Article published online: 2024-11-21

Reducing Vancomycin Dosage in Children on ECMO with Renal Impairment

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Thorac Cardiovasc Surg 2024;72:e30–e36.

Abstract

Background Extracorporeal membrane oxygenation (ECMO) can influence pharmacokinetics. We investigated the vancomycin dosage in children on ECMO compared to critically ill children to determine the necessary dosage adjustment on ECMO.

Methods Eight-year, single-center, retrospective cohort study at a tertiary heart center's pediatric cardiac intensive care unit (ICU) of children undergoing ECMO support. Our control group (non-ECMO) was critically ill children with delayed sternal closure after cardiac surgery. We included consecutively all children undergoing vancomycin administration. The starting dose was 10 to 15 mg/kg BW per dose, every 8 to 12 hours depending on age. The vancomycin trough level was maintained in the 10 to 20 µg/ml range.

Results 85 total courses on ECMO and 99 non-ECMO courses were included. The ECMO group's daily vancomycin dose was significantly lower than non-ECMO's at a median of 33.3 and 38.5 mg/kg/d, respectively ($p < 0.001$). Vancomycin serum trough levels were similar between groups and within the target range. The ECMO group's daily vancomycin dose dropped faster over time, with a dose on day 3 of 28.7 and 33.7 mg/kg/d, respectively. The impact of renal function on vancomycin dosing was more apparent in the ECMO group. If the renal function was reduced at the start of treatment, the vancomycin dose was lower in the ECMO group compared to the non-ECMO group with renal impairment (22.5 vs. 42.1 mg/kg/d; $p < 0.001$). When renal function was normal, the doses were similar between groups.

Conclusion In children on ECMO with impaired renal function at treatment initiation, lower vancomycin doses were necessary. Early therapeutic drug monitoring, even before reaching a steady state, should be considered.

Keywords
- extracorporeal membrane oxygenation
- ECMO
- pediatric
- kidney
- pharmacokinetics
- intensive care

received
May 27, 2024
accepted after revision
September 19, 2024

DOI https://doi.org/10.1055/s-0044-1793908.
ISSN 0171-6425.

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a lifesaving organ support in critically ill patients to support or replace cardiac and respiratory function. The pharmacokinetics of medications on ECMO can be severely altered because of the increased distribution volume, sequestration to tubing and oxygenator, hemolysis, reduced clearance, and inflammatory responses.[1,2] Vancomycin is a frequently used antibiotic in children on ECMO due to their high risk of infection with gram-positive cocci, especially when children have open chest cannulation and delayed sternal closure.[3] Vancomycin is renally eliminated, but kidney function can be critically impaired on ECMO. A recent review described a high percentage of target non-attainment with standard dosing regimens.[4] Published investigations have reported very few children given vancomycin on ECMO, or they involved no control group of critically ill children. We hypothesize children on ECMO require a different vancomycin dose than children without ECMO support. Our aim was to determine vancomycin's necessary dosage adjustment under ECMO compared to critically ill children with delayed sternal closure and hence similar disease severity to extrapolate the influence of ECMO support more accurately on the pharmacokinetics.

Methods

We conducted an 8-year, single-center, retrospective cohort study at our pediatric cardiac intensive care unit (ICU) in a tertiary referral heart center on children (0–18 years) undergoing ECMO support. Critically ill children with delayed sternal closure after cardiac bypass surgery served as the control group (non-ECMO). Data were collected from digital patient charts.

The reason for vancomycin administration was prophylaxis of mediastinitis, surgical site infection, and sepsis. Vancomycin serum levels were collected as trough levels before the next administered dose. The first level was obtained before the third dose and in reduced renal function earlier. Trough levels of 10 to 20 µg/ml were considered in the target range as this was the standard operating procedure on this unit. These levels were predefined by the fact that at our pediatric cardiac ICU, we had only 21 cases of methicillin-resistant *Staphylococcus aureus* out of 238 overall detected *Staphylococcus* and a minimal inhibitory concentration (MIC) of >1 mg/l only in 43/238 cases. Vancomycin serum levels were measured via immunoassay by Cobas 8000 modular analyzer (Roche Diagnostics Deutschland GmbH, Mannheim, Germany). The vancomycin dose was calculated as the total daily dose per kilogram of body weight. The starting vancomycin dose in both cohorts for neonates was (day 0–7 of age) 10 to 15 mg/kg per dose every 12 hours, for neonates (day >7) 10 to 15 mg/kg per dose every 8 hours, for children after the neonatal period 40 mg/kg per day in three single doses. Administration interval was adjusted according to age, renal function, and serum levels at 6, 8, 12, or 24 hours. Vancomycin doses and levels as well as laboratory parameters included in the calculations were of the time on ECMO in the ECMO group, or the open chest time in the non-ECMO group. Laboratory parameters like serum urea, creatinine, alanine aminotransferase (ALAT), cholinesterase, D-dimers, N-terminal fragment brain natriuretic peptide (NT-proBNP), and troponin T were measured repeatedly during ECMO or open chest.

