SYSTEMATIC REVIEW

Open Access

Do patients receiving extracorporeal membrane-oxygenation need antibiotic prophylaxis? A systematic review and meta-analysis on 7,996 patients

Daniele Orso[1*], Caterina Maria Fodale[2], Sara Fossati[1], Sergio Venturini[3], Federico Fonda[1], Francesco Cugini[4], Irene Comisso[1], Massimo Crapis[3], Luisa Cacciavillani[2] and Tiziana Bove[1,5]

Abstract

Background   Patients undergoing Extracorporeal Membrane Oxygenation (ECMO) are particularly susceptible to infections: 42% experience sepsis and 26% develop a nosocomial infection (NI). Whether antibiotic prophylaxis is effective in reducing mortality and its effects on the rate of NIs is currently unclear.

Research question   Can antibiotic prophylaxis decrease 30-day mortality for patients on ECMO? Can antibiotic prophylaxis prevent the occurrence of NIs in these patients?

Study design and methods   A systematic review and meta-analysis was conducted. We searched PubMed, Scopus, and CINAHL libraries from inception to June 12, 2024. Two researchers were involved in abstract screening and three researchers were involved in full text selection.

Results   A pooled population of 7,996 patients is represented by 5 retrospective studies. Reported mortality ranges between 46 and 58% and the NIs rate is between 14 and 62%. Regarding 30-day mortality, the random-effects model ($I^2 = 65\%$) indicates a non-statistically significant difference between the antibiotic prophylaxis group and the non-prophylaxis group (OR 0.76; 95%CI 0.37–1.59). For the NIs rate, a fixed-effect model ($I^2 = 36\%$) shows an OR of 0.81 (95%CI 0.71–0.92) in favor of the antibiotic prophylaxis group, with a number-needed-to-treat (NNT) of 39.7 patients.

Conclusion   According to a very low degree of certainty, antibiotic prophylaxis appears to have no impact on the 30-day mortality rate of ECMO recipients. The risk of NIs seems to decrease with antibiotic prophylaxis, even though the NNT is high. Prospective high-quality studies that address these specific clinical questions are necessary.

Clinical trial registration   PROSPERO: International prospective register of systematic reviews, 2024, CRD42024567037.

Keywords   ECMO, Antibiotic prophylaxis, Nosocomial infection, Meta-analysis, Mortality

*Correspondence:
Daniele Orso
sd7782.do@gmail.com
Full list of author information is available at the end of the article

Orso *et al. BMC Anesthesiology*   (2024) 24:410

Page 2 of 13

Introduction

In recent years, Extracorporeal Membrane Oxygenation (ECMO) has become more popular. The management of both adults and pediatric patients with acute respiratory or cardiac failure in the Intensive Care Unit (ICU) can be improved by using ECMO technique.

ECMO patients are known to be particularly vulnerable to infections. According to the available evidence, approximately 42% of ECMO recipients experience sepsis after cannulation [1]. Patients who received ECMO had a 26% chance of developing nosocomial infections (NIs), according to a recent meta-analysis that included 30 retrospective studies [2]. The prevalence of NIs ranged from 1 to 93% [2]. An infection acquired during ECMO treatment led to a significant increase in mortality rate, with an odds ratio of 1.91 (95% confidence interval of 1.75–2.08) [3].

Although sepsis occurs frequently, there is still a lack of consensus on whether antibiotic prophylaxis can decrease mortality or NIs incidence in these patients [4]. The Extracorporeal Life Support Organization (ELSO) advises against antibiotic prophylaxis for patients undergoing ECMO [5]. Despite this, many ECMO centers frequently use antibiotic prophylaxis using an empirical approach [6]. Antibiotic prophylaxis is prescribed in 74% of cases, as reported in a recent survey [6].

A systematic review was carried out to investigate the impact of antibiotic prophylaxis on 30-day mortality in ECMO patients. The second objective was to assess whether antibiotic prophylaxis has a negative impact on the rate of NIs in patients receiving ECMO treatment.

Study design and methods

A systematic review and meta-analysis of the literature was performed. The protocol of this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO: International prospective register of systematic reviews, 2024, CRD42024567037), and we reported this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [7]. This study has been exempted from approval by the local Institutional Review Board because of the review of data collected from previously approved studies and the unidentifiable subject matter.

Eligibility criteria, search strategy and data collection

We considered any study that investigated the comparison between the administration of an antibiotic prophylaxis and no antibiotic preventive administration. To date, there is no agreement in the literature on a specific definition of antibiotic prophylaxis for ECMO patients. We included all studies that were specifically designed to investigate antibiotic prophylaxis as reported by the study authors.

Our research included randomized controlled trials (RCTs), observational prospective/retrospective studies, retrospective studies with propensity score matching and interventional studies.

The exclusion of editorials, comments, letters to the editor, conference papers, case reports, clinical guidelines, or literature reviews with or without meta-analysis was made.

Studies involving non-adult participants (i.e., < 18 years old), pregnant patients, animal subjects, and those that did not report outcome data were also excluded.

Searches were conducted using the electronic biomedical databases PubMed, Scopus, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) from database inception to June 12, 2024. To ensure a comprehensive synthesis of the available literature, existing meta-analyses on the same topic were retrieved and analyzed during the screening phase to select relevant studies for inclusion.

One researcher (DO) created search strings for each database. Search strings were peer-reviewed prior to the execution [8] by an experienced researcher (FF) following the Peer Review of Electronic Search Strategies (PRESS) guidelines checklist [9]. Search results were imported into the Covidence platform by Veritas Health Innovation Ltd. The keywords searched for were "antibiotic prophylaxis", "antibiotic prevention", "chemoprophylaxis" and "ECMO" (in its various extensions and types). Details of search strings are given in the Supplementary Material (Table 1S in the Supplementary Material).

Two phases were involved in the selection process: title/abstract screening and full-text screening. After removing duplicate results, two researchers (DO and FF) performed the screening independently and blindly. By rediscussing conflicting cases, a consensus was reached regarding article eligibility, and the final decision was made after discussion until a third researcher (IC) was involved.

The following data were extracted: name of the author(s), year, study design, sample size(s), number of deaths in the intervention group and in the control group, nosocomial infections events in the intervention group and in the control group, type of ECMO (e.g., Venoarterial vs. Venovenous ECMO); type of cannulation (e.g., upper limbs vs. lower limbs); antibiotic administered. An electronic data extraction form was implemented using the Covidence platform and piloted with at least three of the selected articles to ensure its usefulness, appropriateness, and feasibility [8, 10]. The data was extracted cooperatively by two data extractors (DO and FF) who were previously trained and had the appropriate topic knowledge. Rediscussing conflicting cases resulted in a

consensus for data extraction, and the final decision was made after that consensus was established.

