JPPT | A Systematic Review

Vancomycin Area Under the Curve to Minimum Inhibitory Concentration Ratio for Treatment Effectiveness in Pediatric and Neonatal Staphylococcal Infections: A Systematic Review

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OBJECTIVE To review pediatric data on vancomycin exposure threshold against methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MR-CoNS).

METHODS A systematic review was conducted through July 2023. Publications in English that explored vancomycin effectiveness threshold against MRSA, CoNS, or *S aureus* in pediatrics were eligible. Effectiveness examined included clinical improvement, microbiologic sterilization, recurrence, and mortality, as defined by each individual study.

RESULTS Twelve studies were eligible. One on MRSA bacteremia (MRSA-B) identified an area under the curve to minimum inhibitory concentration ratio (AUC:MIC) of 300 mg × hr/L associated with rapid bacteremia clearance. Two on CoNS bacteremia (percentage of MR-CoNS unreported) demonstrated an AUC of 300 mg x hr/L regardless of MIC and an AUC:MIC of 280 mg × hr/L for bacteriologic cure, respectively; and one on *S aureus* bacteremia (25.5% MRSA) found an AUC:MIC of 400 mg × hr/L for clinical improvement.

CONCLUSIONS There is overall limited pediatric data, and the observed AUC:MIC thresholds should be interpreted as hypothesis generating only. Further, the effectiveness outcome could be refined in future research by using time to bacteremia clearance only, as odds of complications increase with each additional day of MRSA-B, whereas the definition of recurrence is not standardized, and mortality is low. Additionally, extrapolating AUC:MIC for MRSA to CoNS is beyond the stated usage of current guidelines. To achieve an AUC:MIC ratio against CoNS with a MIC of >1 mg/L would require higher AUC with potential nephrotoxicity. More data on AUC (regardless of MIC) for MR-CoNS bacteremia are needed.

ABBREVATIONS AUC:MIC, area under the curve to minimum inhibitory concentration ratio; BMD, broth microdilution; CoNS, coagulase-negative staphylococci; EMBASE, Excerpta Medica Database; ICU, intensive care unit; MR, Methicillin resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSA-B, methicillin-resistant *Staphylococcus aureus* bacteremia; OFID, Open Forum Infectious Diseases; PD, pharmacodynamic; PK, pharmacokinetic; WOS, Web of Science

KEYWORDS pediatrics; treatment effectiveness; vancomycin; vancomycin AUC:MIC

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Introduction

Vancomycin is widely used in the treatment of infections caused by resistant Gram-positive pathogens. Although other factors—including adequate control of the source of infection, such as removal of infected indwelling medical devices if feasible—are crucial to treatment success, therapeutic drug monitoring of vancomycin is essential in ensuring bacterial killing, preventing resistance, and minimizing drug toxicity.[1–3] The 2020 revised consensus guideline on vancomycin recommends that an individualized target of the area under the curve to minimum inhibitory concentration determined by broth microdilution (AUC:MIC_{BMD}) ratio of 400 to 600 mg × hr/L (assuming a vancomycin MIC_{BMD} of 1 mg/L) should be advocated for patients with suspected or definitive serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections, to achieve clinical efficacy while improving patient safety, primarily avoiding or minimizing nephrotoxicity.[4]

The advantages of the current vancomycin AUC-guided dosing strategy include potential reduced risk of acute kidney injury, whereas the historical serum

vancomycin trough concentration goal of 15 to 20 mg/L against invasive MRSA infections would require aiming at a trough of >15 mg/L, which has been shown to increase the risk of nephrotoxicity by 2.7-fold in pediatric patients.[5] Additionally, AUC estimation can be performed before steady state for more timely dosing optimization.[6] Further, AUC can be predicted in children with ~80% accuracy across all weight groups including children with overweight and obesity, compared with the poor fit between serum vancomycin trough data and weight-based dosing.[7] However, the specific AUC:MIC ratio threshold for effectiveness against MRSA has mostly been based on adult findings,[4,8,9] whereas pediatric data are limited and would be a helpful next step.

Caution is also advised to extrapolate guideline recommendations for MRSA to other bacteria such as coagulase-negative staphylococci (CoNS).[4] Despite debates over pathogenic role, CoNS can cause significant clinical disease in immunologically immature premature neonates who often rely on invasive devices for their care, and vancomycin remains the mainstay of therapy against CoNS owing to the long-standing clinical experience in neonates. An AUC-based vancomycin exposure goal balancing efficacy with limited to no nephrotoxicity is needed for neonates and young infants born prematurely while their kidneys are still functionally immature.

Vancomycin is commonly used to treat MRSA, CoNS, or *S aureus* infections, and the AUC-based monitoring strategy is gradually increasing in the clinical practice in pediatrics. Therefore, the objective of this qualitative systematic review was to assess published pediatric studies that have examined the vancomycin AUC:MIC ratio threshold for treatment effectiveness in pediatric patients with these culture-proven infections.