This retrospective data analysis was approved by the ethical review committee (Freiburg University 23-1000-S1-retro) and in accordance with the ethical review committee, the request for parental consent was waived. Data are presented as median and its interquartile range (IQR). Boxplots depict the median, hinges the IQR, and whiskers the largest value up to 1.5*IQR from the hinge and beyond outlier points. Statistical analysis with Wilcoxon's rank-sum test was performed for not normally distributed variables. *p*-values <0.05 were considered statistically significant. RStudio 2021.09.1 was used for statistical analysis and graph creation.

Results

Patient enrollment and exclusions are listed in ►**Fig. 1**. We included a total of 85 courses on ECMO in 82 children and 99 non-ECMO courses in 92 children receiving vancomycin (►**Table 1**). Our patients were mainly on venoarterial ECMO (93%), with the majority undergoing open chest cannulation postcardiotomy if they could not be safely

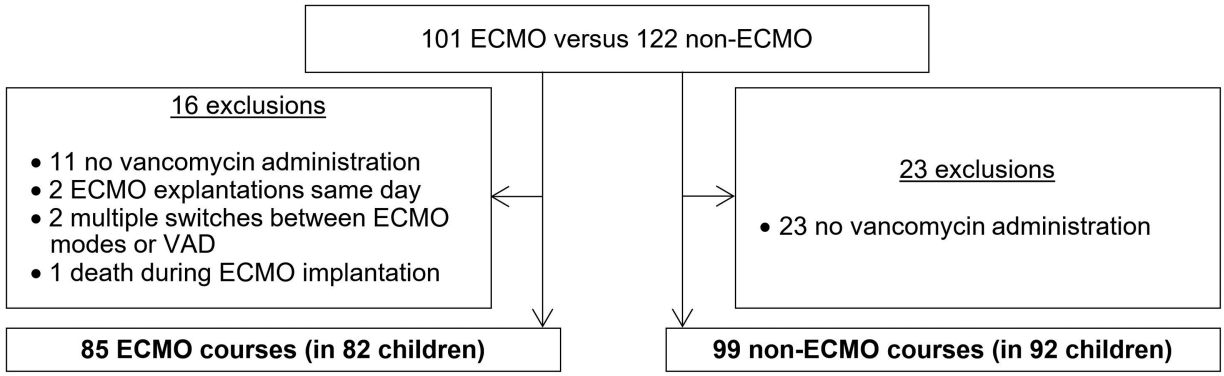

Fig. 1 Patient enrollment in the ECMO and non-ECMO groups. ECMO, extracorporeal membrane oxygenation.

