Nosocomial infections during extracorporeal membrane oxygenation in neonatal, pediatric and adult patients: A comprehensive narrative review

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Abstract

Objective: Extracorporeal membrane oxygenation (ECMO) is increasingly used in critically ill patients with refractory cardiopulmonary failure. Nosocomial infection acquired during ECMO represents one of the most frequent complications but the available evidence on the risk of infection and its association with outcomes has not been comprehensively analyzed. We performed a narrative review examining the epidemiology of nosocomial infection during ECMO; association with clinical outcomes; and preventive strategies.

Data sources: We searched PubMed, Web of Science, EMBASE, and the Cochrane Library between 1972 and June 2018.

Study selection: We included any article which detailed nosocomial infection during ECMO. Articles were excluded if they were not written in English, detailed ECMO use for infections acquired prior to ECMO, or used other forms of extracorporeal support such as ventricular assist devices.

Data extraction: Two reviewers independently assessed eligibility and extracted data. We screened 984 abstracts and included 59 articles in the final review.

Data synthesis: The reported risk of nosocomial infection among patients receiving ECMO ranged from 3.5 to 64% per ECMO run, while the incidence of infection ranged from 10.1 to 116.2/1000 ECMO days. Nosocomial infections during ECMO were consistently associated with longer duration of ECMO and, in several large multicenter studies, with increased mortality. Risk factors for nosocomial infection included duration of ECMO; mechanical and hemorrhagic complications on ECMO; and use of venoarterial and central ECMO. Biomarkers had low specificity for infection in this population. Few studies examined strategies on how to prevent nosocomial infection on ECMO.

Conclusions: Nosocomial infections in ECMO patients are common and associated with worse outcomes. There is substantial variation in the rates of reported infection and thus it is possible that

some may be preventable. The evidence for current diagnostic, preventive and therapeutic strategies for infection during ECMO is limited and requires further investigation.

Introduction

Over the past decade, extracorporeal membrane oxygenation (ECMO) has been more widely used to treat refractory respiratory and cardiac failure around the world. ECMO is associated with a number of potentially life-threatening complications, in particular bleeding, thrombosis and infection (1-5). While recent improvements in technology may have lowered the risk of thrombosis and hemorrhage (1,2), nosocomial infections pose particular challenges both for diagnosis and management. ECMO support can last for weeks or even months, with consequent risks of blood stream infections (BSI), ventilator-associated pneumonia (VAP), and cannula-site infections. Diagnosing infection in patients on ECMO can be challenging because exposure of blood to the artificial surface of the machine can elicit a systemic inflammatory response even in the absence of infection and the heater-cooler used to regulate body temperature makes detection of a febrile response to infection difficult.

Nosocomial infection during ECMO has received comparatively little attention until recently (2). Since the influenza A(H1N1) pandemic in 2009 and the subsequent adoption of ECMO by many adult hospitals (6-10), there has been a substantial increase in studies reporting on this issue. These studies report considerable differences in the rates and sites of infection during ECMO.

In order to design strategies addressing the diagnosis, management, and prevention of infection during ECMO more effectively, a comprehensive analysis of the available literature is required. We conducted a comprehensive narrative review in order to examine the epidemiology of nosocomial infections during ECMO, risk factors for infection, and association with outcomes.

Methods

We conducted a literature search using the databases from PubMed, Web of Science, EMBASE, and the Cochrane Library for articles published between 1972 (the first reported use of ECMO (4)) and June 2018. The search was performed using the Preferred Reporting Items for Systematic Review

and Meta-analyses (PRISMA) as a guideline (http://www.prisma-statement.org). Articles which were in press and available online were also reviewed. The following search terms were used: 'extracorporeal membrane oxygenation', 'extracorporeal life support', 'infection', 'sepsis', 'nosocomial', 'ventilator associated pneumonia', 'urinary tract infection', 'bloodstream infection', 'central line associated bloodstream infection', 'device associated infection', 'bacteremia', '*Clostridium difficile*', 'pseudomembranous colitis', 'healthcare associated infection', 'fungal infection', 'neonatal', 'pediatric', 'adult'. Studies were included if they contained data on infectious complications acquired during ECMO, including incidence, risk, prevalence, outcomes, risk factors, diagnostic tools, or preventive strategies. Studies were excluded if they (i) were not published in English, (ii) consisted solely of case reports, conference abstracts, or editorial correspondence, (iii) were duplicate publications, (iv) detailed ECMO use in the treatment of specific infections, ie. those acquired prior to ECMO rather than during it, (v) or referred to other forms of extracorporeal support such as ventricular assist devices.

