Outcomes of Fungemia in Patients Receiving Extracorporeal Membrane Oxygenation

Melissa M. Rosas,1 Michal J. Sobieszczyk,1 Whitney Warren,1 Phillip Mason,2 Robert J. Walter,1 and Joseph E. Marcus3,

1Pulmonary and Critical Care Division, Department of Medicine, Brooke Army Medical Center, Joint Base San Antonio, Texas, USA, 2Critical Care Division, Emergency Medicine, Brooke Army Medical Center, Joint Base San Antonio, Texas, USA, and 3Infectious Disease Division, Department of Medicine, Brooke Army Medical Center, Joint Base San Antonio, Texas, USA

There are limited data on the treatment of fungal infections complicating extracorporeal membrane oxygenation (ECMO). In 14 patients who developed fungal bloodstream infections on ECMO, 8 (57%) survived to discharge. Of the 5 patients completing treatment prior to decannulation, 2 (40%) developed recurrent fungal infections.

Keywords. COVID-19; extracorporeal membrane oxygenation; fungemia.

Extracorporeal membrane oxygenation (ECMO) provides cardiopulmonary support in patients with refractory respiratory or cardiac failure. The use of ECMO has grown over the last decade [1]. Patients receiving ECMO are at increased risk of nosocomial infections due to their underlying illness, immune dysregulation, and prolonged hospitalizations [1, 2]. Currently, limited data exist on treatment of nosocomial infections for those patients requiring ECMO support. Management of these infections can be challenging due to potential for microorganism colonization of devices, unpredictable antibiotic pharmacokinetics related to blood–membrane interface, and challenges in exchanging or removing ECMO cannulas for source control [3].

Yeast are the most common pathogens, which cause clinical line–associated bloodstream infections [4]. Fungemia is associated with a high attributable mortality [5]. There are clinical practice guidelines to guide treatment duration, surgical management, and suppressive therapy for complicated candidemia and its complications such as endocarditis, cardiac devices, and other foreign body infections [6, 7]. However, despite Candida being the most frequently isolated pathogens in adults receiving ECMO, there are no agreed treatment guidelines specifically for candidemia in patients receiving ECMO [8, 9]. Additionally, equipoise exists regarding the necessity of suppressive antifungal therapy after treatment [10]. This study presents a single institution’s experience with treating fungemia in patients receiving ECMO.

METHODS

A retrospective review of medical records was conducted for patients admitted to Brooke Army Medical Center between January 2012 and September 2021 who required ECMO support. Blood cultures were reviewed, and all patients with isolation of fungal species were included. For patients within this cohort, demographics, admission diagnosis, dates of cannulation and decannulation, positive cultures, treatment, metastatic foci, and outcomes were obtained. Patient records were additionally reviewed for subsequent episodes of fungemia.

All blood cultures at our institution were obtained based upon clinical suspicion and not part of an existing surveillance protocol. No antibiotic or antifungal prophylaxis was administered at our facility. This protocol was reviewed by the Army Regional Health Command–Central Institutional Review Board, and this protocol was approved by the San Antonio Institutional Review Board, with a waiver for informed consent.

RESULTS

Of the 273 patients who received ECMO during the review period, 14 (5%) patients developed fungal bloodstream infections (3.5 infections/1000 ECMO days). The most common fungal organism isolated was Candida albicans (n = 6 [43%]), followed by Candida tropicalis (n = 3 [21%]). The cohort was predominantly male (n = 12 [86%]) with a median age of 34 years (interquartile range [IQR], 30–43 years) (Table 1). All Candida species were susceptible to fluconazole, except for the Candida glabrata isolated from patient 8, which was susceptible-dose dependent, and patient 9, which was resistant. The most common indication for admission was severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (n = 6 [43%]), followed by thermal burn (n = 3 [21%]) and influenza (n = 3 [21%]). All patients had a venovenous ECMO configuration at the time of fungemia. Before developing fungemia, patients were hospitalized for a median of 25 days (IQR, 10–48 days) and were cannulated for a median of 15 days (IQR, 6–36 days). The majority of patients (12 [86%]) had a transthoracic echocardiogram. Five patients had isolation of the same yeast at other sites at time of fungemia including fungal empyema (n = 2 [40%]), fungal empyema and infected thrombus (n = 1 [20%]), corneal infection (n = 1 [20%]), and wound infection (n = 1 [20%]).