Table 1 Patients' characteristics

Characteristics median (interquartile range) or *n* (%)	ECMO	non-ECMO	*p*-value
Treatment courses	85	99	
Patients	82	92	
Age, days	144 (10–940)	63 (7–296)	**0.048**
Body weight, kg	4.6 (3.4–11.5)	3.9 (3.4–7.2)	0.133
Days on ECMO or open chest	4 (2–6)	3 (2–4)	**0.001**
VA ECMO/VV ECMO	79 (93%)/6 (7%)	–	–
Surgery			
Duration, minutes	455 (152–550)	391 (300–479)	0.340
Cardiopulmonary bypass time, minutes	218 (0–282)	197 (150–236)	0.506
Aortic cross-clamp time, minutes	70 (0–128)	82 (47–134)	0.062
Nadir temperature, °C	29.9 (25.0–33.8)	29.7 (25.5–33.7)	0.903
Blood transfusions, mL/kg/day			
Red blood cell concentrates	16.0 (7.4–36.0)	0 (0–5.5)	<**0.001**
Fresh frozen plasma	6.9 (2.0–21.7)	3.0 (0–9.6)	<**0.001**
Platelet concentrates	10.7 (4.4–22.0)	0 (0–2.9)	<**0.001**
Renal failure[a]			
Day 0	18 (21%)	13 (13%)	0.148
Last day of treatment	32 (38%)	21 (21%)	**0.014**
GFR at day 0, mL/min/1.73 m^2	55.5 (35.7–77.7)	51.9 (39.4–78.9)	0.575
Renal replacement therapy	19 (22%)	9 (9%)	**0.013**
Hemodialysis	7 (8%)	0	**0.004**
Peritoneal dialysis	15 (18%)	9 (9%)	0.087
In-hospital deaths	40 (47%)	8 (8%)	<**0.001**
Time to death, days	8 (5–17)	8 (6–18)	0.220
Overall vancomycin dose, mg/kg/day	33.3 (19.1–44.4)	38.5 (29.4–44.1)	<**0.001**
Age 0–7 days, mg/kg/day	29.0 (21.3–35.1)	30.8 (28.6–39.0)	0.355
Age >7 days, mg/kg/day	33.1 (24.4–46.1)	40.3 (33.0–44.7)	**0.044**
GFR normal at day 0, mg/kg/day	37.5 (21.9–46.9)	38.2 (29.4–43.5)	0.299
GFR reduced at day 0, mg/kg/day	22.5 (13.8–33.3)	42.1 (30.4–47.6)	<**0.001**
Vancomycin dose on day X			
Day 0, mg/kg/day	39.1 (33.3–44.3)	38.8 (30.3–43.5)	0.631
Day 3, mg/kg/day	28.7 (13.3–42.7)	33.7 (28.9–43.1)	0.071
Vancomycin level, µg/mL	11.2 (7.1–16.4)	11.5 (8.9–16.7)	0,055
Serum urea, mg/dL	42 (27–69)	32 (23–49)	<**0.001**
Creatinine, mg/dL	0.54 (0.34–0.85)	0.53 (0.40–0.70)	0.552
ALAT, U/L	36 (20–68)	24 (16–41)	<**0.001**
D-dimer, mg/L	4.6 (1.7–14.7)	1.9 (0.6–4.7)	<**0.001**

Abbreviations: ALAT, alanine aminotransferase; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; VA, venoatrial; VV, venovenous.
Characteristics of ECMO and non-ECMO groups. Data are presented as median (interquartile range) or *n* (%).
[a]Defined by glomerular filtration rate less than age-related normal range calculated by revised Schwartz equation.

weaned from cardiopulmonary bypass (86%). The remaining patients were cannulated via neck or femoral cannulation not postcardiotomy (14%). All 85 ECMO courses were on new-generation rotary ECMO blood pumps: 77 on Medos Deltastream DP3 (Fresenius, Bad Homburg, Germany), 7 on Sorin Revolution Centrifugal pump (Livanova, London, United Kingdom), and 1 on CentriMag Blood Pump (Abbott, Illinois, United States). Depending on the calculated cardiac

output, we used the following oxygenators: Medos Hilite 800 LT (Fresenius, Bad Homburg, Germany), Newborn A.L.One 14 days (Eurosets S.r.l., Medolla, Italy), or Medos Hilite 2400 LT (Fresenius, Bad Homburg, Germany). Both groups presented similar body weight (4.6 kg in ECMO vs. 3.9 kg in non-ECMO) although the ECMO group children were slightly older (144 vs. 63 days). There were no significant differences between the ECMO and non-ECMO groups in surgical duration, cardiopulmonary bypass time, aortic cross-clamp time, or lowest body temperature during surgery. However, the amount of blood transfusions—including red blood cell concentrates, fresh frozen plasma, and platelet concentrates—was significantly higher in the ECMO group ($p < 0.001$ for all). For all patients' characteristics, see ►**Table 1**.

Death while on ECMO occurred during nine ECMO courses (11%). ECMO weaning failed with death within ≤24 hours after ECMO explantation in 13 courses (15%). Patients were not put back on ECMO if the prognosis was truly dire and we had the parents' consent. We observed successful weaning entailing survival >24 hours after ECMO explantation in 63 courses (74%). Unadjusted survival probability at the end of our 30-day follow-up period was 59% in ECMO (95% CI: 49–70%) and 93% in the non-ECMO group (95% CI: 88–98%; ►**Supplementary Fig. S1** [available in the online version only]). Adjustments for age, gender, ECMO support, dialysis, and the total vancomycin dose demonstrated an association between survival and greater age ($p = 0.046$), non-ECMO support ($p < 0.001$), and a higher overall vancomycin dose ($p = 0.007$). The proportion of renal failure defined by the glomerular filtration rate (GFR) under the age-related normal range calculated by the revised Schwartz equation tended to be higher but not significantly different on day 0 in the ECMO group (►**Table 1**). This number rose until the ECMO group's last day of ECMO support and the last day of the open chest in the non-ECMO group to 38% and 21% ($p = 0.014$), respectively. The ECMO group underwent renal replacement therapy (RRT) more often (22% in ECMO vs. 9% in non-ECMO), as hemodialysis only in the ECMO group (7 vs. 0 times), and as peritoneal dialysis more often in the ECMO group (15 vs. 9 times), but this did not differ significantly.

