Vancomycin Dosing in Pediatric Extracorporeal Membrane Oxygenation: Potential Impacts of New Technologies

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OBJECTIVES The objective of the current study was to evaluate the doses of vancomycin used to obtain therapeutic drug concentrations in pediatric patients on extracorporeal membrane oxygenation (ECMO), using new ECMO technologies.

METHODS This was a single-center, retrospective study of patients treated with vancomycin while receiving ECMO using low-volume circuit technology.

RESULTS A total of 28 patients were included in the analysis of the primary endpoint. Patients had a median age of 6 weeks (0–11 years) and a median weight of 3.45 kg (2.44–37.2 kg). Ultrafiltration was used in 89.3% of patients at initiation of ECMO regardless of baseline renal function, resulting in a median urine output of 2 mL/kg/hr at the time of the final vancomycin dose. Most patients started vancomycin at the same time as ECMO. The median total daily dose was 30 mg/kg/day. The median total daily dose in a subset of patients less than one year of age was 20 mg/kg/day. Nearly all patients had at least 1 therapeutic trough serum vancomycin concentration. A total of 16 patients completed their vancomycin course using an interval of every 12 hours or shorter. Half-life was calculated in a subset of 11 patients and the mean was found to be 12.3 ± 2.8 hours.

CONCLUSIONS An initial dosing interval of every 12 hours to provide a total daily dose of 30 mg/kg/day is a possible option in pediatric patients on ECMO provided that renal function is normal at baseline. Monitoring of serum vancomycin concentrations for adjustment of dosing is required throughout therapy and is still warranted.

ABBREVIATIONS ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; pRIFLE, Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease

KEYWORDS extracorporeal membrane oxygenation; pharmacokinetics; vancomycin

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of cardiopulmonary bypass used in both respiratory and cardiac failure or as a bridge to surgery. It is a complex system composed of a mechanical blood pump, gas-exchange device, heat exchanger, circuitry tubing, and various other ports used for both obtaining blood samples for laboratory tests and administering drugs.^{1–3} The use of ECMO cannulas carries a risk of infection as about 12% of patients on ECMO will go on to develop an infection.² In many cases, broad-spectrum antibiotics are used to treat these infections. Vancomycin is often chosen for its efficacy in treating Gram-positive infections including methicillin-resistant *Staphylococcus aureus* and coagulase-negative *Staphylococcus* infections.⁴

By adding volume to patients as well as introducing opportunities for drug sequestration, ECMO can change

the pharmacokinetics of many drugs, including vancomycin.⁵ Several earlier studies^{6–9} have investigated the pharmacokinetics of vancomycin in pediatric ECMO patients. These early pharmacokinetic studies revealed that vancomycin has a greater volume of distribution, clearance, and half-life. The mean half-life of vancomycin in these studies ranged from 6.53 to 16.9 hours. The half-lives suggested by these studies best represent the infant population, as only 1 study used samples from older children. From the half-life calculated in these studies, their authors recommended a dosing interval of 18 to 24 hours. In addition, it has been suggested that at least some vancomycin is sequestered in the circuit although this changes over time as binding sites become saturated.⁵

In recent years, advancements have been made in ECMO technology to allow for a smaller circuit volume. In addition to this reduced circuit volume, new technol-

ogy has included hollow-fiber oxygenators, spinning motor centrifugal pumps, and biocompatible tubing. Older pharmacokinetic data may not apply to dosing requirements for current pediatric patients on ECMO. A recent matched cohort study in adult ECMO patients receiving vancomycin therapy suggested that clearance and volume of distribution were similar between ECMO and non-ECMO patients.¹⁰ Additional recent adult data suggest that vancomycin is often underdosed in patients on ECMO and that subtherapeutic serum concentrations are obtained initially, possibly in part due to a hemodilutional effect from added volume.¹¹ The goal of this study was to determine the typical dose requirements for vancomycin and its half-life in neonatal and pediatric patients on ECMO.

Materials and Methods

A single-center, retrospective chart review was completed in order to answer the study questions. Patients were identified by using an institutional ECMO database and a report was generated of all ECMO patients who received intravenous vancomycin during the course of their hospital stay. Patients were included if they were younger than 18 years and admitted to the institution between July 1, 2011, and November 24, 2015. They were required to have received a minimum of 3 doses of vancomycin while on ECMO and to have had at least 1 obtained drug concentration. Patients were excluded if the use of vancomycin was not simultaneous with the use of ECMO. The dates selected for this study were chosen to include only those patients using reduced-volume circuits. These circuits used heparin-coated tubing (1/4" × 3/32" for patients weighing less than 10 kg and 3/8" × 3/32" for patients weighing 10 kg or greater), a bladder (Better Bladder, Circulatory Technology Inc, Oyster Bay, NY), a centrifugal pump, and a hollow-fiber polymethylpentene oxygenator (Quadrox iD, Maquet Cardiopulmonary AG, Rastatt, Germany). ECMO circuits were only changed if a clot formed within the circuit.

