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The Morbidity and Mortality of Patients with Fungal Infections Before and During Extracorporeal Membrane Oxygenation Support

Thomas Pluim, MD[1], **Natasha Halasa, MD, MPH**[2], **Sharon E. Phillips, MSPH**[3], and **Geoffrey Fleming, MD**[1]

[1]Department of Pediatrics, Division of Critical Care, Vanderbilt University School of Medicine, Nashville, TN

[2]Department of Pediatrics, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, TN

[3]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN

Abstract

Objective—To evaluate the prevalence of fungal infections (both pre- and post-cannulation) while on extracorporeal membrane oxygenation (ECMO) support and the associated morbidity and mortality.

Design—Retrospective cohort study.

Patient and Methods—The Extracorporeal Life Support Organization (ELSO) database is an international voluntary registry of clinical data for patients placed on ECMO. The database was queried for all patients on ECMO from 1997–2009. Patient and ECMO data collected included age, support type, length of support, infection status and organism code, discharge status, complications and component failures. Outcomes of interest were mortality, ECMO related patient complications, and mechanical component failures.

Results—From 1997–2009, there were 21,073 patient ECMO runs analyzed of which 12,933 were in the neonatal group (0–30 days), 6,073 were in the pediatric group (31 days-< 18 years old), and 2,067 were in the adult group (≥ 18 years). The prevalence of fungal infection during ECMO varied by age group and timing of infection and ranged from 0.04% to 5%. Fungal infections pre- and on-ECMO conferred a statistically significant higher relative risk of mortality for all age groups and varied by support type and timing of infection. ECMO related complications and component failures were not statistically significantly affected by infection status.

Conclusions—Fungal infection before or during ECMO increases the odds of mortality and the magnitude of this effect is dependent upon age-group and timing of infection. This increased mortality was not the result of increased patient or mechanical complications during ECMO. For patients with fungal infections pre-ECMO, 82–89% demonstrated presumed clearance during ECMO. Although the risk of mortality increased with fungal infections, it does not appear that

Contact Information: Geoffrey M. Fleming MD, 5112 Doctors Office Tower, 2200 Children's Way, Nashville, TN 37232, Ph: 615-936-3983, Fax: 615-936-3467, Geoffrey.fleming@vanderbilt.edu.

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fungal infection before or during ECMO is a contraindication to initiation or continuation of support.

Keywords

ECMO; mycoses; respiratory failure; cardiac failure; neonate; child; adult

Background

Nosocomial infections are known complications for patients managed in intensive care units (ICUs) and are associated with increased mortality in this group. Multiple factors put this patient population at increased risk for infection including critical illness, co-morbid medical conditions, multi-organ failure and decreased innate immunity. Additionally, therapeutic tools such as indwelling vascular lines, endotracheal and urinary catheters may promote microbial overgrowth by bypassing natural protective barriers and further increasing infection risk. Concomitant use of antimicrobial agents may alter both colonization burdens and antimicrobial resistance further increasing the risk and effect of infections. Catheter associated blood stream infections (CA-BSI) in pediatric ICU's are estimated to account for 21–39% of nosocomial infections, depending on the age of the patient [1–3], with an overall unadjusted mortality of approximately 27% vs. 8.1% in those patients without a CA-BSI. [4, 5] Bacterial pathogens remain the predominant causative organisms in CA-BSI's [1, 2]; however fungal pathogens are significant contributors, especially in patients treated with broad-spectrum antibiotics.[6, 7] *Candida* species have been found to be the fifth most common cause of nosocomial infections [1, 5, 8, 9] and the third most common cause of CA-BSI.[10]

Patients on extracorporeal membrane oxygenation (ECMO) support have many of the risk factors for nosocomial infections listed above, including additional large bore indwelling catheters and often have multi-organ failure.[2, 3, 11, 12] From previous reports, the most common causative organisms for infections while on ECMO are bacterial, but fungal organisms are notable contributors to nosocomial infections.[6, 13, 14] The rates of CA-BSI's are much higher in ECMO patients than the critically ill population and infections on ECMO are associated with an increased mortality.[6, 15, 16] Previous work from the Extracorporeal Life Support Organization (ELSO) registry found that neonates on ECMO with fungal infections had a much higher mortality as compared to bacterial infections, 57.7% vs. 30.6% respectively.[16] To date no comprehensive study of the demographics and epidemiology of fungal infections during ECMO outside of limited patient groups, organism classifications or individual center experiences exsits.[17–21] A recent study of infections, both bacterial and fungal, from the ELSO registry reported that fungal infection was the second most frequently acquired infection during ECMO.[22]