Risk of bias assessment

Two authors (DO and FF) independently assessed the risk of bias. Robins-I (Risk Of Bias In Non-randomized Studies - of Interventions) was utilized [11]. In the event of contradictory judgments, the authors discussed until they came to a consensus to resolve any disagreements.

Assessing the quality of evidence

Two reviewers (DO and FF) independently and in duplicate applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [12] to assess the quality of evidence for each outcome. We used the GRADEpro software (GRADEpro GDT; GRADEpro Guideline Development Tool [Software], McMaster University; 2020) to create the evidence profile.

Statistical analysis

In the execution of the meta-analysis, a binary outcome (number of events for each of the two groups) was identified. Fixed-effect and random-effect analyses were conducted. In the first model, the odds ratio (OR) was determined by the Mantel-Haenszel method. In the second model, the inverse-variance method was used. The I^2 statistic was used to assess between-study inconsistency. The forest plots were employed to present the meta-analysis findings.

Our research focused on the 'outliers' to identify the potential causes of heterogeneity in studies. We conducted an Influence Analysis to determine the most influential cases that contribute to the heterogeneity between studies. We performed various sub-analyses based on the characteristics of the groups. To identify possible causes of heterogeneity among studies, a meta-regression (mixed-effect model) was conducted using the main features of the included studies. A Funnel Plot was used to evaluate publication bias.

Finally, we used a multivariate regression approach using structural equation modeling (SEM) to test the interaction between outcomes. The model was created by converting the effect size from OR to Hedges' g and analyzing variance and covariance between the two outcome data sets.

The analysis was carried out with R version 4.3.2 and the packages meta, dmetar, tidyverse, metafor, ggplot2, gridExtra, robvis, esc, and metaSEM.

Results
Study selection

The initial identification process yielded 81 records. After removing non-relevant and duplicate records, we examined 28 studies through full text analysis (Fig. 1). The systematic review and quantitative synthesis [13–17] included 5 studies, accounting for a pooled population of 7,996 patients. The excluded studies were either not observational or did not include 30-day mortality or incidence of NI among the outcomes considered.

Characteristics of the studies included

The main characteristics of the studies included are reported in Table 1. The studies were published between 2016 and 2023. Four studies are retrospective, but two used a Propensity Score Matching technique to reduce the imbalance between the characteristics of the two groups [13, 14]. A quasi-experimental trial is performed in a single study [15].

The study by Kondo et al. [14] has a larger sample size (about 9,600 patients), followed by Tagami et al. (about 2,800 patients) [13]. The remaining three studies enrolled fewer than 500 patients globally (e.g., 484 patients). Only two studies provided information on the type of patients enrolled. Tagami et al. enrolled patients treated with VA-ECMO following an out-of-hospital cardiac arrest (OHCA) [13], while Uçar et al. included patients treated with VV-ECMO for treatment of acute respiratory distress syndrome (ARDS) [16].

The mortality rate reported in the studies is between 45% in Shah et al. [15] to 58% in Kondo et al. [14]. The NIs rate ranges from 14% in Kondo et al. [14] to 62% in Uçar et al. [16].

Regarding the type of ECMO, two studies considered both Venoarterial (VA) and Venovenous (VV)-ECMO [15, 17]. One study only considered VV-ECMO [15]. In the remaining two studies the type of ECMO is not specified.

The cannulation site is not specified for most studies. In two studies, the site of cannulation is mentioned, either with the lower limbs [16], or both the lower and upper limbs [15].

Most studies do not provide information on the antibiotic class used in prophylaxis or specify the antibiotic choice (and combination). Kondo et al. reports that they used a first or third generation of cephalosporins and glycopeptide [14]. The combination of cephazolin and glycopeptide is reported by Shah et al. [15].

The duration of prophylaxis is not reported in the studies.

The use of anti-fungal agents in prophylaxis is only reported in Shah et al. [15]. Two other studies [14, 17] did not use anti-fungal prophylaxis.

Risk of bias (RoB)

The selection of patients is a potential cause of bias (Fig. 2). In retrospective studies, selection bias is more likely to occur. Propensity score matching and

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

Fig. 1 PRISMA flowchart. Eighty-one records were found during the initial identification process. Five studies were finally included and analyzed in the systematic review and quantitative synthesis, accounting for a pooled population of 7,996 patients

quasi-experimental design are used in three studies [13–15] to reduce potential bias in selection.

Misconception may have resulted from the definition of intervention, particularly antibiotic prophylaxis. Despite the unique definition given by Kondo et al., most studies vary in their selection of antibiotics and timeframe [14]. Shah et al. examined three different antibiotic protocols in their study, which made it challenging to compare them [15]. Two studies are at a critical risk of bias because they did not use a clear definition, deeming any antibiotic given within the first 48 h of cannulation as 'antibiotic prophylaxis' [13, 16].

The study by Uçar et al. is deemed to have a potential bias in selecting the outcome due to multiple sub-analyses [16]. Due to the retrospective nature of the studies and small sample sizes, casual results are more likely to occur.

Quantitative synthesis for 30-day mortality
The fixed-effect model shows an OR of 0.87 (95% confidence interval 0.79–0.95) for the antibiotic prophylaxis group when compared to the non-prophylaxis group (Fig. 3). Since the between-studies inconsistency is significant ($I^2 = 65\%$), we only considered the random-effects model, which exhibited an OR of 0.76 (95%CI 0.37–1.59). Due to the confidence interval passing through the unit

(Fig. 3), the result is not statistically significant. The differences in 30-day mortality between two groups of patients are not significant, even in studies using a Propensity Score Matching (OR 0.67; 95%CI 0.01–38.66) or quasi-experimental design (OR 1.21; 95%CI 0.78–1.88).

The study by Tagami et al. is particularly different from the other studies in terms of mortality rate [13]. Excluding this study, the corresponding OR is 0.88 (fixed-effect model; 95%CI 0.80–0.96; $I^2 = 35.1\%$).

Neither the type of ECMO nor the type of cannulation seems to determine a different outcome (Figs. 1S and 2S in the Supplementary Material). Mortality rates are reported in either VA-ECMO or both VA- and VV-ECMO studies, but no studies have exclusively reported mortality data for VV-ECMO (Fig. 1S in the Supplementary Material).

