

Continuous Versus Intermittent Vancomycin Infusions in Infants: A Randomized Controlled Trial

Amanda Gwee, MBBS, FRACP, DTM&H,^{a,b,c} Noel Cranswick, MBBS, FRACP, BMedSc,^{a,b,c} Brendan McMullan, MBBS, FRACP, BMed(Hons),^{d,e} Elizabeth Perkins, RM,^c Srinivas Bolisetty, MBBS, FRACP, MD,^{e,f} Kaya Gardiner, BN,^c Andrew Daley, MMed(ClinEpi),^{a,b,c} Meredith Ward, MBBS, FRACP,^{e,f} Roberto Chiletto, CICM, MD,^{a,c} Susan Donath, MA,^{a,c} Rodney Hunt, BMBS, MMed, MRCP(UK), FRACP, PhD,^{a,b,c} Nigel Curtis, BA, MBBS, MA, DCH, MRCP, DTM&H, MRCPCH, FRCPCH, PhD^{a,b,c}

abstract

BACKGROUND: In adults, continuous infusions of vancomycin (CIV) are associated with earlier attainment of target drug concentrations, require fewer blood samples for monitoring, and may reduce drug toxicity. We aimed to determine, in young infants, if CIV or intermittent infusions of vancomycin (IIV) better achieves target vancomycin concentrations at the first steady-state level and to compare the frequency of drug-related adverse effects.

METHODS: In a multicenter randomized controlled trial in 2 tertiary neonatal units over a 40-month period, young infants aged 0 to 90 days requiring vancomycin therapy for at least 48 hours were randomly assigned to CIV and IIV.

RESULTS: Of 111 infants randomized, 104 were included in the intention-to-treat analysis. Baseline characteristics were similar for both groups. The proportion of infants achieving target concentrations at the first steady-state level was higher for CIV compared with IIV (45 in 53 [85%] vs 21 in 51 [41%]; $P < .001$). Fewer dose adjustments were required in the CIV group (median 0; range 0–1) compared with the IIV group (median 1; range 0–3; $P < .001$). The mean daily dose required to achieve target concentrations was lower with CIV compared with IIV (40.6 [SD 10.7] vs 60.6 [SD 53.0] mg/kg per day, respectively; $P = .01$). No drug-related adverse effects occurred in either group.

CONCLUSIONS: In young infants, CIV is associated with earlier and improved attainment of target concentrations compared with IIV. Lower total daily doses are required to achieve target levels with CIV. There is no difference in the rate of drug-related adverse effects.

^aDepartment of Paediatrics, The University of Melbourne, Parkville, Australia; ^bThe Royal Children's Hospital Melbourne, Parkville, Australia; ^cMurdoch Children's Research Institute, Parkville, Australia; ^dSydney Children's Hospital, Randwick, Australia; ^eDepartment of Paediatrics, University of New South Wales, Sydney, Australia; and ^fRoyal Hospital for Women, Randwick, Australia

Dr Gwee conceptualized and designed the study, drafted the initial protocol and manuscript, designed the data collection instruments, collected data, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Cranswick and Curtis conceptualized and designed the study and reviewed and revised the manuscript; Drs Chiletto, McMullan, Daley, Bolisetty, and Ward collected data and reviewed and revised the manuscript; Dr Hunt and Ms Perkins contributed to the protocol design, collected data, and reviewed and revised the manuscript; Ms Gardiner assisted with the protocol and design of the data collection instruments and reviewed and revised the manuscript; Ms Donath oversaw the statistical analysis plan, assisted with data analysis, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

WHAT'S KNOWN ON THIS SUBJECT: In adults, continuous infusions of vancomycin (CIV) are associated with earlier attainment of target drug concentrations, require fewer blood samples for monitoring, and may reduce drug toxicity. There are no trials comparing CIV to intermittent infusions of vancomycin in children.

WHAT THIS STUDY ADDS: CIV is associated with earlier and improved attainment of target concentrations compared with intermittent infusions of vancomycin. Additionally, lower total daily doses are required to achieve target levels with CIV. There is no difference in the rate of drug-related adverse effects.