The ELSO registry (Ann Arbor, MI) provides a unique opportunity to study fungal infection on ECMO as it represents the near complete experience for this cohort of patients. Previously published reports of infections from the ELSO database were focused on neonates and pediatric patients with sepsis, of whom a small subgroup was identified with fungal etiologies. [23, 24] To make recommendations regarding antimicrobial practices, it is important to understand the full breadth and scope of the issue, including the association of patient and support-type variables associated with fungal infection. The purpose of this study is to describe the prevalence of fungal infections during extracorporeal life support and describe the effect of infection on morbidity and mortality. The authors hypothesize that the presence of fungal infection during ECMO increases component failure, complications and mortality. This study will give a broader context in which to interpret surveillance and prophylaxis practices which have been previously described in the literature. Additionally,

these data will likely help practitioners with patient selection and management practices in the face of fungal infection.

Methods

The ELSO database is an international voluntary registry of clinical data for adult, pediatric and neonatal patients placed on ECMO, in which de-identified patient information data are submitted to the Registry. IRB approval for study was obtained from the sponsoring institution prior to data collection and included a waiver of consent for this study. We queried the ELSO Registry for neonatal, pediatric and adult patients on ECMO from 1997–2009. This period was chosen to best reflect current practice and outcomes driven by perceived changes in ICU practice, antimicrobial resistance patterns, and newer antimicrobial agents.

Patient and ECMO data collected included age, support type, length of support, infection status and organism code, discharge status, component failure, complications and year of support. Infection was considered to have occurred if the database contained an organism code on the registry data-form. The data-form contains two entry points for organism code, Pre-ECMO and On-ECMO without further time stamp, and patients could have organism codes reported pre-ECMO, on-ECMO or in both fields (all-ECMO). Fungal infections were divided into four mutually exclusive infection groups; None (no fungal organism code), Cleared (pre-ECMO organism only), Acquired (on-ECMO organism code only), Persistent (same organism code in both Pre-ECMO and On-ECMO). Of note, the registry at the time did not provide further data such as culture reports, site of infection or timing of infection. The organism codes were sub-divided into *Candida* and Non-*Candida* species. Patient age was divided into three groups: neonate (0–30 days old), pediatric (31 days-<18 years old) and adult (≥ 18 years old) patients. Support type was categorized as venoarterial if the registry included an arterial component (i.e. VA, or VVA) or venovenous if there was no arterial component (VV, VVV, double lumen VV, etc.). Outcomes of interest studied were mortality, patient complications and component failures. Patient complications and mechanical component failures listed in the registry are shown in Appendix 1.

All initial ECMO runs were incorporated in the analysis and were considered independent events for the purposes of analysis. Subsequent ECMO runs for an individual patient were excluded from analysis. Runs were excluded if information from the data fields of interest were missing, including year, gender, discharge status, support type, and patient age.

Statistical Analysis

Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Inc. Cary, NC) and R version 2.11 (2010-05-31) (R Foundation for Statistical Computing). Separate multivariable analyses were performed using logistic regression for all patients and for each age subgroup to examine the effect of fungal infection on mortality. Independent variables included in the model were total hours on ECMO, total number of complications, age, pre-ECMO fungal infection status, on-ECMO fungal infection status, gender, and support type. These variables were chosen *a priori* by the authors based on previously published findings.

Baseline and outcome characteristics were examined within each age group using the Welch Two Sample t-test or the Nonparametric Kruskal-Wallis test for continuous variables and the Chi Square test for categorical variables. A p-value <0.05 was considered to be significant. Between groups analysis was not performed on the three age groups studied (neonates were not compared with pediatric and adult patients). Within each age group studied, differences in outcome were examined by infection status for all variables of interest including timing of infection, fungal species and ECMO support type.