Materials and Methods

Search Strategy. The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews checklist.[10] The literature search was conducted in 5 electronic databases, including the Cochrane Library, Excerpta Medica Database (EMBASE), Open Forum Infectious Diseases (OFID), PubMed, and Web of Science (WOS) from inception through July 31, 2023, using search terms *vancomycin*, *AUC*, *children* or *pediatric*. Given that research on vancomycin therapeutic drug monitoring is often conducted with focus on serum trough concentrations, whereas studies on AUC are focused on treatment outcomes instead of therapeutic drug monitoring or a target concentration attainment, the search term *AUC* was used instead to retrieve as many relevant records as possible. Items identified were exported into a Microsoft Excel spreadsheet (Microsoft, Redmond, WA). The screening started with the author and title review for duplicates and relevance, followed by review of the abstract and text for eligibility based on the inclusion and exclusion criteria as described below. In addition, references of included studies, narrative reviews, guidelines, commentaries, author replies, letters, and editorials were manually checked to identify any additional sources. Three authors (R-YC, BAH, HT) independently applied the inclusion and exclusion criteria to identify eligible studies. Non-concordance was reviewed and resolved by consensus agreement.

Inclusion and Exclusion Criteria. All publications were eligible if they met the inclusion criteria defined according to the Population, Intervention, Comparison, Outcome and Study design (PICOS) process as follows[11]: Population: pediatric patients (age ≤18 years) who received intravenous vancomycin against culture-proven MRSA, CoNS, or *S aureus*; Intervention: vancomycin therapy was guided by AUC:MIC ratio; Comparison: AUC:MIC ratio above a threshold was considered the exposure, compared with those below this threshold; Outcome: treatment effectiveness, which can be any combination of measurements of clinical improvement (i.e., symptoms and/or surrogate markers), microbiologic clearance, frequency and/or time to recurrence, and incidence of mortality, as defined by each individual study; and Study designs: all published articles or abstracts, either retrospective or prospective, observational or experimental.

Exclusion criteria were studies not published in English; nonhuman or adult (>18 years old) studies; publications without original data; studies not addressing clinical or microbiologic treatment effectiveness outcomes; studies that enrolled patients with presumed infections without documented positive cultures in their assessment for treatment effectiveness target; studies without assessment of the vancomycin AUC:MIC ratio threshold for effectiveness despite data presented on AUC:MIC and treatment outcomes; and studies that enrolled patients with a variety of infection types where less than 90% were MRSA, CoNS, or *S aureus* on cultures.

Data Reporting. Data collected from eligible studies included the first author, country and year of publication, study design, number of participating sites, study period, primary objective, inclusion and exclusion criteria, determination methods for vancomycin AUC, pathogen MIC, distribution of MICs, AUC:MIC ratio threshold for treatment effectiveness, characteristics of participants and of the subgroup of patients, if applicable, in the analysis of AUC:MIC threshold for effectiveness, and major findings on the AUC/MIC ratio threshold for treatment effectiveness outcomes. Data on concurrently administered antibiotics were not collected. Comparable to adult literature on MRSA bacteremia (MRSA-B), additional data were collected from eligible pediatric MRSA-B studies including common comorbidities, intensive care unit (ICU) status, and presence of high-risk infectious foci, as previously defined, with clinical manifestations indicative of a source within the

endovascular system, lower respiratory tract, abdomen, or central nervous system.[12,13] Data may be missing in some enrolled studies. However, no attempt was made to obtain additional unpublished clinical data from enrolled studies owing to the requirement of approval from multiple institutional review boards.

Quality Assessment. The Newcastle-Ottawa scale for non-randomized studies,[14] as used in a recent systematic review on mortality from *S aureus* bacteremia,[15] was used for evaluation of the methodologic quality of enrolled individual non-randomized studies (Supplemental Table S1a). Of note, some enrolled studies reported the relationship between AUC or AUC:MIC and treatment effectiveness as a secondary outcome from a subgroup of their study participants who had AUC, MIC, and treatment outcome data available. For these studies, the quality assessment was focused on their subgroup analysis, such as the representativeness of the subgroup.

Results

Literature Search. A combined 1020 records from Cochrane, EMBASE, OFID, PubMed, and WOS were identified. No other studies were added through individual citation reference list. Of these 1020 identified records, 312 were removed for duplicates, 362 were taken out for irrelevance, and 334 were excluded on the basis of assessment of eligibility (see Supplemental Table S1 and Supplemental Figure). The remaining 12 studies were eligible and included for data extraction. All 12 studies, including 10 articles and 2 abstracts, were cohort observational studies published between 2015 and 2022, reporting 559 patient encounters on vancomycin against MRSA, CoNS or *S aureus* across different geographic regions, reflecting the global prevalence of use of vancomycin in pediatrics.