Clinician-guided treatment for fungemia varied in this cohort (Table 2). Two patients (patient 7 and 9) died within
2 days of diagnosis without antifungal treatment or follow-up cultures to document clearance and were excluded from antifungal duration calculations. Eight (57%) patients had a circuit change after developing fungemia, though the reason for circuit change was not due to fungemia. Two (14%) patients had circuit reconfigurations, with only 1 (patient 3) reconfiguration completed due to fungemia and visualized thrombus. The majority of patients (11/12 [92%]) were initially treated with an echinocandin prior to the addition or switching to other antifungals. The median time to culture clearance was 3 days (IQR, 2–4 days). The median number of days of antifungal therapy after clearance was 15 days (IQR, 13–23 days). Of the 12 patients who were treated with antifungals, 10 (83%) survived to antifungal therapy completion. The median number of days on ECMO after initial clearance was 16.5 days (IQR, 8–38 days) and number of hospital days after initial clearance was 37 days (IQR, 26–52 days). Five (50%) patients completed antifungal therapy prior to decannulation and 5 completed therapy after decannulation.

Of the 5 patients who completed antifungal therapy on ECMO, 2 patients developed recurrent C. albicans infections. One patient, patient 3, developed recurrent fungemia 29 days after completing a 10-day course of micafungin. With second episode of candidemia, a circuit reconfiguration was performed due to visualized thrombus on a cannula, but the patient remained fungemic for 15 days after procedure. An additional patient, patient 4, had a recurrent Candida empyema 51 days after completing a 14-day course of micafungin.

There were 6 (43%) deaths in our cohort. Two patients died prior to clearance and 2 died after clearance but during their initial treatment for fungemia. The 2 patients who completed treatment prior to decannulation (patient 4 and 6) died 99 and 37 days, respectively, after their original fungemia clearance due to complications of their underlying SARS-CoV-2 infection; these deaths were thought to be unrelated to fungemia.

**DISCUSSION**

This single-center case series describes the treatment and outcomes for fungemia in a cohort of patients receiving ECMO. In a setting without suppressive antifungal therapy, 2 of 5 patients who remained on ECMO after completion of therapy had an additional fungal infection. This finding suggests possible benefit of extending antifungal courses or offering suppressive therapy in patients who complete therapy while remaining cannulated.

In ECMO, there are limited data on fungal bloodstream infections. The prevalence of fungal bloodstream infections has been reported at 1.2%–6.0% [1, 3, 11] and with increasing incidence associated with longer ECMO duration [12]. In line with these data, our center has a 5% infection rate. With this prevalence, only 2% of ECMO centers routinely provide antifungal prophylaxis, which using prudently is essential for stewardship and to decrease selection pressures associated with widespread antifungal use [12, 13]. As in other reports, C. albicans was the most commonly isolated species in the blood [11, 14]. Furthermore, mortality in our cohort was high at 43%, with 2 deaths prior to initiation of therapy and 2 deaths during treatment. This is consistent with data from the worldwide registries as well as single-center studies, which describe a similarly high mortality of 64.1%–82% in patients with fungemia [3, 11]. It is unclear whether pathogen or patient factors that predispose to infection are the cause of this high mortality in patients receiving ECMO.

