrations (<5 mg/L)

BW, birth weight; CoNS, coagulase-negative staphylococci; CrCL, creatinine clearance; GA, gestational age; IQR, interquartile range; MRSA, methicillin-resistant Staphylococcus aureus; PK, pharmacokinetic; PMA, postmenstrual age; Vd, volume of distribution; VLBW, very low birth weight

* See Supplemental Table for vancomycin dosing regimens.

† High dose is defined as using the higher end of the dosing range.

‡ Neofax 2011[7]; Neofax 2010.[25]

Table. Clinical Studies of Vancomycin Dosing and Monitoring in Neonates *(cont.)*

Reference	Study Objectives	Patient Population	Results
Vancomycin Monitoring: Correlation Between Trough Concentrations and AUC/MIC			
Chen[26]	Predict percentage of Chinese neonates receiving vancomycin dosing regimen who achieve AUC/MIC ≥400	Neonates (n = 213) with median GA 37 (range, 25–42) wk and PMA 40 (range, 28 – 48) wk Vancomycin dosing regimen from Neofax 2011[‡]; vancomycin serum concentrations (n = 330)	Vancomycin trough concentrations and AUC/MIC ≥400 for MIC ≤0.5 mg/L • 88% achieved AUC/MIC ≥ 400 with vancomycin trough concentrations <5 mg/L; 95% with trough concentrations 5–10 mg/L; 100% with trough concentrations >10 mg/L Vancomycin trough concentrations and AUC/MIC ≥400 for MIC of 1 mg/L • 6% achieved AUC/MIC ≥400 with vancomycin trough concentrations < 5 mg/L; 15% with trough concentrations 5–10 mg/L; 14% with trough concentrations 10–15 mg/L; 55% with trough concentrations >10 mg/L Vancomycin trough concentrations and AUC/MIC ≥400 for MIC of 2 mg/L • No infants achieved AUC/MIC ≥400
Tseng[27]	Determine minimum vancomycin trough concentration range predictive of achieving AUC/MIC ≥400 in Asian neonates	Neonates (n = 76) with median GA 26 (IQR, 25–29) wk and PMA 30 (IQR, 28–36) wk. Vancomycin serum concentrations (n = 184)	• 75% of vancomycin trough concentrations achieving AUC/MIC ≥ 400 • Minimum vancomycin trough concentration of 8–8.9 mg/L was predictive of achieving AUC/MIC ≥400 in >90% of neonates for MRSA isolates with vancomycin MIC of ≤1 mg/L • Almost 100% of vancomycin trough concentrations between 10–20 mg/L achieved AUC/MIC ≥ 400 • As PMA increased from 24 wk to 46 wk, the minimum vancomycin trough concentration range predictive of achieving AUC/MIC ≥ 400 also increased from 7–7.9 mg/L to 9–9.9 mg/L
Vancomycin Monitoring: Correlation Between Coagulase-Negative Staphylococci and AUC/MIC			
Padari[24]	Identify vancomycin dosing regimen needed for 80% and 90% probability of target attainment of AUC/MIC ≥400 and AUC/MIC ≥300 with MIC of CoNS isolates in neonates. Correlate individual AUC/MIC with clinical outcome	Neonates (n = 76) with a mean GA of 29 wk and PMA of 31 wk Vancomycin dosing regimen from Neofax 2010[‡]. Vancomycin serum concentrations (n = 186)	• Target AUC/MIC ≥400 and AUC/MIC ≥300 achieved <25% and 40%, respectively, with vancomycin dosing regimen for treating CoNS bacteremia • 12% of neonates achieved AUC/MIC ≥400 and 34% for AUC/MIC ≥300 for CoNS bacteremia • The median AUC/MIC ratio for neonates with clinical success was higher (269; IQR, 131–327) than for those with clinical failure (210; IQR, 140–319)

BW, birth weight; CoNS, coagulase-negative staphylococci; CrCL, creatinine clearance; GA, gestational age; IQR, interquartile range; MRSA, methicillin-resistant Staphylococcus aureus; PK, pharmacokinetic; PMA, postmenstrual age; Vd, volume of distribution; VLBW, very low birth weight

[*] See Supplemental Table for vancomycin dosing regimens.