In addition, most studies do not furnish any information about the site of cannulation (Fig. 2S in the Supplementary Material). The cannulation of both the upper and lower limbs was reported by Shah et al. [15]. No data is available for separate cannulation of the upper and lower limbs.

The 30-day mortality is not reduced by prophylactic administration of an antifungal agent (1.21 vs. 0.87) (Fig. 3S in the Supplementary Material). The only study [15] that employed prophylaxis with an anti-fungal agent

Table 1 Characteristics of the studies included in the systematic review. PSM: propensity score matching; NS: not specified; HAP: hospital-acquired pneumonia; AKI: acute kidney Injury; MRSA: Methicillin-Resistant Staphylococcus aureus; PM: pacemaker; ICD: Implantable cardioverter-defibrillator; ICU-LOS: ICU length of stay; VV: Venovenous; LL: lower limbs; C. Diff: Clostridioides difficile

Study	Design	Sample size	Timeframe	Type of ECMO	Cannulation	Antibiotic protocol	Outcome	Mortality rate	Nosocomial Infections rate
Tagami et al. 2016 [13]	Retrospective with PSM	2,803	2007–2013	NS	NS	All antibiotics administered within 2 days after cannulation	Primary: 30-day mortality Secondary: incidence of HAP	53%	NS
Kondo et al. 2021 [14]	Retrospective with PSM	9,615	2010–2017	NS	NS	1st or 3rd generation cephalosporins (cefazoline, cefalotin, and cefsulodin) and glycopeptides (vancomycin or teicoplanin)	Primary: 30-day mortality; incidence of HAP Secondary: incidence of AKI, diarrhoea.	58%	14%
Shah et al. 2021 [15]	Quasi-experimental interrupted time series analysis	338	2011–2014 (no protocol) 2014–2017 (first protocol) 2018–2019 (second protocol)	Mixed	Mixed	Cefazoline/vancomycin (if colonized by MRSA) + fluconazole or vancomycin + cefepime + fluconazole if implantation PM, ICD, prosthetic valves (first protocol) Cefazoline/vancomycin (if colonized by MRSA) + fluconazole (second protocol)	Primary: 30-day mortality Secondary: ICU LOS, duration of mechanical ventilation and nosocomial infections rate	45%	17%
Uçar et al. 2023 [16]	Retrospective	50	2018–2021	VV	LL	NS	Primary: Nosocomial infections rate	NS	62%
Kishk et al. 2018 [17]	Retrospective	96	2009–2012	Mixed	NS	NS	Primary: Nosocomial infections rate Secondary: Multidrug resistent bacteria isolation, C. diff. isolation	46%	39%

has no significant effect on 30-day mortality (OR 1.21; 95%CI 0.78–1.88).

The Egger test does not detect any significant publication bias (*p*=0.595) (Fig. 4).

Quantitative synthesis for NIs rate
For the outcome of NIs rate, the fixed-effect model shows an OR of 0.81 (95%CI 0.71–0.92) in the antibiotic prophylaxis group compared to the non-prophylaxis group, with a number-needed-to-treat (NNT) of 39.7 patients. The between-studies inconsistency is low (I^2=36%), so we only considered the fixed-effect model (Fig. 5). No studies were found to be outliers. The only study that used a propensity score matching [14] shows a significant reduction in NIs rate (OR 0.82; 95%CI 0.72–0.94) while the study by Shah et al. (quasi-experimental design) is not statistically significant (OR 0.99; 95%IC 0.56–1.77).

In the study that included VV-ECMO patients, the antibiotic prophylaxis group is found to have a lower OR than the ones in the studies that included both VA and VV-ECMO (0.25 vs. 0.88) (Fig. 4S in the Supplementary Material). The OR for studies with only lower

limb cannulation is lower than for those with mixed cannulation (0.25 vs. 0.99) (Fig. 5S in the Supplementary Material).

The prophylactic administration of an antifungal agent does not result in a decrease in the incidence of NIs (0.99 vs. 0.81) as shown in Fig. 6S in the Supplementary Material. The only study [15] that employed prophylaxis with an anti-fungal agent has no significant effect on the incidence of NIs (OR 0.99; 95%CI 0.56–1.77).

There is no significant publication bias (*p*=0.397) according to Egger's test (Fig. 6).

Multivariate analysis
To verify the mutual influence between the outcomes considered (i.e., incidence of NIs and 30-day mortality), we performed a multivariate analysis using a SEM approach. The results are inconclusive because of the small sample size and wide confidence intervals (Fig. 7). The fixed-effect model shows an estimated effect of -0.07 (95%CI -0.12 − -0.02; *p*=0.005) for the 30-day mortality outcome; and -0.11 (95%CI -0.18 − -0.04; *p*=0.001) for the NIs rate. The random-effects model shows an estimated effect of 0.03 and -0.003 for the two outcomes,

Fig. 2 Risk of bias in the included studies. For observational studies, the Robins-I was used to assess the risk of bias. The main source of risk of bias was in the definition of intervention (i.e. antibiotic prophylaxis). The two studies considered at risk of critical bias did not use an unambiguous definition, considering any antibiotic administered within the first 48 h of cannulation as an 'antibiotic prophylaxis'

Fig. 3 Forest plots for 30-day mortality. The random effects model exhibited an OR of 0.76 (95%CI 0.37–1.59). Since the confidence interval crosses the unit, the difference was not statistically significant. We considered only the random-effect model since the high between-study inconsistency found (65%)

Fig. 4 Funnel plot for 30-day mortality. Egger's test was not statistically significant (*p* = 0.595)

Fig. 5 Forest plots for nosocomial infections rate. The fixed-effect model showed an OR of 0.81 (95%CI 0.71–0.92) in antibiotic prophylaxis group compared to no prophylaxis group, with a number-need-to-treat (NNT) of 39.7 patients. The between-studies inconsistency was low (I^2 = 36%), so we only considered the fixed-effect model

respectively, but this model is not statistically significant (with a significant amount of heterogeneity: I^2 = 87% for the first outcome and 82% for the second outcome).

Assessment of the quality of evidence

The quality of evidence for both outcomes is very low, highlighting the risks of bias, inconsistency, and possible confounding factors. The assessment is resumed in Table 2. The wide heterogeneity, inconsistency between studies and confounding factors linked to the retrospective nature of the studies make the conclusions reached very uncertain. Furthermore, the RoB score suggests that the selection of patients is the main cause of the low quality of evidence obtained.