The initial management for critically ill patients with fungemia includes an echinocandin or lipid formulation amphotericin B while evaluating for source of infection and removing central venous access, if feasible [6]. Generally, patients are treated for 14 days after clearance, but currently there are limited data and guidelines to direct this therapy for patients receiving ECMO. Existing guidelines on the treatment of
Table 2. Characteristics of Individual Episodes of Fungemia for Patients Receiving Extracorporeal Membrane Oxygenation at Brooke Army Medical Center

| Patient No. | Organism          | Admission Diagnosis | Days on ECMO Prior to Infection | Additional Sites of Isolation | Days Until Clearance | Antifungal After Clearance (Days of Therapy) | Completed Therapy Before Decannulation | Survival to Discharge |
|-------------|-------------------|---------------------|---------------------------------|------------------------------|----------------------|-----------------------------------------------|---------------------------------------|------------------------|
| 1           | Candida albicans  | Thermal burn        | 5                               | Wound                        | 4                    | Micafungin (15), voriconazole/L-AmB (7)      | No                                    | Yes                    |
| 2           | Candida albicans  | Influenza           | 20                              | No                           | 3                    | Micafungin (11), fluconazole (14)            | No                                    | Yes                    |
| 3           | Candida albicans  | COVID-19            | 41                              | Empyema, thrombus            | 6                    | Micafungin (10)                              | Yes                                   | Yes                    |
| 4           | Candida albicans  | COVID-19            | 22                              | Empyema                      | 2                    | Micafungin (14)                              | Yes                                   | No                     |
| 5           | Candida albicans  | COVID-19            | 0                               | No                           | 2                    | L-AmB/isavuconazole (4), isavuconazole (35) | No                                    | Yes                    |
| 6           | Candida albicans  | COVID-19            | 15                              | No                           | 12                   | Micafungin (14)                              | Yes                                   | No                     |
| 7           | Candida dubliniensis | COVID-19            | 14                              | Empyema                      | NA                   | NA; patient died 1 day after initial blood culture | NA                                    | No                     |
| 8           | Candida glabrata  | Chemotherapy toxicity | 51                             | No                           | 4                    | Anidulafungin (8)                            | NA                                    | No                     |
| 9           | Candida glabrata  | Bacterial pneumonia | 73                              | NA                           | NA                   | NA; patient died 2 days after initial blood culture | NA                                    | No                     |
| 10          | Candida tropicalis| Thermal burn       | 11                              | Corneal                      | 2                    | Micafungin (6)                               | NA                                    | No                     |
| 11          | Candida tropicalis| Thermal burn       | 3                               | No                           | 2                    | Micafungin (8), L-AmB/posaconazole (3), fluconazole (16) | Yes                                   | Yes                    |
| 12          | Candida tropicalis| COVID-19            | 8                               | No                           | 2                    | Micafungin (35)                              | No                                    | Yes                    |
| 13          | Candida parapsilosis | Influenza           | 63                              | No                           | 3                    | Micafungin (4), fluconazole (10)             | Yes                                   | Yes                    |
| 14          | Kodamaea ohmeri   | Influenza           | 0                               | No                           | 3                    | Micafungin (11), micafungin/posaconazole (10) | No                                    | Yes                    |

Abbreviations: COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; L-AmB, liposomal amphotericin B; NA, not applicable.

*Antifungals given as combination therapy.

†Recurrent infection 41 days after clearance.

‡Received additional course of antifungals for a recurrent empyema.

§Died while receiving therapy.
fungemia in other invasive devices, such as left ventricular assist devices, recommend treatment with antifungals for 6 weeks in addition to suppressive fungal therapy as long as the device is in place [6]. All patients in our cohort who were decannulated during antifungal therapy survived without recurrence. There was only 1 patient in our cohort who had recurrence of fungemia; this likely occurred due to suboptimal initial length of treatment with antifungals. A different patient had a fungal empyema that occurred 51 days after completing antifungal therapy. These 2 patients, of the 5 who completed antifungal therapy while cannulated, suggest a high recurrence risk in patients who remain cannulated past their antifungal treatment. As antifungal suppression is used in other intravascular devices, this experience suggests a potential area of future studies.

Fungemia treatment often requires removing or exchanging invasive intravascular devices, which may be challenging and/or prohibitive in complex ECMO cases. While 2 patients had circuit reconfigurations, only 1 of these patients had a cannula exchange due to visualized thrombus with persistent candidemia. This was performed 15 days before the patient achieved clearance. Though there may be benefits to cannula exchange, it was not associated with rapid clearance in this single case and more studies are needed to determine the best situations for exchange.