The primary endpoint of study was the total daily dose of vancomycin used for a patient while on ECMO. The dose administered and interval between doses in order to achieve a therapeutic trough serum concentration was also assessed. A secondary endpoint estimated the half-life in a subset of patients for whom 2 concentrations had been drawn following a single dose. It is not common practice to draw 2 serum concentrations after a dose; thus, only a subset of patients was included in the secondary endpoint.

Baseline characteristics were collected from the chart and included patient age, weight, sex, serum creatinine, blood urea nitrogen, and urine output. Both serum creatinine and urine output were collected throughout the patient's vancomycin course. Patients were also categorized according to the pRIFLE (Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease) score based on the point at which their urine output was at

its lowest.¹² Information regarding the ECMO circuitry including indication, type, equipment used, and duration of use was also collected. The chart was also reviewed for the dose and time of vancomycin used as well as its subsequent concentration. Vancomycin orders were placed by using the hospital electronic medical record with a scheduled dosing interval, but clinicians had the option to put in a regimen for a single dose. Vancomycin concentrations were drawn prior to the fourth dose given, approximately 1 hour prior to the dose. Given natural variation in laboratory draws, the exact interval from dose to laboratory draw was recorded. Additional serum vancomycin concentrations drawn after the fourth dose was given were also collected. For the current study, a concentration of 8 to 15 mg/dL was classified as therapeutic. The indication for vancomycin, as well as the time it was started in relation to ECMO, was also noted. Data collection began with the initiation of vancomycin while on ECMO and continued throughout the duration of ECMO, as patients may have received multiple courses of vancomycin. Each patient represented an individual data point even if receiving 2 courses of vancomycin therapy at least 48 hours apart. In cases where 2 dosing intervals were used, the initial dosing interval in the first course was used. Descriptive statistics (mean, standard deviation, median, range, and interquartile range [IQR]) were used to describe the data. The Institutional Review Board approved the completion of this study.

Results

Initial review of the institution's ECMO database yielded 66 individuals who were on ECMO and treated with vancomycin. Twenty-eight patients were included in the analysis of the primary objective and an additional 11 patients were included in the secondary analysis (Figure 1). The patient characteristics included in the study are summarized in the Table. Our study included mostly infants (78.5%). Patients ranged in age from birth to 11 years and ranged in weight from 2.44 to 37.2 kg. There were several indications for ECMO in the study population. These indications included respiratory failure, cardiogenic shock, and cardiac arrest. ECMO was started in the emergent setting secondary to a code event for cardiopulmonary arrest in 15 patients (53.6%). Three of these patients had a code event following repair of a congenital heart defect. Six patients did not start vancomycin therapy within 48 hours of initiating ECMO. Two of these patients started vancomycin prior to ECMO. Ultrafiltration was used as a means of maintaining fluid clearance and preserving renal function. Ultrafiltration was started in all but 5 cases at the initiation of ECMO, regardless of baseline renal function, and continued throughout therapy. Three patients required the use of true countercurrent dialysis. Vancomycin was started in 14 patients (50%) with sepsis or as empiric therapy until sepsis could be ruled

Figure 1. Flow diagram of study participant inclusion.

ECMO, extracorporeal membrane oxygenation.

out. The second most common indication for starting vancomycin was a part of the institution's open-chest protocol (9/28 patients, 32.1%). There were 2 suspected cases of pneumonia and no cases of meningitis in the study patients. Blood cultures came back positive in 6 patients (21.4%). *Staphylococcus aureus* was found in culture results for a single patient. This culture showed methicillin-susceptible *S aureus*.