Results

Of the 21,073 runs analyzed, there were 12,933 neonatal, 6,073 pediatric, and 2,067 adult patients. Two hundred forty five runs were excluded from further analysis due to missing data points (patient sex). Patient demographics for each age group are shown in Table 1. For all age groups, there was a slight male predominance for those patients who received ECMO support. However, for all age groups, there was not a gender difference between the patients who developed fungal infections prior to versus after cannulation.

Entire Cohort

The majority of fungal infections were due to *Candida* species, regardless of patient age or timing of infection. There was not a statistically significant difference in the mortality risk of patients with *Candida* vs. non- *Candida* fungal infections for any age group or support type. (Table 2) Fungal infection was associated with an increased mortality risk as compared to no infection in all age groups studied and varied depending upon the timing of infection and support type in univariate analysis. (Table 3) In multivariable analysis, fungal infection at all time points had a significant effect on odds of mortality, including persistent fungal infection throughout the ECMO course from pre-ECMO to on-ECMO.(Table 5) No effect was seen regarding fungal infection status for patient complications or mechanical component failures in any group analyzed.

Conversion of Infection Status

Patients could have four distinct infection classifications related to ECMO with none, fungal infection acquired during ECMO (on-ECMO organism code), previous fungal infection cleared during ECMO (pre-ECMO organism code) and persistent infection throughout the course of ECMO (all-ECMO). These data are presented in table 4. Of the 12894 neonatal patients who had no infection pre-ECMO, 99% remained culture negative during their ECMO run, and 1% developed a fungal infection on-ECMO. Of the neonatal patients with pre-ECMO fungal infections, 87% had negative organism code entries on-ECMO, while 13% continued to have positive fungal organisms reported. In both the pediatric and adult populations a similar proportion presumably cleared the fungal infection at 82% and 89% respectively. As seen in table 5, fungal infection increased the odds of mortality in both the cleared (pre-ECMO) and acquired (on-ECMO) infection groups, however persistence of fungal infection throughout the ECMO course (all-ECMO) was significantly associated with mortality only in analysis of the entire cohort.

Neonate

For the neonatal group, the prevalence of fungal infections pre-ECMO, on-ECMO, and all-ECMO was 0.26% (34/12,933), 0.9% (118/12,933), and 0.04% (5/12933) respectively. Mortality for the entire neonatal cohort without infection was 35%, 42% for the subgroup of patients on VA support and 15% for patients on VV support. Univariate analysis results of the raw mortality among neonatal patients with fungal infections, and odds ratio of mortality as compared to patients with no infections, divided by timing of infection and support type groups are shown in table 3. Neonates with fungal infections had a significantly greater risk of mortality as compared to neonates without infection, more so in those patients who developed fungal infections on-ECMO with an OR of 4.77 as compared to no infection. There was no statistically significant change in complication or component failure rates for neonatal patients with fungal infection as compared to those without fungal infection. The patient complication rates ranged from 79–85%, whereas the mechanical component failure rates ranged from 31–41% in all groups studied. Multivariable analysis for the risk of mortality demonstrated neonates with on-ECMO fungal infection had a significantly higher

risk of death as compared to no infection when controlling for duration of ECMO, number of complications, age, sex and support type. (Table 4)

Pediatric

In the pediatric group, the prevalence of fungal infections pre-ECMO, on-ECMO, and all-ECMO was 0.96% (58/6,073), 2.8% (173/6073), and 0.21% (13/6,073) respectively. Mortality for the entire pediatric cohort without infection was 54%, 50% for the subgroup of patients on VA support and 69% for patients on VV support. Mortality on VA support was not compared with mortality on VV support, however univariate analysis results for pediatric patients are reported in table 3 by support group and timing of infection. In the pediatric population, fungal infections conferred significantly greater odds of mortality as compared to no infection in all support type and timing of infection groups analyzed and was highest (8.27) in the VV support cleared infection group. (Table 3) There was no statistically significant change in complication or component failure rates for pediatric patients with fungal infection as compared to those without fungal infection. The patient complication rates ranged from 77–94% whereas the mechanical component failure rates ranged from 35–42%. Multivariable analysis for the risk of mortality demonstrates pediatric patients with fungal infection have a significantly higher risk of death in cleared and acquired infection groups as compared to no infection when controlling for duration of ECMO, number of complications, age, sex and support type. (Table 4)