[†] High dose is defined as using the higher end of the dosing range.

[‡] Neofax 2011[7]; Neofax 2010.[25]

in children should be considered, but require further study in patients with serious infections. These higher goal trough concentrations correlate with an AUC/MIC ≥400, a suggested predictor of vancomycin efficacy. The guidelines, however, do not address vancomycin dosing in neonates. Although IDSA provided recommendations for monitoring vancomycin trough concentrations for both efficacy and safety, there are concerns regarding its applicability to neonatal vancomycin dosing and monitoring. The IDSA guideline recommended vancomycin trough concentrations of 15 to 20 mg/L for invasive infections caused by MRSA, which were based primarily on adult PK and PD data that achieved an AUC/MIC of ≥400. However, in neonates, the most common pathogen for LOS is MRSE; hence, the need for vancomycin therapy.[21] Currently, there are no studies evaluating the efficacy of this vancomycin dose for clinical and microbiologic outcomes related to the recommended AUC/MIC ratio in neonates. Although serum trough concentrations are usually obtained as a surrogate marker for vancomycin AUC in routine clinical practice, vancomycin troughs may underestimate the true AUC owing to the high degree of interindividual variability in neonatal and pediatric patients. The AUC or exposure of vancomycin is dependent primarily on total body clearance and volume of distribution, which vary significantly in pediatric patients, particularly neonatal patients. The trough concentration is only reflective of a single point on the concentration-time curve, whereas AUC represents cumulative exposure over a 24-hour period. Chhim et al[22] reported that trough concentrations did not correlate well with predicted AUC in children >2 months to 17 years of age who were receiving vancomycin dosing of 40 to 60 mg/kg/day. More than 60% of those who received vancomycin 40 mg/kg/day and 43% of those who received 60 mg/kg/day had subtherapeutic vancomycin trough concentrations. Only 5% and 16.5% of those receiving 40 mg/kg/day and 60 mg/kg/day, respectively, had trough concentrations of 15 to 20 mg/L. The AUC is based on multiple serum concentrations; however, in this study, only 1 steady-state trough concentration was obtained. Therefore, trough concentrations may be a poor surrogate for the AUC in children.[22]

Based on animal and limited adult studies, AUC/MIC is a predictive PK parameter for measuring the efficacy of vancomycin for the treatment of MRSA and vancomycin-intermediate *S aureus* strains.[20] However, in neonates, CoNS or MRSE is the most common causative agent of neonatal LOS.[21] Although CoNS pathogens are usually not virulent, the organisms are known to be methicillin-resistant and have a higher MIC (median 2 mg/L; range, 0.5–4 mg/L) than MRSA.[13,23] Hence, a target of AUC/MIC ≥ 400 may or may not be enough for the treatment of CoNS bacteremia in neonates. Padari et al[24] aimed to evaluate a lower AUC/MIC ratio by using MIC of CoNS isolates as determined by Etest from their hospital and to correlate individual AUC/MIC ratios with clinical outcomes. An AUC/MIC ≥300 and AUC/MIC ≥400 were only achieved in 34% and 12% of neonates with CoNS bacteremia, respectively. The median AUC/MIC ratio for those with clinical success (defined as bacteriologic cure with clinical improvements) was higher than for those with clinical failure (268.6 with IQR of 130.7–326.5 vs 210.1 with IQR of 149.5–319.1, respectively); both were lower than target AUC/MIC ≥300 to 400. Using the recommended vancomycin dosing from Neofax,[25] target AUC/MIC ≥400 and AUC/MIC ≥300 would be achieved in less than 25% and 40% of cases, respectively, suggesting that the current vancomycin dosing regimen is not optimal for the achievement of this predefined AUC/MIC target in neonates with CoNS (Table).[24]