Determination of Vancomycin AUC:MIC Ratio Threshold for Effectiveness. Regarding the determination of vancomycin AUC:MIC threshold for treatment effectiveness, 4 studies had set an AUC:MIC ratio threshold of 400 mg × hr/L adopted from adult literature *a priori* and compared efficacy outcomes between patients with AUC:MIC ratio above and below 400 mg × hr/L.[16–19] Two studies divided their patients into treatment success and failure groups and compared the median AUC:MIC ratio between these 2 groups.[20,21] Four studies used statistical methods to identify an AUC:MIC ratio breakpoint associated with effectiveness,[22–25] and the remaining 2 did not provide the method they used to determine the AUC:MIC ratio threshold for treatment effectiveness.[26,27]

The vancomycin AUC:MIC ratio value is derived from the vancomycin AUC estimate and the MIC reported from the microbiology laboratory. Various methods were used by these studies to determine MICs, including BMD,[17,19,20,24,25] gradient diffusion,[16,18,21,26] automated systems,[16,20–22,24,27] and 1 study did not report the methodology.[23] The MICs from different susceptibility testing methods across these studies may not be entirely consistent.

Similarly, 2 studies did not provide descriptions of AUC calculation.[17,26] The remaining 10 studies[16,18-25,27] used various methods to estimate AUC, including published validated methods by Chang et al[28] or Le et al,[29] trapezoidal rule,[18] or various pharmacokinetic (PK) modeling/Bayesian estimates incorporating either one,[19,21,27] two,[24] or unknown number of vancomycin serum concentrations.[16,25] Notably, as stated in one study,[18] the trapezoidal method requires actual vancomycin concentration from patients, whereas the methods by Chang et al[28] and Le et al[29] were developed from Monte Carlo simulation. This study found that the AUC values were not similar between the different PK methods that were used to calculate AUC.[18]

Risk of Bias Assessment. All 12 eligible studies were observational in design. As demonstrated in Supplemental Table S1b, all studies enrolled patients to represent pediatric or neonatal populations admitted at their institutions except 4 studies that enrolled patients younger than 3 years,[19] 2 months to 17 years of age,[20] both pediatric and young adults with ages of 17.2 ± 6.9 years (mean ± SD),[23] or with more extensive exclusion criteria.[24] Similarly, 5 studies reported their assessments of vancomycin AUC:MIC breakpoint for treatment effectiveness on a subgroup of study participants owing to microbiology and clinical outcome data availability,[18,21,24,26,27] and did not provide descriptions of the representativeness of the selected subgroup. All 12 studies used electronic medical records to retrieve data on exposure and outcomes, although only 2 studies specified inclusion criteria of first clinical episode to ensure the outcome of interest, such as persistence of bacteremia, was not present at the start of study.[22,27] Lastly, only 1 study made statements on participants lost to follow-up, which can affect the determination of outcome of interest such as mortality.[22]

Vancomycin AUC:MIC Threshold Against MRSA. There were 5 studies involving MRSA, including 4 addressing bacteremia and 1 involving patients with cystic fibrosis, as shown in Table 1. Yoo et al[22] enrolled 73 children with first-episode MRSA-B. The most frequently reported underlying diseases were congenital heart disease (28.8%), malignancy (16.4%), neurologic diseases (6.8%), and chronic lung disease (5.5%). In their multivariate analysis adjusting for age, coinfection, indwelling medical device, and presence of primary focus of MRSA-B, an initial AUC:MIC of <300 was the only statistically significant risk factor associated with persistent bacteremia at 48 to 72 hours (adjusted OR, 3.05; 95% CI, 1.07–8.68) and therefore, could be used as a predictor of persistent MRSA-B. Of note, approximately 13.7% of their patients had a MIC of 2 mg/L. Although the overall incidence of acute kidney injury was 4.1% (defined in this study as an increase in serum

