Heart & Lung 48 (2019) 236–239

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Epidemiology of blood stream infection in adult extracorporeal membrane oxygenation patients: A cohort study

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ARTICLE INFO

Article history:
Received 17 December 2018
Received in revised form 4 January 2019
Accepted 13 January 2019
Available online 24 January 2019

Keywords:
ECMO
Infection
Shock
Respiratory failure

ABSTRACT

Purpose: The purpose of our study was to characterize the epidemiology of blood stream infection (BSI) in adult extracorporeal membrane oxygenation (ECMO) patients at a single tertiary care academic medical center with standardized post-cannulation antibiotic prophylaxis practices.
Methods: A single-center retrospective cohort study was performed over a five-year period. BSI incidence was characterized and patients who developed BSI during ECMO were compared with those who did not.
Results: Nineteen of 145 VV ECMO patients (13.1%) developed BSI while 7 of 123 VA ECMO patients (5.7%) developed BSI. When accounting for total ECMO days, the incidence rate was 8 BSIs per 1,000 ECMO days for both VV and VA ECMO patients. VV ECMO patients with BSI had longer ECMO runs and more red blood cell transfusion (both $p<0.05$). VA ECMO patients who developed BSI had longer ECMO runs and more platelet transfusion (both $p<0.05$). In VV ECMO patients there was an association between renal failure and BSI and in VA ECMO patients there was an association between hepatic failure and BSI.
Conclusions: BSIs are common in ECMO patients even with post-cannulation antimicrobial prophylaxis and are associated with ECMO duration, blood transfusion, and organ failure. Further work is needed to clarify the optimal duration and type of antimicrobial prophylaxis, as well as surveillance strategies for BSIs during adult ECMO.

Introduction

Blood stream infection (BSI) is associated with mortality of around 25% and in critically ill patients with cardiovascular disease the mortality is as high as 50%.[1-2] Patients requiring extracorporeal membrane oxygenation (ECMO) are at risk for BSI for a number of reasons. First, cardiogenic shock increases the risk for infection.[3] Second, both veno-arterial (VA) and veno-venous (VV) ECMO patients require large indwelling cannulas that cannot easily be exchanged if infected. Third, ECMO patients frequently require central venous catheters (CVCs) for vasoactive medications and arterial catheters for hemodynamic monitoring, both of which increase BSI risk.

The use of adult ECMO has grown with almost 10,000 adult ECMO runs reported in 2017.[4] Mortality remains relatively high, 40% for VV ECMO and 60% for VA ECMO, in part because of serious complications during ECMO.[4] One important complication that may impact survival during ECMO is infection. In a previous cohort study that included over 20,000 adult, pediatric, and neonatal ECMO patients the incidence of new infection during adult ECMO was 30.6 infections per 1000 ECMO days with VA ECMO patients having a higher risk for infection than VV ECMO patients.[5] This study did not specifically examine BSIs and it was unclear what type of antimicrobial prophylaxis patients received, as data from multiple ECMO centers were pooled in the study. Several other smaller studies have specifically explored the incidence of BSI during ECMO, but these studies were

Conflicts of Interest: None
Financial disclosures: None
Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
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https://doi.org/10.1016/j.hrtlng.2019.01.004
0147-9563/$ - see front matter © 2019 Elsevier Inc. All rights reserved.

relatively small. In one study of 16 VV ECMO patients, the incidence of BSI was 19 infections per 1000 ECMO days.[6] In a second study of 47 adult ECMO patients, the incidence of BSI was 27.7% and approximately 50% of patients with BSI had bacterial colonization of their ECMO cannulas after removal.[7] Finally, in a study of 121 VV ECMO patients, the incidence of BSI was 17% during the first 6 ECMO days. In this study, allogeneic blood transfusion was associated with increased BSI risk.[8]

The purpose of our study was to characterize the epidemiology of BSI in adult ECMO patients at a single tertiary care academic medical center where post-cannulation antibiotic prophylaxis is standardized. We hypothesized that new BSIs during ECMO would be associated with in-hospital mortality and that patients with organ failure would more frequently experience BSIs.