Correlation between Vancomycin Trough Concentrations and AUC/MIC. Recent PK modeling studies demonstrated lower vancomycin trough concentrations were needed to achieve the target AUC/MIC in neonates.[15, 26,27] Frymoyer et al[15] demonstrated that at a vancomycin trough concentration of 10 to 11 mg/L, more than 90% of the neonates achieved an AUC/MIC > 400. In addition, vancomycin trough concentrations of 7 to 11 mg/L are highly predictive of an AUC/MIC of ≥400 across a range of PMA, serum creatinine levels, and vancomycin doses in neonates with a median GA of 34 weeks and PMA of 39 weeks. They also reported that the AUC/MIC ranged up to 3-fold across neonates for a given trough concentration and that higher trough concentrations of 15 to 20 mg/L may increase the risk for toxicity.[15] Two recent studies using samples collected for therapeutic drug monitoring and population PK analysis also reported lower vancomycin trough concentrations needed to reach the target AUC/MIC ≥400. Chen et al,[26] using a cohort of 213 neonates (median GA of 37 weeks and PMA of 40 weeks), demonstrated that an AUC/MIC of ≥400 was achieved in 95% of the neonates with vancomycin trough concentrations of 5 to 10 mg/L for MIC values ≤0.5 mg/L. Achievement of target AUC/MIC decreased to 15% when the MIC increased to 1 mg/L, with trough concentrations of 5 to 10 mg/L. No infants achieved the target when MIC was 2 mg/L.[26] The authors also suggested that vancomycin doses of 14 and 15 mg/kg every 12 hours were needed to reach the target AUC/MIC ≥400 in 90% of infants with a PMA of 30 to 32 and of 32 to 34 weeks, respectively, with trough concentrations of 5 to 15 mg/L.[26] In a cohort of 76 neonates with a median GA of 26 weeks and PMA of 30 weeks, the authors reported that a minimum vancomycin trough concentration of 8 to 8.9 mg/L was predictive of achieving an AUC/MIC of ≥400 in >90% of neonates for MRSA isolates with vancomycin MIC of ≤1 mg/L. They further identified a proportion of infants with trough concentrations of 15 to 20 mg/L and AUC/MIC of >700.[27] These 3 studies demonstrated that higher vancomycin trough concentrations of 15 to 20 mg/L are

not necessary and may result in VIN (Table). Bhargava et al[28] reported a statistically significant association between acute kidney injury (AKI) and vancomycin trough concentrations > 15 mg/L (p = 0.04) in 110 neonates with a mean GA of 27 weeks. The incidence of AKI was 18.2% in those with vancomycin trough concentrations greater than 15 mg/L compared to 1.39% in those with trough concentrations less than 10 mg/L.[28] Regression analysis demonstrated a positive correlation value of 0.32 (p < 0.05) between increasing vancomycin trough concentrations and serum creatinine levels post vancomycin administration.

Revised IDSA Vancomycin Guideline. Since the 2011 IDSA guideline, numerous studies evaluating vancomycin's clinical efficacy and toxicity in adults and pediatric patients have been published.[29] Based on these newer findings, a revised consensus guideline, issued by the American Society of Health-System Pharmacists, IDSA, Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists in 2020, does *not* recommend monitoring vancomycin trough concentrations in adult patients with serious MRSA infections because higher trough concentrations of 15 to 20 mg/L have been associated with nephrotoxicity.[29] An AUC/MIC of 400 to 600 is the recommended target to achieve clinical efficacy while reducing the incidence of nephrotoxicity. Therapeutic monitoring should begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections. There are limited clinical outcomes data in pediatric and neonatal patients to support the target AUC found in adult patients for efficacy. Some of the differences that might affect target AUC in these populations include variation in vancomycin clearance among pediatric populations and differences in tissue site-of-infection drug exposure (osteomyelitis is more common in pediatrics while endocarditis is more common in adults) between pediatric and adult populations. Furthermore, the incidence of VIN in neonates is lower than in adults.[30] The guideline urges more studies, incorporating the assessment of clinical outcomes in pediatric patients with MRSA infections, to identify the optimal dosing strategies of vancomycin. Until then, the AUC/MIC target of 400 to 600 appears to be the most appropriate initial target for vancomycin in all pediatric age groups including neonates. AUC-guided therapeutic dosing and monitoring for vancomycin, preferably with Bayesian estimation, may be an optimal approach to individualize vancomycin dosing in pediatric populations, since it allows the incorporation of different ages, weights, and renal function. To achieve an AUC of 400 (MIC 1 mg/L) in neonates, vancomycin dosing regimens of 15 to 20 mg/kg/dose every 8 to 12 hours, depending on PMA and serum creatinine, are needed. Additionally, clinicians should consider a lower AUC/MIC target for CoNS infections. However, the guideline did not provide target AUC/MIC parameters, nor did it provide literature to support this recommendation. The guideline *does* recommend that clinicians continue to monitor vancomycin trough concentrations and renal function, since vancomycin clearance and creatinine clearance are not always well correlated in pediatric populations. Furthermore, similar to adults, vancomycin AUC/MIC should be lower than 800 and trough concentration ≤ 15 mg/L to minimize the risk of AKI in pediatric patients. The guideline did not provide recommendations on the target AUC/MIC for minimizing the risk of AKI in neonates. This may be due to the low incidence of AKI, ranging from 1% to 9%, in this population.[29]

