Continuous Infusion Vancomycin in Pediatric Patients: A Critical Review of the Evidence

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OBJECTIVE To evaluate the use of continuous infusion vancomycin in pediatric patients.

DATA SOURCES AND STUDY SELECTION PubMed, Cochrane Library, International Pharmaceutical Abstracts, and Google Scholar were searched to identify relevant published articles (1977 to November 2019) using the following search terms: vancomycin, neonates, pediatrics, infusion, continuous, administration, children, nephrotoxicity, pharmacokinetics, and pharmacodynamics. All English-language primary references that evaluated continuous infusion vancomycin in pediatric patients were included in this review.

DATA SYNTHESIS Vancomycin is typically administered with intermittent infusions, but continuous infusion is an alternative delivery method used to improve achievement of target serum concentrations. Fifteen articles were reviewed that evaluated continuous infusion vancomycin in pediatric patients. Study data were heterogeneous with limited evidence to support improved clinical or microbiologic outcomes as compared with intermittent dosing. Potential benefits and limitations of continuous infusions are discussed.

CONCLUSIONS Currently available evidence is lacking to support routine implementation of continuous infusion vancomycin in pediatric patients. However, it is a therapeutic option in certain clinical conditions and could be beneficial for individuals with serious Gram-positive infections where rapid achievement of target serum concentrations is critical. Continuous infusions may also benefit individuals who do not achieve target concentrations or who experience significant red man syndrome with traditional dosing, particularly when high daily doses are required. Optimal dosing and ideal target serum concentrations have not been established and may vary for different populations. Future prospective randomized clinical trials should be performed to identify optimal dosing and monitoring regimens and determine comparative safety and efficacy with traditional intermittent dosing in various pediatric populations.

ABBREVIATIONS AUC, area under the concentration-time curve; CF, cystic fibrosis; CIV, continuous infusion vancomycin; CoNS, coagulase-negative staphylococci; Cpss, steady-state concentration; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; D5W, dextrose 5% in water; GA, gestational age; GFR, glomerular filtration rate; IIV, intermittent intravenous vancomycin; IV, intravenous; LD, loading dose; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; PCA, postconceptual age; PICU, pediatric intensive care unit; PMA, postmenstrual age; PNA, postnatal age; SCr, serum creatinine; TPN, total parenteral nutrition; UOP, urine output; VAN, vancomycin; VSC, vancomycin serum concentration

KEYWORDS administration; continuous infusion; intermittent; neonate; pediatrics; vancomycin; vancomycin infusion

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Introduction

Vancomycin is often used as empiric and targeted treatment for a wide variety of systemic Gram-positive infections, including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA), which place a large burden on the health care system.¹ Vancomycin exhibits concentration-independent bactericidal activity, and the pharmacodynamic parameter traditionally associated with efficacy was time above the minimum inhibitory concentration (MIC). Clinical guidelines for the treatment of complicated MRSA infections in adults

recommend target serum trough concentrations of 15 to 20 mg/L.² Despite extensive investigation into therapeutic monitoring and years of clinical experience, there remains controversy about the optimal vancomycin dosing approach that maximizes efficacy and safety. Recent studies in adults suggest that the area under the concentration-time curve to minimum inhibitory concentration ratio (AUC/MIC) is predictive of clinical outcome.² Target AUC/MIC ratios of 400:1 or greater are suggested to maximize clinical efficacy when treating serious *S aureus* infections.² Because AUC-guided dosing and monitoring is complicated when using inter-

mittent intravenous vancomycin (IIV), target trough concentrations of 15 to 20 mg/L can serve as a surrogate marker in adults with normal renal function when the *S aureus* MIC is ≤ 1 mg/mL.^{2,3} These trough ranges can be difficult to achieve when using IIV in certain patient populations with rapid drug clearance, such as children and patients with cystic fibrosis (CF), and they have also been associated with nephrotoxicity.⁴⁻⁷ In fact, use of these vancomycin trough ranges is controversial when treating children with serious staphylococcal infections. Recent data suggest that trough concentration ranges of 15 to 20 mg/L result in excessively high AUC/MIC ratios in children, increasing the risk of nephrotoxicity.⁸⁻¹⁰ When targeting an AUC/MIC of 400:1 in children and adolescents, the trough range that corresponds (about 7–11 mg/L and 10–12.5 mg/L, respectively) is lower than the surrogate adult target goal of 15 to 20 mg/L.^{8,9,11-13} This can be explained by increased renal clearance in children and adolescents. As compared to intermittent administration, continuous vancomycin administration simplifies therapeutic drug monitoring through easier AUC estimation methods and avoids use of surrogate trough concentrations that are not well established in all patient populations or clinical scenarios.

Continuous infusion vancomycin (CIV) has been used in pediatric patients where target serum trough concentrations have not been achieved with standard IIV administration. Attaining target serum concentrations with IIV in children requires larger mg/kg doses and more frequent dosing intervals as compared to adults and, in some cases, is not achievable even with doses as high as 100 mg/kg/day.^{14,15} In adults, use of CIV following an initial loading dose shortens the time to therapeutic concentration achievement, demonstrates longer duration above target concentrations, and reduces toxicity, particularly among critically ill patients and those with serious infections.¹⁶⁻²⁴ Continuous administration avoids the transiently elevated serum peak concentrations that occur with IIV dosing, which results in smaller total daily doses that are needed to achieve target serum concentrations. Nephrotoxicity has been thought to be related to excessive drug exposure in terms of AUC, which may be reduced with smaller total daily doses needed to achieve desired plateau concentrations with CIV as compared to the larger daily doses needed to achieve target trough serum concentrations with IIV.^{5,10,18,23,25}

There is evidence available from cohort studies and randomized controlled trials to support the use of CIV in the critically ill adult population.^{18-21,26} The purpose of this review is to provide an evidence-based recommendation for use of CIV in pediatric patients.

Data Sources and Study Selection

PubMed, Cochrane Library, International Pharmaceutical Abstracts, and Google Scholar were comprehensively searched to retrieve primary studies using

Figure. QUOROM diagram of systematic search used to identify articles for review.

the following search terms: vancomycin, neonates, pediatrics, infusion, continuous, administration, children, nephrotoxicity, pharmacokinetics, and pharmacodynamics. Specific search limits were placed to yield solely primary references that were published between 1977 and November 2019. Next, articles included in this review must have been published in the English language and must have evaluated vancomycin use in children (birth through 18 years). Studies that did not include use of vancomycin continuous infusion were excluded from this review.

The Figure is a QUOROM diagram of the systematic search that illustrates the process used to identify primary articles included in this review. From the original identified citations (n = 302), articles were excluded that did not include pediatric patients and were not published in English. From the remaining citations (n = 49), articles that were not primary references evaluating use of continuously infused vancomycin were excluded, resulting in 15 articles that are summarized in this review.

Clinical Evidence

Studies of CIV in pediatrics have used various dosing regimens with different target serum plateau con-

centrations in a variety of patient populations (Tables 1 and 2). Only 1 randomized controlled trial has been performed in pediatric patients to compare the efficacy and safety of CIV with IIV. Patients with augmented renal clearance (creatinine clearance greater than 120 mL/min/1.73 m²) and critically ill patients are more likely to have subtherapeutic vancomycin concentrations early in the treatment course; therefore, most of the studies have used a loading dose to achieve target serum concentrations more quickly with the goal of optimizing therapy and increasing the likelihood of clinical success in a population with compromised immunity.