Methods

Subjects

The Institutional Review Board at the University of Maryland, Baltimore approved the study. The study was checked against the STROBE statement checklist for cohort studies. All adult patients that required ECMO between March 1st 2010 and March 1st 2015 were identified and included. For all patients we collected demographic data (age and sex), medical history (diabetes mellitus, hypertension, left ventricular ejection fraction, right ventricular dysfunction, chronic lung disease, and active malignancy), and ECMO data (indication, cannulation strategy, total ECMO days, and allogeneic blood transfusion).

ECMO details

General criteria for VA ECMO in our institution are refractory cardiogenic shock or rapidly deteriorating cardiogenic function with lactic acidosis or mixed venous oxygen saturation less than 45%. Criteria for VV ECMO are severe hypoxemia with a Murray score $\geq$3 or hypercarbia (PCO2$>$60 mmHg) in patients younger than 66 years of age. The standard ECMO circuit includes a Rotaflow centrifugal pump (Maquet, Wayne NJ, USA) and Quadrox oxygenator (Maquet, Wayne NJ, USA). In VA ECMO patients blood flow is adjusted to maintain systemic mean arterial blood pressure greater than 65 mmHg and cardiac index greater than 2.0 L/min/m^2. Patients on VV ECMO have blood flow adjusted to maintain arterial hemoglobin oxygen saturation greater than 85% and sweep gas flow to maintain $PaCO_2$ between 35–45 mm Hg; however, adjustments are made based upon a particular patient's condition. Patients are cannulated in our critical care resuscitation unit, emergency room, or cardiac surgery intensive care unit (ICU) by cardiac surgeons or by credentialed trauma surgeons or intensivists.

After peripheral cannulation, VA ECMO patients receive 48 hours of prophylactic antimicrobial therapy with vancomycin and ceftriaxone. Post-cannulation antimicrobial prophylaxis is not routinely administered after VV ECMO cannulation; however, targeted antibiotics are often given to VV ECMO patients if they have evidence of pulmonary infection (e.g., oseltamivir or other agents required to treat atypical causes of severe pneumonia). VA ECMO patients with an open sternum and central cannulation who are cannulated in the operating room receive prophylactic antimicrobial therapy with vancomycin and cefazolin and VA ECMO patients who are cannulated in the intensive care unit receive prophylactic antimicrobial therapy with vancomycin and piperacillin-tazobactam. Prophylactic antimicrobial therapy is discontinued 48 hours after sternal closure in these patients. Routine surveillance is not performed for BSI. Instead, blood cultures are sent when there is clinical suspicion for BSI (eg: leukocytosis, fever, or purulence at a catheter entry site).

ICU infection prevention practices

Patients in our ICUs are screened for methicillin-resistant *Staphylococcus aureus* (MRSA) at admission, each week, and at the time of ICU discharge. High-risk patients are also screened for multidrug-resistant gram-negative organisms including carbapenem-resistant Enterobacteriaceae (CRE) and multidrug-resistant *Acinetobacter baumannii*. Chlorhexidine bathing is performed daily in all patients, unless they have an allergy. Our facility uses minocycline/rifampin-coated central venous catheters and clinicians assess the need for lines daily. For patients with new MRSA nasal colonization, mupirocin is administered intranasally for 10 days.

Blood stream infection

Definitions from the Centers for Disease Control/National Healthcare Safety Network were used when identifying BSI. BSI was defined by two separate positive blood cultures with a pathogenic organism and signs of infection including leukocytosis, leukopenia, fever, or hypothermia. The causative organism for each BSI was recorded.

Outcomes

For all patients data were collected on in-hospital mortality, acute hepatic failure (defined as: international normalized ratio $>$1.5, new hepatic encephalopathy, and elevated total bilirubin), and acute renal failure requiring renal replacement therapy.