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Sepsis is a leading cause of death in young infants worldwide.¹ In industrialized countries, infection with Gram-positive bacteria, particularly coagulase-negative staphylococci (CONS) and *Staphylococcus aureus*, are among the most common pathogens causing late-onset sepsis. As a result, vancomycin, a glycopeptide antibiotic, is often used in the treatment of young infants with suspected or proven sepsis, particularly in the hospital setting.

Vancomycin is routinely administered as intermittent infusions multiple times per day. Therapeutic drug monitoring (TDM) is required to ensure that antibiotic levels are sufficient for effective bacterial killing. In young infants, this involves the measurement of trough concentrations (immediately before a dose), with target vancomycin levels ranging from 10 to 20 mg/L.² There is no consensus on the optimal dosing regimen for vancomycin in this age group, and this is reflected by the wide diversity in the dosing regimens of intermittent infusions of vancomycin (IIV) used worldwide. Studies reveal that these current dosing recommendations result in poor attainment of target vancomycin levels.³⁻⁵ Another problem with IIV dosing is the incorrect timing of trough samples, resulting in inappropriate dose adjustments.⁶

Continuous infusions of vancomycin (CIV) are an attractive alternative to IIV in young infants. Data from adult studies reveal an improved attainment of target vancomycin levels and a reduced incidence of drug-related nephrotoxicity with CIV compared with IIV.⁷ An additional benefit is that the timing of blood samples can be more flexible because they can be taken any time at steady state rather than requiring trough levels. This allows for TDM sampling at the same time as other blood tests, which is particularly important in the NICU setting, where infants are often

having repeated blood tests.⁸ However, potential disadvantages of CIV include the risks of drug incompatibilities and reduced line availability.

We report a randomized controlled trial (RCT) of CIV versus IIV in young infants to determine which results in improved attainment of target concentrations at the first steady-state level.

METHODS

The complete study protocol is published in an open-access journal, and the trial was registered at www.clinicaltrials.gov (identifier NCT02210169).⁹ Ethics approval was obtained from The Royal Children's Hospital (RCH) Melbourne Human Research Ethics Committee (34030) and the South Eastern Sydney Local Health District Human Research Ethics Committee (SSA 16/G/335).

Trial Design

This was a multicenter, nonblinded, RCT conducted over a 40-month period (September 2014–December 2017).

Three main changes were made to the initial trial protocol after commencement: (1) the inclusion of infants with a postnatal age of 0 to 90 days (from 0 to 30 days) because many young infants in the neonatal unit were >30 days of age; (2) for vancomycin courses >7 days, baseline blood tests were repeated weekly instead of every 48 hours to minimize repeated blood tests; and (3) change in the timing of vancomycin TDM for patients receiving 4-hourly dosing to recommend that it is taken before the fourth dose instead of before the third dose.

Participants

The study sites included the NICU and PICU at RCH Melbourne and the NICU at The Royal Hospital for Women (RHW) in Sydney.

Participants were eligible if they were aged between 0 and 90 days and it was anticipated that vancomycin therapy would be administered for ≥ 48 hours. Exclusion criteria included: corrected gestational age (CGA) <25 weeks, known glycopeptide allergy, renal impairment, infants receiving extracorporeal membrane oxygenation, vancomycin administration within the previous 72 hours, and previous randomization in the study.

Interventions

Before randomization, the treating clinician or study investigator provided both written and verbal information to the parents and obtained consent. Patients were randomly assigned in a 1:1 ratio to receive either standard care, consisting of IIV (dose recommended in the *British National Formulary for Children*¹⁰), or CIV after a loading dose of 15 mg/kg infused over 1 hour (dose published by Patel et al⁶; Tables 1 and 2). The target trough level for IIV was 10 to 20 mg/L, and the steady-state level for CIV was 15 to 25 mg/L.^{6,11} A protocol for dose adjustment was also provided (Tables 3 and 4).

All patients had the following blood tests taken at or before randomization: full blood examination; urea, electrolytes, and creatinine; C-reactive protein (CRP); albumin level; and blood culture if a new infection was suspected. A full blood examination and urea, electrolytes, and creatinine testing was repeated every 48 hours for the first week then weekly thereafter during vancomycin therapy. Repeat measurements of CRP were done every 48 hours only if the first CRP measurement was elevated. A repeat blood culture was taken the day after clinical staff were notified of a positive result whenever possible.