Table 1. Description of Studies on MRSA Infections

Reference	Design	Primary Objective	Inclusion Criteria	Exclusion Criteria	Number; Age; MIC	High-Risk Source, %	Most Seen Comorbidity	ICU Care, %	Treatment Outcomes	Major Findings on AUC:MIC Threshold for Outcomes
Yoo, 2021, South Korea[22]	Retrospective, single center, 2010–2018	The impact of initial vancomycin exposure on the outcomes of MRSA-B	Age 2 mo to 18 yr, first episode of MRSA-B within 4 wk, on vancomycin ≥48 hr, trough before the fourth or fifth dose	Chronic renal diseases on renal replacement therapy, or in NICU	N = 73; age, median (IQR) 12.4 (5.3–36.1 mo); 86.3% MIC ≤1 mg/L	13.7	Congenital heart disease 28.8%	47.5	Persistent bacteremia 39.7% (2–3 days); recurrence 19.4 (30 days); mortality 9.7% (30 days, all-cause)	An initial AUC:MIC <300 mg·hr/L was the only significant risk factor associated with persistent bacteremia at 2 to 3 days but not associated with 30-day all-cause mortality, by ROC curve and multivariate logistic regression analysis
Regen, 2019, USA[20]	Retrospective, single center, 2005–2015	The rate of vancomycin treatment failure in MRSA-B	Age 2 mo to 17 yr with MRSA-B, on vancomycin with a steady-state trough	Vancomycin <5 days, NICU, or non-weight–based dosing	N = 67; age, median (IQR) 4 (1.4–12 yr); 96% MIC ≤0.5 mg/L	16.4	n/a	n/a	Persistent bacteremia 8.9% (≥7 days); recurrence 3% (30 days); mortality 1.5% (30 days, all-cause)	No difference in the median $AUC_{24\ hr.}$:MIC ratios between groups with treatment success and failure (bacteremia ≥7 days, recurrence of bacteremia within 30 days, or 30-day all-cause mortality)
Murai, 2017, Japan[17]	Retrospective, single center, 2010–2017	Whether early achievement of AUC:MIC >400 mg × hr/L improved MRSA-B outcomes	Children with MRSA-B on vancomycin	No dose or MIC, on extracorporeal membrane oxygenation, or cases of contamination	N = 56; age, median (IQR) 9 (1.8–120.5 mo); 96.4% MIC ≤1 mg/L	n/a	n/a	n/a	Data n/a on persistent bacteremia, recurrence, and mortality	There was no difference in persistent bacteremia on days 3 and 7, mortality at 30 days, or the recurrence of MRSA-B between patients who achieved the predefined AUC:MIC >400 mg × hr/L prior to the fourth or fifth dose and those who did not

(Table cont. on page 56)

Table 1. Description of Studies on MRSA Infections *(cont.)*

Reference	Design	Primary Objective	Inclusion Criteria	Exclusion Criteria	Number; Age; MIC	High-Risk Source, %	Most Seen Comorbidity	ICU Care, %	Treatment Outcomes	Major Findings on AUC:MIC Threshold for Outcomes
Hahn, 2015, USA[16]	Retrospective, single center, 2010–2013	Whether $AUC_{24\ hr}$:MIC <400 mg × hr/L was predictive of MRSA-B treatment failure	Age <18 yr, on vancomycin ≥3 days for MRSA-B	No level or creatinine, or on concurrent antibiotic to which the MRSA was susceptible	N = 59; age, median (IQR) 2.95 (1.2–9.3 yr); MIC distribution n/a	20.3	Gastrointestinal 22%	45.8	Persistent bacteremia 29.5% (3 days); recurrence 7.3% (30 days) and no attributable mortality (30 days)	A predefined AUC:MIC of ≥400 mg × hr/L did not show improved outcomes (bacteremia ≥3 days, 30-day mortality, or recurrence of bacteremia within 30 days of end of treatment)
Fusco, 2017, USA[23]	Retrospective, single center, 2012–2014	To assess the vancomycin trough and changes in pulmonary function in patients with CF with acute pulmonary exacerbation and MRSA	Patients with CF, age ≥6 yr, admitted for acute pulmonary exacerbation with ≥1 sputum culture positive for MRSA within 30 days of admission, on vancomycin for ≥ 48 hr and had ≥1 appropriately measured trough, as well as ≥2 sets of PFTs during their admissions.	Lung transplant or pregnancy	N = 49; age, mean ± SD 17.2 ± 6.9 yr; MIC distribution n/a	n/a	n/a	n/a	FEV_1 at admission and at discharge (mean ± SD) was 65.2 ± 15.9 and 78.8 ± 15.6, respectively ($p < 0.001$). 85.7% patients returned to their baseline FEV_1	AUC:MIC ratio was not a significant predictor of change in FEV_1 or return to baseline FEV_1 on multivariate analysis

AUC:MIC, area under the cure to minimum inhibitor concentration ratio; CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus; MRSA-B, methicillin-resistant Staphylococcus aureus bacteremia; n/a, not available; NICU, neonatal intensive care unit; PFT, pulmonary function test; ROC, receiver operating characteristic

creatinine concentrations by 0.5 mg/dL), no data were provided on nephrotoxicity experienced in these patients who might have required an AUC of >600 mg × hr/L to achieve their goal of AUC:MIC of 300 mg × hr/L, or an alternative antibiotic was used instead.

Hahn et al[16] performed a study in 59 pediatric patients with MRSA-B. The most common underlying conditions seen in their study patients were gastrointestinal disease (22%), neurologic disease (13.6%), lung disease (13.6%), and genetic/metabolic disease (11.9%). They found no statistically significant differences between those with an $AUC_{24\,hr}$:MIC ≥400 and <400 in treatment failure, defined as bacteremia ≥3 days, 30-day mortality, or recurrence of bacteremia within 30 days of end of treatment. Similarly, Regen et al[20] and Murai et al[17] did not observe an impact of vancomycin AUC:MIC ratio on treatment effectiveness. However, these studies dichotomized their patients on the basis of either a predefined AUC:MIC cutoff of 400 mg × hr/L to compare outcomes,[16,17] or on treatment outcome of success vs failure to compare median AUC:MIC ratio values.[20] These comparisons were limited statistically to identify an AUC:MIC breakpoint for effectiveness.