Statistical analysis

Statistical analysis was performed using SAS 9.3 (SAS Corporation, Cary, NC, USA). Patients were stratified by whether they required VA or VV ECMO. Continuous variables were summarized as the median and interquartile range and categorical variables were summarized as the number and percentage of patients. Patient characteristics were compared between patients with and without a BSI during ECMO using either the Wilcoxon Rank Sum Test or Chi-Squared Test as appropriate. For study outcomes, crude odds ratios with 95% confidence intervals were calculated using logistic regression. Appropriate logistic regression diagnostics were applied, including goodness-of-fit testing (Hosmer-Lemeshow test), analysis of Pearson's and deviance residuals, and influence plots. A p value less than 0.05 was considered statistically significant and all tests were two-tailed.

Results

Two hundred sixty seven ECMO patients were included in the cohort. VV ECMO patient characteristics are summarized in Table 1 and VA ECMO patient characteristics are summarized in Table 2. The majority of patients (57.3%) in the cohort were on VA ECMO for cardiogenic shock, while a smaller number were on VV ECMO for severe acute respiratory failure.

Twenty-six patients (9.7%) developed a BSI during ECMO. The incidence of BSI during VV ECMO was 13.1% and the incidence of BSI during VA ECMO was 5.7%. There were a total of 2336 VV ECMO days and 888 VA ECMO days for patients in the cohort, resulting in an incidence rate of 8 BSIs per 1000 VV ECMO days and 8 BSIs per 1000 VA ECMO days. Patients who developed a BSI during VV ECMO were transfused more RBCs (median 20 units versus 13 units, $p = 0.04$) and were on ECMO longer (median 18 days versus 9 days, $p = 0.0007$). Patients who developed a BSI during VA ECMO received more platelet transfusion during ECMO ($p = 0.05$) and were on ECMO longer (median 17 days versus 6 days, $p = 0.02$). The most common organisms causing BSI in VV ECMO patients were *Candida* species and gram-negative rods including: *Pseudomonas aeruginosa,*

Table 1
VV ECMO patients with and without blood stream infection

Variable	No BSI N = 126	BSI N = 19	p value
Age	44 [29, 56]	46 [27, 61]	0.70
Sex (% male)	70 (55.6)	11 (57.9)	0.85
Diabetes mellitus	23 (18.3)	2 (10.5)	0.41
Hypertension	47 (37.3)	4 (21.1)	0.17
LVEF (%)	60 [50, 65]	58 [55, 65]	0.82
Chronic lung disease	40 (31.8)	5 (26.3)	0.63
Malignancy	9 (7.1)	0 (0.0)	0.23
RV dysfunction			0.40
Mild	24 (22.4)	4 (25.0)	
Moderate	13 (12.2)	4 (25.0)	
Severe	7 (6.5)	0 (0.0)	
Cannulation			1.0
Peripheral	116 (92.8)	18 (94.7)	
Central	9 (7.2)	1 (5.3)	
RBC (units)	13 [5, 24]	20 [9, 36]	0.04
FFP (units)	1 [0, 4]	1 [0, 7]	0.54
Platelet (units)	1 [0, 5]	2 [0, 7]	0.26
ECMO days	9 [5, 19]	18 [13, 35]	0.0007

BSI=blood stream infection, ECMO=extracorporeal membrane oxygenation, FFP=fresh frozen plasma, LVEF=left ventricular ejection fraction, RBC=red blood cell, RV=right ventricle.