For infants receiving IIV, vancomycin levels were measured within 1 hour

TABLE 1 IIV Empirical Dosing Regimen

| CGA, wk | Dose, mg/kg per Dose | Dose Interval |
|---------|----------------------|---------------|
| <29 | 15 | 24 hourly |
| 29–35 | 15 | 12 hourly |
| 36–44 | 15 | 8 hourly |
| >44 | 15 | 6 hourly |

Adapted from Paediatric Formulary Committee. *British National Formulary for Children 2011-2012*. London, UK: Pharmaceutical Press; 2012.

after the first dose (peak level), before (trough level), and peak level after the third dose. If the participant was receiving 4-hourly dosing, levels were measured before and after the fourth dose. If the trough vancomycin level fell within the target range of 10 to 20 mg/L, an additional trough level was taken before the sixth dose, and if this second level was within range, trough levels were then repeated every 3 days. If the trough vancomycin level was <10 mg/L or >20 mg/L, after dose adjustment, trough and peak levels were taken before and after the third adjusted dose.

For those infants receiving CIV, a vancomycin level was measured immediately after the loading dose and 18 to 30 hours after the commencement of infusion. Samples were taken at the same time as other blood tests whenever possible. If the steady-state level was within the target range of 15 to 25 mg/L, the level was repeated 18 to 30 hours after the last level, and if this second level was within range, the level was repeated every 3 days. If CIV was paused to enable the administration of a drug that was incompatible with vancomycin, this was recorded.

Study involvement ceased when vancomycin therapy was

discontinued. Treating clinicians documented any adverse events.

Outcomes

The primary outcome measure was the difference in the proportion of participants achieving target vancomycin levels at their first steady-state level (when the drug level is in equilibrium).

Secondary outcomes included (1) the difference in the proportion of participants who experienced drug-related adverse effects, (2) the time taken to achieve target vancomycin levels, and (3) determining the pharmacokinetics and pharmacodynamics of vancomycin by using nonlinear mixed-effects modeling (outcomes 2 and 3 are reported in a separate article). No changes were made to the trial outcomes after commencement.

Sample Size Calculation

The sample size of 200 young infants was calculated by using Pearson's χ^2 test to detect a difference of 20% in the proportion of participants achieving target vancomycin levels between the 2 groups with a power of 80%. An interim analysis was not done.

TABLE 2 CIV Empirical Dosing Regimen

| Serum Creatinine, $\mu\text{mol/L}$ | CGA, wk | Dose, mg/kg per d |
|-------------------------------------|-----------|-------------------|
| <40 | ≥ 40 | 50 |
| <40 | <40 | 40 |
| 40–60 | All | 30 |
| >60 | All | 20 |

Adapted from Patel AD, Anand D, Lucas C, Thomson AH. Continuous infusion of vancomycin in neonates. *Arch Dis Child*. 2013;98(6):478–479.

Randomization

The randomization schedule was prepared by an independent statistician using random permuted blocks and stratified by the 2 sites. Infants were randomly assigned by the treating clinician or a member of the study team. At RCH, allocation was concealed in consecutively numbered, opaque, sealed envelopes, and at RHW, an online randomization procedure in a Research Electronic Data Capture program was used.

Statistical Methods

Randomly assigned infants who had the first trough vancomycin level (IIV) or steady-state level (CIV) measured were included in the intention-to-treat analysis. The difference in proportions was assessed by using a χ^2 test together with a 95% confidence interval (CI). Normally distributed continuous outcomes were compared by using paired *t* tests. Median values were compared by using a Wilcoxon rank test, and CIs for the difference of medians were compared by using bootstrap. Data were analyzed by using Stata 15 (Stata Corp, College Station, TX).

RESULTS

Over the 40-month study period, 2023 young infants were screened for eligibility. Of these, 486 were approached for consent, and we obtained consent for 298 (61%) of them. At RCH, infants who were thought likely to need vancomycin were preconsented for participation in the trial. In total, 111 young infants were randomly assigned, 54 to IIV and 57 to CIV, of whom 51 and 53, respectively, were included in the intention-to-treat analysis (Fig 1). On the basis of previous vancomycin usage at RCH, it was anticipated that recruitment would take 24 months. However, because of a change in antibiotic policy and the resultant reduced usage of vancomycin, the recruitment rate was slower than