Other than these 4 studies addressing MRSA-B, Fusco et al[23] performed a study in 49 patients with cystic fibrosis with acute pulmonary exacerbation and MRSA on sputum culture. The authors concluded that only younger age and lower admission lung function, but not AUC:MIC ratio values, were significant predictors for a positive vancomycin response in pulmonary function tests by multivariate analysis. As stated by the authors, both younger patients who have not had time to develop advanced lung disease yet and those patients with lower admission pulmonary function might experience a greater change in pulmonary function test values between admission and discharge. Therefore, a more defined patient population or a wider distribution of serum vancomycin trough concentrations (and therefore, AUC values derived from serum troughs) might be necessary to further define the optimal target.

Vancomycin AUC:MIC Threshold Against CoNS. All 4 studies against infections caused by CoNS were performed in neonates and young infants, as presented in Table 2. Gwee et al[25] enrolled 30 young infants with postnatal age ≤90 days who developed staphylococcal bacteremia (93% with CoNS, defined as CoNS from at least 2 blood cultures, and 7% MRSA-B). The authors reported that 33% of MICs of CoNS were >1 mg/L (range, 0.5–4.0) by BMD and a target $AUC_{0–24\,hr}$ and $AUC_{24–48\,hr}$ of 300 and 424 mg × hr/L, respectively, increased the chance of microbiologic cure by 7.8- and 7.3-fold, respectively, regardless of MIC. Of note, the authors found that the presence or absence of central venous catheters did not have a predictive value in their pharmacodynamic (PD) model linking vancomycin exposure metrics to time to bacteremia clearance, despite the general recommendation of removal of contaminated device if feasible (data not available). The authors concluded the importance of early target attainment on microbiologic cure with a proposed rationale of being able to prevent CoNS to form biofilms in indwelling venous catheters, which would make eradication more challenging.

Chen et al[24] explored the vancomycin effectiveness threshold from 54 neonates with CoNS infection, defined as CoNS from at least 2 blood cultures or with a positive tracheal culture and imaging evidence in ventilated patients (65% and 35% of the subgroup, respectively). The authors reported that an AUC:MIC ratio >280 mg × hr/L was a predictor of culture sterilization within 72 hours and/or clinical improvement. It is worth noting that this study had extensive exclusion criteria (Table 2). Therefore, the findings might not be generalizable to other patients who would have been excluded from their study. Furthermore, the current guideline targeting AUC:MIC ratio of 400 to 600 mg × hr/L is for severe MRSA infections assuming a vancomycin MIC of 1 mg/L. In contrast, this study was focused on CoNS infection and 54% of their isolates had a MIC of >1 mg/L by BMD. Aiming at their proposed goal AUC:MIC ratio of 280 mg × hr/L in these patients would require an AUC of 560 mg × hr/L or higher, which likely exceeded the average AUC of 500 mg × hr/L observed by them for nephrotoxicity, defined by the authors as an increase in serum creatinine by 26.5 µmol/L within 48 hours, or an increase by 1.5 times or higher within 7 days.

The other 2 studies from Padari et al[21] and Viel-Thériault et al[27] in patients with CoNS infections did not observe a correlation between AUC-based strategy and clinical outcomes, although both studies required only 1 positive blood culture for inclusion and no description was given to distinguish between true pathogens and contaminants. It is possible that the efforts to identify a potential AUC or AUC:MIC ratio goal for vancomycin efficacy against CoNS may have been negated because of less strict inclusion criteria for CoNS infections, given some patients with only 1 positive blood culture, treated by vancomycin for 3 to 5 days, may represent contamination instead of true infection. Moreover, none provided data of whether the CoNS were methicillin resistant or susceptible, which makes identification of an AUC or AUC:MIC breakpoint for efficacy difficult.

Vancomycin AUC:MIC Threshold Against *S aureus*. Literature findings addressing *S aureus* infections are presented in Table 3, including 2 for bacteremia and 1 for pneumonia. For *S aureus* bacteremia, Ruiz et al[19] found that the predefined efficacy goal of a vancomycin AUC:MIC ratio of 400 mg × hr/L was associated with early clinical but not microbiologic response or mortality in 51 children younger than 3 years (25.5% MRSA-B), whereas Kishk et al[18] concluded no difference in time to first negative blood culture or clinical outcomes between those who achieved the predefined vancomycin AUC:MIC target of 400 mg × hr/L and those who did

