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

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<tr><td>STUDY</td><td>Continuous Versus Intermittent Vancomycin Infusions in Infants: A Randomized Controlled Trial</td></tr>
<tr><td>BACKGROUND</td><td>

Vancomycin is routinely administered as intermittent infusions multiple times per day
No consensus on optimal dosing regimen in young infants
Current dosing recommendations result in poor attainment of target vancomycin levels and inappropriate dose adjustments
Continuous infusions of vancomycin (CIV) are an attractive alternative to IIV in young infants: improved attainment of target levels, reduced incidence of drug-related nephrotoxicity, more flexible therapeutic drug monitoring (TDM)

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<tr><td>OBJECTIVE</td><td>

To determine, in young infants, if CIV or IIV better achieves target vancomycin concentrations at the first steady-state level and to compare the frequency of drug-related adverse effects (AEs)

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<tr><td>METHODS</td><td>

Design: parallel, multi-center, non-blinded, randomized controlled trial
Duration: mean of 5 days
Inclusion Criteria: between 0 and 90 days of age with an infection requiring treatment with vancomycin as determined by the treating physician (with anticipation that therapy would be administered for ≥48 hours)
Exclusion Criteria: corrected gestational age (CGA) <25 weeks, known glycopeptide allergy, renal impairment, infants receiving extracorporeal membrane oxygenation, vancomycin administration within the previous 72 hours, previous randomization in the study, and need for a drug that is incompatible with vancomycin
Number Enrolled: 111 (104 included in intention-to-treat analysis)
Regimen: Randomly assigned in 1:1 ratio to receive IIV (target trough level of 10-20 mg/L) or CIV after loading dose of 15 mg/kg infused over 1 hour (target trough level of 15-20 mg/L)
Primary Outcome: difference in proportion achieving target vancomycin levels at first steady-state level
Secondary Outcomes: (1) difference in proportion of participants who experienced drug-related AEs; (2) time to achieve target vancomycin levels; and (3) determining the pharmacodynamics (PD) and pharmacokinetics (PK) of vancomycin by using nonlinear mixed-effects modeling (Note: results from outcome 3 not included)
Power: 80% based on a 200-infant sample size
Data Handling Method: Intention-to-treat

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<tr><td>RESULTS</td><td>
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<tr><th colspan="3">Study Completion</th></tr>
<tr><td colspan="3">111 randomly assigned (54 to IIV and 57 to CIV)
51 in IIV group and 53 in CIV group were included in intention-to-treat analysis</td></tr>
<tr><th colspan="3">Primary Outcome</th></tr>
<tr><td colspan="3">Proportion of infants who achieved target concentrations at the first steady-state level was 21 of 51 (41%) in IIV group versus 45 of 53 (85%) in CIV group (P<0.001)</td></tr>
<tr><th colspan="3">Secondary Outcomes</th></tr>
<tr><th>Drug-Related AEs</th><th>Time to Achieve Target Levels</th><th>Other Results</th></tr>
<tr><td>No increase in creatinine levels at the end versus the start of therapy in IIV group (35.4-31.2; SD 19.6-16.2; P=0.01) or in CIV group (29.3-28.1; SD 12.1-10.7; P=0.5)</td><td>Mean time to achieve target concentration was greater in IIV group (33.6 hours; SD 38.8 hours) versus CIV group (27.1 hours; SD 10.8 hours; P=0.003)</td><td>Mean times to clearance of bacteremia: 55.3 hours (SD 14.9 hours) with IIV and 46.1 hours (SD 10.3 hours) with CIV (P=0.62)
MIC determined for 16 of 18 Gram-positive isolates</td></tr>
<tr><th colspan="3">Authors' Conclusions</th></tr>
<tr><td colspan="3">CIV is associated with earlier and improved attainment of target concentrations compared with the current standard of care (IIV)
Lower daily doses and fewer dosage adjustments are required to achieve therapeutic levels with CIV
Vancomycin-related drug toxicity was rare with both CIV and IIV</td></tr>
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<tr><td>STRENGTHS/ LIMITATIONS</td><td>
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<tr><th>Strengths</th><th>Limitations</th></tr>
<tr><td>Similar baseline characteristics between groups
Randomized controlled trial
Intention-to-treat data handling method used
Baseline and repeated blood tests remained consistent
Protocols for dose adjustments in place depending on trough level</td><td>Small sample size
Short duration of therapy
Adherence not addressed (did some participants miss a dose for any reason during study?)
Concomitant antibiotics not addressed
PD and PK outcome measures not reported
Unsure if the study ensured consistency in the times trough levels were obtained
Variability of time to reach steady-state depending on type of infection treated
Included patients with Gram – infections</td></tr>
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		• Cost addressed but not included • Ototoxicity purposefully not addressed • Not all patients were included in the AE analysis • Not powered to detect nephrotoxicity • Unclear if patients were handled similarly • Drew conclusions on results that were not studied
CONCLUSION	I think that this study is a good start. Although many of the results proved to be statistically significant, the question remains if these are also clinically significant and can be extrapolated to clinical practice. The only clinical outcome addressed in the study, mean time to clear bacteremia, was not statistically or clinically significant. Because vancomycin-related drug toxicity and AEs were similar between the groups, lower daily doses and fewer dosage adjustments could not be as relevant to clinical practice. The study was also not powered to detect nephrotoxicity. The most relevant finding that could be considered as clinically significant was the earlier attainment of drug concentrations with CIV; this could be applied in clinical practice when deciding between IIV versus CIV in young infants, especially if they are more acutely ill. However, this is ultimately inconclusive because vancomycin therapy differs depending on the type of infection treated. Therefore, the time to steady-state could differ and this was not taken into account in the study. Because this was the first randomized controlled trial addressing the difference between CIV and IIV in infants, future research needs to be done with a larger sample size and adequate power. More randomized controlled trials done in the United States, for a longer duration, and in more distinct age subsets of pediatric patients, are needed to further assess the difference between CIV and IIV, particularly in AEs. These should also include a comparison of vancomycin in infants who have a known indication for therapy, as well as assess for more specific clinical outcomes like symptom improvement. In addition, it is undetermined if CIV could be further supported by being a cost-effective alternative to IIV. Therefore, cost analyses should be done in this study and further studies to determine cost-effectiveness of CIV versus IIV.	
REFERENCE	Gwee A, Cranswick N, McMullan B, et al. Continuous Versus Intermittent Vancomycin Infusions in Infants: A Randomized Controlled Trial. *Pediatrics.* 2019 Jan 30. 143(2):e20182179.	

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