TABLE 3 IIV Dose Adjustment Protocol

| Current Regimen | Trough <10 mg/L | Trough >20 mg/L ^a |
|-----------------|-----------------|------------------------------|
| 6 hourly | 4 hourly | 8 hourly |
| 8 hourly | 6 hourly | 12 hourly |
| 12 hourly | 8 hourly | 18 hourly |
| 18 hourly | 12 hourly | 24 hourly |
| 24 hourly | 18 hourly | 30 hourly |

^a If the level is >20 mg/L, the dose is withheld, and the trough level is repeated before each due dose. Once the vancomycin level is ≤20 mg/L, dosing is restarted at a lower dose frequency.

anticipated. Recruitment was therefore terminated after a 40-month period.

Baseline Characteristics

Of the 104 infants included in the intention-to-treat analysis, 44% were boys with a mean birth weight of 2271 g and current weight of 2549 g. The mean gestational age was

34.0 weeks and postnatal age was 23 days (Table 5). The most common underlying diagnoses were prematurity (66%), exomphalos and/or gastroschisis (16%), bowel obstruction (13%), and congenital heart disease (12%). Indications for vancomycin therapy included suspected sepsis (65%), preceding positive blood culture result (11%),

TABLE 4 CIV Dose Adjustment Protocol

| CIV Dose Adjustment Calculation |
|---|
| Adjusted dose (mg per d) will be calculated by last maintenance dose × (target concentration (20 mg/L)/last vancomycin concentration) |

skin and soft tissue infection (11%), necrotizing enterocolitis (5%), and surgical prophylaxis (5%). Of the 92 infants who had blood cultures taken, 23 (25%) had a positive result, with CONS (58%), *Enterococcus* spp (9%), and Gram-negative bacteria (9%) being the most frequently isolated. In 3 of the blood cultures, 2 CONS species were isolated and therefore deemed to be contaminants. The mean duration of therapy was 5 days. Baseline characteristics were similar between both groups.

Attainment of Target Levels

The proportion of infants who achieved target concentrations at the first steady-state level was 21 of 51 (41%) in the IIV group compared with 45 of 53 (85%) in the CIV group ($P < .001$). No patients in either group had supratherapeutic concentrations at the first steady-state level.

For the infants who received IIV, achievement of target levels was low in all CGA dosing groups, with 15 of 34 (44%) in the 36- to 44-week CGA group, 5 of 12 (42%) in the 29- to 35-week CGA group, and 1 of 5 (20%) in the <29-week CGA group attaining target levels. In the CIV group, achievement of target concentrations was 8 in 10 (80%) and 24 in 30 (80%) for infants with a serum creatinine of <40 μmol/L and CGA of ≥40 weeks and <40 weeks, respectively. Target concentrations were achieved in all infants receiving CIV with a serum creatinine of 40 to 60 μmol/L (9 of 9; 100%) and >60 μmol/L (4 in 4; 100%).

Overall, 43 of 51 (84%) infants in the IIV group achieved target levels by the end of the study period compared