Adult

The prevalence of fungal infections in adult patients pre-ECMO, on-ECMO, and both pre- and on-ECMO was 1.6% (33/2,067), 5% (106/2,067) and 0.2% (4/2067) respectively. Mortality for the entire adult cohort without infection was 45%, 35% for the subgroup of patients on VA support and 62% for patients on VV support. Univariate analysis results of the raw mortality among adult patients with fungal infections, and odds ratio of mortality as compared to patients with no infections, divided by timing of infection and support type groups are shown in Table 3. Although age group, support type and timing of fungal infection impacted the mortality risk of neonatal, pediatric and adult patients, adult patients with cleared fungal infections who were placed on VA ECMO had the highest OR for mortality of any patient sub-group in the entire analysis. There was no statistically significant change in complication or component failure rates for adult patients with fungal infection as compared to those without fungal infection. The patient complication rates ranged from 81–87% whereas the mechanical component failure rates ranged from 38–44%. Multivariable analysis for the risk of mortality demonstrated adults with cleared fungal infection have a significantly higher risk of death as compared those without infection when controlling for duration of ECMO, number of complications, age, sex and support type. (Table 4)

Discussion

This study supports our *a-priori* hypothesis that fungal infections increase the risk of mortality for patients on ECMO in all age groups. However, contrary to our hypothesis, we found ECMO complications and component failures were not increased in the setting of a fungal infection. Additionally, we demonstrate 82–89% of all individuals with fungal infection pre-ECMO became fungal culture negative on-ECMO representing the group with potentially cleared infections.

The increased mortality associated with fungal infections is consistent with anecdotal experience in critically ill patients as well previously published associations with infection and mortality during ECMO.[16] The presence of fungal infection was associated with

increased risk of mortality, however, overall mortality rates were not substantially higher than other groups supported with ECMO.[25] Contrary to previously published data, ECMO complication and component failure rates were not affected by fungal infection status in this study.[24] We hypothesized *a priori* there would be higher rates of complication and component failures associated with fungal infection, yet there was little variance in either of these outcomes. The authors conclude that the presence of fungal infection should not be the primary determining factor in a practitioner's decision to initiate or discontinue ECMO support, although it remains an important co-morbidity to be considered. The exception to this finding is the sub-group of adult patients with fungal infections prior to requiring VA support who have a 10 fold increase in odds of death compared to patients with no fungal infection.

The infection conversion status data demonstrate that >80% of pre-ECMO fungal infections are presumably cleared during ECMO. This study does not provide sufficient evidence to determine the variable associated with clearance such as anti-fungal administration, and a recent survey of ECMO center practices demonstrates a wide variation in antifungal practices.[26] However, this topic will become an important avenue of research as acquisition and clearance of infection is associated with changes in survival, both in the current study and a recent ELSO analysis of infections acquired on ECMO.[22] Subgroup analysis of mortality by age group found slight differences based on the timing of infection and likely reflect differences in severity of illness, baseline age group ECMO survival and multiple organ dysfunction. No specific variables were collected or analyzed to determine the exact etiology of the difference in mortality risk by age group. Additionally, the graded response to infection resembles the overall age group survival rate on ECMO with neonates having survival rates far greater than adults in general. Further studies could investigate the impact of specific organisms (i.e. *Candida* subspecies), infection surveillance and control practices and specific diagnoses (ARDS, trauma, etc) on patient mortality during fungal infection.

This study has multiple limitations all related to the retrospective analysis of a data registry repository. A significant limitation of this study is the lack of more specific data regarding the timing of infection, including absence of an organism code in the on-ECMO category because of death prior to obtaining the culture. Patient management strategies beyond ECMO are not reported, yet may have had significant effects on outcomes, such as timing, duration and choice of antimicrobial agents. Infection site (blood, trachea, urine) was not included in the registry at the time and is an important limitation of this analysis as site of infection is likely to affect outcomes. Additional limitations of this study beyond the registry include lack of uniformity in practice of infection control, chemo-prophylaxis and screening for infection in the ECMO population among all participating centers. Finally, no severity of illness score exists in the registry.