Neonates and Infants Younger Than 90 Days. Most of the evidence available for CIV is in the neonatal population, of which 7 studies with over 500 neonates are included in this review. In an early French study, Pawlotsky et al²⁷ prospectively studied 2 different dosing schemes in 53 critically ill neonates with proven or suspected Gram-positive infections (Table 1). CIV doses were determined by using postconceptual age (PCA) dosing strata. Dosages in group 1 were generally smaller than the doses in group 2, and a loading dose was administered only to patients in group 2. The investigators targeted a steady-state serum concentration of 10 to 30 mg/L, where steady state was defined as the average of serum concentrations obtained at 48 hours and 72 hours. The regimen used in group 2 achieved the target steady-state serum concentration in 88% of neonates (75% within 24 hours) as compared to 56% in group 1 (55% within 24 hours, $p < 0.01$). No infusion-related reactions were observed with either dosing scheme, but 1 patient in group 2 developed a reversible increase in serum creatinine (SCr) during treatment for sepsis. This study showed that a loading dose helped reach target serum concentrations faster in neonates. Use of larger weight-based doses for a given PCA stratum also resulted in improved attainment of target serum concentrations. A limitation of this study was that the authors used a complicated stratified dosing scheme in group 2 that may not be as easily introduced into clinical practice. Also, the lower end of the target serum concentration range was below that used in more recent studies, which may not be effective for treating infections caused by organisms with vancomycin MIC of 1 mg/L or greater. Finally, the authors did not describe any dose adjustments that were made during therapy, did not indicate the duration of therapy, and did not discuss the relationship between the increased attainment of target serum concentrations and clinical or bacteriologic efficacy.

In another French study, Plan et al²⁸ prospectively evaluated 2 simplified CIV dosing regimens based on weight and SCr in 145 preterm neonates and their impact on serum concentrations and antibacterial efficacy (Table 1). Neonates with necrotizing enterocolitis or severe congenital malformations were excluded from the study. Loading doses were not administered and

all neonates received amikacin for at least the first 48 hours of vancomycin treatment. Blood samples were drawn at 48 hours to assess culture results and serum vancomycin and creatinine concentrations. If cultures were negative, antibiotics were discontinued. If infection was confirmed, vancomycin doses were adjusted to achieve a target serum concentration range of 10 to 25 mg/L and treatment was continued for 8 days after the first negative blood culture. There was no difference between the 2 groups in the percentage of neonates (75%) reaching target serum concentrations at 48 hours; however, there were significantly more neonates in group 2 with high serum concentrations and significantly more neonates in group 1 with low serum concentrations ($p = 0.0006$). Bacteriologic efficacy at 48 hours was similar with both dosage regimens (71%) for documented coagulase-negative staphylococcal infection. After 96 hours of treatment, 92% of patients had negative blood cultures without requiring removal of central venous lines. Serum creatinine changes were not observed in either group, but results were only reported for the first 48 hours of therapy. The authors proposed that the doses used in group 2 were preferred. Higher serum vancomycin concentrations did not correlate with improved efficacy, as similar percentages of patients had negative cultures at 48 hours despite significantly different average serum concentrations obtained between the 2 groups (13 mg/L and 19 mg/L for groups 1 and 2, respectively; $p < 0.005$). This could be related to infections that were caused by highly sensitive staphylococci, but MIC values were not reported. Additional study limitations are that loading doses were not used, and there was no mention of dose adjustments, duration of CIV therapy, or adverse reactions.

Patel et al²⁹ prospectively evaluated a CIV protocol used in a neonatal unit at a single British hospital, which was implemented because of historically poor achievement of desired serum concentrations with IIV at their facility coupled with inappropriate blood sampling that led to excessive venipunctures and inappropriate dose adjustments (Table 1). The protocol included a loading dose followed by a CIV dose based on SCr, postmenstrual age (PMA), and weight. Serum concentrations were obtained within 12 to 24 hours of treatment initiation or dose changes and when routine blood samples were scheduled (when possible) to avoid additional venipunctures. A review of the first 60 CIV courses revealed that 68% of concentrations were within the target serum concentration range of 15 to 25 mg/L, but 30% of initial concentrations exceeded this range. High serum concentrations occurred most often with doses of 60 mg/kg/day, so the maximum dose was reduced to 50 mg/kg/day for the subsequent 60 CIV courses. The dose change achieved satisfactory serum concentrations in 82% of samples and only 5% had serum concentrations above the target range. No

Table 1. Summary of Continuous Infusion Vancomycin Studies in Neonates and Infants Younger Than 90 Days

Reference	Study Population	Target VSC, mg/L	Dosing Regimen	Measured VSC, mg/L	Comments
Pawlotsky ²⁷	NICU pts with proven or suspected Gram + infections Group 1: n = 24; PCA 33.5 wk (27–41)* Group 2: n = 29; PCA 33.9 wk (28–51.5 wk)*	10–30 (Cpss = avg of VSC at 48 and 72 hr)	Group 1: no LD; CIV 10–30 mg/kg/day (admixed with TPN) Group 2: LD 7 mg/kg; CIV 10–40 mg/kg/day (diluted in 24 mL of D5W; infused via separate pump) CIV dose calculated on wt and PCA increments Group 1: 5 dosing strata Group 2: 11 dosing strata	Group 2: after LD: $15 \pm 8.1^{\dagger}$ After 24 hr: Group 1: $10.7 \pm 3.7^{\dagger}$ Group 2: $12 \pm 3.8^{\dagger}$ After 48 hr: Group 1: $10.7 \pm 3.3^{\dagger}$ Group 2: $14.9 \pm 6.7^{\dagger}$ After 72 hr: Group 1: $11 \pm 3.6^{\dagger}$ Group 2: $16 \pm 3.8^{\dagger}$	13 pts (24.5%) had documented infection (organisms NR); all recovered Group 1 (17%) and Group 2 (24%) were < 10th percentile in wt for GA at birth No hypotension or red man syndrome; 1 case of reversible increase in SCr during <i>Klebsiella</i> sepsis
Plan ²⁸	Preterm NICU pts with suspected CoNS sepsis Group 1: n = 73; PCA 28 wk (26–29) [‡] Group 2: n = 72; PCA 27.5 wk (26–29) [‡]	10–25	No LD Group 1: 15 mg/kg/day if SCr > 1.02 mg/dL or 25 mg/kg/day if SCr ≤ 1.02 mg/dL Group 2: 20 mg/kg/day if SCr > 1.02 mg/dL or 30 mg/kg/day if SCr ≤ 1.02 mg/dL Dose adjusted by ± 5 mg/kg/day for VSC < 10 mg/L or > 25 mg/L CIV diluted in D5W to 5 mg/mL; infused via separate pump	After 48 hr: Group 1: 13 (10–17) [‡] Group 2: 19 (15–23) [‡]	VSC at 48 hr: <10 mg/L - Group 1: 24%; Group 2: 5% >25 mg/L - Group 1: 1.4%; Group 2: 19% Bacteriologic efficacy at 48 hr: Group 1: 69% Group 2: 73% Proportion of patients with wt > 2 SD below NL at start of VAN: Group 1: 16% Group 2: 40% Older PNA (OR 1.39; 95% CI, 1.09–1.96) and heparin use (OR 5.3; 95% CI, 1.37–21.9) associated with >risk of continued infection at 48 hr of CIV; No changes in SCr at 48 hr in either group

avg, average; CIV, continuous infusion vancomycin; CoNS, coagulase-negative staphylococci; Cpss, steady-state concentration; D5W, dextrose 5% in water; GA, gestational age; ILV, intermittent intravenous vancomycin; LD, loading dose; NICU, neonatal intensive care unit; NL, normal; NR, not reported; PCA, postconceptional age; PMA, postmenstrual age; PNA, postnatal age; pts, patients; SCr, serum creatinine; TPN, total parenteral nutrition; VAN, vancomycin; VSC, vancomycin serum concentration; wt, weight

* Mean (range).

[†] Mean $\pm$ standard deviation.

[‡] Median (IQR).

[§] Dose selected on the basis of GA, PNA, and renal function.

[¶] Low concentrations occurred most often in hospital 3, which did not use an LD, while high concentrations occurred most often in hospital 2, which used an LD and a fixed weight-based dose regardless of GA, PMA, or SCr.

[#] Dose calculation using a complex equation that included birth weight, current weight, PNA, SCr, and desired vancomycin serum concentration in addition to a personalized LD.

Table 1. Summary of Continuous Infusion Vancomycin Studies in Neonates and Infants Younger Than 90 Days (cont.)