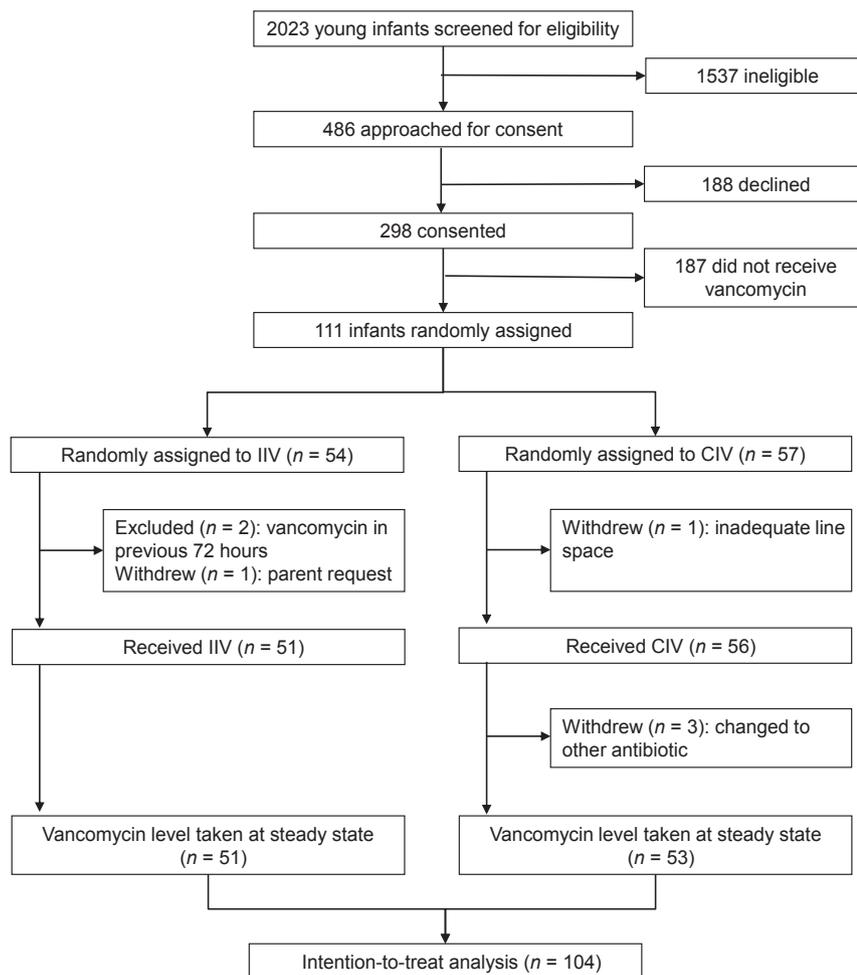


FIGURE 1
Consort diagram.

with 51 of 53 (97%) infants in the CIV group ($P = .04$). The mean time to achieve the target concentration was greater for the IIV (33.6 hours; SD 38.8 hours) compared with the CIV group (27.1 hours; SD 10.8 hours; $P = .003$). Fewer dose adjustments were required to achieve target levels in the CIV group (median 0; range 0–1) compared with the IIV group (median 1; range 0–3; $P < .001$).

Six infants (12%) in the IIV group had supratherapeutic trough levels, ranging from 22 to 30 mg/L after the initial trough level. Similarly, there were 5 infants (9%) in the CIV group who subsequently had supratherapeutic steady-state levels, ranging from 26 to 29 mg/L.

The overall mean daily dose required to achieve target concentrations was 60.6 (SD 53.0) mg/kg per day with IIV and 40.6 (SD 10.7) mg/kg per day with CIV ($P = .01$; Table 6).

Adverse Events

Serum creatinine levels were determined between 48 hours before initial dosing and 72 hours after vancomycin therapy in 48 of 51 (94%) infants in the IIV group and 51 of 53 (96%) infants in the CIV group. There was no increase in the creatinine levels at the end compared with at the start of therapy in the IIV group (35.4–31.2 $\mu\text{mol/L}$; SD 19.6–16.2 $\mu\text{mol/L}$; $P = .01$) or in the CIV group (29.3–28.1 $\mu\text{mol/L}$; SD 12.1–10.7 $\mu\text{mol/L}$; $P = .50$). One infant in each of the groups had a rise in creatinine level >1.5 times the baseline creatinine (IIV, 18–32 $\mu\text{mol/L}$; CIV, 24–45 $\mu\text{mol/L}$). Vancomycin was well tolerated, with no infants experiencing red man syndrome and no documented vancomycin-related adverse effects in either group.

Data on vascular access devices were available for 49 of 51 infants in the IIV group and all infants in the CIV