Table 2. Description of Studies on Coagulase-Negative Staphylococcal Infections

Reference	Design	Primary Objective	Inclusion Criteria	Exclusion Criteria	Characteristics of Entire Group	Characteristics of the Subgroup for Efficacy	Major Findings on AUC:MIC Threshold for Treatment Effectiveness
Gwee, 2022, Australia[25]	Retrospective, single center, 2016–2020	Therapeutic target of vancomycin in young infants with staphylococcal infections	PNA ≤90 days on vancomycin with level available for MRSA from 1 or same CoNS species from 2 separate blood cultures	n/a	N = 30, PMA, median (IQR) 40.6 (38.3–44.7 wk)	Entire group of 30 patients, among them 28 had CoNS and 2 had MRSA-B; 33% CoNS had MIC >1 mg/L	An $AUC_{0–24\ hr}$ ≥300 or $AUC_{24–48\ hr}$ ≥424 mg × hr/L increased the chance of bacteriological cure by 7.8- and 7.3-fold, respectively, by a time-to-event pharmacodynamic model to link the AUC, with the event being the first negative blood culture
Chen, 2022, China[24]	Retrospective, single center, 2016–2021	The optimal exposure target in neonatal CoNS infections	PNA ≤28 days and on vancomycin ≥3 days, with level and records available	Level was not determined or exceeded the detection limit, on renal replacement therapy, abnormal immune function, chronic/underlying conditions, major congenital malformations, pneumonia from aspiration or a specific obstruction, or lack of relevant information	N = 153, age n/a	A subgroup of 54 patients with MIC of CoNS available, and not on other antibiotics to which the CoNS was susceptible; age n/a; 65% with 2 positive blood cultures and 35% with positive trachea culture and imaging evidence while on a ventilator; 54% MIC >1 mg/L	In this subgroup of patients, an AUC:MIC of >280 was a predictor of negative culture at 72 hr or clinical improvement by multivariate regression analysis
Viel-Theriault, 2020, Canada[27]	Retrospective, single center, 2012–2017	To characterize the residual vancomycin concentrations	NICU patients on the first course of vancomycin, with ≥1 vancomycin C_{min} at steady state and relevant clinical data available	Incomplete medical records	N = 120; PMA, median (IQR) 32 (28–38 wk)	A subgroup of 22 patients on vancomycin ≥5 days, and ≥1 CoNS on blood culture with AUC:MIC available; age and MIC distribution n/a	In this subgroup of patients, there was no correlation between the $AUC_{0\text{-}tau}$ or the $AUC_{0\text{-}tau}$:MIC and the duration of CoNS bacteremia (statistical method for correlation n/a)
Padari, 2016, Estonia[21]	Retrospective, single center, 2010–2012	Vancomycin doses required to achieve AUC:MIC >400 and >300 mg × hr/L in neonates	PNA <90 days with ≥1 vancomycin level available	n/a	N = 76; PMA, mean ± SD 30.9 ± 4.8 wk	A subgroup of 46 patients with proven Gram-positive pathogen from a blood culture (95% CoNS) and treated with vancomycin for ≥3 days; PMA, mean ± SD, 29.3 ± 4.1 wk; 41 cases of CoNS had MIC >1 mg/L	In this subgroup of patients, the mean AUC:MIC values were similar between groups with treatment failure and success, defined as culture negative and/or clinical improvement within 72 hr

AUC:MIC, area under the cure to minimum inhibitor concentration ratio; CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant Staphylococcus aureus; MRSA-B, methicillin-resistant Staphylococcus aureus bacteremia; n/a, not available; NICU, neonatal intensive care unit; PMA, post-menstrual age; PNA, postnatal age

not in 29 children (percentage of MRSA not reported). McNeil et al[26] performed a study in 23 children with *S aureus* pneumonia and found no correlation between values of AUC:MIC and duration of bacteremia, clinical improvement, or mortality.

Discussion

Only unbound vancomycin is pharmacologically active and available for clearance. The unbound vancomycin fraction in general decreases from 90% in neonates and young infants to 70% in critically ill children to 50% in adults, and there is a large variability within and between patients.[30–32] Owing to the decreased protein binding, aiming for a similar unbound vancomycin exposure for effectiveness in neonates, young infants, or critically ill children might result in a goal AUC (which is based on total vancomycin concentration) that is different from that reported in adults.

Among host-level factors captured in these retrospective pediatric MRSA-B studies, the percentage of pediatric patients with MRSA-B and requiring ICU level care (45.8% and 47.5%),[16,22] as a marker of illness severity, appears to be within the range of that previously reported for adults (5.5%–73.3%).[12,33–43] However, the most frequently encountered comorbidities in these enrolled pediatric studies, such as congenital heart disease and gastrointestinal diseases, were distinct from those typically reported in adults, which include diabetes, injection drug use, renal impairment, and malignancy.[12,33–47] In addition, the proportions of high-risk foci infections in enrolled pediatric MRSA-B studies (13.7%, 16.4%, and 20.3%)[16,20,22] corroborated with those observed in pediatric epidemiologic studies (12.7% and 16.8%).[48,49] These numbers were numerically at the lower end of adult data (9.2%–34%),[12,34–46] including a nationwide estimate (30%) in adults.[45] Taken together, other than the difference in vancomycin protein binding, the dissimilarity in host comorbidities and numerically lower frequencies of high-risk foci infections might also partly explain why a predefined AUC:MIC ratio of 400 mg × hr/L adopted from adults has not been demonstrated to improve treatment effectiveness in pediatric MRSA-B.

