

Sepsis Associated with Extracorporeal Membrane Oxygenation

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Abstract

Keywords

- ▶ extracorporeal membrane oxygenation
- ▶ sepsis
- ▶ ventilator-associated pneumonia

Sepsis in patients on extracorporeal membrane oxygenation (ECMO) remains a serious complication. Its presence is a poor prognostic marker and increases overall mortality. Adult patients with prolonged duration on ECMO are at high risk of developing sepsis. Ventilator-associated pneumonia and bloodstream infections are the main sources of infection these patients. A strong early suspicion, drawing adequate volume for blood cultures, and early and timely administration of empirical antibiotics can help control the infection and decrease the morbidity and mortality. The diagnostic and the treatment are both challenging. Cardiac patients have increased risk of nosocomial infection while on ECMO, which may be in part due to longer cannulation times, as well as increased likelihood of undergoing major procedures or having an open chest.

Introduction

With a better understanding of the principles used in extracorporeal membrane oxygenation (ECMO), there is a growing number of centers performing ECMO. Sepsis in patients on ECMO remained a serious complication. Its presence is a poor prognostic marker and increases overall mortality. Adult patients with a prolonged duration of ECMO are at high risk of developing sepsis. Ventilator-associated pneumonia (VAP) and bloodstream infections (BSIs) in these patients are the main sources of infection. A strong early suspicion, drawing adequate volume for blood cultures, and early and timely administration of empirical antibiotics can help control the infection and decrease morbidity and mortality. Utmost care should be undertaken to maintain sterility and integrity of the ECMO circuit while managing these patients. Regular hand washing, keeping the sample sites cleaned and closed, and regular follow-up of the inflammation markers are some of the

standard practices that can be instituted in every patient on ECMO. These practices are of paramount importance in infection control in this high-risk population.¹

ELSO Data on Infections Associated with ECMO

The Extracorporeal Life Support Organization (ELSO) registry was created in the year 1989 to facilitate the advancement of extracorporeal life support (ECLS) care through research and benchmarking. The first original ECMO registry included a total of 50,667 ECMO runs. Survival to discharge in the adults was 55%, in the pediatric age group it was 56%, and in the neonates it was 75%. The respiratory complication with culture-positive infections was 20.9% and reported as the leading adverse event.

In a study by Bizzaro et al, a total of 20,741 (11.7%) ECMO cases were included and overall, 2,418 infections were

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reported for a rate of 15.4 per 1,000 ECMO days. Rates were highest in the adult versus the pediatric and neonatal populations (30.6 vs. 20.8 vs. 10.1 infections per 1,000 ECMO days, respectively) and those necessitating extracorporeal cardiopulmonary resuscitation (ECPR) 24.7 infections per 1,000 ECMO days. Prevalence of infection increased with the duration of ECMO support from 6.1% of those requiring ECMO for less than or equal to 7 days to 30.3% of those requiring ECMO for more than 14 days ($p < 0.001$).²

According to the ELSO Registry International Report 2016, on 78,397 patients there was 58% survival to hospital discharge. The patient's age at the time of ECMO deployment was categorized as neonatal (≤ 30 days), pediatric (respiratory ECLS > 30 days to less than or equal to 18 years; cardiac ECLS: > 30 days to 16 years), and adult (respiratory ECLS > 18 years and cardiac ECLS > 16 years). The infection was associated with 7.1% of the total adverse events in neonates on ECMO, 11% in pediatric patients on ECMO, and 13% in adult patients on ECMO.³

In a review by Abrams et al, published in 2020, sepsis was mentioned as one of the most commonly reported adverse events during ECLS. Although it was difficult to ascertain if the infections were sequelae of prolonged clinical illness or were hospital-acquired, they may not be attributable to the presence of ECLS itself.⁴

A study by multiple correspondence analysis and hierarchical ascendant classification on complications of ECMO has demonstrated that out of the 145 patients studied, 65 (44.8%) finally developed sepsis, as determined by the Simplified Acute Physiology score. The median duration of ECMO was 7 (4–11) days. Overall, 15.9, 22.1, 25.6, 24.1, and 12.4% of patients presented, respectively, with zero, one, two, three, and more than three of the five complications studied (all variables except death, i.e., sepsis, major transfusion, thrombotic event, major bleeding, and renal replacement therapy).⁵

Peitz et al studied the incidence and characterization of sepsis in the ECMO population and showed that out of 89 patients included in the study, 41.6% developed sepsis after ECMO cannulation. Factors contributing to sepsis include high severity of underlying illness, disease-induced compromised immune systems, and a large number of indwelling medical devices.⁶

NI Associated with ECMO

The Centre for Disease Control-defined ECMO-associated nosocomial infection (NI) as occurring within 24 hours of the institution of ECMO or 48 hours of discontinuation of ECMO.