Conclusions

Fungal infections in patients who require ECMO support are associated with an increased risk of mortality that is not driven by patient complications or component failures. Despite this increased risk of mortality, most patient groups had a likelihood of survival within the range of other groups reported from the ELSO registry. From these data the authors conclude that ECMO is a viable support option for most patients with fungal infection, with a significant proportion of patients presumably clearing the infection on-ECMO. Further investigation will be needed to identify the specific strategies associated with modulation of and prevention for fungal infections on ECMO.

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Table 1

Patient demographics, divided by age groups (neonate, pediatric, adult). VA: venoarterial, VV: venovenous.

	Neonate	Pediatric	Adult
Total N	12933	6073	2067
VA Support % (N)	74%(9542)	83% (5014)	61% (1260)
VV Support % (N)	26% (3391)	17% (1059)	39% (807)
Mean Age	4.1 (days)	3.7 (yrs)	44.6 (yrs)
Male % (N)	58% (7514)	53% (3205)	60% (1246)
Mean Duration of Support (hrs)	187.7	206.7	185.2

Table 2

Demographics of fungal infections in ECMO patients, separated by timing of infection and fungal species. Fungal species are designated as *Candida* or non-*Candida* species. For each subgroup, the specific prevalence and associated patient mortality is shown. Univariate analysis of mortality between fungal species groups within each age group demonstrated no significant differences with $p > 0.05$.

Neonates	***Candida* Sp**	**Non-*Candida* Sp**	**p value**
Prevalence of Pre-ECMO Infection	91.2% (31)	8.8% (3)	
Mortality of Patients with Pre-ECMO Infection	61% (19/31)	33% (1/3)	0.3475
Prevalence of On-ECMO Infection	84% (99)	16% (19)	
Mortality of Patients with On-ECMO Infection	70% (69/99)	89% (17/19)	0.0757
Pediatrics	*Candida* Sp	Non-*Candida* Sp	p value
Prevalence of Pre-ECMO Infection	92% (52)	8% (6)	
Mortality of Patients with Pre-ECMO Infection	69% (36/52)	50% (3/6)	0.3419
Prevalence of On-ECMO Infection	84% (145)	16% (28)	
Mortality of Patients with On-ECMO Infection	58% (84/145)	57% (16/28)	0.9384
Adults	*Candida* Sp	Non-*Candida* Sp	p value
Prevalence of Pre-ECMO Infection	82% (27)	18% (6)	
Mortality of Patients with Pre-ECMO Infection	81% (22/27)	67% (4/6)	0.4220
Prevalence of On-ECMO Infection	81% (86)	19% (20)	
Mortality of Patients with On-ECMO Infection	50% (43/86)	35% (7/20)	0.2261

Table 3

Odds Ratio of mortality of ECMO patients with fungal infections, as compared to patients on ECMO with no fungal infection. Age group data are divided by ECMO support type sub-group. Significant increases in mortality as compared to no infection are indicated in **bold** typeset. Four distinct infection categories exist; no infection, infection acquired during ECMO (on-ECMO), previous fungal infection cleared during ECMO (pre-ECMO) and persistent infection throughout ECMO (all-ECMO). OR = Odds Ratio