The abstracts from the combined search were reviewed independently by two authors (GM and LS) and those meeting inclusion criteria underwent full-text review for data extraction. No formal quantitative methodology was used to formally assess quality or bias. Neonates were defined as infants less than one month old, pediatric patients as children between 1 month and <18 years, and adult patients 18 years old or older.

Results

The literature search identified 984 articles of possible relevance. Nine hundred and seventeen were excluded following review of title and abstract. The remaining 67 articles were reviewed as full texts (11-77). A further 8 articles were excluded, leaving 59 articles for review (Figure 1). No further articles were identified through the reference sections of the identified articles or other searches.

The publication dates of the 59 studies ranged from 1994 to 2018, showing a substantial increase in publication frequency in recent years (Supplementary Digital Content - Figure 2). Thirty-eight (64%) of these publications were observational studies which presented original data on the incidence or risk of acquiring nosocomial infections during ECMO, including six (10%) using the international, multicenter database of the Extracorporeal Life Support Organization (the ELSO Registry). Of these 38 studies, 6 (16%) focused exclusively on neonatal patients, 11 (29%) on a combination of neonatal and pediatric patients, 18 (47%) on adult patients, and 3 (8%) included patients of all ages. The remaining 21 studies reported complications of ECMO as a whole without focusing exclusively on or in detail about infection, or they examined specific problems such as the diagnostic utility of biomarkers. There were no randomized studies of strategies to prevent infection

Epidemiology

The definitions of nosocomial infection during ECMO varied markedly between studies. In the 38 reports cited that presented comprehensive original data, 4 (11%) did not provide any definition of hospital-acquired infection (11,13,15,27). Eighteen (47%) provided their own definitions, ranging from any positive bacterial culture to clinical suspicion of infection (16,17,19,20,21,26,30,34,38,49,50,59,61,66,69,70,71,77). Sixteen (42%) studies used established definitions: 13 employed those recommended by the Centers for Disease Control (CDC) and Prevention National Healthcare Safety Network (18,25,28,31,32,36,39,48,51,56,57,60,72), two used the Infectious Diseases Society of America criteria (55,73), and one used the UK Public Health Laboratory Service Nosocomial Infection National Surveillance Scheme 1997 criteria (24).

Early studies of the epidemiology of nosocomial infection during ECMO measured the risk of infection (cumulative incidence per ECMO run) rather than the incidence (incidence per day). These studies were confined to neonates and observed a risk of nosocomial infection during ECMO support between 3.5-4.6% (11,13,15), with a mean duration on ECMO in one study of 225 (±130) hours in those with nosocomial infection compared to 140 (±88) hours without (13)

Single-center studies of pediatric patients observed a higher risk of infection, ranging from 15-42% (17,21,27,60,61,69). Single-center studies of adult patients reported a risk of infection ranging from 8-64% (18,25,28,36,38,39,48,49,51,55-57,66,70,72,73). In a study of the ELSO Registry published in 2011 which combined data from over 100 centers, 2418 (11.7%) of 20,741 patients of all ages were found to have acquired infection during ECMO (26). The incidence rate was 10.1/1000 ECMO days in neonates, 20.8/1000 days in pediatric patients, and 30.6/1000 days in adult patients. A considerably higher incidence of infection has been noted in some single center studies (Table 1). In the six studies of adult patients within the last decade which employed the CDC definition of infection, the incidence of blood-stream infection ranged from 2.98 to 16.0/1000 ECMO days (25,28,36,39,56,72).