AUC/MIC Measurements. AUC concentrations can be estimated by using 2 concentrations (peak and trough) with simple analytic PK equations. Bayesian software programs such as DoseMe (Tabula Rasa HealthCare, Inc, Moorestown, NJ) can also be used to estimate vancomycin AUC value by using minimal PK sampling (e.g., 1 or 2 concentrations) and providing AUC-guided dosing recommendations in real-time.[31] The software uses vancomycin population PK model as the Bayesian prior, in conjunction with the individual patient's drug concentrations, to calculate the optimal dosing regimen. Kumar et al[31] evaluated the user-friendliness of the 3 Bayesian programs, namely, DoseMe, TDMx (S.G. Wicha, Hamburg, Germany), and InsightRx (Insight Rx, Inc, San Francisco, CA), according to clinical pharmacists in 3 Australian children's hospitals. The authors concluded that DoseMe was rated as the most user-friendly with 70%, followed by 41% for TDMx and 37% for InsightRx (p = 0.02). The ease of data entry and graphical displays of the 3 programs, in particular, were appreciated by the participants.[31]

Vancomycin Susceptibility Testing. The discrepancies of MIC reporting among institutions (using broth microdilution [BMD], agar dilution, or Etest) also need to be examined. Since AUC/MIC has been proposed to be the most appropriate measure to predict clinical outcomes for the treatment of invasive MRSA infections, MIC methodology must be taken into consideration when interpreting susceptibility and evaluating MIC trends. Rybak et al[32] compared 4 different MIC tests (Phoenix, MicroScan, Vitek-2, and Etest) to BMD reference method among 200 MRSA strains. Compared to BMD, the Phoenix test produced the highest agreement at 66.2% followed by MicroScan (61.8%) and Vitek-2 (54.3%). The Etest had the lowest agreement at 36.7% and tended to produce results that were 1 to 2 dilutions higher. In addition, Etest identified a MIC of 2 mg/L 80% of the time, when compared to BMD.[32] Another study[33] reported that BMD testing resulted in a 96.3% agreement with Vitek-2 and MicroScan and 88.8% with Phoenix, while the Etest had the lowest agreement of 76.4%, with results consistently higher by 1 to 2 dilutions. This high variability of MIC poses a challenge to clinicians making clinical treatment decisions using AUC-guided vancomycin dosing. Given this variability, the use of AUC (assuming a MIC_{bmd90} of 1 mg/L) to

guide empiric vancomycin dosing is further supported. Consistent reporting of MICs among institutions will allow for standardization of AUC/MIC calculations. Clinicians should be aware that the current target AUC/MIC of ≥400 was derived by using the reference BMD method; therefore, adjustments to this target need to be made when calculating AUC/MIC ratio using other MIC testing methods.