Patients receiving ECMO are also at risk of developing typical intensive care unit (ICU)-related NIs, for example, VAP, BSIs, urinary tract infections, in addition to ECMO-specific infections, such as localized infections at peripheral cannulation insertion sites or mediastinitis in the setting of central cannulation. The overall NI rate ranged between 9 and 65% in different case series.^{7–10}

Schmidt et al in their study on 220 patients reported a rate of NI of 64% for their 220 patients under VA-ECMO.¹¹ VAP, BSIs,

cannula infections, and mediastinitis infections occurred in 55, 18, 10, and 11% of the patients, respectively. More critical condition at ICU admission, but not antibiotics at the time of ECMO cannulation, was associated with subsequently developing NIs (hazard ratio, 0.73; 95% confidence interval [CI], 0.50–1.05; $p = 0.09$). Infected patients had longer durations of mechanical ventilation, ECMO support, and hospital stay. Independent predictors of death were infection with severe sepsis or septic shock (odds ratio, 1.93; 95% CI, 1.26–2.94; $p = 0.002$) and Simplified Acute Physiology Score II (SAPS II) whereas immunosuppression and myocarditis as the reason for ECMO support were associated with better outcomes.¹¹

A recent single-center observational study of 92 patients by Grasselli et al, receiving ECMO (87% venovenous ECMO), in whom infections were systematically and prospectively identified through the application of well-established clinical practice guidelines,^{12,13} reported high rates of NIs (55%), with VAP and multidrug-resistant organisms, found to be common.¹⁴ Those who acquired NIs had higher overall mortality, longer mechanical ventilation, and ECMO durations, and spent longer in the ICU. Younger age (2–35 years old) was independently associated with a higher risk of NIs.¹⁵

The ELSO registry data documenting positive cultures during ECMO administered for respiratory failure, cardiac failure, and cardiac arrest. ECMO for respiratory failure showed the highest rate of positive cultures during ECMO (64.9%), whereas ECPR showed the lowest rate (22%). The distribution of pathogens during ECMO was found to be similar to the pre-ECMO pattern. The survival rates of individuals with positive cultures during ECMO administered for respiratory failure or cardiac failure were lower than the overall survival rates of all ECMO recipients over a similar timeframe (54.3 vs. 61.1% and 38.0 vs. 44.2%),¹⁵ whereas survival among culture-positive ECPR patients was the lowest of the three groups but comparable to that observed in the general ECPR population (30.2 vs. 29.9%).¹⁶

Mediators of Infection and Inflammation

The systemic inflammatory syndrome initiated by the infection of the whole blood and the extracorporeal circuit is mediated by complements like proinflammatory cytokines (interleukin-6 [IL-6], IL-8) and tumor necrosis factor-alpha. Following an initial immune response, ECMO induces a further risk of developing sepsis. A full septic screen, including bronchoalveolar lavage for microbial examination, choosing appropriate antibiotic coverage covering unusual organisms along with the local patterns of pathogens and resistance can help control infection and sepsis. The use of a computed tomography (CT) scan to rule out any abdominal and pelvic collection and early drainage of the such collection can help aggressive early source control.¹⁷

Organisms Isolated in Patients on ECMO

The results of an ELSO registry search for all infectious organisms identified on culture between 2012 and 2019 were summarized. The registry data search revealed 5,492

positive cultures before the initiation of 17,374 distinct ECMO runs for respiratory failure (31.6%). Positive cultures before ECLS appeared to be much more common in the case of ECMO administered for respiratory failure than for cardiac indications (8.8% of cardiac failure runs; 7% of runs for ECPR), with the respiratory tract being the most frequent site throughout.

Regardless of ECMO indication, *Staphylococcus aureus* and yeast were consistently reported among the most common respiratory tract pathogens. Notably, influenza A was the most commonly identified organism in the respiratory tract in patients receiving ECMO for respiratory failure, accounting for 12.7% of all organisms identified. Yeast, *Escherichia coli*, and *Enterococcus* were common pathogens in the urine.

The most commonly isolated organisms in patients developing VAP on ECMO were gram-negative (70%) with the highest incidence for *Pseudomonas aeruginosa* (18–26%), while coagulase-negative staphylococci were the most commonly isolated gram-positive organisms. *Candida* species and *Enterococcus* were also commonly reported. This should be considered when selecting antibiotics for empiric therapy.^{7,15,18}

Recommendations by ELSO for Infections during ECMO¹⁹

- The ECMO circuit must be treated as a protected central line. Avoid “breaking” the line unnecessarily. Routine sampling from the circuit should be avoided if other sites are accessible.
 - Use needleless hubs
 - Use chlorhexidine prep rather than alcohol or betadine
- Only continuous infusions should be administered via the circuit to minimize “breaking” the sterility of the lines, including heparin, inotropes, vasopressors, narcotics, and sedation.
- Avoid pairing the care of ECMO patients with other patients with highly resistant organisms or with grossly contaminated wounds or serious infections.
 - Frequent hand washing and easy access to cleansing solutions.