Site of infection and causative pathogens

Thirty studies provided a breakdown on the type of infection. These included bloodstream infections, VAP, cannula-site infection, and urinary tract infection. In patients who had surgery prior to ECMO, surgical site infections accounted for fewer than 10% of infections (31,36,38,59). Blood-stream infections were common in neonatal and pediatric patients (21,24) while VAP was the most common type of infection in adult patients (36,38,55).

Thirty-one studies presented the causative pathogens for nosocomial infection during ECMO. The most common pathogens were coagulase-negative *Staphylococcus* species (spp), *Pseudomonas aeruginosa*, and *Candida* spp (15,18,19,21,24,26,31,34,36,48,56,57,60,61,71). Enterobacteriaceae (typically *E*.coli and *Klebsiella pneumoniae*) were the most common pathogens in two studies (39,66) while environmental Gram-negative bacteria such as *Stenotrophomonas maltophilia* or *Acinetobacter* spp were most commonly identified in four series (28,51,55,73). Neonatal and pediatric studies commonly reported infections with coagulase negative staphylococci and *Candida* spp (15,19,21,26,77).

Three studies described unusual organisms causing infections in ECMO patients, related to contamination of the heater-cooler with environmental Gram-negative organisms such as *Ralstonia picketii*, leading to bacteremia in the patients (74-76). More recently, *Mycobacterium chimaera* was identified in the heater-cooler units and was subsequently found in patients' respiratory tracts (75,76).

Diagnostic strategies

Early diagnosis of nosocomial infection in ECMO patients is difficult because of the heater-cooler device maintaining constant body temperature, thus making any underlying fever challenging to detect. One strategy used to identify infection is to send surveillance cultures from multiple sites at regular intervals. In one study of 187 neonatal patients, daily surveillance cultures were sent from blood and endotracheal tube aspirates (20). Urine samples were sent every other day. Of 2423 cultures taken, 155 (6.4%) were positive but only thirteen (0.9%) of 1370 blood cultures were positive, in comparison to 137 (16%) of 850 tracheal aspirates and 5 (2.3%) of 203 urine cultures. The authors concluded that surveillance cultures were not helpful because only one blood culture out of 1370 led to a change in management. The authors estimated that abandoning the practice of surveillance cultures would save at least USD$1000 per patient. The Extracorporeal Life Support Organization subsequently recommended that surveillance cultures should not be performed because of a lack of evidence supporting their use and because they are unlikely to be cost-effective (78).

A potentially more promising strategy is the use of biomarkers to identify infection before it becomes clinically apparent. Only 4 studies were found reporting on infection markers, in a total of 65 adult patients and 47 children (32,37,58,65). One study of 27 ECMO patients investigated the sensitivity and specificity of procalcitonin and C-reactive protein (CRP) at identifying patients subsequently confirmed to have infection (32). Combining the results of both assays showed good sensitivity (87%) but poor specificity (26%). Another study of 38 patients did not demonstrate any

association between procalcitonin levels and the occurrence of nosocomial infection during ECMO (65). Similarly conflicting results were found in both pediatric studies (37,58).

Risk factors for nosocomial infection

Thirty studies identified risk factors for developing nosocomial infection during ECMO. A consistent observation across many studies was that longer duration of ECMO was associated with increasing incidence of infection (Table 2). In one multicenter retrospective study of 20,741 patients, nosocomial infections during ECMO were associated with significantly longer duration of support, irrespective of age (26). Those receiving ECMO for less than one week had 6.1% risk of infection, compared to 15.7% of those patients receiving ECMO for between 8-14 days, and 30.3% for those receiving ECMO for more than 2 weeks ($p < 0.001$). In the adult patients in this study, the risk of infection was 12.8% in those receiving ECMO for less than a week, compared to 51.6% in those receiving ECMO for more than two weeks ($p < 0.001$).