Further, as shown in Table 1, the percentage of patients with persistent bacteremia from enrolled pediatric MRSA-B studies, defined as a positive culture after 48 to 72 hours of vancomycin treatment (29.5% and 39.7%),[16,22] was in agreement with a pediatric epidemiologic study (27.6% after 3 days),[48] whereas previously reported persistent bacteremia in adult literature (8.7% to 76%) was defined as a positive culture after 7 days of vancomycin treatment.[33–38,40,43,44,50] Additionally, the reported percentages of pediatric patients with recurrent MRSA-B within 30 days was 3%, 7.3%, and 19.4%,[16,20,22] compared with the 30-day recurrence rate of 3% previously reported in a pediatric epidemiologic study that was defined as a new positive blood culture separated by at least 7 days from the last positive blood culture for MRSA.[48] In contrast, the observed rate of recurrence in adults ranged from 2.6% to 8.1%, using a variety of cutoffs for recurrence such as during the same admission, or within 30 or 60 days.[33,35,37,41,43]

More importantly, the 30-day all-cause mortality rate reported in enrolled pediatric MRSA-B studies was 1.5% and 9.7%.[20,22] This is consistent with pediatric epidemiology (3.5%–8.7%)[49,51,52] and probably is lower than that observed in adult institution-based studies (10.2% to 40%),[12,33–37,39–44,46,47] or in a systematic review across different periods to account for changes over time in patient care (33.4%, 25.9%, and 23.4% for years prior to 2001, 2001 to 2010, and 2011 onward, respectively).[15] As mortality is a critical part of the composite endpoint of treatment effectiveness for MRSA-B, the observed rates of mortality in pediatrics suggest that these studies may be underpowered to answer the question as to whether a specific target for vancomycin AUC:MIC ratio is associated with improved outcomes with low mortality.

A pediatric MRSA-B epidemiologic study has demonstrated that every 1-day increase in the duration of MRSA-B is associated with a 50% increase in the odds of developing a complication, including progression of infection and development of metastatic foci of infection or septic emboli.[48] Therefore, the composite outcome for treatment effectiveness, including microbiologic clearance, recurrence, and mortality, could be refined in future studies by using time to bacteremia clearance only, given the potential severe complications from prolonged bacteremia, the observed low mortality, and the lack of widely adopted definitions on recurrent bacteremia. Although a median vancomycin trough concentration of <10 mg/L within the first 72 hours from historic trough-based monitoring has also been associated with a longer duration of MRSA-B in children, 47% of those trough concentrations were obtained before the third dose and may be lower than the true steady-state trough for some patients.[53]

All included studies against CoNS were performed in neonates and young infants, because CoNS infection was strongly related to lower gestational age and birth weight.[54] In contrast to the complications from delayed clearance of MRSA-B, a study involving 4364 infants with CoNS bloodstream infection from 348 neonatal ICUs found there was no significant difference in 30-day mortality, and the median duration of bacteremia was 1 day longer for infants who received delayed vancomycin therapy, started 1 to 3 days after the first positive blood culture.[55] This finding suggests that the PD properties of vancomycin against CoNS may vary from those of MRSA, and could affect the vancomycin PK/PD exposure goal.

Further, as opposed to MRSA-B, which typically is reported to have a vancomycin MIC ≤1 mg/L in these pediatric studies and in the guidelines,[4] more than

Table 3. Description of Studies on *Staphylococcus aureus* Infections

Reference	Design	Primary Objective	Inclusion Criteria	Exclusion Criteria	Characteristics of Entire Group	Characteristics of the Subgroup for Efficacy	Major Findings on AUC:MIC Threshold for Treatment Effectiveness
Ruiz, 2022, Spain[19]	Retrospective, single center, 2010–2016	AUC:MIC >400 mg × hr/L on *S aureus* bacteremia clinical and microbiologic treatment response	Age <3 yr on vancomycin for *S aureus* bacteremia	n/a	N = 51; age, mean ± SD, 7.2 ± 1 mo	Entire group of 51 patients, 25.5% MRSA, 35.3% MIC >1 mg/L	Achieving the predefined AUC:MIC goal of 400 mg × hr/L between days 2 and 3 was associated with early clinical response but not with microbiologic sterilization by 72 hr by a multivariate analysis or 30-day all-cause mortality using Kaplan-Meier method
Kishk, 2017, USA[18]	Retrospective, single center, 2007–2013	Vancomycin dosing to achieve an AUC:MIC >400 mg × hr/L	Age 2 mo to 18 yr with *S aureus* bacteremia on vancomycin for ≥2 doses and a trough available	On dialysis, abnormal serum creatinine for age or trough drawn inappropriately	N = 36, age n/a, 50% MRSA, 67% MIC >1 mg/L	A subgroup of 29 patients on vancomycin ≥24 hr; age and MRSA percentage n/a	Hospital or ICU stay and time to first negative blood culture was not different between those who achieved a predefined AUC:MIC ≥400 and those <400 mg × hr/L
McNeil, 2017, USA[26]	Retrospective, 2011–2016	Vancomycin trough and AUC:MIC on outcomes of pediatric *S aureus* pneumonia	*S aureus* pneumonia on vancomycin	On vancomycin for <48 hr	N = 36, median age 0.74 yr, 75% MRSA	A subgroup of 23 patients with AUC:MIC determination possible; age and MRSA percentage n/a; 88% MIC ≥1.5 mg/L	No correlation between values of AUC:MIC and length of ICU or hospital stay or any combination of duration of fever, bacteremia or ICU stay >75%-tile, need for re-operation, and mortality (statistical method for correlation n/a)