In the primary endpoint, the total daily dose of vancomycin used to obtain a therapeutic serum concentration had a median of 30 mg/kg/day (IQR 17.5–30 mg/kg/day) (Figure 2). To obtain a total daily dose of 30 mg/kg/day, a 12-hour dosing interval was most commonly used with a 15-mg/kg dose. At the completion of therapy, 16 patients (57.1%) were dosed using an interval of 12 hours or shorter with 10 patients (35.7%) using a 12-hour dosing interval. All patients were started on either 10 mg/kg or 15 mg/kg of vancomycin. One-half of the patients finished on a dose of 15 mg/kg, while 2 patients (7.1%) completed therapy on 20 mg/kg and 12 patients (42.9%) used 10 mg/kg. Subgroup analysis was also performed to assess any differences between the infant population (patients younger than 1 year) and older pediatric patients. The median total daily dose was smaller (20 mg/kg/day) in the younger patient group (n = 21) with an IQR of 15 to 30 mg/kg/day. The median total daily dose in the older patient group (n = 7) was 30 mg/kg/day with an IQR of 15 to 45 mg/kg/day.

Serum creatinine remained constant throughout the duration of ECMO treatment. The initial and final values are represented in the Table. Although this variable was collected throughout the patient's course of vancomycin, only 2 patients saw a 50% increase in serum creatinine. In those cases, the vancomycin was not adjusted in response to the changes in serum creatinine. Patients had small changes in urine output over the course of their ECMO run. The median urine

output at the start of vancomycin therapy was 2.45 mL/kg/hr and the median decreased to 2 mL/kg/hr. There was greater variation in the day-to-day urine output as compared to serum creatinine. A pRIFLE score was assigned to 7 patients (25%) on the basis of urine output throughout their course of vancomycin. Two patients met the definition of risk with urine output dropping below 0.5 mL/kg/hr for at least 8 hours and 1 patient met the definition of injury with urine output below 0.5 mL/kg/hr for at least 16 hours. Another 3 patients met the definition of failure, based on urine output less than 0.3 mL/kg/hr for at least 24 hours.¹² One patient had end-stage renal disease. All patients in the Risk or Injury categories quickly regained urine output without changes in vancomycin dosing. There were 2 patients with oliguria at the onset of ECMO, including the patient with end-stage renal disease.

A total of 157 concentrations were drawn in the full sample of 28 patients at a point in time no sooner than before the fourth dose. Most patients (27/28, 96.4%) were able to obtain a therapeutic drug concentration at some point in their therapy. The single patient unable to obtain a concentration in the 8- to 15-mg/dL range had a subtherapeutic serum concentration, and therapy was discontinued prior to any subsequent checks of the concentration. Thirteen patients (46.4%) had subtherapeutic troughs at one point in their treatment course. All of these patients were started on an initial dosing regimen of 12 hours or greater. In 10 patients (35.7%), this was the first vancomycin concentration drawn, indicating a potential delay in achieving therapeutic efficacy of the medication. On the other end of the spectrum, 6 patients (21.4%) had a concentration of greater than 20 mg/dL. These patients included 1 patient who required continuous renal replacement therapy and another patient on peritoneal dialysis. One of these patients had end-stage renal disease at baseline with oliguria and a serum creatinine of 3.7 prior to starting ECMO. In addition, all 6 patients with concentrations greater than 20 mg/dL were included in the secondary analysis of half-life, representing 54.5% of the 11 patients. These patients were either dosed on the basis of obtained concentrations or used an extended interval of 18 or 24 hours between doses. With the exception of the patient with baseline renal dysfunction, the initial regimens selected for these patients did not greatly differ from those of other patients. The use of longer intervals did enable all of these patients to eventually obtain a therapeutic drug concentration. The half-life calculated in the subset of patients who had 2 obtained concentrations after a single vancomycin dose was 12.3 ± 2.8 hours. The median age of these patients was 1 month with the oldest patient at 6 months of age. Six of these patients were placed on ECMO for rest or in an emergent setting following cardiac surgery. All patients in whom half-life could be calculated had a concentration greater than 15 mg/dL and required a dosing interval of at least 12

Table. Characteristics of Study Participants

Demographics	Value
Age, median (IQR)	6 wk (2 wk–10.5 mo)
Weight (kg), median (IQR)	3.45 (2.7–10.5)
Male, No. (%)	17 (60.7)
Renal function	
Initial serum creatinine (mg/dL), median (IQR)	0.6 (0.45–0.75)
Serum creatinine at time of last dose (mg/dL), median (IQR)	0.6 (0.5–0.8)
Initial urine output (mL/kg/hr), median (IQR)	2.45 (1.1–3.45)
Urine output at time of last dose (mL/kg/hr), median (IQR)	2 (1–3.2)
pRIFLE score, No. (%)*	7 (25)
R (Risk)	2 (7.1)
I (Injury)	1 (3.6)
F (Failure)	3 (10.7)
L (Loss)	0 (0)
E (End-stage)	1 (3.6)
Venoarterial ECMO, No. (%)	27 (96.4)
Days of ECMO therapy, median (IQR)	9 (5–13)
Ultrafiltration or renal support, No. (%)	25 (89.3)
Vancomycin	
Vancomycin prior to ECMO, No. (%)	1 (3.6)
Days of vancomycin, median (IQR)	5.5 (3–11)
Doses of vancomycin, median (IQR)	8 (5.5–13)