Studies identified several risk factors for nosocomial infection. Venoarterial ECMO was associated with the highest infectious risk irrespective of age (26). Central cannulation appeared to be associated with higher risk of infection than peripheral cannulation. The incidence of nosocomial infection was 24.9/1000 ECMO days in all patients in one study but 65.1/1000 ECMO days in children receiving central ECMO (24). Peripheral ECMO was associated with significantly fewer infections than central ECMO (OR 0.08, 95%CI 0.01-0.5, $p=0.007$). In another study of 141 neonatal and pediatric patients, 36% with an open chest developed at least one episode of nosocomial infection compared to 19% with peripheral ECMO ($p=0.003$)(21). In a study of 58 children receiving ECMO after cardiac surgery, nosocomial infection was more commonly seen in patients who required mediastinal re-exploration, suggesting that even brief periods of opening the chest may increase the infection risk (27% vs 6%, $p=0.02$)(27).

Another risk factor for nosocomial infection related to the conduct of ECMO was the number of mechanical complications. In one multicenter study of 38,661 patients, mechanical complications such as oxygenator failure or pump malfunction were significantly associated with infection (OR 1.16, 95%CI 1.01-1.33, p=0.04 in pediatric patients; OR 1.54, 95%CI 1.22-1.95, p<0.001 in adult patients)(30). Hemorrhagic complications during ECMO and a history of immunosuppression also appear to be associated with an increase in the risk of nosocomial infection (28,56,73).

Outcomes

The earliest studies of nosocomial infection during ECMO were exclusively of neonatal patients and consistently showed significantly increased mortality in those who developed nosocomial infection, ranging from 35-52% mortality in those with infection compared to 13-21% in those without (11,13,15). These studies also demonstrated an increase in both mechanical and patient complications, including circuit thrombosis, oxygenator failure, seizures, gastrointestinal bleeding and renal dysfunction, seen in those with infection. While the majority of more recent single center studies have not demonstrated a consistent association between nosocomial infection and mortality (Table 3), the largest multicenter studies have observed a positive association (26,30). For example, in a study of 38,661 ECMO patients, mortality was significantly higher in those with infection, irrespective of age (30). Nosocomial infection is also commonly associated with a longer duration of hospital stay (36,39).

A number of studies have demonstrated an association between the infecting microbe and survival, with some reporting worse outcomes seen in fungal and Gram negative infections (15,30,31,70). However, this is not a consistent observation, particularly in adult patients (34,71).

Prevention

Four studies assessed the effects of an intervention aimed at preventing infection in ECMO patients. None of these studies were randomized and only one was conducted prospectively. No studies of

the effectiveness of basic ICU management strategies such as VAP prevention bundles or improving pressure care were identified. One single center prospective study examined the introduction of a sequential policy change in the pediatric ICU to reduce the incidence of nosocomial infection (24). These changes included (i) re-education for the ICU team; (ii) a change in the caps facilitating access to the ECMO circuit, preventing blood from coming into contact with air at any time; (iii) electively pre-priming the ECMO circuit; and (iv) reducing the use of central ECMO when feasible.

The effect of these changes was a reduction in the incidence of infection episodes from 29.3/1000 ECMO days to 20.1/1000. There were marked changes in patients on ECMO for respiratory support, with a reduction in neonatal patients from 28/1000 to 6.2/1000 and in pediatric patients from 42.4/1000 to 16.9/1000. However, there was no comparable reduction in the incidence of infection in those children on ECMO for cardiac support, despite a significant reduction in the number of children managed with an open chest (83% vs 36%, $p<0.001$).

A retrospective study attempted to address the question of whether using antifungal prophylaxis in children during ECMO for cardiac support might be associated with improved outcomes (31). Lack of antifungal prophylaxis was associated with an increased risk of any fungal infection (OR 2.8, 95%CI 1.2-6.7, $p=0.016$). However, there was no difference in the rates of candidemia between those receiving prophylaxis and those who did not (2.4% vs 4.5%, p value not significant). We did not identify any interventional studies providing evidence to support the use of routine prophylactic antibiotics in ECMO patients to prevent nosocomial infection.

