Treatment and outcome of *Staphylococcus aureus* bacteremia in patients receiving extracorporeal membrane oxygenation

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Running Title: Staph aureus bacteremia in ECMO

Keywords: *Staphylococcus aureus,* bacteremia, extracorporeal membrane oxygenation

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Word Count:
Abstract: 50/50
Manuscript: 1467/1500
References: 10/10

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Abstract:

There are limited data on the treatment of infections complicating extracorporeal membrane oxygenation. This case series describes the treatment and outcomes of 12 patients with *Staphylococcus aureus* bacteremia. In this cohort, infections occurred early after cannulation with no cases of infective endocarditis and were treated with 4-6 weeks of antibiotics.

Introduction

Extracorporeal membrane oxygenation (ECMO) provides continuous life support for critically ill patients with reversible cardiac or pulmonary failure by connecting the patients to an external circuit through one to two large bore cannulas. The use of ECMO has grown rapidly over the past decade and infections are common in this patient population. However, there are no published data on specific treatments of patients who develop nosocomial infections on ECMO[1,2]. The treatment of infections on ECMO are challenging for multiple reasons including pharmacokinetic and pharmacodynamic changes associated with surface area of the circuit[3]. Additionally, the technical difficulties of removing and replacing cannulas means they are often retained in infections, which has been associated with metastatic complications in other patient populations[4].

Staphylococcus aureus bacteremia (SAB) is commonly seen in critically ill patients and is associated with approximately 20% mortality[5]. In reviews of the

Extracorporeal Life Support Organization registry, *Staphylococcus aureus* is the third most common pathogen isolated in ECMO infections[6]. In other invasive devices, such as left ventricular assist devices, there are standard protocols for the evaluation of SAB including a transesophageal echocardiogram (TEE), and guidance on duration of therapy as well as the need for surgical debridement[7]. However, there are no guidelines for SAB in ECMO and many questions remain. This case series describes a single center's experience treating SAB in ECMO.

Methods:

Positive blood cultures from patients undergoing ECMO between March 2012 and March 2021 at Brooke Army Medical Center were retrospectively analyzed. Patients with SAB after cannulation were identified as part of this sub-study. Demographics, admission diagnosis, dates of cannulation and decannulation, positive cultures, diagnostic workup, treatment, and outcomes including death or discharge were obtained. All blood cultures at our institution are obtained for clinical presentation and not part of a surveillance protocol, and no periprocedural antibiotic prophylaxis is administered for ECMO cannulation. The protocol was approved by the 59th Medical Wing IRB as exempt research.

Cases

In this cohort, there were twelve cases of SAB in 11/242 (5%) patients who received ECMO (**Table)**. The majority of cases were caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) (n=8, 67%). Patients had a median age of 42 (IQR: 28-

44) and were predominantly male (n=7, 58%). The most common indication for admission was COVID-19 (n=7, 58%) followed by thermal burn (n=3, 25%). All patients had a veno-venous ECMO configuration at time of infection. Infections tended to occur early in the patient's ECMO course (median days: 2, IQR: 1-3) and hospitalization (median day: 14, IQR: 7-21). Almost all patients (n=11, 92%) received a transthoracic echocardiogram as well as an infectious diseases consult and most (n=7, 58%) received a TEE. No patient was found to have infective endocarditis. Of the 8 (75%) patients who had central lines at the time of bacteremia, 7 (88%) were removed within 72 hours of first positive blood culture. Only one patient, patient 11, had an ECMO cannula replaced. This occurred on the patient's second day of bacteremia, which did not clear for an additional 10 days. The median time to culture clearance was 4 days (IQR: 2-6). No patients underwent nuclear medicine studies such as positive emission tomography.

The median number of days of antimicrobial therapy after clearance of cultures was 28 days. Of the eight isolates that were MSSA, five were treated with cefazolin, one with oxacillin, and one with vancomycin. Additionally, one patient received ertapenem for concurrent *Enterobacter cloacae* pneumonia. For methicillin-resistant *Staphylococcus aureus* (MRSA) isolates, vancomycin was used for three patients and combination ceftaroline/daptomycin was used for one patient. The median days with positive cultures was 2 (IQR: 1-3) and median days until clearance was 5 (IQR: 2-7). The median number of days on ECMO after clearance was 19 (IQR: 3-45) and the median number of days in the hospital after clearance

was 54 (IQR: 31-71).

Of the ten patients who completed therapy, four (40%) patients were decannulated from ECMO circuit before completion of antibiotic therapy, and six (60%) remained cannulated past the duration of the antibiotic course. Of the patients who remained on ECMO, one (17%) had a second case of SAB after completing a 28 day course of Vancomycin for MRSA with a negative TEE at the time of first episode of bacteremia and at onset of recurrence. He cleared his recurrent bacteremia after one day of vancomycin, and completed an additional 28 day course of vancomycin for treatment. The source of second bacteremia was thought to be a new infection introduced via a central line, which was subsequently removed.

There were five patient (42%) deaths in this cohort. Two patients, both with burn injuries, died while undergoing treatment for SAB. The remaining three patients, all with COVID-19, died a median of 68 days after original bacteremia clearance due to complications from COVID-19.

Discussion

This single center case series is the first to describe the treatment and outcomes of patients receiving ECMO complicated by SAB. Despite the small size of the study group, there were several findings of this study that provide insight into the pathogenesis as well as treatment of patients with SAB receiving ECMO.