Conclusion

In summary, vancomycin remains the drug of choice for neonatal sepsis caused by CoNS and MRSA at MICs ≤1 mg/L. At this time, it is unknown if the goal AUC/MIC of 400 to 600 (for MICs ≤ 1 mg/L) is appropriate for neonates. Dosing strategies for vancomycin in neonates should be based on body weight, PMA, and serum creatinine. Lower trough concentrations of 7 to 11 mg/L may be adequate for treating Gram-positive organisms in neonates. Owing to limited data, a high degree of PK variability in neonates, the risk of nephrotoxicity, and common need for MRSE coverage, judicious use of higher target vancomycin trough concentrations (e.g., 15 to 20 mg/L) is warranted and may be considered in those with severe invasive MRSA bacteremia not responding to lower vancomycin trough concentrations. AUC-guided therapeutic dosing and monitoring should be considered in neonates, using traditional peak and trough concentrations or preferably with Bayesian estimation. A lower AUC/MIC target may be considered for those with CoNS bacteremia. The NeoVanc project, which aims to identify optimal PD targets and compare the efficacy and safety (VIN and ototoxicity) of current standard and optimal vancomycin dosing regimens in neonates with Gram-positive bacteremia, particularly CoNS and enterococci, is currently underway.[34] Optimizing vancomycin dosing by using PK/PD principles can lead to increased efficacy and reduced emergence of resistant organisms. Larger studies are needed to determine the optimal AUC/MIC ratio for the treatment of Gram-positive organisms in neonates, to identify optimal vancomycin dosing to achieve these targets, and to assess clinical outcome data as well as adverse effects with this target AUC/MIC ratio.

ARTICLE INFORMATION

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REFERENCES

1. Hornik CP, Fort P, Clark RH, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. *Early Hum Dev*. 2012;88(suppl 2):S69–S74.
2. Puopolo KM, Lynfield R, Cummings JJ, Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of infants at risk for group B streptococcal disease. *Pediatrics*. 2019;144(2):e20191881. doi:10.1542/peds.2019–2350
3. Tröger B, Göpel W, Faust K, et al. Risk for late-onset blood-culture proven sepsis in very-low-birth weight infants born small for gestational age: a large multicenter study from the German Neonatal Network. *Pediatr Infect Dis J*. 2014;33(3):238–243.
4. Tsai MH, Hsu JF, Chu SM, et al. Incidence, clinical characteristics, and risk factors for adverse outcome in neonates with late onset sepsis. *Pediatr Infect Dis J*. 2014;33(1):e7–e13.
5. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing*. Wayne, PA: Clinical and Laboratory Standards Institute; 2006. CLSI-approved standard M100-s16.
6. Smits A, Pauwels S, Oyaert M, et al. Factors impacting unbound vancomycin concentrations in neonates and young infants. *Eur J Clin Microbiol Infect Dis*. 2018;37(8):1503–1510.
7. Thomas Reuters Clinical Editorial Staff. *Neofax 2011*. 24th ed. PDR Network; 2011.
8. Kimberlin DW, Long SS, Brady MT, Jackson MA. *Red Book 2018: Report of the. Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018.
9. Bateman DA, Thomas W, Parravicini E, et al. Serum creatinine concentration in very-low-birth-weight infants from birth to 34-36 wk postmenstrual age. *Pediatr Res*. 2015;77(5):696–702.
10. Taketomo CK, Hodding JH, Kraus DM. *Pediatric and Neonatal Dosage Handbook*. 23rd ed. Hudson, OH: Lexicomp; 2016.
11. Bhongsatiern J, Stockmann C, Roberts JK, et al. Evaluation of vancomycin use in late-onset neonatal sepsis using the area under the concentration-time curve to the minimum inhibitory concentration ≥ 400 target. *Ther Drug Monit*. 2015;37(6):756–7865.
12. Kato H, Hagihara M, Nishiyama N, et al. Assessment of optimal initial dosing regimen with vancomycin pharmacokinetics model in very low birth weight neonates. *J Infect Chemother*. 2017;23(3):154–160.