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; pRIFLE, Risk, Injury, Failure, Loss, End-stage Renal Disease

* pRIFLE score based on urine output at lowest point.

hours. These patients were often started on a dosing interval of 12 to 18 hours, which was extended during the course of their therapy. All patients who ultimately used a dosing interval of 18 hours or greater were included in the half-life analysis. The range in half-life was from 7.4 to 16.2 hours.

Discussion

Earlier studies have suggested that the dosing interval of vancomycin should be automatically extended out to 18 or 24 hours for patients on ECMO with a total daily dose of 15 to 20 mg/kg/day. However, the results of this study suggest that this recommendation may not be uniformly useful; using newer forms of ECMO technology and a shorter dosing interval may be warranted in some cases. The total daily dose used by many of the patients in the current study represents a slight increase from the dose suggested by earlier studies. Many of the changes made to ECMO technology seem to favor a shorter dosing interval, closer to that used in pediatric patients not on ECMO. The reduced volume of the circuits may contribute to a smaller volume of distribution for vancomycin. Use of ultrafiltration has

expanded since the previous studies were performed and may help to preserve renal function. Rates of use cited in earlier literature (12%) are much lower than the rates seen in this study (89.3%).⁵ The use of ECMO has traditionally been accompanied by a decline in renal function over the course of therapy, but changes in creatinine or urine output were not commonly seen within the current study. Of the 7 patients with a pRIFLE score, 3 quickly recovered without any changes made to their vancomycin dose and 2 had renal dysfunction prior to initiation of ECMO. In many patients, urine output and serum creatinine were normal at initiation of ECMO. There was little change in these parameters over the course of therapy in a majority of patients, indicating an ability to preserve renal function in most patients. It permitted over half of the included patients to use a dosing interval of 12 hours or shorter.

For the purposes of this study, a concentration range of 8 to 15 mg/dL was considered to be a therapeutic trough. The decision to use this range stems from literature highlighting the increased risk of nephrotoxicity in pediatric patients with vancomycin troughs > 15 mg/dL.¹³ Previous literature has documented that lower troughs are sufficient to achieve an area under the curve/mini-

Figure 2. Total daily dose of vancomycin.

imum inhibitory concentrations ratio of >400 and that clinical resolution of infection may still be achieved in children.^{14,15} This is also the trough commonly targeted by clinicians in our institution. The targeted serum trough concentration was not compared to indication, nor were the minimum inhibitory concentrations analyzed given the relatively infrequent finding of *S aureus* in patient cultures. Blood cultures had a relatively low yield for patients in this study, preventing a greater discussion of acceptable troughs for a particular organism.

The half-life seen in this study was longer than the half-lives seen in earlier studies with the exception of 1 study that found a half-life of 16.9 hours. This could in part be explained by the large number of infants included in this subset of patients and the number of patients placed on ECMO after surgery. The neonatal population would be expected to have a longer half-life than older pediatric patients and the studies which included a greater variety of patients would be more likely to show shorter half-lives. The postoperative patients were predisposed to a period of oliguria after surgery and may have prolonged clearance. In addition, there was an inherent bias in the inclusion of patients in this subset. It is not common practice to draw 2 concentrations after a single dose of vancomycin in order to perform true pharmacokinetic calculations. It does occur in certain patients when there is a high concentration and the optimal time to dose the medication needs to be determined. These cases occur when clearance is reduced or at least slower than would otherwise be expected. As a result, these are patients with longer half-lives. Our half-life analysis included all patients with a concentration > 20 mg/dL and most patients with a concentration greater than 15 mg/dL and best represented those patients who had some difficulty eliminating vancomycin.