The total number of vancomycin administration days while on ECMO or while opened chest, respectively, was 416 in the ECMO and 372 in the non-ECMO group. The ECMO group's necessary total daily vancomycin dose was significantly lower than the non-ECMO group's (33.3 vs. 38.5 mg/kg/d; ►**Fig. 2A**). At treatment initiation on day 0, both groups' doses were similar (39.1 and 38.8 mg/kg/d, respectively). During the later treatment course, doses required adjustment to maintain the vancomycin serum trough level within the target range of 10 to 20 µg/ml. The total number of measured vancomycin serum levels was 259 in the ECMO and 189 in the non-ECMO group. Both groups' total vancomycin serum trough levels were similar and in the target range (11.2 and 11.5 µg/ml, respectively; ►**Fig. 2B**). To achieve that range, the ECMO group's daily vancomycin dose declined over the treatment faster than the non-ECMO group (►**Fig. 2C**).

A subgroup analysis of normal and reduced GFR at the start of treatment on day 0 showed that if GFR was normal at the start, the total daily vancomycin dose over the whole ECMO support period or delayed sternal closure period was similar between groups (►**Fig. 3A**). But if GFR fell below the age-related range, the ECMO group's vancomycin dose

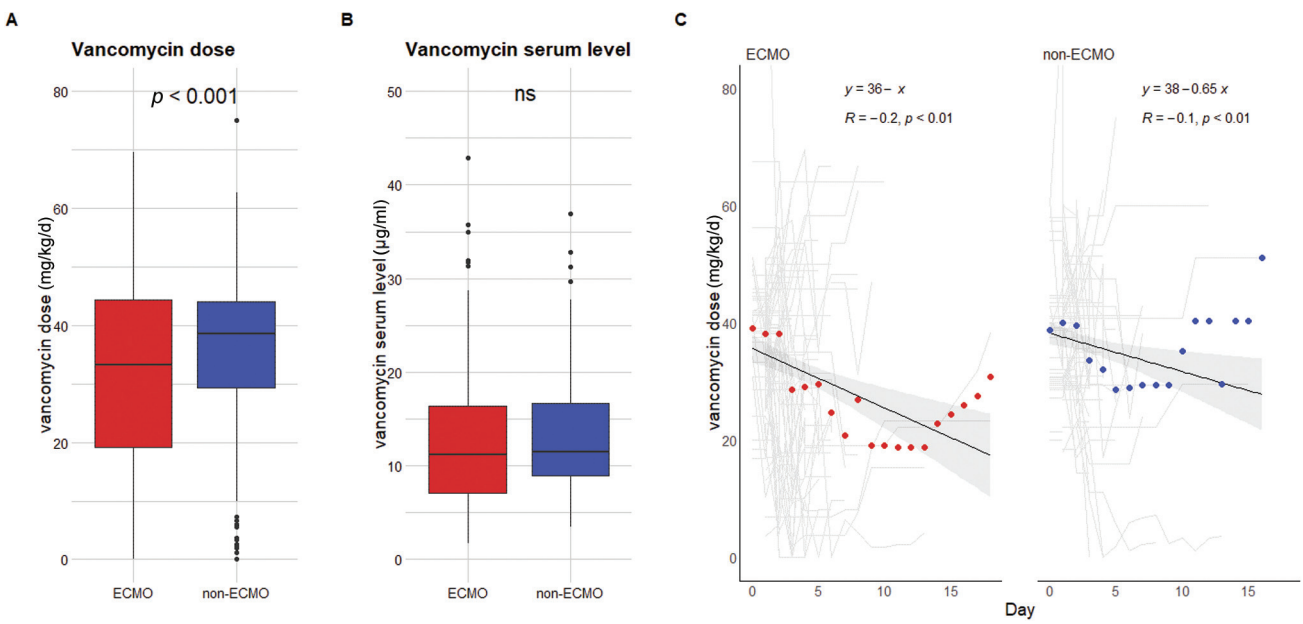

Fig. 2 Overall vancomycin doses (**A**) and serum levels (**B**) in ECMO and non-ECMO groups. Median vancomycin doses by day on treatment with linear regression and patients' trajectories (**C**). ECMO, extracorporeal membrane oxygenation.