Neonates	**Acquired**		**Cleared**		**Persistent**	
	N	**OR (95% CI)**	**N**	**OR (95% CI)**	**N**	**OR (95% CI)**
All Neonates	86/118	**4.77** (3.18–7.17)	20/34	**2.51** (1.26–4.97)	3/5	2.63 (0.44–15.72)
VA Support	79/102	**4.54** (2.85–7.24)	18/29	**2.14** (1.01–4.53)	3/3	
VV Support	7/16	**3.97** (1.47–10.7)	2/5	3.38 (0.56–20.27)	0/2	
Pediatrics	**Acquired**		**Cleared**		**Persistent**	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
All Pediatrics	100/173	**1.59** (1.17–2.15)	39/58	**2.36** (1.36–4.10)	10/13	**3.82** (1.05–13.88)
VA Support	78/131	**1.49** (1.05–2.12)	28/44	1.76 (0.95–3.27)	8/11	
VV Support	22/42	**2.51** (1.35–4.66)	11/14	**8.27** (2.29–29.84)	2/2	
Adults	**Acquired**		**Cleared**		**Persistent**	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
All Adults	50/106	0.72 (0.49–1.06)	26/33	**3.09** (1.33–7.14)	3/4	2.46 (0.26–23.67)
VA Support	34/59	0.73 (0.43–1.24)	18/19	**10.03** (1.33–75.37)	3/3	
VV Support	16/47	0.77 (0.41–1.42)	8/14	2.03 (0.7–5.92)	0/1	

Table 4

Infection status conversion by patient group. Four distinct infection status categories exist; no infection, infection acquired during ECMO (on-ECMO), previous fungal infection cleared during ECMO (pre-ECMO) and persistent infection throughout ECMO (all-ECMO).

			Pre-ECMO	
			None, n(%)	**Fungal, n(%)**
On-ECMO	Neonates		n=12894	n=39
		None, n (%)	12776 (99)	34 (87)
		Fungal, n(%)	118 (1)	5(13)
	Pediatrics		n=6002	n=71
		None, n (%)	5829 (97)	58 (82)
		Fungal, n(%)	173 (3)	13 (18)
	Adults		n=2030	n=37
		None, n (%)	1924(95)	33 (89)
		Fungal, n(%)	106 (5)	4 (11)

Table 5

Multivariable analysis of risk of mortality. Independent variables included in the model were total hours on ECMO, total number of complications, age, timing of fungal infection and support type. Fungal infections as an independent variable conferred an increased odd risk of mortality for the entire cohort in all infection timing subgroups. Significant increases in odds ratio of mortality are indicated in **bold** typeset. Four distinct infection status categories exist; no infection, infection acquired during ECMO (on-ECMO), previous fungal infection cleared during ECMO (pre-ECMO) and persistent infection throughout ECMO (all-ECMO). OR= Odds Ratio

	Acquired	Cleared	Persistent
Age Group	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
All Patients	**1.46** (1.17–1.82)	**2.19** (1.46–3.27)	**3.29** (1.19–9.10)
Neonates	**2.54** (1.63–3.95)	1.34 (0.62–2.87)	3.35 (0.47–23.7)
Pediatrics	**1.43** (1.04–1.97)	**2.11** (1.19–3.73)	3.45 (0.92–12.98)
Adults	0.73 (0.48–1.10)	**2.91** (1.21–6.97)	1.73 (0.14–21.47)

Appendix 1

Patient complications and component failure (listed as mechanical complications) encoded in the ESLO registry.

System	Complications
Cardiovascular	Cardiac arrhythmia, CPR required, Hypertension requiring vasodilators, Inotropes on ECLS, Myocardial stun by echo, PDA: bidirectional/ L->R, Tamponade: air/ blood
Hemorrhagic	Cannulation site bleeding, Disseminated intravascular coagulation (DIC), GI hemorrhage, Hemolysis (Hgb > 50 mg/dl), Surgical site bleeding
Infectious	Culture proven infection; WBC < 1,500
Metabolic	Glucose < 40, Glucose > 240, Hyperbilirubinemia (> 2 direct or > 15 total), pH < 7.20 or > 7.60
Neurologic	Brain death clinically determined, CNS hemorrhage by US/CT, CNS infarction by US/CT, Seizures: clinically determined, Seizures: EEG determined
Pulmonary	Pneumothorax requiring treatment, Pulmonary hemorrhage
Renal	CAVHD required, Creatinine > 3.0, Creatinine 1.5 – 3.0, Dialysis required, Hemofiltration required
Mechanical	Cannula problems, Clots: bladder/ bridge/ hemofilter/ other/ oxygenator, Cracks in pigtail connectors, Other tubing rupture, Oxygenator failure, Mechanical: Pump malfunction, Raceway rupture