Reference	Study Population	Target VSC, mg/L	Dosing Regimen	Measured VSC, mg/L	Comments
Patel ²⁹	NICU pts (number NR); GA 24–42 wk PMA 26–62 wk 120 CIV courses assessed	15–25	LD: 15 mg/kg followed by initial CIV dose of 20–60 mg/kg/day VAN dose dependent on SCr and PMA: SCr < 0.45 mg/dL and PMA ≥ 40 wk: 50 mg/kg/day SCr < 0.45 mg/dL and PMA < 40 wk: 40 mg/kg/day SCr 0.45–0.68 mg/dL: 30 mg/kg/day SCr > 0.68 mg/dL: 20 mg/kg/day CIV doses diluted in D5W (final concentration of 4.17 mg/mL) and infused via same line as TPN	NR	No VAN-related adverse effects, IV access problems, or incompatibilities reported
Zhao ³⁰	NICU pts (N = 116) Hospital 1: mean PMA = 32.4 wk, PNA = 23 days Hospital 2: mean PMA = 33.5 wk, PNA = 35 days Hospital 3: mean PMA = 35.3 wk, PNA = 23 days	15–25	Hospital 1: LD 10–15 mg/kg; then 15–35 mg/kg/day§ Hospital 2: LD 15 mg/kg; then 30 mg/kg/day§ Hospital 3: no LD used; 30 mg/kg/day (20 mg/kg/day if SCr > 1.02 mg/dL)§ CIV administration details not reported	Hospital 1: 20.3 (8.9–44)* Hospital 2: 21.6 (11–61.5)* Hospital 3: 16.8 (5.1–50)*	Data from 3 hospitals prior to use of optimized regimen: 41% (n = 48) desired VSC range 30% (n = 35) < 15 mg/L 28% (n = 32) > 25 mg/L¶ Prospective validation study in 58 neonates using an optimized patient-tailored regimen 71% in desired VSC range 6–12 hr after starting VAN; mean concentration 20 mg/L (10th to 90th percentile: 12.8–26.5 mg/L)
Demirel ³¹	Preterm NICU pts with suspected/proven late-onset sepsis Group 1: (n = 41) mean GA 29.3 wk, median PNA 9 days; Group 2: (n = 36) mean GA 28.6 wk, median PNA 11 days	Group 1: 5–10 Group 2: 15–20	Group 1: IIV dose and dosing frequency as recommended by Neofax Group 2: LD 10 mg/kg; then CIV dose as recommended by Neofax (IIV total daily dose given as 24-hr infusion). VAN diluted in D5W to 5 mg/mL	At 48 hr: Group 1: median 8 (range, 5–10.5) Group 2: median: 17 (range, 11–21)	At 48 hr: Supratherapeutic VSC: Group 1 (39%) and Group 2 (6%), p = 0.002 Subtherapeutic VSC: Group 1 (27%) and Group 2 (42%), p = 0.002 Clinical or bacteriologic outcome and adverse events were not statistically different Aminoglycosides were not given concomitantly

avg, average; CIV, continuous infusion vancomycin; CoNS, coagulase-negative staphylococci; Cpss, steady-state concentration; D5W, dextrose 5% in water; GA, gestational age; IIV, intermittent intravenous vancomycin; LD, loading dose; NICU, neonatal intensive care unit; NL, normal; NR, not reported; PCA, postconceptional age; PMA, postmenstrual age; PNA, postnatal age; pts, patients; SCr, serum creatinine; TPN, total parenteral nutrition; VAN, vancomycin; VSC, vancomycin serum concentration; wt, weight

* Mean (range).

† Mean ± standard deviation.

‡ Median (IQR).

§ Dose selected on the basis of GA, PNA, and renal function.

¶ Low concentrations occurred most often in hospital 3, which did not use an LD, while high concentrations occurred most often in hospital 2, which used an LD and a fixed weight-based dose regardless of GA, PMA, or SCr.

Dose calculation using a complex equation that included birth weight, current weight, PNA, SCr, and desired vancomycin serum concentration in addition to a personalized LD.

Table 1. Summary of Continuous Infusion Vancomycin Studies in Neonates and Infants Younger Than 90 Days (cont.)

Reference	Study Population	Target VSC, mg/L	Dosing Regimen	Measured VSC, mg/L	Comments
Tauzin ³²	NICU pts (N = 75) with suspected infections caused by beta-lactam-resistant Gram + bacteria; GA 27 wk (26–30.5) [‡] PNA 15 days (9–33) [‡] 91 CIV treatment courses	20–30	LD 15 mg/kg; then CIV 30 mg/kg/day	21.1 (16.3–29.7) [‡] at 18 hr	74% (n = 67) had negative blood cultures; 19% (n = 17) had CoNS 1st sample assay: 44% had VSC < 20 mg/L and 25% had VSC > 30 mg/L 2nd sample assay (n = 49): 37% of VSC were within the target range, 6% had VSC > 40 mg/L Multivariate logistic regression revealed PNA > 14 days and PMA ≥ 32 wk were associated with low VSC; SCR > 0.79 mg/dL associated with elevated VSC
Gwee ³³	104 infants with suspected infections, expected to receive at least 48 hr of VAN GA: mean 34.0 wk PNA: mean 23 days	IIV: 10–20 (trough) CIV: 15–25 (Cpss)	IIV: doses and frequency recommended by British National Formulary based upon PMA (15–60 mg/kg/day) CIV: LD 15 mg/kg; then 20–50 mg/kg/day based upon PMA and SCR (using regimen of Patel ²⁹) CIV administration details not reported	NR	Time to achieve target VSC (p = 0.003): IIV: 33.6 ± 38.8 hr [†] CIV: 271 ± 10.8 hr [†] Number of dose adjustments (range) to achieve target VSC (p < 0.001): IIV: 1 (0–3) [*] CIV: 0 (0–1) [*] Time to clearance of bacteremia (p = 0.62): IIV: 55.3 ± 14.9 hr [†] CIV: 46.1 ± 10.3 hr [†] PMA of 36–44 wk required significantly larger VAN doses with IIV vs CIV (67.7 ± 59.3 mg/kg/day [†] vs 43.8 ± 9.7 mg/kg/day [†] , p = 0.02); Concomitant gentamicin: 73% (IIV) and 81% (CIV) of patients

avg, average; CIV, continuous infusion vancomycin; CoNS, coagulase-negative staphylococci; Cpss, steady-state concentration; D5W, dextrose 5% in water; GA, gestational age; IIV, intermittent intravenous vancomycin; LD, loading dose; NICU, neonatal intensive care unit; NL, normal; NR, not reported; PCA, postconceptional age; PMA, postmenstrual age; PNA, postnatal age; pts, patients; SCR, serum creatinine; TPN, total parenteral nutrition; VAN, vancomycin; VSC, vancomycin serum concentration; wt, weight

* Mean (range).

† Mean ± standard deviation.

‡ Median (IQR).

§ Dose selected on the basis of GA, PNA, and renal function.

¶ Low concentrations occurred most often in hospital 3, which did not use an LD, while high concentrations occurred most often in hospital 2, which used an LD and a fixed weight-based dose regardless of GA, PMA, or SCR.
Dose calculation using a complex equation that included birth weight, current weight, PNA, SCR, and desired vancomycin serum concentration in addition to a personalized LD.