Discussion

This review highlighted that nosocomial infections during ECMO are common and appear to more frequently affect older children and adult patients. These infections are associated with longer duration of ECMO and, in the largest studies, increased mortality. Risk factors for nosocomial

infection other than the duration of ECMO include mechanical and bleeding complications on ECMO and the use of venoarterial and central ECMO. Diagnosis of nosocomial infection in these patients remains challenging and there is a lack of evidence to support the routine use of surveillance cultures or of biomarkers such as procalcitonin and C-reactive protein. Few studies have been conducted attempting to assess the effectiveness of anti-infective preventive measures on ECMO. Overall, the quality of studies was low with the vast majority being retrospective single-center or registry-based multicenter studies. Prospective observational studies were scarce and no randomized controlled trials were identified.

The review highlighted considerable variation in the epidemiology of infection during ECMO. This may have been due to changes in clinical practice over the 25 years of the studies analysed in this review, the heterogeneity of the patient populations studied, or differences in the definitions of nosocomial infection. Almost all studies were conducted in high-income countries, predominantly Europe and North America, with two exceptions from middle-income countries, China and Turkey (53,60). The preponderance of single center studies and the lack of granularity in the ELSO Registry make it difficult to assess the degree to which local management policies may influence epidemiology. One consistent finding was the relationship between longer ECMO duration and increasing risk of infection. It seems likely that longer ECMO runs are simultaneously both a risk factor for and a consequence of nosocomial infection.

Preventing infection in ECMO patients has received comparatively little attention. A simple means of preventing infection might be the administration of prophylactic antimicrobial agents. Although there is no evidence to support using prophylactic antibiotics, two surveys with responses from 132 and 85 ECMO centers, published in 2011 and 2016 respectively, reported that between half to three-quarters of the responding centers used antibiotic prophylaxis regardless (29,45). There is slightly more evidence to support the use of antifungal prophylaxis (31), but there are substantial limitations to the available studies, including reporting bias and poor internal validity. No report has evaluated

using prophylactic antibiotics for the duration of the ECMO run, although it has been advocated in specific circumstances such as central ECMO (24). A more recent international survey again demonstrated that surveillance cultures, biomarkers, and prophylactic antibiotics are commonly used, despite the lack of evidence (79).

This review identified a number of limitations with existing studies. First, the majority were retrospective, single-center studies. Those reports which used multicenter data from the ELSO Registry likely had substantial overlap of patients in some of them. Second, there was considerable variation in the definitions of nosocomial infection used, ranging from established definitions such as those of the Centers for Disease Control, through study-specific definitions with varying degrees of rigor, to no definition of what constituted infection. Several studies did not provide details on how infection and colonisation were differentiated (17,20,26,30,34,38,49,59,61,71) and others reported on specific infections such as BSI but excluded others. These factors are likely to have had a substantial impact on the reported incidence, risk factors and outcomes. Third, most studies estimating excess length of ECMO support due to infection did not adequately control for the onset time of infection during ECMO and thus may have suffered from time-dependent bias (80). Fourth, there was no risk-adjustment for severity of illness and indication for ECMO on the risk of infection. Finally, we identified very little research into how to prevent infection during ECMO.

Limitations to this review are that only English language studies were examined and the heterogeneity of the patient populations and study design of included publications did not facilitate a meta-analysis of the data. The nature of the reports included did not allow attribution of cause and effect but merely demonstrated associations.

In conclusion, nosocomial infections during ECMO are common and are strongly associated with adverse outcomes. The overall quality of studies in this field was low, with substantial heterogeneity in study design, case definitions, and outcomes, which limit the generalizability of the findings. Prospective, multicenter studies characterizing the early diagnosis, treatment and prevention of

these infections in ECMO patients are required. The use of consistent, established definitions such as those of the CDC is vital in future research, which may facilitate the development of practice guidelines to standardize care of ECMO patients in this regard, limit the use of unnecessary antibiotics and improve outcomes.

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Figure legends

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart

Supplementary Figure 2: Publications by year, from 1972 until June 2018