Antifungal Prophylaxis for Adult Recipients of Veno-Venous Extracorporeal Membrane Oxygenation: A Cautionary Stance During the COVID-19 Pandemic

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The ongoing global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent of novel coronavirus disease 2019 (COVID-19), has resulted in over 1 million deaths worldwide and many more cases of respiratory failure.[1] The propensity of SARS-CoV-2 to cause catastrophic pneumonia fulfilling criteria for the acute respiratory distress syndrome (ARDS) has not only strained the capacity of intensive care units (ICUs) to provide mechanical ventilation but has also led to a spike in utilization of veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) for respiratory failure not seen since the H1N1 influenza pandemic.[2] The explosion in the use of extracorporeal support is likely to magnify unresolved controversies surrounding the management of patients receiving ECMO. One such controversy is whether administration of prophylactic antifungal therapy reduces the incidence of *Candida* bloodstream infection (C-BSI) associated with vascular cannulation.

The concern about C-BSI in the setting of ECMO is not trivial. Together with Gram-negative bacilli and enterococci, *Candida* spp. are among the three most common pathogens implicated in central venous catheter-related BSI (CVC-BSI) in critically ill patients.[3] The impact of COVID-19 on the contribution of *Candida* to CVC-BSI in intensive care units remains to be elucidated, although such infections have likely increased during the pandemic.[4] Although there are conflicting data on whether ECMO cannulation confers greater risk of CVC-BSI than conventional catheterization,[5,6] routine antibacterial prophylaxis of ECMO patients was reported by 42% of participating centers in the Extracorporeal Life Support Organization (ELSO) in a 2011 study.[7] Routine antifungal prophylaxis, on the other hand, was reported by a mere 2% of programs that year. By 2017, however, 47% of international respondents reported the use of antifungal prophylaxis.[8] An impromptu survey of the authorship of this *Brief Communication*, which consists of experts who have developed clinical practice guidelines on fungal diagnostics[9] and therapeutics,[10] revealed that antifungal prophylaxis of ECMO recipients is currently a common practice in the represented institutions. Given the possibility that this may be a growing phenomenon in the management of the ECMO patient, the consensus among the author group is that routine antifungal prophylaxis of the immunocompetent adult patient receiving V-V ECMO for acute respiratory failure can only be judged in the context of available indirect evidence as it has never been studied directly.

A subset of ECMO patients, namely pediatric cardiac veno-arterial (V-A) ECMO recipients[11] and adults on V-A ECMO following orthotopic heart transplantation[12] appear to be at especially high risk for C-BSI. Recognizing this, the ELSO Infectious Disease Task Force advocates for "cautious but aggressive" use of antifungal prophylaxis in patients deemed to be at particularly high risk, including those with compromised immunity.[13] Of note, the only study to have assessed the impact of antifungal prophylaxis (with fluconazole) in ECMO patients was performed in the pediatric cardiac V-A ECMO population and showed a nonsignificant reduction in the incidence of fungemia with prophylaxis (2.4%) compared with the already low incidence in the no-prophylaxis group (4.5%).[11] In an unselected adult population of ECMO recipients, the prevalence of candidemia is remarkably low: 1.2% in a study of 19,697 such patients from the ELSO registry.[14] Even *Candida* colonization rates of ECMO cannulas have been found to range from 0% to only 10%, and when present, *Candida* colonization is less common than Gram-positive and Gram-negative bacterial colonization.[15,16] Although in aggregate bacterial isolates exceed fungal ones in ECMO patients with BSI, there has been no indication to date that even antibacterial prophylaxis reduces bacterial infection rates.[17,18]

In evaluating the justification for routine antifungal prophylaxis of immunocompetent adult V-V ECMO recipients, it is helpful to draw on existing prophylaxis data in immunocompetent critically ill non-ECMO populations. In the seminal prospective surgical ICU study by Pelz *et al.*,[19] fluconazole prophylaxis significantly reduced the incidence of invasive candidiasis (IC) from 15.4% in the placebo arm to 8.5% in the intervention arm. When added to a selective digestive decontamination regimen in a mixed ICU population, fluconazole likewise significantly reduced IC incidence from 16% with placebo to 5.8% with active prophylaxis.[20] Despite a comparable sample size to these earlier studies, a significant