Table 2
VA ECMO patients with and without blood stream infection

Variable	No BSI N = 116	BSI N = 7	p value
Age	56 [44, 64]	55 [22, 66]	0.47
Sex (% male)	7 7 (66.4)	6 (85.7)	0.29
Diabetes mellitus	26 (22.4)	0 (0.0)	0.16
Hypertension	71 (61.2)	2 (28.6)	0.09
LVEF (%)	25 [15, 40]	30 [10, 40]	0.91
Chronic lung disease	18 (15.5)	0 (0.0)	0.26
Malignancy	3 (2.6)	1 (14.3)	
RV dysfunction			0.43
Mild	9 (7.8)	1 (14.3)	
Moderate	25 (21.6)	0 (0.0)	
Severe	54 (46.6)	3 (42.9)	
Cannulation			1.0
Peripheral	58 (50.0)	4 (57.1)	
Central	58 (50.0)	3 (42.9)	
RBC (units)	17 [8, 29]	23 [11, 73]	0.44
FFP (units)	6 [1, 13]	15 [2, 23]	0.33
Platelet (units)	3 [1, 8]	11 [2, 19]	0.05
ECMO days	6 [3, 9]	17 [5, 20]	0.02

BSI=blood stream infection, ECMO=extracorporeal membrane oxygenation, FFP=fresh frozen plasma, LVEF=left ventricular ejection fraction, RBC=red blood cell, RV=right ventricle.

Acinetobacter Baumannii, Burkholderia cepacia, and *Enterobacter aerogenes* Table 3. The most common organisms in VA ECMO patients were gram-negative rods including: *Aeromonas hydrophila/caviae, Klebsiella Pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, Table 3. There were no increased odds of BSI in VV or VA ECMO patients who died, Table 4. Increased odds of BSI were observed in VV ECMO patients who developed acute renal failure (OR=3.31, 95% CI=1.21 to 9.01) and increased odds of BSI were observed in VA ECMO patients who developed acute hepatic failure (OR=11.56, 95% CI=2.31 to 57.91).

Discussion

BSIs during ECMO remain a serious patient safety issue and are associated with both substantial morbidity and increased cost.[9-11] ECMO patients are likely to be more susceptible to BSIs because of femoral cannulation, immunocompromised status, and prolonged use of CVCs. In our cohort, the overall incidence of BSI in adult ECMO patients at a single academic medical center with standardized post-cannulation antimicrobial prophylaxis was 9.7%. The incidence rate of BSI for both VV and VA ECMO patients was 8 BSIs per 1000 ECMO days, which is lower than what has been previously described for VA ECMO patients.[6] The relatively low rate of BSI observed in our center could be in part due to our use of post-cannulation antimicrobial prophylaxis in VA ECMO patients.

Table 3
Organisms causing BSI in ECMO patients

Organism	n (%)
VV ECMO	
Candida species	5 (26.3)
Gram negative rod*	5 (26.3)
Staphylococcus or streptococcus species	4 (21.1)
Enterococcus species	3 (15.8)
Polymicrobial	2 (10.5)
VA ECMO	
Gram negative rod**	5 (71.4)
Candida species	1 (14.3)
Polymicrobial	1 (14.3)

ECMO=extracorporeal membrane oxygenation, VA=veno-arterial, VV=veno-venous.
* Gram negative rods were *Burkholderia cepacia, Enterobacter aerogenes, Acinetobacter baumannii*, and *Pseudomonas aeruginosa.*
** Gram negative rods were *Aeromonas hydrophila/caviae, Klebsiella Pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa.*

Table 4
Outcomes in patients with and without BSI

Outcome	No BSI	BSI	OR [95% CI]
VV ECMO			
In-hospital death	45 (36.0)	9 (47.4)	1.60 [0.61 to 4.22]
ARF requiring dialysis	43 (34.1)	12 (63.2)	3.31 [1.21 to 9.01]
Acute liver failure	5 (4.0)	1 (5.3)	1.35 [0.15 to 12.18]
VA ECMO			
In-hospital death	64 (55.2)	6 (85.7)	4.87 [0.57 to 41.75]
ARF requiring dialysis	49 (42.2)	5 (83.3)	6.84 [0.77 to 60.37]
Acute liver failure	12 (10.3)	4 (57.1)	11.56 [2.31 to 57.91]

ARF=acute renal failure, BSI=blood stream infection, CI=confidence interval, OR=odds ratio, VA=veno-arterial, VV=veno-venous.