Discussion

This systematic review is the first to use rigorous selection criteria for the studies it encompasses. Our review suggests that antibiotic prophylaxis has no significant effect on reducing 30-day mortality. Antibiotic

Fig. 6 Funnel plot for nosocomial infections rate. Egger's test was not statistically significant ($p=0.397$)

Fig. 7 Multivariate meta-analysis model (SEM). Due to the small sample size, the results were inconclusive due to the wide confidence intervals. The fixed-effect model showed an estimated effect of -0.07 (95%CI -0.12 – -0.02; $p=0.005$) for the 30-day mortality outcome; and -0.11 (95%CI -0.18 – -0.04; $p=0.001$) for the nosocomial infections rate. The random-effects model showed an estimated effect of 0.03 and -0.003 for the two outcomes, respectively, but this model was non statistically significant (with a significant amount of heterogeneity: $I^2=87\%$ for the first outcome and 82% for the second outcome)

prophylaxis seems to reduce the incidence of NIs, with a NNT of around 40 patients. Due to the high NNT found, the clinical application of antibiotic prophylaxis to decrease the incidence of NIs remains uncertain. The results may be biased due to the retrospective nature

of the studies included. The poor quality of the studies included is affecting both conclusions.

Lee et al. found that the predictive factors of 30-day mortality are both the development of renal failure, hypotension, and failure to wean from ECMO [18]. According to the literature, cardiac and renal function

Table 2 A summary of the GRADE evaluation for assessing the quality of evidence

Antibiotic prophylaxis for ECMO treatment

Patient or population: patients with ECMO treatment
Settings: Intensive care unit
Intervention: Antibiotic prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Antibiotic prophylaxis				
30-day Mortality	**593 per 1000**	**525 per 1000** (350 to 698)	**OR 0.76** (0.37 to 1.59)	7946 (4 studies)	⊕⊖⊖⊖ **very low**	
Nosocomial Infections rate	**159 per 1000**	**133 per 1000** (119 to 148)	**OR 0.81** (0.71 to 0.92)	7783 (4 studies)	⊕⊖⊖⊖ **very low**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

are the most significant predictors of 30-day mortality in VA-ECMO [19–21]. The outcomes of patients undergoing ECMO for ARDS are influenced by several factors, potentially intertwining with a synergistic effect, and are not easily discernible [22]. Sepsis is a common occurrence in these patients, but its impact on the outcome is uncertain. Although NIs have an impact on survival, with increases reported in the risk of death up to 63% in infected patients, an antibiotic prophylactic strategy does not appear to significantly alter the prognosis of these patients [3, 23]. Our meta-analysis suggests that the outcome is not significantly affected by the use or absence of antibiotic prophylaxis. The study by Tagami et al. [13], which focused on OHCA patients, showed a significant decrease in 30-day mortality. It is uncertain whether this outcome is due to the patient population or the study design. More research is recommended to focus on specific populations that are undergoing ECMO.

Due to the scarce data regarding the different mortality and impact of antibiotic prophylaxis depending on the type of ECMO (i.e., VA-ECMO vs. VV-ECMO), conclusions in this respect can only be provisional. The influence of the cannulation site on mortality in the presence of antibiotic prophylaxis is still unknown based on available data.

NIs in this population are mostly ventilation-related pneumonia and bloodstream infections. In both cases, the most implicated microorganisms are Pseudomonadaceae, Enterococcus species, and Candida species [23, 24]. Gram-positive bacteremia has been reported to occur with isolates of Enterococcus species and Staphylococcus species in other studies [25]. Given this epidemiology, it is probable that the use of third and fourth-generation cephalosporins has a positive impact on reducing the incidence of NIs in this population [26]. But the effectiveness of such prophylactic choices is strongly correlated with the implicated microorganism. The effect observed in the group of patients receiving prophylaxis with the addition of a glycopeptide is something that should be taken into consideration. Glycopeptide usage could be burdened by several high-impact adverse events, such as hypotension and pancytopenia [27].

The incidence of NIs in patients with ECMO has been observed to partially be influenced by the clinical severity and duration of treatment, as well as by the antibiotic therapy itself [28]. The probability of bloodstream infection increases after 7 to 10 days after cannulation [29]. Extending antibiotic prophylaxis or starting early or preventive empirical therapy for cases of ECMO support beyond this period is still a matter of uncertainty. Information on the duration of antibiotic prophylaxis was not provided in the studies included, and the literature does not adequately address this clinical variable. According to the available data, the duration of ECMO treatment directly affects the incidence of nosocomial infections [16]. However, they show that antibiotic prophylaxis is associated with an increase in the duration of ECMO treatment [15].

The risk of infection seems to be higher for patients who receive VA-ECMO than those who receive VV-ECMO. During VA-ECMO initiation, the immune response was demonstrated to be characterized by immunosuppressive cytokines that were linked to an increased risk of infection in critical illness [30]. According to literature data, VA-ECMO and VV-ECMO have distinct differences not only in susceptibility to infections, but also in the bacteria involved and onset time [31]. The absence of information about the various types of ECMO, along with 30-day mortality, prevents us from determining if certain subpopulations can benefit from antibiotic prophylaxis to prevent NIs. In addition, the site of cannulation may be affected differently from antibiotic prophylaxis in terms of the risk of NIs. Unfortunately, the studies included lack sufficient data to draw conclusions

on this point. The goal of future research is to determine if antibiotic prophylaxis is more effective for various types of ECMO and cannulation, which could result in more precise patient selection.

Antifungal agents seem to have no effect on the effectiveness of prophylaxis. In a single study, anti-fungal prophylaxis was utilized, but there was no statistically significant improvement in 30-day mortality or NIs observed [15]. The guidelines currently suggest the use of anti-fungal prophylaxis in individuals with hematopoietic malignancies or neutropenia [32]. Patients may be exposed to drug interactions and may experience a synergistic effect on prolonging the QT interval on ECG when using triazole agents [32]. Moreover, antifungal agents, especially fluconazole, exhibit comparable pharmacokinetic properties to glycopeptides. A decrease in serum concentrations can be caused by a drug seizure caused by circuit and membrane [33, 34].