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Table 1. Summation of Five Available Studies,[16,23–26] All Retrospective, of Immunocompetent Adult ECMO Recipients From Which the Incidence of Bloodstream Infection Caused by *Candida* spp. Could Be Derived Specifically for Those Connected to Veno-Venous Support*

Study/Year	V-V or Mixed	N (Patients)	Incidence C-BSI (%)	C-BSI Fraction of BSI (%)
Pieri *et al.* 2013[23]	Mixed	22	2/22 (9.1)	2/4 (50)
Austin *et al.* 2017[24]	Mixed	34	0/34 (0)	0/1 (0)
Kutleša *et al.* 2017[25]	V-V	100	1/100 (1)	1/35 (2.9)
Thomas *et al.* 2017[16]	V-V	103	8/103 (7.8)	8/43 (18)
Na *et al.* 2018[26]	V-V	121	5/121 (4.1)	5/21 (23.8)
Totals	Two mixed, three V-V	380	16/380 (4.2)	16/104 (15.4)

Included studies were either exclusively of V-V ECMO or of both V-V and veno-arterial (*i.e.*, mixed) but from which the incidence in the V-V population could be determined separately. The incidence of C-BSI as a proportion of all BSI is also provided.

*Eligible studies were obtained through a PubMed search up to the current date using the terms "extracorporeal membrane oxygenation AND fungal" as well as "extracorporeal membrane oxygenation AND *Candida*." Search results selected for full-text review were limited to those in the English language and those of adult patients. Information needed to populate the table was abstracted from the relevant studies thus identified.

BSI, bloodstream infection; C-BSI, *Candida* bloodstream infection; ECMO, extracorporeal membrane oxygenation; V-V, veno-venous.

reduction was not achieved in a subsequent trial of caspofungin prophylaxis limited to medical ICU patients in whom the incidence of IC in the placebo group was only 4.8%.[21] Although much lower than expected by the study authors, the 4.8% incidence was actually higher than the 3.1% incidence of candidemia registered in a prospective cohort of 1,655 non-neutropenic mixed ICU patients.[22] Returning to the question of antifungal prophylaxis during immunocompetent adult V-V ECMO use, when the cumulative incidence of C-BSI in such cases is calculated from the major available studies reporting this metric, a figure of 4.2% is obtained (Table 1). This is of relevance because aforementioned studies of critically ill populations in which the baseline incidence of candidemia or IC was in the range of 4.2–4.8% have not shown benefit of antifungal prophylaxis.

Extrapolation of the above IC incidence analysis to V-V ECMO in COVID-19 pneumonia is potentially confounded by, among other factors, the frequent provision of immunomodulatory therapy for this disease.[27,28] Nonetheless, if the incidence of C-BSI in V-V ECMO patients is accepted to be under 5% as suggested by aggregate data, we submit that universal antifungal prophylaxis cannot be supported at the present time assuming adherence to recommended circuit maintenance protocols.[13] This generalization may not apply to ECMO programs with outlying C-BSI rates. Although generally well tolerated, widespread administration of antifungal agents for prolonged periods raises concerns about cost, toxicity, and selection for resistant isolates. With the ongoing SARS-CoV-2 pandemic showing no signs of abating, the current "boom" in V-V ECMO use is expected to continue as ICUs across the globe admit patients with catastrophic respiratory failure on an unprecedented scale. The transition of ECMO from an exceptional management strategy in normal times to a widely adopted rescue maneuver during a respiratory virus outbreak magnifies the importance of associated decisions such as antifungal prophylaxis. Previously an overlooked issue in intensive care medicine, antifungal prophylaxis in the ECMO recipient now merits greater attention. While challenging in many ways, current pandemic conditions may paradoxically offer a singular window of opportunity to prospectively investigate the impact of antifungal prophylaxis on C-BSI in adult patients with respiratory failure connected to V-V ECMO.

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