In this cohort, SAB generally occurred early in the patient's ECMO course with almost all infections within the first week of ECMO, except for two cases that were believed to be a central line associated blood stream infection later in the patient's ECMO course. The known risk factors for infections on ECMO include greater time on the ECMO circuit and older patient age[1,6], which are non-modifiable. The early infections in this cohort could suggest a relationship between infection and either the patient's underlying disease process or is related to the cannulation process itself.

As in other populations, SAB in this group was associated with significant mortality, with two deaths occurring during treatment. Despite most patients receiving a TEE, which is associated with rates of infective endocarditis in SAB between 14 and 28%, there were no cases of infective endocarditis in these patients[8]. While this may be an artifact of the small sample size, this result is surprising. One possible explanation is that all infections were likely hospital acquired, occurring in patients that were being closely monitored with early initiation of antimicrobials, whereas community acquired infections may present later in the course of infection. Another possibility is that the high flow rate of the ECMO circuit leads to high flows through the heart that make it more difficult for bacteria to form vegetations.

The initial management for SAB involves identifying the source of infection, assessing for metastatic foci of infection, removing unnecessary vascular access, and a course of antibiotics that ranges from 2-6 weeks from time of culture clearance.

Interventions that have been proven to improve mortality in SAB, including infectious disease consultation, were generally followed[9]. With the exception of one case all patients were treated as complicated infections per the 2011 MRSA guidelines[10]. In the patients who were rapidly decannulated from ECMO without any other intravascular cannulas, there may be utility in investigating shorter treatment treatments, such as 14 days of antibiotics after bacterial clearance.

Cannulas remained in place for the entirety of therapy in most patients. There was only a single case of SAB re-infection from a central line associated catheter infection and no cases of recurrence. This study supports the current practice of not using suppressive antibiotics after treatment of SAB in ECMO with retained cannulas due to the low incidence of recurrence.

An additional consideration was the need to exchange ECMO cannulas in patients with bacteremia. Only one patient had a cannula exchange. In this patient, the exchange occurred on the second day of bacteremia, which was 10 days before clearance. She did not have any additional episodes of SAB. This study suggests that cannula exchange may not necessary to prevent recurrence.

There are several shortcomings from this single center case series that may affect the generalizability of the results. All patients received veno-venous ECMO and it is unclear how management may different for other configurations. Additionally, due to improvement of their admitting disease processes, two patients were

decannulated shortly after the patient was determined to be bacteremic and the removal of cannulas may have contributed to recovery. Due to the rarity of specific ECMO infections, trials designed to determine the optimal therapeutic strategy will likely need multiple centers to account for the diversity of cases now requiring ECMO.

This study shows the outcomes of twelve patients who developed SAB while receiving ECMO. In this setting, there were no cases of infective endocarditis, and treatment of complicated bacteremia with four weeks of antimicrobials was associated with clearance. Future studies are needed to see the incidence of deep seeded infections on ECMO as well as optimal treatment duration in patients with rapid decannulation as well as those with retained cannulas. As ECMO utilization increases, these infections will likely be more common and best practices are needed.

Acknowledgements: This work was funded by the 59th Medical Wing Office of Science and Technology.

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Table
Treatment and outcomes of patients with *Staphylococcus aureus* bacteremia

Patient Number	Age	Sex	Isolate	Admission Diagnosis	Days on ECMO/Inpatient until infection	Antibiotic Course^	Days until clearance	TTE/TEE	Days on ECMO/Inpatient after clearance	Survival to Hospital Discharge
1	42	M	MRSA	Thermal Burn	1/5	Vancomycin (duration not specified)	6	Y/N	0/0	N
2	33	F	MRSA	Cavitary Pneumonia	0/1	Ceftaroline +Daptomycin, 28 days	4	Y/Y	0/7	Y
3	44	F	MRSA	COVID-19	1/29	Vancomycin, 28 days	2	Y/Y	36/45	Y
4	49	M	MRSA	COVID-19	3/19	Vancomycin, 28 days	4	Y/Y	104/104	N
	49	M	MRSA	COVID-19	95/111	Vancomycin, 28 days	1	Y/Y	13/13	N
5	54	M	MSSA	Thermal Burn	4/7	Vancomycin (duration not set)	6	N/N	9/17	N
6	21	M	MSSA	Coccidioidomycosis	43/55	Cefazolin, 14 days	1	Y/N	29/101	Y
7	28	M	MSSA	COVID-19	8/13	Cefazolin, 42 days	11	Y/Y	0/47	Y
8	28	M	MSSA	Thermal Burn	0/6	Cefazolin, 28 days	2	Y/Y	5/61	Y
9	42	F	MSSA	COVID-19	1/25	Oxacillin, 28 days	5	Y/N	4/46	Y
10	45	M	MSSA	COVID-19	3/9	Cefazolin, 28 days	12	Y/Y	68/68	N
11	29	F	MSSA	COVID-19	2/15	Cefazolin, 42 days	12	Y/Y	61/61	N
12	43	F	MSSA	COVID-19	2/16	Cefazolin, 42 days	3	Y/N	41/58	Y

^Days of therapy after clearance

Abbreviations: MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-susceptible *Staphylococcus aureus*, TTE: Transthoracic echocardiogram, TEE: Transesophageal echocardiogram