TABLE 5 Characteristics of Infants Included in the Intention-To-Treat Analysis

| | IIV ($n = 51$) | CIV ($n = 53$) |
|--|--------------------------|-------------------------|
| Birth wt, g, mean (SD) | 2294 (1033) ^a | 2248 (1036) |
| Current wt, g, mean (SD) | 2503 (1137) | 2595 (970) |
| Gestational age, wk, mean (SD) | 34.4 (5.2) | 34.0 (4.4) |
| Postnatal age, d, mean (SD) | 23 (21) | 23 (19) |
| Male sex, n (%) | 27 (53) | 25 (47.2) |
| Underlying diagnosis, ^b n (%) | | |
| Prematurity | 32 (63) | 37 (70) |
| Exomphalos and/or gastroschisis | 10 (20) | 7 (13) |
| Bowel obstruction | 7 (14) | 7 (13) |
| Congenital heart disease | 6 (12) | 7 (13) |
| Chronic lung disease | 5 (10) | 3 (6) |
| Gastrointestinal atresia and/or TOF | 3 (6) | 6 (11) |
| HMD and/or RDS | 3 (6) | 4 (8) |
| Neurologic disease | 3 (6) | 3 (6) |
| Genetic disease (with T21) | 3 (6) | 5 (9) |
| NEC | 2 (4) | 4 (8) |
| CDH | 2 (4) | 3 (6) |
| IUGR | 2 (4) | 2 (4) |
| Surgical airway disease | 1 (2) | 4 (8) |
| Other | 7 (14) | 10 (19) |
| Indication for treatment, n (%) | | |
| Suspected sepsis | 34 (67) | 34 (64) |
| Preceding positive blood culture result | 10 (20) | 1 (2) |
| SSTI | 5 (10) | 6 (11) |
| Surgical prophylaxis | 4 (8) | 4 (8) |
| Gastrointestinal infection (including NEC) | 3 (6) | 5 (9) |
| Respiratory tract infection | 2 (4) | 2 (4) |
| Endocarditis | 2 (4) | 0 |
| Septic ileus | 1 (2) | 1 (2) |
| Urinary tract infection | 0 | 4 (8) |
| Other | 2 (4) | 4 (8) |
| Positive blood culture result, n (%) | 12 of 46 (26) | 11 of 46 (24) |
| CONS | 7 (15) | 6 (13) |
| <i>Enterococcus</i> spp | 1 (2) | 1 (2) |
| MSSA | 0 | 1 (2) |
| GBS | 0 | 1 (2) |
| <i>Streptococcus mitis</i> group | 1 (2) | 0 |
| Gram-negative organism | 1 (2) | 1 (2) |
| 2 different CONS bacteria | 2 (4) | 1 (2) |
| Days of treatment, mean (SD) | 4.5 (2.6) | 5.5 (9.0) |
| Albumin level, g/L, mean (SD) | 26.0 (6.0) | 24.9 (5.6) ^c |
| Time to repeat blood culture, h, mean (SD) | 37.3 (16.6) | 36.8 (21.8) |
| Concomitant gentamicin use, n of N (%) | 37 of 51 (72.5) | 43 of 53 (81.1) |

CDH, congenital diaphragmatic hernia; GBS, group B *Streptococcus*; HMD, hyaline membrane disease; IUGR, intrauterine growth restriction; MSSA, methicillin-sensitive *S aureus*; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; SSTI, skin and soft tissue infection; TOF, tracheoesophageal fistula; T21, trisomy 21.

^a Birth wt not available for 1 participant.

^b Infants could have multiple underlying diagnoses.

^c Albumin level available for 50 infants.

group. The median number of vascular access devices was 1 in the IIV group and 1.5 in the CIV group ($P = .06$; CI -0.412 to -0.003). One patient in the CIV group was administered a drug that was incompatible with vancomycin through the same line, with no clinical adverse effects observed for the patient.

Clinical Outcomes

Of the 9 infants in the IIV group and the 9 infants in the CIV group with Gram-positive bacteremia, repeat blood cultures were taken in 8 and 7 infants, respectively. The mean times to the clearance of bacteremia were 55.3 hours (SD 14.9 hours) with IIV and 46.1 hours (SD 10.3 hours) with

CIV ($P = .62$). The vancomycin minimum inhibitory concentration (MIC) (the lowest antibiotic concentration that will inhibit bacterial growth) was determined for 16 of the 18 Gram-positive isolates (Table 7). No infants died of sepsis; however, 1 infant in the CIV group died because of complications of congenital heart disease.

DISCUSSION

This is the first RCT of vancomycin dosing in a pediatric population. We show that, compared with IIV, CIV results in earlier and improved attainment of target levels, requires only 1 dose adjustment, and lower total daily doses to achieve therapeutic levels. Vancomycin dosing is an important issue in young infants because, as was found in our trial, current IIV dosing regimens are associated with subtherapeutic levels in the majority of young infants.^{3,4,6,12} Furthermore, difficulties with taking accurately timed trough samples in a busy clinical environment is a common problem.⁶ One study in young infants reported that in 24% of vancomycin samples, the timing of the sample was missing, and 54% of samples required a repeat blood test because the time documented could not be interpreted. CIV provides an easier alternative for dosing and monitoring vancomycin in young infants.