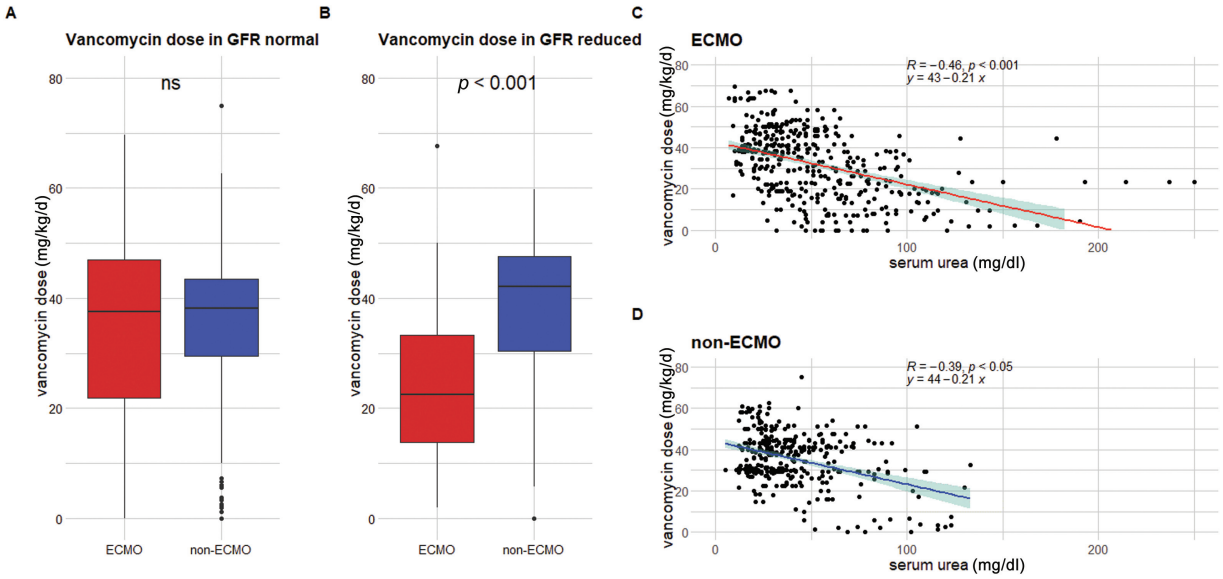

Fig. 3 Vancomycin dose in subgroups with normal GFR (calculated by revised Schwartz equation) at the start of treatment on day 0 (**A**) versus reduced GFR on day 0 (**B**). Linear regression between serum urea and vancomycin dose for ECMO (**C**) and non-ECMO group (**D**). ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate.

required to maintain serum levels within the target range was significantly lower (22.5 vs. 42.1 mg/kg/d; ►**Fig. 3B**). Both groups revealed a similar correlation between higher serum urea concentrations and lower required vancomycin doses (►**Fig. 3C, D**).

The ECMO group's total serum urea, ALAT, and D-dimers were higher than the non-ECMO group's (►**Supplementary Fig. S2** [available in the online version only]), while creatinine, cholinesterase, troponin T, and NT-proBNP did not differ significantly.

Discussion

In our study with a cohort including 85 ECMO courses, we compared the necessary vancomycin doses between children on ECMO and critically ill children to highlight the effects of ECMO support. Our cohorts, ECMO and non-ECMO groups differed slightly in age with younger children in the non-ECMO group. However, because kidney function matures during the first year of life, our ECMO group's lower vancomycin dose—although they were slightly older children—might even lead to an underestimation of the dose discrepancy, given the less mature renal function of the non-ECMO group while required higher vancomycin dose.[5] Nevertheless, as there was no difference in body weight and length, the two groups are comparable. Our non-ECMO group children with delayed sternal closure had undergone heart–lung machine surgery; such children are, often hemodynamically unstable, in an increased inflammatory condition, and are more prone to infections because of their open chest and multiple catheters inserted.[6] The similar state of critical illness of both groups is also supported by similar surgical duration, cardiopulmonary bypass time, aortic cross-clamp time, lowest body temperature during surgery, levels of creatinine, cholinesterase, troponin T, and NT-proBNP, which did not differ significantly. Hence, our non-ECMO group, being critically ill children, is suitable for comparison to the ECMO group—thus highlighting the ECMO circuit's impact and less the ECMO group's critically ill state.