AUC:MIC, area under the cure to minimum inhibitor concentration ratio; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus; n/a, not available; S aureus, Staphylococcus aureus

one-third of CoNS isolates in enrolled studies had a vancomycin MIC of >1 mg/L (Table 2), which approximates the published data from 33 medical centers in the United States and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) database[56,57] that CoNS MICs are more frequently >1 mg/L in

comparison to MRSA. However, the MICs from different susceptibility testing methods are not entirely consistent. The same discrepancies between the Etest and BMD described for *S aureus* were also observed for CoNS; in general, the MICs obtained by Etest were 1- to 2-fold higher than the MICs obtained by BMD.[58] Therefore, consensus on the MIC method is extremely important if the AUC:MIC ratio is used as the PK/PD exposure goal against CoNS.

Likewise, extrapolating the vancomycin AUC:MIC goal for MRSA to CoNS with a MIC of >1 mg/mL would result in dose adjustment to achieve a high AUC with associated risk of nephrotoxicity and is beyond the stated usage of the current guidelines. Further evaluation of vancomycin exposure goal against CoNS is needed, especially if it might be more aptly characterized by AUC regardless of MIC as reported in 1 included study.[25] Alternatively, avoiding high AUC–associated nephrotoxicity by replacing vancomycin with another antibiotic—based on susceptibility—might be considered, although data on vancomycin alternative in premature neonates are limited and discussions on the appropriateness of antibiotic selection are beyond the scope of the review.

Vancomycin therapeutic drug monitoring may be indicated for *S aureus* infections while awaiting antimicrobial susceptibility testing results for definitive treatment. However, identifying a vancomycin exposure goal for efficacy from these patients might be difficult given that empiric treatment of severe infection with *S aureus* isolates from normally sterile sites usually includes concurrent beta-lactam to maximize activity against both MRSA and methicillin-susceptible *S aureus*.

Limitations

To the best of our knowledge, this is the first qualitative systematic review on vancomycin AUC:MIC ratio threshold for effectiveness against culture-proven MRSA, CoNS, and *S aureus* in neonates, infants, and children. Nonetheless, several limitations of this review should be noted.

First, concomitant drug therapy and control of the source of infection, such as removal of infected indwelling medical device, may affect treatment outcomes regardless of the vancomycin exposure goal, but we were unable to determine its impact on outcomes owing to absence of these data in the identified studies. Additionally, pathogenic factors such as the molecular characteristics of MRSA, including the presence of the accessory gene regulator or Panton-Valentine leucocidin, were not available. Further, assessment on treatment success against CoNS may be challenging given lack of data on whether CoNS was pathogenic and not a contaminant.

Second, observational studies are subject to selection bias and unidentified confounding factors and warrant cautious interpretation of study findings. Further, clinical diversity in patient characteristics, inconsistencies in the measurement of exposures, and definition of effectiveness outcomes across studies preclude a meta-analysis. Considering the challenges in performing pediatric research due to limited studies and low study enrollment, this review constituted an accumulation of real-world evidence to encourage further scientific evaluation of the vancomycin exposure goal against MRSA and methicillin-resistant CoNS with consideration of assessment of underlying disease severity, concurrent antibiotics, in addition to a single vancomycin PK/PD marker.

Conclusions

Available pediatric data on the vancomycin exposure threshold for effectiveness included an AUC:MIC of 300, 280, and 400 mg × hr/L for MRSA, CoNS, and *S aureus* bacteremia, respectively, and an AUC of 300 mg × hr/L, regardless of MIC, for CoNS bacteremia. However, there are overall limited data, and these thresholds should be interpreted as hypothesis generating only. Given the advantages of AUC-guided dosing, further research is needed to elucidate the pediatric vancomycin AUC:MIC target against MRSA-B. However, the effectiveness outcome including recurrent bacteremia and mortality could be refined in future research by using time to bacteremia clearance only, as odds of complications increase with each additional day of MRSA-B, whereas the definition of recurrent bacteremia is not standardized, and mortality is low. Similarly, obtaining more data on AUC regardless of MIC against MR-CoNS bloodstream infection remains a priority, because extrapolating AUC:MIC goal to CoNS with a MIC of >1 mg/L would result in dosing adjustment aiming at a high AUC with associated risk of nephrotoxicity and is beyond the stated usage of current guidelines.

Article Information

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