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COMMENTARY: CONTINUOUS INFUSION OF VANCOMYCIN IN NEONATES:

TO USE OR NOT TO USE REMAINS THE QUESTION

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In an effort to identify ways to improve vancomycin treatment of newborns, Gwee et al¹ explored published medical literature regarding vancomycin treatment of newborns by continuous infusion. They point out that vancomycin infusions in adults reach therapeutic concentrations more often and with less toxicity than treatment with intermittent doses. Whether a similar situation occurs in neonates remains to be established.

In some studies, fewer than 50% of neonates reach therapeutic concentrations of vancomycin with intermittent dosing.^{2,3} Such an observation must be considered within the context of the population being treated and the dosages used in the studies. If the dosage does not produce therapeutic concentrations, it is inherently the wrong dosage for the population. Exactly what constitutes a therapeutic concentration is often not certain.

The authors imply that renal function in newborns is predictable enough to allow selection of appropriate dosages for vancomycin infusions to reach desired therapeutic concentrations. Renal development is not linear. Glomerular filtration is relatively low, but increasing until 32–34 weeks post menstrual age when glomerulogenesis ends.^{4–6} Birth itself stimulates an increase in glomerular filtration rate (GFR).⁶ The relation of serum creatinine (Cr) to GFR at birth is complicated. For the first week after birth, neonatal serum Cr partly reflects a combination of maternal Cr acquired transplacentally, endogenous creatinine released from the newborn's muscle mass and tubular reabsorption of creatinine by the neonatal kidney. The exact age when the newborn's serum Cr reflects only endogenous Cr and GFR has been

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estimated, but is not known precisely. Very recently, a neonatal amikacin covariate model has been reported, which can serve as a GFR ontogeny model that is able to predict the developmental changes in vancomycin clearance in neonates.⁷ Zhao et al⁸ have demonstrated that published vancomycin models in neonates cannot be transferred to different clinical settings because of clinically important variations in the measurements of serum vancomycin and serum creatinine values. In addition, dosage models for vancomycin that incorporate serum Cr are not accurate for at least several days after birth based on aforementioned reasons.

Practical and theoretical issues impact on the use of continuous infusions of vancomycin in newborns. All clinicians have either heard of or seen the “red man” syndrome when histamine released by a rapid infusion of vancomycin causes extreme vasodilatation, hypotension and sometimes frank shock.⁹ Infusion tubing filled with vancomycin 24 hours/d increases the risk of infusing a bolus dose of vancomycin when the intravenous solution is changed or when another medication is infused into the same intravenous tubing. A recent systematic review and meta-analysis in adults showed that target serum vancomycin concentrations vary between 20 and 25 mg/L or 20 and 30 mg/L,¹⁰ but there are major differences in the use of vancomycin between adults and neonates. Vancomycin is not only used routinely for empiric therapy in neonates, but also the coagulase-negative *Staphylococcus* species encountered in the neonatal nursery are not comparable with the methicillin-resistant *Staphylococcus aureus* in adults. Consequently, in neonates it might be prudent to aim for lower target concentrations for coagulase-negative *Staphylococcus* species and also to avoid continuous infusions of vancomycin. Current guidelines for use in adults advocate for a AUC/MIC ratio of greater than 400 being most predictive for clinical cure. This translates in adults for the need to reach trough concentrations of 15–20 mg/L, whereas in the pediatric population an AUC/MIC ratio of 400 can be reached with significantly lower trough concentrations.

Tissue is often the site of action, rather than the circulating blood stream, and vancomycin must diffuse from the circulation to its site of action. A major determinant of tissue penetration is the concentration gradient from the circulation to the tissue. This is higher after an intermittent dose than after a continuous infusion during which the tissue concentration does not exceed that in the circulation. Whether this difference affects effectiveness must be tested prospectively.

Finally, any dosage change for vancomycin must consider its effect on neonatal nephrotoxicity which appears to occur less often than in adults.^{11,12} We acknowledge that the mechanism of vancomycin nephrotoxicity is more uncertain than that of many other nephrotoxic drugs, although risk factors have been identified from studies in adults. Trough concentrations of 15–20 mg/L during intermittent vancomycin dosing in adults are associated with a modest increase in nephrotoxicity.¹³ When vancomycin is combined with other nephrotoxic medications, such as aminoglycosides or amphotericin, or with medications that reduce renal blood flow, such as furosemide or nonsteroidal antiinflammatory drugs, the risk of nephrotoxicity is significantly increased.¹³ Others have noted an increased risk with higher pretreatment serum Cr that increases the area under the concentration time curve during treatment.¹⁴ During continuous vancomycin infusions using

higher concentrations of 20–25 mg/L in adults, nephrotoxicity occurred in 15.7% of patients and risk factors included exposure to aminoglycosides, loop diuretics and steady-state vancomycin concentration ≥ 28 mg/L.¹⁴

Certainly, no one would want to trade off convenient administration for renal damage. Lessons from gentamicin nephrotoxicity illustrate how developmental physiology can influence nephrotoxicity in potentially unpredictable ways.¹⁵ Gentamicin is a small enough molecule that it is fully filtered into urine. Toxicity occurs in the tubular cells into which it is actively transported and wrapped in a lamellar membrane before it releases lysozymes that damage the tubular cell.^{16–19} Immature tubular transport and differences in distribution of intrarenal blood flow in immature animals and likely in premature newborns protect them from tubular cell disruption.²⁰ In more mature animals, nephron function is preserved after tubular cell damage by a robust tubular repair system that is active between doses when the circulating gentamicin concentration falls. Maintaining a constant gentamicin concentration because of decreased clearance is associated with nephrotoxicity, possibly because there is no time for repair.

The mechanism of vancomycin-induced nephrotoxicity is still uncertain, but several animal studies suggest possible mechanisms. Their relevance to neonatal physiology remains to be established. As with many toxic conditions, vancomycin nephrotoxicity may involve oxidative damage to the proximal tubular cells.²¹ Nephrotoxicity has been reduced by antioxidant treatments with superoxide dismutase,²² erythropoietin²³ and thymoquinone.²⁴ As with gentamicin, immaturity may provide protection to the newborn from vancomycin toxicity that is more commonly seen in adults. However, exposure to potentially nephrotoxic drugs during active glomerulogenesis might jeopardize the ultimate acquisition of anatomically available glomeruli and therefore increased pharmacovigilance is indicated until at least the postconceptional age of 35 weeks.

As for many areas of newborn therapeutics, vancomycin administration by continuous infusion represents a novel approach that warrants testing in a prospective, controlled study with careful attention to toxicity and effectiveness. Certainly, the challenge of congenital and nosocomial staphylococcal infections deserves careful attempts to improve treatment. The design of these attempts must be guided by a thorough recognition of developmental renal physiology and pharmacology.

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