Table 2. Summary of Continuous Infusion Vancomycin Studies in Children Older than 30 Days

Reference	Study Population	Target VSC, mg/L	VAN Dosing Regimen	Measured VSC, mg/L	Comments
Non-critically ill children McKamy ²⁴	Children with pneumonia (n = 10) or osteomyelitis (n = 5) and normal renal function (baseline SCr < 0.9 mg/dL, GFR > 100 mL/min/1.73 m ² , and UOP > 1 mL/kg/hr) Age: 5.8 ± 61 yr*	15–20	<p>ILV initially, then converted to CIV if VAN trough < 15 mg/L</p> <p>CIV 55–60 mg/kg/day initiated immediately after next scheduled intermittent infusion dose (serves as an LD; should be at least 15 mg/kg or maximum of 1500 mg given over 1–2 hr)</p> <p>CIV given through dedicated intravenous line (central access preferred)</p>	<p>Initial (24–36 hr after starting CIV): 20.2 ± 5.2* Plateau (average during CIV): 19.1 ± 3.05*</p>	<p>VAN dosage at the end of CIV therapy was 44.3 ± 12.8* mg/kg/day</p> <p>No nephrotoxicity (defined as increase in SCr ≥ 0.5 mg/dL or 50% increase from baseline on 2 consecutive days, or UOP < 1 mL/kg/hr)</p> <p>1 patient lost peripheral IV access during CIV</p>
	Hurst ¹⁵ 240 children aged > 30 days to < 18 yr with normal renal function Most had central nervous system infection, bacteremia/sepsis, or meningitis	10–15 (n = 76) 15–20 (n = 164)	<p>Transitioned from ILV to CIV: dose dependent upon goal VSC:</p> <p>10–15 mg/L <2 yr: 45 mg/kg/day 2–8 yr: 40 mg/kg/day >8 yr: 35 mg/kg/day</p> <p>15–20 mg/L <2 yr: 50 mg/kg/day 2–8 yr: 45 mg/kg/day >8 yr: 40 mg/kg/day</p>	<p>Initial steady-state at ≥23 hr of CIV at Goal 10–15 mg/L (p = 0.077): <2 yr: 10.4 ± 1.6* 2–8 yr: 11.2 ± 2.4* >8 yr: 12.5 ± 3.4* Goal 15–20 mg/L (p = 0.009): <2 yr: 13.4 ± 4.5* 2–8 yr: 13.6 ± 3.7* >8 yr: 15.6 ± 3.1*</p>	<p>Doses required to achieve VSC of: 10–15 mg/L (p < 0.005): <2 yr: 48.4 ± 4.6 mg/kg/day* 2–8 yr: 45.6 ± 5.5 mg/kg/day* >8 yr: 39.4 ± 7.3 mg/kg/day 15–20 mg/L (p = 0.008): <2 yr: 50.2 ± 7.2 mg/kg/day* 2–8 yr: 50.6 ± 6.3 mg/kg/day* >8 yr: 44.7 ± 10.2 mg/kg/day* 9% had decreased renal function 19 had CrCl reduction of 25%–49% 1 had CrCl reduction of 50%–74% 1 had CrCl reduction of >75%</p>

AUC, area under the concentration-time curve; CIV, continuous infusion vancomycin; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; D5W, dextrose 5% in water; GFR, glomerular filtration rate; ILV, intermittent intravenous vancomycin; LD, loading dose; MLC, minimum inhibitory concentration; NR, not reported; pt, patient; PICU, pediatric intensive care unit; UOP, urine output; SCr, serum creatinine; VAN, vancomycin; VSC, vancomycin serum concentration

* Mean ± SD.

† Median (IQR).

‡ Median (range).

Table 2. Summary of Continuous Infusion Vancomycin Studies in Children Older than 30 Days (cont.)

Reference	Study Population	Target VSC, mg/L	VAN Dosing Regimen	Measured VSC, mg/L	Comments
Critically ill children					
Cies ³⁵	11 children with acute kidney injury in PICU, treated with CRRT using Prismaflex system Age: 10 yr (1–15) [†]	15–30	LD: 15–20 mg/kg over 1 hr; then CIV via CRRT solution, dialysate, or replacement fluid with final VAN concentrations ranging from 18–30 mg/L	21.8 (20.9–25) [†]	91% (n = 10) achieved target VSC within 8 hr of initiating CRRT admixed with VAN; the last pt achieved target VSC of 23.5 mg/L within 16 hr
Genuini ³⁶	28 critically ill pts with suspected or proven resistant Gram + infection Age: 2 yr (1 mo to 17 yr) [†]	15–30	LD: 15 mg/kg over 1 hr; then CIV 45 mg/kg/day via central or peripheral catheter; VAN diluted with D5W to 20 mg/mL	First VSC: 14.1 (range, 9.8–25.6) [†] ; After dose adjustment: 15.5 (range, 10–25.7) [†]	50% (n = 14) required 1–7 dose adjustments to achieve target VSC; 79% (n = 11) required dose increases 11% (n = 3) had renal dysfunction (≥2-fold increase in SCr) during CIV; all were receiving concomitant nephrotoxic drugs
Children with hematologic-oncologic conditions					
Guilhaumou ³⁷	121 pts with febrile neutropenia: Hematologic malignancies (n = 61) Age 9.1 ± 5.7 yr* Solid tumors (n = 60) Age 7.1 ± 5.4 yr*	20–25	LD: 10–15 mg/kg over 1 hr; then CIV 30–40 mg/kg/day CIV administration details NR Authors proposed an optimized dosing based on pharmacokinetic modeling that incorporated malignancy type, body weight, and concomitant use of cyclosporine	VSC within target range: Hematologic: 16% Solid tumors: 16% VSC < 20 mg/L: Hematologic: 52.1% Solid tumors: 70.5%	Hematologic malignancy protocol: All patients received VAN and ceftazidime (± aminoglycoside) Solid tumor protocol: VAN added to ceftazidime + amikacin after 24 hr if still febrile Blood cultures positive in 37.5%; staphylococcal species most common (43.8% methicillin resistant) Optimized dosing model was not validated as part of this study
Hoegy ³⁸	94 children with hematologic or oncologic disease and normal renal function Age 4.3 mo to 17.9 yr	14–21	LD not used CIV: <2 yr: 50–55 mg/kg/day 2–6 yr: 45–50 mg/kg/day 6–12 yr: 40–45 mg/kg/day >12 yr: 40 mg/kg/day CIV administration details NR	NR	VSC target range: 59% (n = 55) VSC < 14 mg/L: 33% (n = 31) VSC 11–14 mg/L: 87% (n = 31)

AUC, area under the concentration-time curve; CIV, continuous infusion vancomycin; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; D5W, dextrose 5% in water; GFR, glomerular filtration rate; ILV, intermittent intravenous vancomycin; LD, loading dose; MLC, minimum inhibitory concentration; NR, not reported; pt, patient; PICU, pediatric intensive care unit; UOP, urine output; SCr, serum creatinine; VAN, vancomycin; VSC, vancomycin serum concentration

* Mean ± SD.

[†] Median (IQR).

‡ Median (range).

Table 2. Summary of Continuous Infusion Vancomycin Studies in Children Older than 30 Days (cont.)

Reference	Study Population	Target VSC, mg/L	VAN Dosing Regimen	Measured VSC, mg/L	Comments
Cystic fibrosis					
	Fung ³⁹	15–20	CIV dose: Patient 1: 50 mg/kg/day Patient 2: 40 mg/kg/day Patient 3: 50 mg/kg/day CIV administration details NR	After 24 hr: Patient 1: 14.2 mg/L Patient 2: 22.5 mg/L Patient 3: 26.8 mg/L at steady state	Patient 3 final dose was 31 mg/kg/day with AUC/MIC 436
	McKinzie ⁴⁰	20–25	Day 1: CIV 64 mg/kg/day Day 9: 53 mg/kg/day CIV administration details NR	Range: 21.8–27.7 mg/L during 15 days	Developed hives on day 15; and VAN discontinued

AUC, area under the concentration-time curve; CIV, continuous infusion vancomycin; CrCl, creatinine clearance; CRRT, continuous renal replacement therapy; D5W, dextrose 5% in water; GFR, glomerular filtration rate; IIV, intermittent intravenous vancomycin; LD, loading dose; MIC, minimum inhibitory concentration; NR, not reported; pt, patient; PICU, pediatric intensive care unit; UOP, urine output; SCr, serum creatinine; VAN, vancomycin; VSC, vancomycin serum concentration

* Mean $\pm$ SD.

† Median (IQR).