13. Dao K, Guidi M, Padre P, et al. Optimisation of vancomycin exposure in neonates based on the best level of evidence. *Pharmacol Res*. 2020;154:104278. doi:10.1016/j.phrs.2019.104278
14. Frymoyer A, Stockmann C, Hersh AL, et al. Individualized empiric vancomycin dosing in neonates using a model-based approach. *J Pediatric Infect Dis Soc*. 2019;8(2):97–104.
15. Frymoyer A, Hersh AL, El-Komy MH, et al. Association between vancomycin trough concentration and area under the concentration-time curve in neonates. *Antimicrob Agents Chemother*. 2014;58(11):6454–6461.
16. Stockmann C, Hersh AL, Roberts JK, et al. Predictive performance of a vancomycin population pharmacokinetic model in neonates. *Infect Dis Ther*. 2015;4(2):187–198.
17. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis*. 2006;42(suppl 1):S35–S39.
18. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am*. 2003;17(2):479–501.
19. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66(1):82–98.
20. 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: executive summary. *Clin Infect Dis*. 2011;52(3):285–292.
21. Bizzarro M, Shabanova V, Baltimore R, et al. Neonatal sepsis 2004-2013: the rise and fall of coagulase-negative staphylococci. *J Pediatr*. 2015;166(5):1193–1199.
22. Chhim RF, Arnold SR, Lee KR. Vancomycin dosing practices, trough concentrations, and predicted area under the curve in children with suspected invasive staphylococcal infections. *J Pediatr Infect Dis Soc*. 2013;2(3):259–262.
23. Paiva RM, Mombach AB, Machado P, et al. Vancomycin MIC for methicillin-resistant coagulase-negative *Staphylococcus* isolates: evaluation of the broth microdilution and Etest methods. *J Clin Microbiol*. 2010;48(12):4652–4654.
24. Padari H, Oselin K, Tasa T, et al. Coagulase negative staphylococcal sepsis in neonates: do we need to adapt vancomycin dose or target? *BMC Pediatr*. 2016;16(1):206. doi: 10.1186/s12887-016-0753-0.
25. Young TE, Magnum B. *Neofax 2010, A Manual of Drugs Used in Neonatal Care*. 23rd ed. Thomas Reuters Clinical Editorial; 2010.
26. Chen Y, Wu D, Dong M, et al Population pharmacokinetics of vancomycin and AUC-guided dosing in Chinese neonates and young infants. *Eur J Clin Pharmacol*. 2018;74(7):921–930.
27. Tseng SH, Lim CP, Chen Q, et al. Evaluating the relationship between vancomycin trough concentration and 24-hour area under the concentration-time curve in neonates. *Antimicrob Agent Chemother*. 2018;62(4):e01647–617.
28. Bhargava V, Malloy M, Fonseca R. The association between vancomycin trough concentrations and acute kidney injury in the neonatal intensive care unit. *BMC Pediatrics*. 2017;17:50. doi:10.1186/s12887-017-0777-0
29. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835-864
30. Lestner JM, Hill LF, Heath PT, Sharland M. Vancomycin toxicity in neonates: a review of the evidence. *Curr Opin Infect Dis*. 2016;29(3):237–247.
31. Kumar AA, Burgard M, Stacey S, et al. An evaluation of the user-friendliness of Bayesian forecasting programs in a clinical setting. *Br J Clin Pharmacol*. 2019;85(1):2436–2441.
32. Rybak MJ, Vidaillac C, Sader HS, et al. Evaluation of vancomycin susceptibility testing for methicillin-resistant *Staphylococcus aureus*: comparison of Etest and three automated testing methods. *J Clin Microbiol*. 2013;51(7):2077–2081.
33. Kruzel MC, Lewis CT, Welsh KJ, et al. Determination of vancomycin and daptomycin MICs by different testing methods for methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. 2011;49(6):2272–2273.
34. Hill LF, Turner MA, Lutsar I, et al. NeoVanc Consortium. An optimised dosing regimen versus a standard dosing regimen of vancomycin for the treatment of late onset bacterial sepsis due to Gram-positive microorganisms in neonates and infants aged less than 90 days (NeoVanc): study protocol for a randomised controlled trial. *Trials* 2020;21(1):329:2-11.
35. Janssen EJH, Valitalo PAJ, Allegaert K, et al. Towards rational dosing algorithms for vancomycin in neonates and infants based on population pharmacokinetic modeling. *Antimicrob Agents Chemother*. 2016;60(2):1013–1021.
36. Vancomycin. In: *Neonatal Formulary: Drug Use in Pregnancy and the First Year of Life*. 7th ed. West Sussex, United Kingdom: John Wiley & Sons, Ltd; 2015.