The use of CIV was initially proposed to optimize the time above which the vancomycin concentration exceeds the bacterial MIC when the drug was thought to exhibit time-dependent bacterial killing. A retrospective cohort study of adults with methicillin-resistant *S aureus*

TABLE 7 MIC Values Determined by Using Etest (bioMérieux, Crappone, France) of Gram-positive Isolates From Blood Cultures ($n = 16$)

| Organism | Vancomycin MIC | | | |
|-------------------------------|----------------|--------|--------|--------|
| | 0.5 mg/L | 1 mg/L | 2 mg/L | 4 mg/L |
| <i>S epidermidis</i> | — | — | 4 | 5 |
| <i>Staphylococcus capitis</i> | — | — | 3 | 1 |
| <i>S mitis</i> group | 1 | — | — | — |
| <i>S aureus</i> | 1 | 1 | — | — |
| <i>Enterococcus faecalis</i> | — | — | 1 | — |

—, not applicable.

pneumonia revealed a reduction in mortality when vancomycin was administered as a continuous infusion.¹³ However, a meta-analysis of 1 RCT and 5 observational studies in adults revealed no difference in mortality, but the authors did report a lower risk of nephrotoxicity associated with CIV (relative risk 0.6; 95% CI 0.4 to 0.9; $P = .02$).⁷ Two subsequent systematic reviews revealed conflicting results: 1 revealed no difference in the rate of nephrotoxicity,¹⁴ whereas the other revealed a reduction in the incidence of nephrotoxicity (relative risk 0.61; 95% CI 0.47 to 0.80; $P < .001$).¹⁵ This difference was largely influenced by the inclusion of 1 retrospective observational study.¹⁶

CIV dosing regimens have been studied in 5 prospective cohort and 2 retrospective studies in young infants.^{6,11,17–21} However, in only 2 studies was CIV compared with IIV. The 1 prospective study in which researchers compared the 2 dosing regimens revealed an improved attainment of target concentrations with CIV (82%) compared with IIV (46%).⁶ A retrospective study also revealed that a greater proportion of patients achieved target levels with CIV compared with IIV (52.8% with CIV versus 34.1% with IIV). However, interpretation of this study is limited

because target trough levels for IIV were low (between 5 and 10 mg/L).²⁰ Overall, 4 studies of CIV (each using different dosing regimens) in young infants reported attainment of target vancomycin levels $>80\%$.^{6,17,19,21} Importantly, in these studies, CIV was not associated with drug incompatibility⁶ or infusion-related side effects.^{6,17} As in our study, there was no difference in creatinine levels in young infants treated with IIV versus CIV.⁶

The evidence for target drug concentrations when using CIV is scarce. In a systematic review of adult studies in which researchers compared IIV and CIV, 5 of 6 studies targeted concentrations of 20 to 25 mg/L or 20 to 30 mg/L,⁷ whereas in the studies of young infants, target levels ranging from 10 to 15 mg/L to 25 to 30 mg/L have been used.⁸ Although existing data support a pharmacodynamic target for *S aureus* infections of an area under the concentration-time curve over 24 hours (AUC_{24})/MIC >400 , the target for CONS infections (the most common pathogen causing late-onset sepsis in young infants) is poorly defined. The authors of in vitro pharmacodynamic studies have described time-dependent killing for *Staphylococcus epidermidis*,^{22,23} and the authors of an in vivo murine model reported no significant difference in the mortality rate in mice with a higher AUC_{24} /MIC ratio.²⁴

Although there are population pharmacokinetic models that allow for the calculation of AUC with IIV dosing,²⁵ the use of CIV enables the AUC_{24} to be easily calculated by using