‡ Median (range).

adverse effects were reported with CIV. The authors concluded that continuous infusions were more effective at achieving target serum concentrations than IIV and resolved problems related to improper monitoring and dose adjustments. Some significant limitations of this study include the lack of detailed information available in the publication, including the number of patients and infection-related information, treatment duration and dose adjustments, and clinical outcome data. Also, the investigators measured vancomycin serum concentrations 12 to 24 hours after treatment initiation or dose changes were made, which may not be reflective of steady state in a patient population where the vancomycin half-life is likely to be 6 to 10 hours or greater.

Zhao et al³⁰ used non-linear mixed effects modeling to create an optimized CIV dosing equation using 207 vancomycin serum concentration measurements obtained from 116 neonates who were managed with 1 of 3 different French neonatal intensive care unit (NICU) dosing protocols (Table 1). A total of 58 neonates participated in the prospective validation study using the patient-tailored optimized dosing equation. After receiving personalized doses (which included a loading dose), 71% achieved target serum concentrations within 6 to 12 hours of starting vancomycin. After subsequent dose adjustments, all neonates achieved serum concentrations in the desired range when the dose adjustment protocol was followed. The authors concluded that, even with use of an optimized dosing equation based on pharmacokinetic modeling, therapeutic drug monitoring was still required to ensure that target serum concentrations were achieved when CIV was administered to neonates because of large inter-individual variability. The pharmacokinetic model was advantageous because it allowed for dose calculation based upon the desired target serum concentration. While use of personalized dosing was fairly successful for achieving target serum concentrations early in therapy, this dosing strategy used a complex calculation and 30% of patients still required individualized dose adjustments, which is not distinctly different from earlier studies that used less complex dosing equations. This suggests that equations incorporating simpler parameters, such as gestational age and SCr, may be more useful in everyday practice. Also, there was no evaluation of clinical outcomes, bacteriologic efficacy, or toxicity in this study.

Demirel et al³¹ retrospectively compared the microbiologic outcomes, clinical response, and adverse events of CIV with IIV in 77 preterm infants with suspected or proven late-onset sepsis in an Istanbul NICU (Table 1). Daily vancomycin doses were determined by using gestational age and postnatal age (PNA) and administered either as IIV or as CIV-initiated postloading dose. Vancomycin serum concentrations were obtained between 48 and 72 hours of treatment and doses were

adjusted to maintain target concentrations. Clinical failure was defined as death from infection or deterioration in clinical, laboratory, or radiologic status despite vancomycin treatment. Adverse effects attributed to vancomycin and reasons for treatment discontinuation were also compared. Target serum concentrations at 48 hours were obtained more frequently with CIV than IIV (53% versus 34%, $p = 0.002$). More dose adjustments were necessary with IIV than with CIV to reach target serum concentrations (66% versus 54%), but this was not statistically significant ($p = 0.2$). No statistical differences in clinical, bacteriologic, or adverse outcomes were observed between the groups. The authors concluded that while CIV was not superior to IIV in clinical or microbiologic outcomes, it may be advantageous because it requires fewer dose adjustments and less blood sampling with a lower propensity for timing errors. Limitations of this study include its retrospective nature and inherent challenges associated with this study design, the small sample size that limits the ability to detect potentially significant differences between groups, lack of randomization, and absence of AUC/MIC calculations.

Tauzin et al³² evaluated the efficiency of a simplified CIV regimen to achieve target serum concentrations in a French NICU and compared their results to other published dosing regimens to determine which would be the most adequate for their population (Table 1). The study evaluated 91 vancomycin courses from 75 preterm neonates, of which 53% were born before 28 weeks' gestation. The target serum concentration range was reached in only 31% of courses at the first assay (minimum of 18 hours after starting CIV postloading dose). At the first assay or after dose titration, the target range was achieved in 62% of courses, which occurred at a median time of 34 hours. When compared to other published CIV regimens in neonates, only 1 would have been more suitable to minimize concentrations outside of the target range by using a CIV dose that was based upon PMA and SCr (regimen used by Patel et al²⁹). The authors concluded that a simplified CIV dosing regimen is not appropriate for the high interindividual variability and pharmacokinetic changes inherent in a preterm neonatal population and that therapeutic drug monitoring is essential. Limitations of this study include its retrospective nature, lack of clinical outcome data, and the low blood culture positivity rate in order to characterize MICs and assess bacteriologic efficacy.

Gwee et al³³ recently published the only randomized controlled trial of CIV versus IIV in children (Table 1). This multicenter, non-blinded study included 104 infants aged 0 to 90 days, treated at 2 NICUs in Australia. Infants were excluded if their PMA was less than 25 weeks, if they had known glycopeptide allergy or renal impairment, or required extracorporeal membrane oxygenation. The primary outcome was the difference in the proportion of patients who achieved target serum

concentrations at the first steady-state level. The first steady-state level was defined as the serum concentration before the fourth or fifth dose for IIV or the serum concentration at 18 to 30 hours postloading dose and after starting CIV. The most common reason for vancomycin therapy was suspected sepsis (65%) and the most commonly isolated organisms from blood were coagulase-negative staphylococci (13/23, 57%). The average vancomycin treatment duration was 5 days. Significantly more infants in the CIV group achieved target serum concentrations at the first steady-state level than those who received IIV (85% vs 41%, $p < 0.001$). The average time to achieve target serum concentrations and the number of dose adjustments were significantly greater with IIV than with CIV. The average daily dose required to achieve desired serum concentrations was smaller and less variable with CIV (40.6 ± 10.7 mg/kg/day) than with IIV (60.6 ± 53.0 mg/kg/day, $p = 0.01$). There were no differences between the groups in terms of adverse effects or clinical outcomes. The authors concluded that CIV achieved earlier and improved target serum concentrations with smaller total daily doses and fewer dose adjustments than standard intermittent dosing. Despite the stronger study design than that of previously published studies, the findings are limited by the lack of power to detect differences in toxicities and mortality, the low culture positivity rate and subsequent microbiologic efficacy assessment, and lack of cost comparison.

Pediatric Patients Older Than 30 Days. McKamy et al³⁴ evaluated a pediatric CIV dosing guideline developed at their California hospital for pediatric patients who were unable to achieve target serum troughs of 15 to 20 mg/L with intermittent doses of 60 mg/kg/day or larger (Table 2). Patients older than 6 months with normal renal function were eligible for CIV therapy if they had pneumonia or osteomyelitis known or presumed to be caused by Gram-positive organisms. The primary outcomes included rate of target serum concentration attainment at 24 to 48 hours, the adequacy of the empiric dosing strategy, and adverse effects. Fifteen patients experienced conversion to CIV after 4 to 7 days of IIV with doses of 68.4 ± 5.8 mg/kg/day and trough concentrations of 9.2 ± 4.6 mg/L. The mean initial vancomycin concentration during continuous infusion was 20.2 ± 5.2 mg/L compared to 6.6 ± 2.3 mg/L with intermittent dosing. Twelve patients (80%) achieved steady-state serum concentrations of ≥ 15 mg/L within 24 to 36 hours of CIV initiation. Adolescents had the highest initial vancomycin serum concentrations and required dose reductions of up to 50%, suggesting that the optimal empiric CIV dose for these patients is ≤ 40 mg/kg/day. Two of 3 patients who developed infusion-related reactions with intermittent dosing that required diphenhydramine were able to discontinue its use during CIV. No patients developed nephrotoxicity while on CIV with an average duration of therapy of 15.3 ± 23.1

days. The authors concluded that converting to CIV is safe and well tolerated in select pediatric patients who are not able to achieve target serum concentrations with intermittent dosing. A significant limitation of this study is the small sample size and inclusion of patients with only pneumonia or osteomyelitis. These patients initially received IIV and were switched to continuous dosing, so there is no information on the ability to achieve target serum concentrations with continuous infusions at the onset of therapy and the resultant effect on clinical outcome. In fact, clinical effectiveness was not a measured study objective. Lastly, this study did not include patients younger than 6 months.