There are several limitations to this retrospective single-center study. First, treatment plans were not standardized and varied between patients. All patients in this study were on venovenous ECMO and it is unclear how treatment would differ for other configurations. The population was young and predominantly male, and our institution does not offer transplants, which may lead to different results in other populations. Finally, no patient received suppressive antifungal agents, so their benefit could not be evaluated.

CONCLUSIONS

This study demonstrates the outcomes of 14 patients who developed fungemia while on ECMO in a single institution. In this study, mortality was high and recurrence was frequently seen in patients who completed antifungal therapy while cannulated. As ECMO use continues to increase, nosocomial infections will rise and best practices will need to be developed and standardized. Future studies are needed to address therapy length in relation to decannulation, the role of suppressive antifungal agents, and the role of circuit reconfigurations.

Notes

Disclaimer. The views expressed in this article reflect the results of research conducted by the author and do not necessarily reflect the official policy or position of the Department of the Army and Air Force, Department of Defense, or the United States government.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Biffi S, Di Bella S, Scaravalli V, et al. Infections during extracorporeal membrane oxygenation: epidemiology, risk factors, pathogenesis and prevention. Int J Antimicrob Agents 2017; 50:9–16.
2. Grasselli G, Scaravalli V, Di Bella S, et al. Nosocomial infections during extracorporeal membrane oxygenation: incidence, etiology, and impact on patients’ outcome. Crit Care Med 2017; 45:1726–33.
3. Cavayas YA, Yusuff H, Porter R. Fungal infections in adult patients on extracorporeal life support. Crit Care 2018; 22:98.
4. Weiner-Lagtinger LM, Haass K, Gross C, et al. Pathogens attributed to central line-associated bloodstream infections in US acute care hospitals during the first year of the COVID-19 pandemic. Infect Control Hosp Epidemiol 2022. doi: 10.1017/ic.2022.16.
5. Mai PB, Olsen MA, Stawalley D, et al. Attributable mortality of Candida bloodstream infections in the modern era: a propensity score analysis. Clin Infect Dis 2022. doi: 10.1093/cid/ciaa004.
6. Pappas PG, Kaufman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 62:1–50.
7. Cornely OA, Bassetti M, Calandra T, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect 2012; 18:19–37.
8. Bizzarro MJ, Conrad SA, Kaufman DA, et al. Infections acquired during extracorporeal membrane oxygenation in neonates, children, and adults. Pediatr Crit Care Med 2011; 12:277–81.
9. Aubron C, Cheng AC, Pilcher D, et al. Infections acquired by adults who receive extracorporeal membrane oxygenation risk factors and outcome. Infect Control Hosp Epidemiol 2013; 34:24–30.
10. Poth JM, Schewe JC, Putensen C, et al. Impact of invasive fungal diseases on survival under veno-venous extracorporeal membrane oxygenation for ARDS. J Clin Med 2022; 11:1949.
11. Monk EJM, Rautema-Richardson R, Felix T, et al. Incidence of candidaemia in prolonged veno-venous extracorporeal membrane oxygenation. J Hosp Infect 2022; 119:49–53.
12. Epelbaum O, Carmona EM, Evans SE, et al. Antifungal prophylaxis for adult recipients of veno-venous extracorporeal membrane oxygenation: a cautionary stance during the COVID-19 pandemic. ASAIO J 2021; 67:611–3.
13. Pieri M, Agradchena N, Fumagalli L, et al. Infections occurring in adult patients receiving mechanical circulatory support: the two-year experience of an Italian national referral tertiary care center. Med Intensiva 2013; 37:468–75.
14. Sun HY, Ko WI, Tsai PR, et al. Infections occurring during extracorporeal membrane oxygenation use in adult patients. J Thorac Cardiovasc Surg 2010; 140:1125–32.e2.