The cost-effectiveness ratio of a prophylactic antibiotic strategy is unclear, particularly when considering the possibility of early diagnosis through Polymerase Chain Reaction techniques and the use of biomarkers [35, 36]. According to epidemiology and the prevalence of bacteria, on-demand treatment could appear to be the most efficient approach [5]. The potential risks of antibiotic resistance, drug interactions, intestinal microbiota depletion, and Clostridioides difficile (C. difficile) colitis can lead to the burden of routine antibiotic prophylaxis [37]. The emergence of antibiotic resistance is due to the use of antibiotics that are overused or inappropriate, along with the incorrect duration or dosage of therapy. The rate of drug-resistant bacteria infecting patients is steadily rising: 131 infections per 100,000 patients, and 63% are attributed to health-care facilities (hospitals and other health-care settings). Drug-resistant bacteria infections have a significant risk of death of 6.44 per 100,000 patients [38]. The costs and duration of hospitalizations have increased due to the emergence of multi-resistant bacterial infections [38]. Kishk et al. found no difference in the incidence of multidrug-resistant bacterial infections between the group treated with antibiotic prophylaxis and the group not treated with antibiotic prophylaxis [17]. The small sample size of this monocentric study makes it challenging to obtain definitive conclusions.

An increase in intestinal bacterial translocation may be caused by low blood perfusion through a non-occlusive intestinal ischemia mechanism [39], but C. difficile infection has been linked to damage to the intestinal epithelium and an increased incidence of bacterial translocation [40]. It is well-known that the primary cause of C. difficile infections is the use of systemic antibiotic therapy [41]. What impact antibiotic prophylaxis in ECMO recipients can have on this scenario, especially considering the need for infection prevention strategies in this particularly susceptible population, is therefore an open field of research. Among the studies included in this systematic review, Kondo et al. found no significant difference in the incidence of diarrhea between the antibiotic prophylaxis group and the non-prophylaxis group [14]. More specifically, Kishk et al. did not find an increase in the incidence of C. difficile infections in the group treated with antibiotic prophylaxis [17]. Due to the small sample size and number of cases, further investigation is needed to draw conclusions in this case as well.

By using ECMO, serum levels of drugs, particularly antibiotics, can be reduced [42]. A mechanism dependent on serum concentration plays a role in the effectiveness of vancomycin or teicoplanin. Some authors suggest a therapeutic drug monitoring approach to reduce side effects and increase effectiveness [43, 44]. Failure to achieve minimum dosing can result in clinical ineffectiveness, and overdosing can increase the risk of renal failure and mortality [45, 46]. However, the study by Kondo et al. did not find a higher incidence of acute kidney injury (AKI) in patients who received antibiotic prophylaxis than in the control group [14]. Neither Tagami et al. nor Kondo et al. demonstrated a higher requirement for continuous renal replacement therapy (CRRT) in the antibiotic-treated group of patients [13, 14].

Multiple treatments that involve extra-corporal circuits are common for critically ill patients admitted to the ICU. In these circumstances, it is a challenge to determine the influence of ECMO on both pharmacokinetic interactions and effects. The concomitant use of CRRT and ECMO has been reported to increase the clearance of several antibiotics (e.g. cefepime, meropenem, piperacillin-tazobactam) and antifungals [47–51]. The interaction between various devices should always be considered.

Specific clinical guidelines are necessary for extracorporeal life support patients in an era of growing interest in antimicrobial stewardship due to their specific characteristics [52]. Further research is needed to determine the indication for prophylaxis, the most appropriate molecules for prophylaxis, and the epidemiological context. Moreover, it is crucial to compare these variables to collateral damage that may result from adverse events. There are currently no randomized controlled trials (RCTs) in the literature that have addressed the topic of this systematic review. Due to the retrospective nature of the studies included, the conclusions of this review are only provisional and not completely reliable.

In summary, to determine whether antibiotic prophylaxis is useful in reducing the mortality of the patients treated with ECMO or the incidence of NIs, further controlled studies as RCTs are needed to answer several clinical questions raised in this review.

Limitations

The impact of antibiotic prophylaxis on the outcome of ECMO patients is extremely challenging to determine. The first methodological limitation lies in the absence of agreement on a specific definition of antibiotic prophylaxis for ECMO patients, leading to heterogeneity in clinical interventions between studies. The difficulty is further exacerbated due to the influence of different factors on the mortality of these extremely critically ill patients. All the studies that have evaluated the effects of antibiotic prophylaxis are notably different from each other in terms of the type of patients included, the type of antibiotic used, the duration of the prophylaxis, etc. Despite this inevitable and emerging heterogeneity, our systematic review and meta-analysis is an attempt to summarize all the available evidence to raise the attention of clinicians and researchers to this patient-centred topic, stimulating further research on the field. Some variables among those not reported in the studies or reported inconsistently, such as previous exposure to antibiotic therapy or the duration of ECMO treatment, could be relevant to determine a significant impact on mortality or incidence of NIs. The reliability of our results can be biased due to the lack of data.

Furthermore, the Kondo et al. study enrolled a significantly larger number of participants than the other studies. This study may have had an adverse impact on the outcome.

Despite using methods to correct potential imbalances in patient characteristics in at least three of five studies, they are all retrospective studies, which could be affected by selection bias or other confounding bias. Due to this reason, the evidence supporting our review's conclusions is very limited and provisional.

Conclusions

According to a very low degree of certainty, antibiotic prophylaxis appears to have no impact on the 30-day mortality rate of ECMO recipients. While antibiotic prophylaxis appears to decrease the risk of NIs, the NNT is high (40 patients treated to prevent one nosocomial infection). Due to the absence of prospective controlled studies, these conclusions are circumstantial and provisional. Conducting high-quality prospective studies that are specifically focused on antibiotic choice, prophylactic duration, and clinical predictors of infection, as well as other unanswered clinical questions, is necessary. RCTs are currently justified and necessary. Presently, due to the lack of strong evidence, following the guidelines is the most appropriate approach.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02796-z.

Supplementary Material 1

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Emergency, University Hospital of Udine, Azienda Sanitaria Universitaria Friuli Centrale, "Santa Maria della Misericordia", Piazzale Santa Maria della Misericordia 15, Udine 33100, Italy
[2]Department of Cardio-Thoraco-Vascular Sciences and Public Health, University Hospital of Padua, Via Giustiniani, 2, Padua 35128, Italy
[3]Department of Infectious Diseases, Community Hospital of Pordenone, Azienda Sanitaria Friuli Occidentale, "Santa Maria degli Angeli", Via Montereale 34, Pordenone 33170, Italy
[4]Department of Emergency Medicine, Community Hospital of San Daniele del Friuli "Ospedale Sant'Antonio", Azienda Sanitaria Friuli Centrale, Viale Trento Trieste 33, San Daniele del Friuli 33038, Italy
[5]Department of Medicine, University of Udine, Via Colugna 51, Udine 33100, Italy