Hurst et al¹⁵ described their experience with a CIV dosing guideline at a Colorado hospital in 240 patients aged 31 days or older with various infections (Table 2). Patients were transitioned from IIV to CIV, most of whom were unable to achieve desired serum concentrations prior to the switch. They were included in the study if a steady-state serum concentration was recorded at least 23 hours after CIV initiation. Patients with baseline renal insufficiency or those who received extracorporeal membrane oxygenation were excluded. The study outcomes included the total daily CIV dose required to obtain target serum concentrations according to age strata, the frequency of obtaining target serum concentrations, and safety. The total daily doses that resulted in target serum concentrations were significantly larger in children younger than 8 years. There was no difference in the time needed to achieve target serum concentrations between the age strata. For patients with a target serum concentration range of 15 to 20 mg/L, there were significantly more patients older than 8 years who reached this target range than those younger than 8 years ($p < 0.005$). Two patients (0.8%) experienced a creatinine clearance reduction of over 50% from baseline; both received concomitant nephrotoxic drugs, including amphotericin, and both returned to normal before discharge. No infusion-related reactions were reported. The authors concluded that CIV is an effective and safe dosing strategy that can serve as an alternative to escalating intermittent doses when unable to attain goal serum concentrations. Children younger than 8 years require larger daily doses to achieve desired serum concentrations. Although this is the largest pediatric CIV study to date, it is limited by its retrospective design and lack of clinical outcome evaluation.

Critically Ill Children. Cies et al³⁵ retrospectively evaluated the achievement of target serum concentrations when CIV was administered by adding vancomycin to continuous renal replacement therapy (CRRT) solutions in 11 critically ill children with acute kidney injury in a pediatric intensive care unit (PICU) in Philadelphia (Table 2). Following a loading dose, vancomycin was added directly to CRRT solution, dialysate, and/or replacement fluid with final vancomycin concentrations ranging

from 18 to 30 mg/L. The first serum concentration was measured 8 hours after initiating CRRT and vancomycin solution concentrations were adjusted to maintain a target serum plateau of 15 to 30 mg/L. Once the target serum concentration was achieved, vancomycin concentrations were measured daily for the duration of CRRT that included admixed vancomycin. Median estimated glomerular filtration rate calculated by using the updated Schwartz equation was 26.7 mL/min/1.73 m² (IQR, 18.8–42.7 mL/min/1.73 m²) at the onset of CRRT. The median vancomycin serum plateau concentration was 21.8 mg/L, and 91% of patients achieved the target concentration within 8 hours of CRRT initiation. The median duration of CRRT use with vancomycin was 3 days (IQR, 2–3 days) with the longest duration of 25 days in a 6-year-old patient with Stevens-Johnson syndrome. No instances of drug precipitation within the CRRT solution or circuit were reported. The authors concluded that the addition of vancomycin to CRRT solutions is an effective way to deliver a continuous infusion that ensures rapid achievement of target serum drug concentrations, and that it may be advantageous for safety by eliminating the risk of inappropriate drug infusion while CRRT is interrupted. Limitations of this study are the small sample size, retrospective description of use in a single PICU, and the absence of microbiologically proven infections that required vancomycin therapy. Future prospective studies of this novel dosing approach would be beneficial to address these limitations and evaluate if this method leads to improved clinical outcomes in critically ill children.

Genuini et al³⁶ retrospectively evaluated a CIV regimen used in 28 critically ill pediatric patients for suspected or proven beta-lactam-resistant Gram-positive infection in a French PICU or intermediate care unit (Table 2). After a loading dose and CIV dosed at 45 mg/kg/day, vancomycin serum concentrations were measured during the first 48 hours of treatment and after each dose adjustment, but specific times and frequency of monitoring were not standardized. To assess the standardized regimen, AUC was calculated for each patient during the first 3 days of therapy. Using a previously published model from Le et al,⁹ pharmacokinetic parameters were derived for each patient along with a calculated covariate-adjusted dose based upon age, weight, and SCr that would achieve a day 1 target AUC/MIC ratio of 400. On day 1, only 12 of 28 patients (43%) reached the target serum concentration range of 15 to 30 mg/L with a median AUC of 355 mg-hr/L (range, 261–1101). Seven patients (25%) reached a target AUC/MIC of >400 during the first 24 hours of treatment. Dose adjustments were made in 14 patients (50%), but 5 patients still had serum concentrations less than 15 mg/L with only 32% of patients reaching the AUC/MIC target. None of the patients had renal dysfunction when CIV was initiated, but 3 children experienced renal dysfunction while on CIV. All 3 received concomitant

nephrotoxic drugs during CIV and all recovered without requiring renal replacement therapy. The authors determined that if the calculated covariate-adjusted dose would have been used instead of the initial standardized dose, 57% of patients would have achieved the target AUC/MIC with an average dose of 53 mg/kg/day (range, 39–69 mg/kg/day) resulting in an AUC of 409 mg-hr/L (range, 341–593). Limitations of this study include its retrospective design, small and heterogeneous patient population, the lack of routine MIC value determination, and no clinical or microbiologic efficacy evaluation.

Children With Hematologic-Oncologic Conditions.

Guilhaumou et al³⁷ evaluated the pharmacokinetics of CIV administered to 121 children in France with febrile neutropenia and developed an optimized dosage regimen based on pharmacokinetic modeling that was designed to achieve target serum concentrations of 20 to 25 mg/L (Table 2). Empiric antibiotic algorithms differed by malignancy type. After a loading dose was given, CIV at 30 to 40 mg/kg/day was initiated with doses adjusted to achieve target serum concentrations at least 24 hours postloading dose. Approximately 16% of serum concentrations were in the target range, while most observed concentrations were below 20 mg/L. Variables found to correlate with vancomycin clearance were body weight, malignancy type, and coadministration of cyclosporine. These were included in the final pharmacokinetic model and tested through repeated simulations using different maintenance doses for varying body weights designed to obtain serum concentrations of 20 to 25 mg/L. Larger doses were necessary (up to 75 mg/kg/day) in children weighing less than 15 kg, those with solid tumors, and those not receiving cyclosporine. The authors concluded that vancomycin pharmacokinetics are altered in this patient population and that considerably larger doses than normal are required to obtain desired serum concentrations, particularly in those with lower body weight. Limitations of this study include a lack of detail regarding clinical outcomes, adverse effects, dose adjustments, and duration of therapy. Presumably, the final pharmacokinetic model was derived from serum concentrations obtained after 24 hours of therapy but validated testing of the proposed dosage regimen was not performed; therefore, the clinical benefit and risks of the optimized regimen are not clear. Prospective study of their dosage recommendations is necessary before they can be adopted in clinical practice.

Hoegy et al³⁸ prospectively evaluated an age-based CIV dosing regimen in 94 children with hematologic or oncologic diseases and normal renal function and identified variables that affected achievement of target serum concentrations. The age-based regimen was determined from retrospective pharmacokinetic data and Bayesian adjustments in 161 children at their center who received CIV that was dose adjusted to obtain

serum plateau concentrations of 15 to 20 mg/L. Plateau serum concentrations were measured after 48 hours of therapy and categorized as adequate (14–21 mg/L), low (<14 mg/L), or high (>21 mg/L). Concentrations were adequate in 59% of patients as compared to 33% and 9% that were categorized as low or high, respectively. The only identified variable that affected attainment of serum concentrations was hematopoietic stem cell transplantation: 33% of those who underwent transplant achieved the desired range, while 63% of those who did not undergo transplant achieved the target range ($p = 0.031$). The authors concluded that target serum concentration attainment was acceptable following the use of an age-based nomogram in this patient population, but it should be noted that a loading dose was not used. Other limitations of this study include its small sample size and heterogeneous population, lack of clinical and microbiologic outcome data, and lack of adverse event reporting.

