Elevated nosocomial infection rates in patients with COVID-19 requiring extracorporeal membrane oxygenation

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ABSTRACT:

A retrospective cohort compared nosocomial infections for patients receiving extracorporeal membrane oxygenation (ECMO) for influenza or COVID-19. COVID-19 was associated with more infections per 1000 patient days (37.3 vs. 17.7, p=0.04) and infections earlier in patient's ECMO course (median [IQR] 5 days (3-7) vs. 16 (10-21), p=0.03) compared to influenza.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has had tremendous impact in the global healthcare system creating a surge of patients requiring hospitalization. To prevent in-hospital outbreaks, contact and airborne precautions have been implemented for patients with COVID-19 with demonstrated success in preventing transmission to healthcare workers and other patients[1]. Despite this increase in the use of personal protective equipment (PPE), there are a limited data on the rates of nosocomial infections in patients is hospitalized with COVID-19[2]. While early studies showed low rates of nosocomial infections in patients with COVID-19[3], more recent studies in both larger populations and sicker populations have shown elevated rates of nosocomial infection [4,5].

Extracorporeal membrane oxygenation (ECMO) can be used for pulmonary bypass in patients with reversible respiratory failure and poses a significant risk of nosocomial infections[6]. ECMO is currently only recommended in COVID-19 for younger patients with few comorbidities and without severe multisystem organ failure[7]. ECMO has been utilized worldwide for patients with COVID-19, but there are no data on nosocomial infections in these patients[8]. This study aims to differentiate the rates of infections on ECMO for patients with COVID-19 from infections for patients who required ECMO for influenza. While both can cause devastating pulmonary disease and are treated with anti-virals, there are differences in patient management. Unlike influenza, patients hospitalized with COVID-19 are treated with immunosuppression. Additionally, COVID-19 has

been associated with high patient volumes which strained healthcare systems. . As such, we hypothesized that there would be more nosocomial infections for patients with COVID-19, despite the increased use of PPE and emphasis on infection prevention.

Methods

All patients who completed a course of ECMO at Brooke Army Medical Center between January 1, 2013 and October 10, 2020 with confirmed influenza or COVID-19 were included in this retrospective analysis. Positive cultures during ECMO course or within 48 hours of decannulation that were determined to be pathogenic by the patient's treatment team were labeled as blood stream, respiratory, or urinary infections based on the site of culture. Cultures that were considered colonizers or contaminants by the treatment team were excluded. Multidrug resistant organisms (MDRO) were defined as resistance to three or more classes of antibiotics.

Comparisons were made between patients with influenza and COVID-19 by demographics, duration of hospitalization prior to ECMO cannulization, length of stay, mortality, number of infections, infection rates per 1000 ECMO patient days, and MDRO rate. Nominal variables and rates were compared by Chi-squared or Fisher's exact test as appropriate, whereas continuous variables were compared by Mann-Whitney U Test. A p-value of 0.05 was determined to be significant.

Results

Of the 210 patients who received ECMO during the study time period, 39 (19%) patients were diagnosed with COVID-19 or influenza. All patients received the venovenous modality of ECMO. Four (10%) patients who completed their ECMO course were still inpatient and thirty-five (90%) patients had completed their hospital course as of October 10, 2020 with a survival rate to hospital discharge of 72%.

There were minimal differences in the demographics of patients who underwent ECMO with influenza or COVID-19 (**TABLE 1**) with no significant difference in age, sex, comorbidities, hours on ECMO, length of hospitalization, or survival to discharge. All patients with COVID-19 were treated with immunosuppression during their hospital course. Patients with COVID-19 were hospitalized longer prior to ECMO cannulization than patients with influenza (median [IQR] 12 [8-14] days vs. 5 [3-8], p=0.001).

For the primary outcome, patients with COVID-19 had greater rates of nosocomial infections while on ECMO (37.3 per 1000 patient days vs. 17.7, p=0.04). There was a trend towards more blood stream infections (21.8 vs. 13.2, p=0.31), and respiratory infections (15.6 vs. 4.4, p=0.19) per 1000 patient days, but neither was statistically significant. Infections occurred earlier after cannulation in patients with COVID-19 (median day 5 [3-8] vs. 16 [10-21], p=0.03). However, there was no difference in day of infection after hospital

admission (19 [14-26] vs. 21 [16-25], p=0.92). MDROs were isolated at similar frequencies between the two groups (17% vs. 36%, p=0.60).

There were no statistical differences between the organisms isolated the two groups (**TABLE 2**). The most common organisms isolated in the blood of patients with influenza were yeasts, while gram positives were most commonly isolated in the blood of patients with COVID-19.

Discussion

This study compares patients with respiratory viruses requiring ECMO support and shows an elevated infection rate for patients with COVID-19. The reasons for these differences are likely multifactorial and includes strain on the healthcare system, the use of immunosuppressants, and possible COVID-19 disease-specific characteristics. Overall, the rate of infections of 37.1 per 1000 patient days in patients with COVID-19 is higher than the national average for all adults who receive ECMO of 30.6[6]. 36% of infections in our COVID-19 cohort were MDRO. Previous studies have shown the use of PPE alone is not been sufficient to prevent the spread of MDROs in intensive care units[9]. This study adds that increased PPE usage and general emphasis on infection prevention are also not enough to prevent nosocomial infections inpatients with COVID-19. Adherence to infection prevention bundles was not assessed during this time. It is also possible that the desire to conserve PPE during COVID-19 related shortages led to consolidation of patient tasks and potentially delay to assessment of the need

for central line dressing changes, positioning checks, and other common practices.