The microbiology of BSI in ECMO patients is likely to be distinct from that of patients with central venous catheters (CVCs). Historically, coagulase-negative staphylococci are found in 40–50% of BSIs, followed by *S. aureus* (10–20%).[9,12-13] In up to one-third of central line associated bloodstream infections (CLABSIs), gram negative organisms (i.e., *Pseudomonas aeruginosa*) are recovered, and *Candida* sp. are responsible for approximately 3–10%.[9,12-13] In our study, *Candida sp.* and gram-negative bacilli were the top causes of BSI in patients requiring VV ECMO and gram-negative bacilli were the top cause in patients requiring VA ECMO. A shift towards more gram-negative infections has been observed in other centers and is thought to be related to changing resistance patterns, biofilm formation, and exposure to multi-drug resistant bacteria in healthcare environments.[14] Other factors such as immunocompetence, prior or concurrent antimicrobial use, and blood culturing practices may explain these trends. Improved skin care, which helps to decrease the bioburden of gram-positive organisms, may also contribute to changes in BSI microbiology. Moreover, fungal etiologies may be more common in ECMO patients, prompting empiric use of antifungals when BSI is suspected. Knowledge of the epidemiology of BSI in patients requiring ECMO is crucial not only for prevention, but also for timely and appropriate antimicrobial therapy.

In our study, BSI in ECMO patients was not associated with in-hospital mortality, although there was an association with organ failure. The lack of association between BSI and mortality may be attributable

to advances in sepsis care and earlier initiation of antibiotics, but our study may also have been underpowered to detect a small association with mortality. Acute renal failure is common in VV ECMO patients and is thought to be related to high doses of vasoactive drugs and severe shock prior to ECMO.[15] It appears that VV ECMO patients with acute renal failure have a higher rate of BSI, which could be related to longer duration of ECMO in these patients or perhaps more frequent blood draws for electrolyte monitoring. Post-cannulation hepatic injury is well described in VA ECMO patients and has been associated with considerable mortality.[16] Prior studies of non-ECMO patients with acute hepatic failure suggest that bacteremia is common, occurring in up to 35% of these patients and impaired bacterial clearance by the failing liver may be a contributing factor.[17-18]

There are several limitations to our work. First, because of our study's retrospective design only association and not causality can be derived. Although it is one of the largest reports of BSI in adult ECMO patients, the relatively small number of patients studied may preclude external generalizability. Second, our work is subject to several biases that are common in observational studies including: time-dependent bias, spectrum bias, and detection bias. Third, BSIs were not classified as primary or secondary. It is possible that risk factors and outcomes for primary and secondary BSIs are different, but we did not perform this analysis. Third, our ability to assess the appropriateness of antimicrobial timing and initial selection was limited. Specialized infectious disease physicians with consistent prescribing practices care for ECMO patients in our center. Nevertheless, we cannot be certain that all patients received optimal antimicrobial therapy at the earliest possible time. Finally, the definitions used for our study are epidemiological definitions intended to be used for surveillance and not for clinical diagnosis due to lower specificity.[19-20]

In summary, BSIs are fairly common in ECMO patients and although not associated with in-hospital mortality, these infections were more common in patients who develop organ failure during ECMO. The microbiology of BSI in ECMO patients may differ from that of other patients with CVCs in intensive care units, which has implications for heightened surveillance and treatment. In our medical center antimicrobial prophylaxis is routinely administered to all VA ECMO patients after cannulation for 48 hours and our incidence rate of BSI in VA ECMO patients is lower than what has been previously reported. Future studies are needed to determine the optimal type and duration of post-cannulation antimicrobial prophylaxis in adult ECMO patients, as well as optimal surveillance strategies.

Acknowledgements

None

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