TABLE 6 Dose in mg/kg per Day Required to Achieve Target Concentrations

| CGA | IIV, Mean (SD) | CIV, Mean (SD) | P | Creatinine | IIV, Mean (SD) | CIV, Mean (SD) | P |
|-------|----------------|----------------|-----|------------|----------------|----------------|------|
| <29 | 37.0 (21.7) | 25.0 (5.6) | .33 | <40 | 72.9 (63.5) | 45.4 (7.2) | .01 |
| 29–35 | 40.8 (14.0) | 33.9 (7.0) | .21 | 40–60 | 41.9 (13.1) | 29.6 (3.3) | .01 |
| 36–44 | 67.7 (59.3) | 43.8 (9.7) | .02 | >60 | 34.8 (7.9) | 19.9 (0.2) | .008 |

the equation $AUC_{24} = \text{serum concentration} \times 24 \text{ mg.h/L}$. Therefore, this also allows for the calculation of the target vancomycin level if the pharmacodynamic target is known. For example, for a *S aureus* isolate with a specific MIC, using the formula $AUC_{24}/MIC > 400$ enables the calculation of the target concentration (ie, target concentration = $[400 \times MIC]/24 \text{ mg/L}$). Similarly, CIV also allows for a simple linear calculation of dose adjustment as is used in our protocol. This resulted in attainment of target concentrations in all infants in our study after 1 dose adjustment.

In contrast to studies in adults,¹⁴ our study revealed that vancomycin-related adverse effects are extremely uncommon in young infants regardless of the method of administration. Importantly, infants in the CIV group required lower total daily doses of vancomycin compared with those in the IIV group. The relationship between vancomycin exposure and nephrotoxicity is poorly understood. However, a recent in vivo study of rats revealed that an increase in urinary acute kidney injury biomarkers was associated with the area under the concentration-time curve over 0 to 24 hours and the maximum drug concentration over a 24-hour period.²⁶ CIV is associated with lower maximum drug concentrations over a 24-hour period and therefore theoretically could be associated with a reduced risk of nephrotoxicity. One of the barriers to the routine use of CIV is a concern about the need for additional line access and the associated potential risks (eg, infection and extravasation). Although our study was not powered to detect this, we did not observe any significant increase in the need for vascular access devices

or issues of drug incompatibility. This is likely explained by the fact that young infants in whom vascular access was limited were excluded, and in addition, CIV was paused to administer incompatible drugs.

One limitation of our study is that it was not powered to detect a difference in vancomycin-related nephrotoxicity or infection-related mortality because these events are infrequent; recruitment of a sufficient sample size to detect this would not have been feasible.^{27,28} Instead, we are developing a population pharmacodynamic model to assess this. A slow recruitment rate attributable to a change in empirical antibiotic guidelines required us to terminate our trial before reaching our planned sample size. However, because the effect size in our trial was considerably larger than the estimate used in our sample size calculation, the primary outcome of our trial was statistically significant. Our trial did not include an analysis of costs, although a RCT in adults revealed a significant reduction in 10-day treatment costs with CIV.²⁹ Audiology assessments were not done specifically for the study because the ototoxicity of vancomycin is controversial, particularly in a population of premature infants receiving concomitant aminoglycosides.^{2,30} AUC_{24}/MIC ratios were calculated by developing a nonlinear mixed-effects model and will be reported separately.

CONCLUSIONS

In young infants, CIV is associated with earlier and improved attainment of target concentrations compared with the current standard of care, IIV. Lower total daily doses and fewer dose adjustments are required to

achieve therapeutic levels with CIV. Vancomycin-related drug toxicity was rare with both CIV and IIV. Future studies should be focused on the impact of CIV compared with IIV on clinical outcomes of Gram-positive infections.

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ABBREVIATIONS

| | |
|---------------------|---|
| AUC ₂₄ : | area under the concentration-time curve over 24 hours |
| CGA: | corrected gestational age |
| CI: | confidence interval |
| CIV: | continuous infusions of vancomycin |
| CONS: | coagulase-negative staphylococci |
| CRP: | C-reactive protein |
| IIV: | intermittent infusions of vancomycin |
| MIC: | minimum inhibitory concentration |
| RCH: | The Royal Children's Hospital |
| RCT: | randomized controlled trial |
| RHW: | The Royal Hospital for Women |
| TDM: | therapeutic drug monitoring |

This trial has been registered at www.clinicaltrials.gov (identifier NCT02210169).

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Address correspondence to Amanda Gwee, MBBS, FRACP, DTM&H, Department of Paediatrics, The University of Melbourne, The Royal Children's Hospital Melbourne, 50 Flemington Rd, Parkville, VIC 3052, Australia. E-mail: amanda.gwee@rch.org.au

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Continuous Versus Intermittent Vancomycin Infusions in Infants: A Randomized Controlled Trial

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