References

1. Gopalakrishnan R, Vashisht R, Sepsis, Indian ECMO, Thorac Cardiovasc J. Surg. 2021;37(Suppl 2):267–74. https://doi.org/10.1007/s12055-020-00944-x. Epub 2020 May 14. PMID: 32421057; PMCID: PMC7223121.
2. Ait Hssain A, Vahedian-Azimi A, Ibrahim AS, Hassan IF, Azoulay E, Darmon M. Incidence, risk factors and outcomes of nosocomial infection in adult patients supported by extracorporeal membrane oxygenation: a systematic review and meta-analysis. Crit Care. 2024;28(1):158. https://doi.org/10.1186/s13054-024-04946-8. PMID: 38730424; PMCID: PMC11088079.
3. Bizzarro MJ, Conrad SA, Kaufman DA, Rycus P, Extracorporeal Life Support Organization Task Force on Infections, Extracorporeal Membrane Oxygenation. Infections acquired during extracorporeal membrane oxygenation in neonates, children, and adults. Pediatr Crit Care Med. 2011;12(3):277–81. https://doi.org/10.1097/PCC.0b013e3181e28894. PMID: 20495508.
4. O'Horo JC, Cawcutt KA, De Moraes AG, Sampathkumar P, Schears GJ. The Evidence Base for Prophylactic Antibiotics in Patients Receiving Extracorporeal Membrane Oxygenation. ASAIO J. 2016 Jan-Feb;62(1):6–10. https://doi.org/10.1097/MAT.0000000000000287. PMID: 26461238.
5. ELSO Guidelines | Extracorporeal Membrane Oxygenation (ECMO) (accessed 5th. July 2024).

6.   Kao LS, Fleming GM, Escamilla RJ, Lew DF, Lally KP. Antimicrobial prophylaxis and infection surveillance in extracorporeal membrane oxygenation patients: a multi-institutional survey of practice patterns. ASAIO J. 2011 May-Jun;57(3):231-8. https://doi.org/10.1097/MAT.0b013e31820d19ab. PMID: 21317768.

7.   Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.

8.   Franco JVA, Garrote V, Vietto V, Escobar Liquitay CM, Solà I. Search strategies (filters) to identify systematic reviews in MEDLINE and Embase. Cochrane Database Syst Rev. 2020;2020(7):MR000054. https://doi.org/10.1002/1465185 8.MR000054. PMCID: PMC7389254.

9.   McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016;75:40 – 6. https://doi.org/10.1016/j.jclinepi.2016.01.021. Epub 2016 Mar 19. PMID: 27005575.

10. Büchter RB, Weise A, Pieper D. Development, testing and use of data extraction forms in systematic reviews: a review of methodological guidance. BMC Med Res Methodol. 2020;20(1):259. https://doi.org/10.1186/s12874-020-0114 3-3. PMID: 33076832; PMCID: PMC7574308.

11. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10. 1136/bmj.i4919. PMID: 27733354; PMCID: PMC5062054.

12. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6. https://doi.org/10.1136/bmj.39489.470347.AD. PMID: 18436948; PMCID: PMC2335261.

13. Tagami T, Matsui H, Kuno M, Moroe Y, Kaneko J, Unemoto K, Fushimi K, Yasunaga H. Early antibiotics administration during targeted temperature management after out-of-hospital cardiac arrest: a nationwide database study. BMC Anesthesiol. 2016;16(1):89. https://doi.org/10.1186/s12871-016-0 257-3. PMID: 27717334; PMCID: PMC5055699.

14. Kondo Y, Ohbe H, Aso S, Matsui H, Fushimi K, Tanaka H, Yasunaga H. Efficacy of Prophylactic Antibiotics during Extracorporeal Membrane Oxygenation: A Nationwide Cohort Study. Ann Am Thorac Soc. 2021;18(11):1861–1867. https://doi.org/10.1513/AnnalsATS.202008-974OC. PMID: 33765406.

15. Shah A, Sampathkumar P, Stevens RW, Bohman JK, Lahr BD, Dhungana P, Vashistha K, O'Horo JC. Reducing Broad-Spectrum Antimicrobial Use in Extracorporeal Membrane Oxygenation: Reduce AMMO Study. Clin Infect Dis. 2021;73(4):e988-e996. https://doi.org/10.1093/cid/ciab118. PMID: 33575744.

16. Uçar H, Yıldırım S, Köse Ş, Kirakli C. Incidence of nosocomial infection and causative microorganism during extracorporeal membrane oxygenation in adult patients, a single center study. Perfusion 2023 Aug 7:2676591231194931. https://doi.org/10.1177/02676591231194931. Epub ahead of print. PMID: 37550246.

17. Kishk OA, Stafford KA, Pajoumand M, Williams C, Thom KA, Kon ZN, Herr DL, Amoroso A. Prophylactic antibiotics for extracorporeal membrane oxygenation in critically ill adults. Int J Acad Med. 2017;3:256–62.

18. Lee Y, Jang I, Hong J, Son YJ. Factors associated with 30-day in-hospital mortality in critically ill adult patients receiving extracorporeal membrane oxygenation: a retrospective cohort study. Intensive Crit Care Nurs. 2023;79:103489. https://doi.org/10.1016/j.iccn.2023.103489. Epub 2023 Jul 12. PMID: 37451086.

19. Sohail S, Fan E, Foroutan F, Ross HJ, Billia F, Alba AC. Predictors of Mortality in Patients Treated with Veno-Arterial ECMO for Cardiogenic Shock Complicating Acute Myocardial Infarction: a Systematic Review and Meta-Analysis. J Cardiovasc Transl Res. 2022;15(2):227–238. https://doi.org/10.1007/s12265-02 1-10140-w. Epub 2021 Jun 3. PMID: 34081255.

20. Hashem A, Mohamed MS, Alabdullah K, Elkhapery A, Khalouf A, Saadi S, Nayfeh T, Rai D, Alali O, Kinzelman-Vesely EA, Parikh V, Feitell SC. Predictors of mortality in patients with refractory cardiac arrest supported with VA-ECMO: a systematic review and a Meta-analysis. Curr Probl Cardiol.

2023;48(6):101658. https://doi.org/10.1016/j.cpcardiol.2023.101658. Epub 2023 Feb 23. PMID: 36828046.

21. D'Arrigo S, Cacciola S, Dennis M, Jung C, Kagawa E, Antonelli M, Sandroni C. Predictors of favourable outcome after in-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. Resuscitation. 2017;121:62–70. https://doi.org/10.1016/j.resuscitation .2017.10.005. Epub 2017 Oct 8. PMID: 29020604.