This study adds to our understanding of newer ECMO technologies and represents a useful update to the baseline information provided by earlier studies. The current study is not without its limitations. It is a small

study at a single institution and its generalizability is dependent upon the technologies used by other ECMO centers. Owing to the retrospective nature of the study, only patients with reduced clearance were included in the secondary analysis. In addition, the use of ultrafiltration served as a potential confounder. The relationship between ultrafiltration rate and dosing interval was not assessed in the current study because the rate of ultrafiltration is often changed multiple times per day and thus prevents an accurate estimate of its effect on the dosing interval of vancomycin. The changing out of ECMO circuits themselves could also potentially impact drug pharmacokinetics by impacting sites for drug binding and sequestration. This is a relatively rare occurrence at our institution, generally occurring once at most in a particular patient; however, the practice was not directly assessed in the current study. An additional possible limitation lies in the risk of sampling before steady state. In general, true steady state is believed to be achieved by about 3 to 5 half-lives. This would have been captured in most patients in the study even using a half-life of 12 hours. However, there is still the possibility that certain patients may have been sampled too early and concentrations found to be lower than they would have been at true steady state. Finally, a lack of a protocol resulted in variation of dosing decisions based upon clinician preference. A prospective study with a well-designed protocol accounting for drug concentrations and patient's renal function would eliminate treatment decision variation. It could also be designed to collect concentrations for pharmacokinetic calculations representing all patients.

The current study highlights that, in some cases, patients may be started on a slightly larger total daily dose (30 mg/kg/day) than previously recommended when on ECMO with close monitoring and adjustments made for drug concentrations. An initial 15-mg/kg dose and 12-hour dosing interval is a reasonable consideration in older patients without underlying renal dysfunction in order to prevent initial subtherapeutic dosing and ensure adequate antimicrobial coverage while still being below toxic concentrations. This recommendation may be less applicable to the neonatal population whose renal function is not fully developed. They are therefore more at risk for supratherapeutic concentrations secondary to poor clearance. In those cases, a more conservative approach may be warranted. In all cases, patients should be monitored throughout therapy for changes in renal function, as an inherent level of unpredictability is present given the overall complexity of the ECMO circuit.

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REFERENCES

1. Lequier L, Horton SB, McMullan DM, et al. Extracorporeal membrane oxygenation circuitry. *Pediatr Crit Care Med*. 2013;14(S5):S7–S12.
2. Butt W, Heard M, Peek, GJ. Clinical management of the extracorporeal membrane oxygenation circuit. *Pediatr Crit Care Med*. 2013;14(S5):S13–S19.
3. Schwartz SM, Schmidt A. Medical and nursing care of the child on mechanical circulatory support. *Pediatr Crit Care Med*. 2013;14(S5):S43–S50.
4. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines of the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: an executive summary. *Clin Infect Dis*. 2011;52(3):285–292.
5. Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. *Clin Pharmacokinet*. 2003;42(5):403–417.
6. Hoie EB, Swigart SA, Leuschen MP, et al. Vancomycin pharmacokinetics in infants undergoing extracorporeal membrane oxygenation. *Clin Pharm*. 1990;9(9):711–715.
7. Amaker RD, DiPiro JT, Bhatia J. Pharmacokinetics of vancomycin in critically ill infants undergoing extracorporeal membrane oxygenation. *Antimicrob Agents Chemother*. 1996;40(5):1139–1142.
8. Buck ML. Vancomycin pharmacokinetics in neonates receiving extracorporeal membrane oxygenation. *Pharmacotherapy*. 1998;18(5):1082–1086.
9. Mulla H, Pooboni S. Population pharmacokinetics of vancomycin in patients receiving extracorporeal membrane oxygenation. *Br J Clin Pharmacol*. 2005;60(3):265–275.
10. Donadello K, Roberts JA, Cristallini S, et al. Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. *Crit Care*. 2014;18(6):632.
11. Kim SJ, Yang JH, Park HJ. Trough concentrations of vancomycin in patients undergoing extracorporeal membrane oxygenation. *PLoS One*. 2015;10(22):e0141016.
12. Soler YA, Nieves-Plaza M, Prieto M, et al. Pediatric risk, injury, failure, loss, end-stage renal disease score identifies acute kidney injury and predicts mortality in critically ill children: a prospective study. *Pediatr Crit Care Med*. 2013;14(4):e189–e195.
13. McKamy S, Hernandez E, Jahng M, et al. Incidence and risk factors influencing the development of vancomycin nephrotoxicity in children. *J Pediatr*. 2011;158(3):422–426.
14. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant *Staphylococcal* infections. *Pediatr Infect Dis J*. 2013;32(10):1077–1079.
15. Le J, Bradley JS, Murray W, et al. Improved vancomycin dosing in children using area under the curve exposure. *Pediatric Infect Dis J*. 2013;32(4):e155–e163.