Risk Factors for the Development of Infections during ECMO

It has been suggested, initially, in patients undergoing cardiopulmonary bypass, that extracorporeal circuitry affects the immune system through multiple mechanisms (e.g., induction of endothelial dysfunction, activation of the contact system, coagulation cascade, neutrophils, and platelets with consequent release of proinflammatory mediators),²⁰ and that the resulting immune system impairment might explain why ECMO may increase susceptibility to infection.

In contrast to this supposed hyperinflammatory response to ECMO, there exist equally compelling data suggesting that ECMO promotes an anti-inflammatory state through improvements in end-organ perfusion and gas exchange in

patients with severe cardiopulmonary failure and reductions in proinflammatory injury (e.g., ventilator-induced lung injury).^{21,22} A prospective observational study of 262 adult patients with severe acute respiratory distress syndrome (ARDS) reported a rapid decline in IL-6 and IL-8 levels within 24 hours of the start of venovenous ECMO. Higher cytokine levels were associated with extrapulmonary causes of ARDS, more aggressive ventilation before ECMO, and mortality.²³ The overall balance between pro- and anti-inflammatory effects (i.e., whether end-organ protective strategies outweigh the injurious effects of ECMO) likely determines the impact on the immune response and the consequent risk of infection. Whether these alterations pose an increased risk of infection after decannulation from ECMO is an area that warrants further investigation.²⁴

Antibiotics

No data to support the routine use of antibiotics for patients on ECMO support simply for prophylaxis, without specific culture or physiologic evidence of ongoing infection. The use of antibiotics in patients with transthoracic cannulation through open chest wounds should be based on clinical judgment. Prophylactic antibiotics for cannulation should follow standard principles of surgical prophylaxis, and a single dose, or at the most 24 hours of coverage can be justified with either open or percutaneous cannulation techniques.

Altered pharmacokinetics can affect the disposition of the commonly used antibiotics during ECMO. Other important factors are hemodynamic instability, concurrent drug therapy, mechanical ventilation, nutrition support, concurrent disease states, protein binding alterations, or endogenous cytokine release. The large surface area of the ECMO tubing and membranes can lead to drug sequestration and therefore induce a large volume of distribution.^{5,25}

Prevention of Systemic Infections

- Follow VAP prevention guidelines.
- Consider early tracheostomy in adult patients.¹⁴
- Early and complete enteral nutrition should be used.
- Dedicated site for hyperalimentation.
- Remove all unnecessary lines, access, and devices.
- Avoid the insertion of new indwelling long-term intravenous access (tunneled or cuffed catheters) while on ECMO due to the risk of hematoma formation and subsequent infection.

Diagnosis of Infection

- Patients who can generate fevers of as little as 101 or greater while on “full-flow” ECMO are likely to have extremely strong inflammatory responses, and should be checked very carefully for other signs of infection and treated appropriately. The reliability of leukocytosis and leukopenia as a predictor of infection or sepsis in patients on ECMO is poor.

- Thrombocytopenia is common.
- The significance of inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate on ECMO is unknown. The chest X-ray is frequently opacified due to inflammatory changes on ECMO, particularly early in the course, and is thus a poor tool for the diagnosis of pneumonia.
- The suspicion and diagnosis of infections and sepsis on ECMO require specific clinical observations of pyuria, purulent secretions at bronchoscopy, or drainage of pus from an open wound, as well as recognition of changes in the general clinical condition, signs of poor perfusion or inadequate oxygen delivery as manifested by increasing lactate levels, decreasing urine output, metabolic acidosis, rise in the hepatic transaminases, general hemodynamics, etc. Procalcitonin is an upcoming prognostic marker of infection in these patients.
- Use of diagnostic tests such as CT scans and bronchoscopy, and the aggressive re-exploration of wounds and body cavities that are at risk of infection.
- Blood, urine, and tracheal cultures should be obtained from patients on ECMO only when there is a significant clinical suspicion of localized or systemic infection. From an infectious disease standpoint ONLY, ECMO circuits sterilely constructed and primed with electrolyte solutions (no glucose, albumin, or blood) may be safely maintained for up to 30 days and possibly beyond, without increased risk of infection.¹⁷

Summary

Among all the complications of ECMO, sepsis stands out prominently. This high-risk patient group is more likely to develop VAP and BSI. VAP on ECMO is associated with increased mortality and a longer ICU length of stay. Although microorganisms involved in VAP on ECMO are similar to classical epidemiology of ventilated ICU patients, the diagnostic and the treatment are both challenging. Cardiac patients have an increased risk of NI while on ECMO, which may be in part due to longer cannulation times, as well as increased likelihood of undergoing major procedures or having an open chest. The reliability of leukocytosis and leukopenia as a predictor of infection or sepsis in patients on ECMO is poor.^{12,13}

Conflict of Interest

None declared.

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