22. Friedrichson B, Mutlak H, Zacharowski K, Piekarski F. Insight into ECMO, mortality and ARDS: a nationwide analysis of 45,647 ECMO runs. Crit Care. 2021;25(1):38. https://doi.org/10.1186/s13054-021-03463-2. PMID: 33509228; PMCID: PMC7841040.

23. Biffi S, Bella SD, Scaravilli V, et al. Infections during extracorporeal membrane oxygenation: epidemiology, risk factors, pathogenesis and prevention. Int J Antimicrob Ag. 2017;50:9–16.

24. Schmidt M, Bréchot N, Hariri S, et al. Nosocomial infections in adult cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. Clin Infect Dis. 2012;55:1633–41.

25. Grasselli G, Scaravilli V, Di Bella S, Biffi S, Bombino M, Patroniti N, Bisi L, Peri AM, Pesenti A, Gori A, Alagna L. Nosocomial Infections During Extracorporeal Membrane Oxygenation: Incidence, Etiology, and Impact on Patients' Outcome. Crit Care Med. 2017;45(10):1726–1733. https://doi.org/10.1097/CC M.0000000000002652. PMID: 28777198.

26. Lador A, Nasir H, Mansur N, Sharoni E, Biderman P, Leibovici L, Paul M. Antibiotic prophylaxis in cardiac surgery: systematic review and meta-analysis. J Antimicrob Chemother. 2012;67(3):541–50. https://doi.org/10.1093/jac/dkr47 0. Epub 2011 Nov 13. PMID: 22083832.

27. Huang V, Clayton NA, Welker KH. Glycopeptide hypersensitivity and adverse reactions. Pharm (Basel). 2020;8(2):70. https://doi.org/10.3390/pharmacy8020 070. PMID: 32326261; PMCID: PMC7357119.

28. Li X, Wang L, Wang H, Hou X. Outcome and clinical characteristics of nosocomial infection in adult patients undergoing extracorporeal membrane oxygenation: a systematic review and Meta-analysis. Front Public Health. 2022;10:857873. https://doi.org/10.3389/fpubh.2022.857873. PMID: 35812481; PMCID: PMC9268548.

29. Menaker J, Galvagno S, Rabinowitz R, Penchev V, Hollis A, Kon Z, Deatrick K, Amoroso A, Herr D, Mazzeffi M. Epidemiology of blood stream infection in adult extracorporeal membrane oxygenation patients: a cohort study. Heart Lung. 2019 May-Jun;48(3):236–9. Epub 2019 Jan 24. PMID: 30686618.

30. Frerou A, Lesouhaitier M, Gregoire M, Uhel F, Gacouin A, Reizine F, Moreau C, Loirat A, Maamar A, Nesseler N, Anselmi A, Flecher E, Verhoye JP, Le Tulzo Y, Cogné M, Roussel M, Tarte K, Tadié JM. Venoarterial extracorporeal membrane oxygenation induces early immune alterations. Crit Care. 2021;25(1):9. https:/ /doi.org/10.1186/s13054-020-03444-x. PMID: 33407728; PMCID: PMC7788860.

31. Kim HS, Park S, Ko HH, Ha SO, Lee SH, Kim YK. Different characteristics of bloodstream infection during venoarterial and venovenous extracorporeal membrane oxygenation in adult patients. Sci Rep. 2021;11(1):9498. https://do i.org/10.1038/s41598-021-89108-4. PMID: 33947970; PMCID: PMC8097062.

32. Vazquez L. Antifungal prophylaxis in Immunocompromised patients. Mediterr J Hematol Infect Dis. 2016;8(1):e2016040. https://doi.org/10.4084/MJHID. 2016.040. PMID: 27648203; PMCID: PMC5016014.

33. Jendoubi A, Pressiat C, De Roux Q, Hulin A, Ghaleh B, Tissier R, Kohlhauer M, Mongardon N. The impact of extracorporeal membrane oxygenation on antifungal pharmacokinetics: a systematic review. Int J Antimicrob Agents. 2024;63(2):107078. https://doi.org/10.1016/j.ijantimicag.2023.107078. Epub 2023 Dec 30. PMID: 38161046.

34. Shekar K, Roberts JA, Mcdonald CI, Ghassabian S, Anstey C, Wallis SC, Mullany DV, Fung YL, Fraser JF. Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care. 2015;19(1):164. https://doi.org/10.1186/s13054-015-0891-z. PMID: 25888449; PMCID: PMC4407324.

35. Rodríguez A, Gómez F, Sarvisé C, Gutiérrez C, Giralt MG, Guerrero-Torres MD, Pardo-Granell S, Picó-Plana E, Benavent-Bofill C, Trefler S, Berrueta J, Canadell L, Claverias L, Esteve Pitarch E, Olona M, García Pardo G, Teixidó X, Bordonado L, Sans MT, Bodí M. Clinical and microbiological impact of implementing a decision support algorithm through Microbiologic Rapid Diagnosis in critically ill patients: an epidemiological retrospective Pre-/Post-Intervention study. Biomedicines. 2023;11(12):3330. https://doi.org/10.3390/biomedicines 11123330. PMID: 38137551; PMCID: PMC10741655.

36. Mearelli F, Fiotti N, Giansante C, Casarsa C, Orso D, De Helmersen M, Altamura N, Ruscio M, Castello LM, Colonetti E, Marino R, Barbati G, Bregnocchi A, Ronco C, Lupia E, Montrucchio G, Muiesan ML, Di Somma S, Avanzi GC, Biolo G. Derivation and Validation of a Biomarker-Based Clinical Algorithm to Rule

Out Sepsis From Noninfectious Systemic Inflammatory Response Syndrome at Emergency Department Admission: A Multicenter Prospective Study. Crit Care Med. 2018;46(9):1421–1429. https://doi.org/10.1097/CCM.0000000000003206. PMID: 29742588.

37. Peña-Lopez Y, Rello J. Antimicrobial stewardship challenges in extracorporeal membrane oxygenation. Clin Microbiol Infect. 2023;29(11):1356–7. https://doi.org/10.1016/j.cmi.2023.07.020. Epub 2023 Jul 27. PMID: 37516384.

38. Giacomini E, Perrone V, Alessandrini D, Paoli D, Nappi C, Degli Esposti L. Evidence of Antibiotic Resistance from Population-Based studies: a narrative review. Infect Drug Resist. 2021;14:849–58. PMID: 33688220; PMCID: PMC7937387.