Patients With Cystic Fibrosis. Data on CIV use in CF is limited to case reports. Fung³⁹ described the use of CIV in 3 CF patients with pulmonary exacerbations associated with MRSA. In 1 patient, desired serum trough concentrations could not be achieved with IIV. In the other 2 patients, CIV was implemented after intermittent administration failed to produce the desired clinical response. The first patient was a 3-year-old female with sputum cultures growing MRSA (MIC 1 mg/L), *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus*. Vancomycin (15 mg/kg/dose every 6 hours) and meropenem were initiated, but after 2 vancomycin dose escalations (up to 19 mg/kg/dose), serum concentrations remained subtherapeutic at 7.5 mg/L. A continuous infusion of 50 mg/kg/day was then initiated that produced a serum concentration of 14.2 mg/L after 24 hours (AUC/MIC of 333). She demonstrated clinical improvement and was discharged on day 6 to complete a 14-day course of antibiotics at home. She remained exacerbation free for 8 months, which was an improvement over historical admissions every 2 to 3 months. The second patient was a 17-year-old female who was rehospitalized following an exacerbation that had been treated with meropenem, tobramycin, and vancomycin 20 mg/kg/dose every 8 hours (steady-state trough of 14.7 mg/L). Upon readmission 2 weeks later, CIV 40 mg/kg/day was initiated along with intravenous levofloxacin and colistimethate (previous sputum cultures grew 2 isolates of MRSA, *P aeruginosa*, and *C albicans*). The serum plateau concentration after 24 hours was 22.5 mg/L, and estimated AUC/MIC ratios were 540:1 (isolate with MIC 1 mg/L) and $\geq 270:1$ (isolate with MIC ≤ 2 mg/L). She received 14 days of antibiotics and remained exacerbation free for 3 months. The third patient was a 15-year-old female with MRSA (MIC 1 mg/L) and *Stenotrophomonas maltophilia*, initiated on vancomycin (22 mg/kg/dose every 8 hours with a steady-state serum concentration of 13.3 mg/L) and meropenem.

The regimen was changed to CIV 50 mg/kg/day with subsequent dose reductions to a final dose of 31 mg/kg/day to obtain an AUC/MIC ratio of approximately 436:1. She successfully completed 21 days of therapy and was exacerbation free for 2 months, which was a slight improvement over her monthly admissions during the previous 6 months. None of the patients experienced changes in SCr, blood urea nitrogen, or urine output during use of continuous vancomycin. The author reported that CIV was more convenient for home use (all 3 of these patients completed intravenous antibiotics at home after hospital discharge), used smaller total daily doses to achieve target serum concentrations than was possible with intermittent infusions, and could be considered a safe and convenient therapy for CF exacerbations caused by MRSA.

An additional case report by McKinzie et al⁴⁰ described the use of CIV in a 12-year-old female with CF and significant drug allergies, being treated for a pulmonary exacerbation from MRSA (MIC 2 mg/L). She was allergic to ceftaroline (hives) and aztreonam (facial swelling) and experienced paresthesias during 2 previous courses of linezolid. After failure of a 3-week outpatient course of tedizolid plus 1 week of oral minocycline, she was admitted and developed hives after initiation of intravenous minocycline. She was then treated with intermittent vancomycin but developed intolerable red man syndrome that did not subside with prolonged infusions and diphenhydramine. A continuous infusion of 64 mg/kg/day was initiated with a target serum concentration of 20 to 25 mg/L. She received 15 days of CIV and required 1 dose adjustment to 53 mg/kg on day 9 because of an elevated serum concentration of 27.7 mg/L. Her pulmonary function returned to normal and her SCr remained stable at 0.4 to 0.5 mg/dL throughout the course of treatment. The authors concluded that CIV can be used to treat MRSA exacerbations in CF patients with multiple drug allergies and antimicrobial resistance that limits therapeutic options. Additional studies that are larger and prospective in nature are needed before use of this dosing approach can be broadly recommended in pediatric patients with CF; however, consideration can be given to its use in certain patients with drug allergies or intolerances, when achieving target serum concentrations is difficult with traditional intermittent dosing, or for improved convenience with home dosing.

Discussion

The optimal vancomycin dosing approach that maximizes safety and efficacy remains controversial despite decades of clinical experience and extensive study of therapeutic monitoring. Continuous infusions have been proposed as an alternative to intermittent administration as a way to achieve target serum concentrations faster while simplifying drug monitoring and potentially reducing toxicity. There are limited

data available to suggest an optimal dosing regimen for CIV in pediatric patients with suspected or proven Gram-positive infections. Only 1 randomized controlled trial compared the safety and efficacy of continuous infusion with intermittent dosing in pediatric patients.³³ Most of the available evidence is limited to case reports or series, retrospective analyses, prospective dose validation studies, and prospective cohort studies in a wide variety of patient populations.

Nearly all pediatric CIV studies have used different dosing strategies in heterogeneous patient populations, and only 1 compared different dosing protocols in the same population.³² In neonates, complex physiologic changes occur during maturation, which are even more pronounced in premature neonates. Similar to intermittent dosing recommendations, neonatal CIV dosing protocols incorporated parameters such as weight, gestational age, PNA, and SCr to account for these physiologic changes and their impact on pharmacokinetics, namely drug distribution and clearance. CIV doses studied in these patients ranged from 10 to 60 mg/kg/day, reflecting the heterogeneity of the population. In addition, underlying effects of diseases like CF, malignancies, renal failure, and sepsis greatly affect vancomycin pharmacokinetics and subsequent dosing recommendations. Success rates in achieving and maintaining target serum concentrations with CIV varied within and between studies, underscoring the need for therapeutic drug monitoring regardless of the chosen dosing regimen.

It is important to attain target serum concentrations quickly to maximize the likelihood of clinical success with vancomycin therapy, particularly when treating critically ill patients with suspected or proven Gram-positive infections.⁴¹ While it seems intuitive that achieving target serum concentrations faster and maintaining them more effectively would result in improved clinical outcomes, there is a lack of evidence to support that CIV improves clinical or bacteriologic efficacy in the pediatric population as compared to IIV. However, CIV has been used effectively to achieve desired serum target concentrations in patients who were unable to attain goal concentrations or desired clinical outcome with intermittent dosing despite significant dose escalations.^{15,34,39} Use of a loading dose prior to CIV initiation can also improve the time to target serum concentration achievement.^{16–23,27,29–31,33–36} Pawlotsky et al²⁷ showed that administration of a 7-mg/kg loading dose in neonates achieved a postloading dose serum concentration of 15 ± 8.1 mg/L, which was within their target range of 10 to 30 mg/L. Zhao et al³⁰ used a patient-tailored optimized dosing regimen that included a loading dose, achieving desired serum concentrations within 6 to 12 hours after starting CIV treatment in over 70% of neonates. Studies in older children, critically ill children, and children with febrile neutropenia used loading doses of 10 to 20 mg/kg in an attempt to rapidly obtain desired

steady-state target concentrations, but their success in achieving the target ranges was dependent upon use of adequate initial CIV doses.^{33,35–37} Although more rapid achievement of target serum concentrations occurs when loading doses are used,^{31,33} there is a lack of clinical data to suggest that loading doses improve therapeutic outcomes. Despite this, it is important to achieve target serum concentrations as early as possible, especially in critically ill children, immunocompromised children, and neonates who do not have fully functional immune systems and who have potentially life-threatening infections. Therefore, loading doses of 10 to 15 mg/kg (up to 20 mg/kg in critically ill children) are recommended before continuous infusions are initiated in treatment-naïve patients.