At the start of treatment on day 0, we noted slightly but not significantly more ECMO-group patients with renal failure (21%) than in the non-ECMO group (13%). However, on the last day of support, a significantly higher number of ECMO patients were suffering from renal failure. This might be because these ECMO patients in such critical condition may also have lost some kidney function because of ECMO's influence on it, for example, through the absence of pulsatility.[7,8] They therefore also required renal replacement therapy (RRT) more often (22%) than did non-ECMO children (9%). Note that only the ECMO group required hemodialysis. Their observed greater occurrence of hemodialysis might be because it is more feasible on ECMO because of the dialysis connection into the ECMO circuit. Furthermore, the RRT indication on ECMO is not only acute kidney injury but also fluid overload caused by capillary leakage, accompanied by increased mortality on ECMO.[9,10] Even though vancomycin is removed via continuous hemodialysis and a higher dose is usually needed, the ECMO group's total required vancomycin dose was lower while being more often on hemodialysis.[11] This fact reveals that the total effect of RRT on dosing is inferior.

The ECMO group's total required vancomycin dose was significantly lower than the non-ECMO group. As ECMO has such a strong and varied impact on pharmacokinetics, dose adjustments of medications in both directions have been observed.[4,12] The present study demonstrates a necessary reduction in the daily vancomycin dose during the initial days of ECMO. Although critically ill children in the non-ECMO group also needed a dose reduction, the ECMO group's required dose was even lower. This evidence supports the assumption that there is no relevant absorption of vancomycin in the circuit because of its low lipophilicity.[13] Hence,

factors like impaired kidney function demand lowering the vancomycin dose, but not exclusively, as in our subgroup with impaired kidney function, only those children on ECMO needed it. This means that neither impaired kidney function without ECMO nor ECMO alone requires reducing the vancomycin dose, but the coexistence of ECMO and reduced kidney function does mandate lowering it. Supporting this, we detected no significant difference between creatinine serum levels and similar GFR at day 0 in both groups. In line with ours and their small prospective study, An et al demonstrated decreased vancomycin clearance in neonates on ECMO and necessary dosing adjustment.[14] Children on ECMO often suffer from acute kidney injury.[8] The vancomycin level and kidney function are interdependent. Vancomycin excretion depends primarily on kidney function. Nephrotoxicity can occur at vancomycin trough levels of >20 mg/l.[15] The nephrotoxicity risk is high, especially when additional nephrotoxic agents have been given. Hence, it is even more essential to prevent overshooting vancomycin levels in patients on ECMO in advance.[16] The novel finding of our study is the time-dependent dose reduction during the initial days of ECMO support which should raise awareness for the uncritical application of a loading dose at the start of vancomycin administration.

Prophylactic vancomycin administration is common in patients on ECMO and those with delayed sternal closure.[3,17,18] However, due to the increasing development of antimicrobial resistance, careful consideration regarding antibiotic stewardship is essential before its use. In our study, vancomycin was often administered prophylactically according to protocol, starting with the initiation of ECMO or with the delayed sternal closure.

According to the pediatric Extracorporeal Life Support Organization registry's report, the rate of survival-to-hospital discharge in a neonatal cohort on cardiac ECMO was 45%, in a pediatric cohort 57%, and overall survival of 52%.[19] We observed 30-day survival of 59% in our ECMO cohort versus 93% in the critically ill non-ECMO group. Moreover, our multivariable analysis revealed that a higher vancomycin dose was associated with longer survival as dose reductions often become necessary in extremely critical conditions.

Limitations of this study are due to its retrospective design, being unable to compare the same severity of disease, thus we may have overestimated the true effect of ECMO on vancomycin dosages because of our ECMO group's more severe illness and more impaired kidney function. Furthermore, trough concentrations are not as good a surrogate parameter for effective antimicrobial treatment and safety as is the area under the concentration–time curve divided by the MIC; to do that, we would have needed sequential blood samples, which were unavailable because of our study's retrospective design.[20]

Conclusion

In pediatric patients on ECMO, careful vancomycin dosing is crucial, especially when renal function is reduced at ECMO initiation. Our data suggest that the recommendation to start with a higher loading dose to account for the greater volume of distribution should be avoided in these cases to prevent overshooting therapeutic levels and further renal impairment. In children on ECMO with reduced GFR, early therapeutic drug monitoring, even before reaching a steady state with trough levels before the second or third vancomycin dose, should be considered to avoid toxicity.

Conflict of Interest

None declared.

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