Infections tended to occur earlier in the ECMO course for patients with COVID-19 than for patients with influenza. Despite the same length of time on ECMO circuit between the two groups, no patient with COVID-19 had an infection after day seventeen on ECMO, whereas there were five infections after that day in patients with influenza. The reason for this difference is unclear. This may imply that there is a physiologic or treatment difference early in the ECMO course of patients with COVID-19 that disappears later in the course. While immunosuppression may be the culprit, further studies are needed to evaluate the individual risk factors contributions to nosocomial infection risk.

There are several limitations to this retrospective single center study including the small number of patients may be underpowered to detect differences in specific type of infections and MDROs. Secondly, COVID-19 and influenza have different pathophysiology and this study cannot differentiate whether nosocomial infections are caused by a failure of infection prevention practices or due to differences in the underlying disease process. Finally, we have no data on adherence to PPE and hand hygiene, although at our institution PPE for patients with COVID-19 was donned and doffed using the buddy system.

This study compared critically ill patients that presented with similar demographics to an established ECMO center with adequate resources throughout the pandemic. It shows that the risk of nosocomial infections is significant for this population. Infection control strategies should continue to be implemented that protect healthcare workers, with ongoing emphasis on adherence to infection and prevention and control bundles. However, there may still be nosocomial infections for COVID-19 patients on ECMO due to unrecognized factors. Larger, multicenter trials, with COVID-19 patients are needed to help determine best practices for treatment of these patients to reduce nosocomial infections.

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Table 1: Characteristics of patients receiving extracorporeal membrane oxygenation (ECMO) with influenza or COVID-19[1]

	All	Influenza (n=22)	COVID-19 (n=17)	P-value[2]
Age, years	43 (34-53)	45 (32-55)	42 (35-49)	0.76
Male	28 (70%)	15 (68%)	13 (76%)	0.72
Comorbidities				
Obesity	25 (63%)	15 (68%)	10 (58%)	0.51
Hypertension	13 (33%)	8 (36%)	5 (29%)	0.74
Diabetes mellitus	11 (28%)	6 (27%)	5 (29%)	1
COPD	3 (8%)	3 (14%)	0	
Sleep apnea	4 (10%)	3 (14%)	1 (6%)	0.61
Tobacco use	2 (5%)	1 (5%)	1 (6%)	1
Asthma	3 (8%)	1 (5%)	2 (12%)	0.57
Days in hospital Before ECMO	8 (4-13)	5 (3-8)	12 (8-14)	0.001
Hours on ECMO	360 (200-610)	360 (196-604)	321 (191-441)	0.93
Length of Hospitalization	38 (27-47)[3]	36 (28-43)	38 (28-54)[3]	0.43
Survival to Discharge	26 (67%)[3]	17 (89%)	9 (69%)[3]	0.46
Days to first ECMO infection after cannulation	8 (5-16)	18 (10-21)	5 (3-7)	0.01
Days to first ECMO infection after	20 (14-26)	21 (16-25)	19 (14-26)	0.92

hospitalization				
Patients with infections				
Any	18 (46%)	8 (36%)	10 (58%)	0.22
Blood Stream Infection (BSI)	13 (33%)	6 (27%)	7 (41%)	0.60
Respiratory Infection (RI)	7 (18%)	2 (9%)	5 (29%)	0.21
Urinary Tract Infection (UTI)	1 (3%)	1 (5%)	0	
Infections per 1000 ECMO Days				
Total	27.2	17.7	37.3	0.04
BSI	16.8	13.2	21.8	0.31
RI	9.1	4.4	15.6	0.19
UTI	1.3	2.2	0	0.79
Multi-drug resistant bacteria	5/17 (29%)	1/6 (17%)	4/11 (36%)	0.6

[1]Presented as number (%) or median (interquartile range)

[2] Chi-squared, Fisher's exact or Wilcoxon Rank Sum

[3]Excludes 4 patients with COVID-19 who were still inpatient as of 10/10/20

Table 2: Causative organisms of nosocomial infections in patients receiving extracorporeal membrane oxygenation[1]
[1]Number of days after cannulation until infection is shown in parentheses

Diagnosis	**Influenza**	**COVID-19**
Blood Stream Infection	*Candida albicans* (20) *Candida parapsilosis (63)* *Enterococcus faecalis* x 2 (22,22) *Kodamaea ohmeri (0)* *Pseudomonas aeruginosa (21)*	*Acinetobater baumannii (6[2])* *Candida dubliniensis (14)* *Enterococcus faecalis (17)* *Staphylococcus epidermidis (5[2])* Methicillin-sensitive *Staphylococcus aureus* x2 (2,8) Methicillin-resisant *Staphylococcus aureus* (3[2])
Respiratory Infection	*Pseudomonas aeruginosa* x2 (10[2],10)	*Enterobacter cloacae* (7) *Klebsiella oxytoca* (9) Methicillin-sensitive *Staphylococcus aureus* (5) *Pseudomonas aerginosa* x2 (2,5[2])
Urinary Tract Infection	*Escherichia coli* (16)	

[2]Multidrug resistant organism