39. Reintam Blaser A, Preiser JC, Fruhwald S, Wilmer A, Wernerman J, Benstoem C, Casaer MP, Starkopf J, van Zanten A, Rooyackers O, Jakob SM, Loudet CI, Bear DE, Elke G, Kott M, Lautenschläger I, Schäper J, Gunst J, Stoppe C, Nobile L, Fuhrmann V, Berger MM, Oudemans-van Straaten HM, Arabi YM, Deane AM. Working Group on gastrointestinal function within the section of metabolism, Endocrinology and Nutrition (MEN Section) of ESICM. Gastrointestinal dysfunction in the critically ill: a systematic scoping review and research agenda proposed by the Section of Metabolism, Endocrinology and Nutrition of the European Society of Intensive Care Medicine. Crit Care. 2020;24(1):224. https://doi.org/10.1186/s13054-020-02889-4. PMID: 32414423; PMCID: PMC7226709.

40. Oliva A, Aversano L, De Angelis M, Mascellino MT, Miele MC, Morelli S, Battaglia R, Iera J, Bruno G, Corazziari ES, Ciardi MR, Venditti M, Mastroianni CM, Vullo V. Persistent systemic Microbial translocation, inflammation, and intestinal damage during Clostridioides difficile infection. Open Forum Infect Dis. 2019;7(1):ofz507. https://doi.org/10.1093/ofid/ofz507. PMID: 31950071; PMCID: PMC6954488.

41. Gateau C, Couturier J, Coia J, Barbut F. How to: diagnose infection caused by Clostridium difficile. Clin Microbiol Infect. 2018;24(5):463–8. https://doi.org/10.1016/j.cmi.2017.12.005. Epub 2017 Dec 18. PMID: 29269092.

42. Kühn D, Metz C, Seiler F, Wehrfritz H, Roth S, Alqudrah M, Becker A, Bracht H, Wagenpfeil S, Hoffmann M, Bals R, Hübner U, Geisel J, Lepper PM, Becker SL. Antibiotic therapeutic drug monitoring in intensive care patients treated with different modalities of extracorporeal membrane oxygenation (ECMO) and renal replacement therapy: a prospective, observational single-center study. Crit Care. 2020;24(1):664. https://doi.org/10.1186/s13054-020-03397-1. PMID: 33239110; PMCID: PMC7689974.

43. Tsutsuura M, Moriyama H, Kojima N, Mizukami Y, Tashiro S, Osa S, Enoki Y, Taguchi K, Oda K, Fujii S, Takahashi Y, Hamada Y, Kimura T, Takesue Y, Matsumoto K. The monitoring of Vancomycin: a systematic review and meta-analyses of area under the concentration-time curve-guided dosing and trough-guided dosing. BMC Infect Dis. 2021;21(1):153. https://doi.org/10.1186/s12879-021-05858-6. PMID: 33549035; PMCID: PMC7866743.

44. Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, Anderson TL, Roberts SA, Warren SJ, Gao W, Howden BP, Johnson PD. Vancomycin AUC/MIC ratio and 30-day mortality in patients with Staphylococcus aureus bacteremia. Antimicrob Agents Chemother. 2013;57(4):1654–63. https://doi.org/10.1128/AAC.01485-12. Epub 2013 Jan 18. PMID: 23335735; PMCID: PMC3623342.

45. Kalil AC, Van Schooneveld TC, Fey PD, Rupp ME. Association between vancomycin minimum inhibitory concentration and mortality among patients with Staphylococcus aureus bloodstream infections: a systematic review and meta-analysis. JAMA. 2014;312(15):1552-64. https://doi.org/10.1001/jama.2014.6364. PMID: 25321910.

46. Ley EJ, Liou DZ, Singer MB, Mirocha J, Srour M, Bukur M, Margulies DR, Salim A. Supratherapeutic vancomycin levels after trauma predict acute kidney injury and mortality. J Surg Res. 2013;184(1):501-6. https://doi.org/10.1016/j.jss.2013.04.047. Epub 2013 May 11. PMID: 23731689.

47. Honeycutt CC, McDaniel CG, McKnite A, Hunt JP, Whelan A, Green DJ, Watt KM. Meropenem extraction by ex vivo extracorporeal life support circuits. J Extra Corpor Technol. 2023;55(4):159–66. https://doi.org/10.1051/ject/2023035. Epub 2023 Dec 15. PMID: 38099629; PMCID: PMC10723574.

48. Novy E, Abdul-Aziz MH, Cheng V, Burrows F, Buscher H, Corley A, Diehl A, Gilder E, Levkovich BJ, McGuinness S, Ordonez J, Parke R, Parker S, Pellegrino V, Reynolds C, Rudham S, Wallis SC, Welch SA, Fraser JF, Shekar K, Roberts JA. Population pharmacokinetics of fluconazole in critically ill patients receiving extracorporeal membrane oxygenation and continuous renal replacement therapy: an ASAP ECMO study. Antimicrob Agents Chemother. 2024;68(1):e0120123. https://doi.org/10.1128/aac.01201-23. Epub 2023 Dec 8. PMID: 38063399; PMCID: PMC10777822.

49. Hunt JP, McKnite AM, Green DJ, Whelan AJ, Imburgia CE, Watt KM. Interaction of ceftazidime and clindamycin with extracorporeal life support. J Infect Chemother. 2023;29(12):1119–25. https://doi.org/10.1016/j.jiac.2023.08.007. Epub 2023 Aug 10. PMID: 37572979; PMCID: PMC11160944.

50. Green DJ, Watt KM, Fish DN, McKnite A, Kelley W, Bensimhon AR. Cefepime extraction by extracorporeal life support circuits. J Extra Corpor Technol. 2022;54(3):212–22. https://doi.org/10.1182/ject-212-222. PMID: 36742220; PMCID: PMC9891479.

51. Hahn J, Min KL, Kang S, Yang S, Park MS, Wi J, Chang MJ. Population Pharmacokinetics and Dosing optimization of Piperacillin-Tazobactam in critically ill patients on extracorporeal membrane oxygenation and the influence of concomitant renal replacement therapy. Microbiol Spectr. 2021;9(3):e0063321. https://doi.org/10.1128/Spectrum.00633-21. Epub 2021 Dec 22. PMID: 34937189; PMCID: PMC8694146.

52. Martínez-Martínez M, Nuvials FX, Riera J. Nosocomial infections during extracorporeal membrane oxygenation. Curr Opin Crit Care. 2022;28(5):480–5. https://doi.org/10.1097/MCC.0000000000000976. Epub 2022 Aug 10. PMID: 35950717.

Publisher's note