The optimal approach to therapeutic monitoring of vancomycin is not well established, but recent evidence supports AUC-based monitoring.² Clinical efficacy is most likely to occur with vancomycin AUC/MIC ratios of 400:1 or greater when treating serious *S aureus* infections.² However, AUC-based monitoring is complicated with intermittent drug administration, so trough serum concentrations of 15 to 20 mg/L have been proposed to serve as a surrogate measure.^{2,3} Similar measures in children have not been well established, and continuous infusion offers a simplified approach to AUC-based monitoring as long as drug clearance is stable. Serum plateau concentrations achieved with continuous infusions can be used to estimate AUC and AUC/MIC ratios, but there is no consensus recommendation for the optimal serum concentration target range. A meta-analysis of CIV in adults recommended target steady-state serum concentrations of 20 to 30 mg/L on the basis of vancomycin MIC in common infecting staphylococcal species in adults and on the drug pharmacokinetic properties, such as protein binding and tissue penetration.^{23,42} The desired serum concentration range may be different for infections caused by coagulase-negative staphylococci, which commonly infect neonates and children with central venous catheters. There is limited evidence to support that a specific AUC/MIC ratio is predictive of clinical or bacteriologic success in neonatal coagulase-negative staphylococcal sepsis.⁴³ Animal models suggest that methicillin-resistant *Staphylococcus epidermidis* is killed or inhibited with vancomycin AUC/MIC ratios that are 2 to 3 times lower than those needed to effectively kill MRSA.⁴⁴ As such, recent CIV studies have targeted lower steady-state serum concentrations of 10 to 25 mg/L in the neonatal population.^{28–31,33} Although optimal serum concentration targets have not been established, CIV can be advantageous for providing personalized AUC-based therapy through use of simplified therapeutic drug monitoring.

Another potential advantage of CIV over intermittent administration is that it requires fewer dose adjustments and blood draws related to its simplified monitoring

approach. Studies in neonates and young infants reported that CIV was associated with significantly fewer dose adjustments than intermittent dosing in achieving desired serum concentrations.^{31,33} Blood sampling errors are less common with continuous administration than with intermittent dosing because of the timing required relative to intermittent scheduled doses.²⁹ Similarly, unlike intermittent administration, AUC estimation with continuous infusion requires only 1 blood draw at steady state, which can be timed accordingly to occur with other scheduled laboratory draws. This may be beneficial in premature or critically ill infants to minimize iatrogenic anemia caused by repeated blood sampling.²⁹

Other potential advantages for continuous vancomycin administration are reduced toxicities and costs. A recent meta-analysis³⁵ demonstrated that CIV significantly reduced the risk of nephrotoxicity as compared to intermittent infusion in adults. Children are less likely to experience nephrotoxicity with intermittent vancomycin infusions than adults,⁴⁵ but serum trough concentrations of ≥ 15 mg/L, $\text{AUC} \geq 800$ mg-hr/L, and daily doses ≥ 60 mg/kg/day are associated with significantly increased risks of nephrotoxicity in children.¹⁰ There is currently no evidence that CIV is less nephrotoxic than IIV in children, but CIV requires significantly smaller total daily doses (30% to 60% less) to achieve target serum concentrations as compared with intermittent infusions.^{15,33,39} Limited adult evidence also suggests that AUC-guided dosing results in smaller total daily vancomycin doses and is associated with reduced nephrotoxicity.^{46,47} Using appropriate CIV doses and monitoring to avoid high daily drug exposure (as defined by AUC) can minimize the risk for toxicity when treating serious Gram-positive infections where it has been common to use larger intermittent daily doses in efforts to achieve target serum troughs of 15 to 20 mg/L.^{15,34,39} There is also no evidence that red man syndrome is less common with CIV than with intermittent dosing, but it was not reported in any of the pediatric studies in this review. In fact, continuous administration may be protective against red man syndrome that often responds to slowed infusion rates with intermittent administration. McKinzie et al⁴⁰ reported the case of 1 patient with intolerable red man syndrome, unresponsive to 3-hour vancomycin infusions and diphenhydramine, that abated after switching to CIV.

Wysocki et al¹⁸ performed a cost-analysis comparing IIV and CIV in adults for treatment of MRSA. They reported that cost was 23% lower with CIV than IIV ($p < 0.001$) for a 10-day treatment course as a result of fewer blood samples and smaller total daily doses in addition to reaching target serum concentrations faster, suggesting that continuous infusion treatment may be a cost-effective alternative to intermittent dosing. Continuous infusions and AUC-based monitoring may allow pharmacists to more effectively monitor vancomycin

drug exposure while lowering daily dose requirements, monitoring costs, and risks for toxicity.⁴⁶

Potential disadvantages to CIV include practical problems associated with reduced intravenous line availability and possible drug-drug incompatibilities with coadministration. Neonates and small children often have limited intravenous access that can limit the practicality of delivering vancomycin continuously over a 24-hour period when other medications may also need to be administered, particularly those known to be incompatible with vancomycin such as piperacillin/tazobactam, ceftazidime, cefepime, imipenem, potassium phosphate, heparin, methylprednisolone, hydrocortisone, phenytoin, valproic acid, and furosemide.^{48,49} In these situations, either additional intravenous access or temporary suspension of vancomycin administration for the duration of the other infusion(s) is required. Pharmacists and nurses should collaborate before initiating CIV in patients because of these potential barriers.

While it is not currently considered the standard approach to vancomycin dosing in the United States, a variety of patient populations may benefit from continuous administration. The bulk of evidence investigating CIV in the pediatric population is in neonates, including premature neonates and those who are critically ill. Continuous infusion is an attractive option in this vulnerable population because of its more rapid achievement of desired serum concentrations and its association with fewer and more appropriately timed blood samples used for therapeutic drug monitoring. Current evidence in neonates supports initial doses of 15 to 40 mg/kg/day (based upon PMA and renal function) initiated after a 10- to 15-mg/kg loading dose to achieve serum plateau concentrations of 15 to 25 mg/L measured 24 to 48 hours after initiation of therapy. Close monitoring of serum concentrations is required because of the wide interindividual pharmacokinetic variation in neonates.

Continuous vancomycin administration has also been studied in older children with a variety of conditions, including pneumonia, osteomyelitis, febrile neutropenia, sepsis with acute kidney injury, and CF.^{15,34–38,39,40} Most were retrospective, single-center studies in small patient populations that used different dosing protocols and target serum plateau concentrations. Altered pharmacokinetics in these populations, including large volumes of distribution and enhanced drug clearance, create difficulty for attaining target serum concentrations with traditional dosing strategies and lead to frequent therapeutic drug monitoring, delays in effective therapy, and use of high total daily doses that may predispose to toxicity or adverse effects. Use of CIV following an appropriate loading dose is an attractive method to reduce these CIV-dosing drawbacks in these patients. Success in achieving target serum concentrations was greater when the target range was lower or broader (e.g., 14–21 mg/L or 15–30 mg/L) and when doses greater than 40 mg/kg/day were

used. Clinical and microbiologic outcomes were not described in most studies and reporting of adverse effects or toxicities with CIV was lacking. Despite these shortcomings, continuous infusion remains a viable treatment option for children who require vancomycin but are unable to achieve target serum concentrations with traditional dosing. Vancomycin can also be added to CRRT solutions directly to minimize elevated serum concentrations often seen with intermittent dosing in critically ill children with acute kidney injury.

Conclusions

There are limited data to support routine implementation of CIV in children. However, continuous administration is a therapeutic option in certain clinical conditions and could be beneficial for individuals with serious Gram-positive infections where rapid achievement of target serum concentrations is critical. CIV may also be beneficial for patients who do not achieve target serum concentrations or who have significant red man syndrome with traditional intermittent dosing, particularly when high daily doses are required. Continuous administration may be less nephrotoxic and more cost-effective than traditional dosing, but practical issues with intravenous access and coadministration of other medications may hinder its use in some patients. There is no universal empiric dose that can be recommended because of the various dosing regimens studied in heterogeneous populations, lack of consistent target serum concentrations, and paucity of randomized clinical trials comparing the efficacy and safety of intermittent and continuous infusions. The ideal target steady-state concentration has not been elucidated, and furthermore, the optimal pharmacodynamic parameter that correlates with positive clinical outcome for coagulase-negative staphylococcal infections has not been established. The data reviewed indicate that CIV is well tolerated in pediatric patients and may improve the attainment of target serum concentrations, particularly early in therapy. However, the reviewed studies did not investigate the correlation between AUC/MIC and steady-state serum concentrations in conjunction with clinical and bacteriologic efficacy of the treatment regimens. Future prospective randomized clinical trials should be performed to identify optimal dosing and monitoring recommendations and to determine comparative safety and efficacy with traditional intermittent dosing regimens in various pediatric populations.

ARTICLE INFORMATION

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