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Nosocomial Infections in Extracorporeal Membrane Oxygenation

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ABSTRACT

Extra corporeal membrane oxygenation (ECMO) has become an important modality in ICU for treating patients with severe hemodynamic and respiratory failure. It helps clinicians gain time for the primary disease to recover with definitive treatment, and aids in cardio pulmonary recovery of the patient. Most of the patients who require ECMO support are quite sick and fragile. Nosocomial infection is second most common complication after hemorrhage in ECMO patients.It affects about two-third of patients receiving ECMO. There is a lack of sufficient knowledge in this particular area. More focused efforts should be made in future to combat nosocomial infection in ECMO patients.

Keywords: Infection, ECMO, ICU, Nosocomial

INTRODUCTION

Extra corporeal membrane oxygenation (ECMO) has become an important modality in ICU for treating patients with severe hemodynamic and respiratory failure. It helps clinicians gain time for the primary disease to recover with definitive treatment, and aids in cardio pulmonary recovery of the patient. The two most common indications for ECMO are cardiogenic shock and acute respiratory distress syndrome (ARDS).[1]

ECMO is an invasive technique requiring insertion of single or double lumen cannulae in to central vessels.

Most of the patients who require ECMO support are quite sick and fragile. By virtue of having more severe disease, these patients are more likely to require other invasive procedures such as bronchoscopy, arterial and central lines, and renal replacement therapy. In addition, there is activation of inflammatory mediators by ECMO circuit that along with primary disease leads to significant immunosuppression in these patients. Thus, with a compromised defense mechanism and abundant exposure to foreign surfaces, these patients are at a higher risk of acquiring secondary infections.

Diagnosis of superadded infections in patients with ECMO is quite challenging and is determined by many confounding factors as discussed further.[2,3]

EPIDEMIOLOGY AND OUTCOME

Nosocomial infection in ECMO has been defined as an infection not present at the start of ECMO support but detected at least more than 24 h after ECMO initiation, or within the first

48 h after ECMO discontinuation, and with a pathogen that is different from that detected within 7 days before ECMO commencement.

Nosocomial infection is second most common complication after hemorrhage in ECMO patients. It affects about two-third of patients receiving ECMO. Among nosocomial infections, ventilator associated pneumonia (VAP), and blood stream infections (BSI) at two most common ones, followed by surgical wound infection urinary tract infection and cannulation related infection.

Several factors associated with increased nosocomial infection risk in patients on ECMO are adult age, immunosuppression, severity of underlying illness, longer duration of ECMO support, longer ICU stay, and use of VA-ECMO. The respiratory tract is most frequently involved site of acquired infection in these patients. BSI is also quite frequent because ECMO patients frequently require multiple cannulations and lines in major vessels disrupting the skin's protective barrier with potential contamination of the multiple entry ports of these devices. Unfortunately, even if BSI occurs in these patients, ECMO catheter removal is not an option as patients are either hemodynamically unstable or severely hypoxic.

Overall prevalence of hospital acquired infection in ECMO in adults has been found to be 21% approximately. It is been found to range from 10% to 12% as per the extracorporeal lung support organization (ELSO) registry, to 9–65% in some of the single center studies. Nosocomial infections in these patients with preexisting delicate clinical state lead to increase mobility and length of hospital stay. The risk of death increases by 38–63% in these patients.[4-6]

ETIOLOGY

For nosocomial respiratory tract infections regardless of the configuration of ECMO support, organisms are similar to those found in VAP in general ARDS patients. Most common organisms are *Staphylococcus aureus*, *Pseudomonas,* and *Klebsiella* species. The prevalence of BSI has been found to range between 3% and 18%, and incidence is about 2.98–20.55 episodes per 1000 ECMO days. The most common organisms are coagulation negative *Staphylococcus* species, *Candida*, *Enterococcus* species, *S. aureus,* and *Klebsiella* species. Candida BSI infection occurs most frequently during the 3rd week of venovenous extracorporeal membrane oxygenation (VV-ECMO), but it hass been found to occur as early as 13 days in patients receiving VA-ECMO.

The precise contribution of the ECMO circuit, concurrent use of central line, arterial line, and the cannulation strategy in nosocomial infection is yet to be explored. As of now, we do not have any clear recommendations regarding the diagnosis of ECMO cannula-related infection and infection of the ECMO circuit. ECMO cannula colonization was found to be as high as 33% with 9% risk of infection in one study. Another retrospective study had shown oxygenator colonization rate of 11.6% that was found to be associated with lower survival as compared to the non-colonized group.[7]

RISK FACTORS

Patients on ECMO are at a higher risk of having new infections when compared to other ICU patients. Multiple factors are supposed to contribute such as immunological impairment, heightened inflammatory response, colonization of ECMO cannula, and disruption of skin protection. Studies have found that longer duration of ECMO puts the patients at increased risk of infection. An association has been observed between nosocomial infection and mechanical complications, cannulation technique and circuit configuration. Central VA-ECMO is supposed to carry the highest risk of infection. Interhospital transport of ECMO patients has not been found to increase the risk of infection.[7-9]

DIAGNOSIS

It is quite often challenging to pick up a new infection in patients on ECMO. This is because the analytical and clinical signs are usually masked by the extracorporeal therapy in the patients. Patients may not spike fever as frequently heat exchanger is used in the circuit to maintain normothermia, and to replace ambient heat lost through the circuit in these patients. Exaggerated inflammatory response with activation of cellular and humoral systems may actually simulate the classical signs of infection. Utility of biomarkers such as C-reactive protein and procalcitonin in discriminating infection from inflammation has also been found to be unconvincing in these patients. In addition, it may be difficult to spot a new radiological shadow on a pre-existing ARDS on chest x-ray in these patients. Therefore, it is essential to have a high level of suspicion and a low threshold for invasive diagnostic procedures such as bronchoscopy or intrahospital transfer for detailed imaging in these patients to establish a masked infection in these patients. Minimal deterioration in clinical condition and signs of tissue hypoperfusion like elevated lactate levels, decreased urine output, deranged liver function tests, and metabolic acidosis may all point toward a brewing infection in ECMO patients.

Routine surveillance blood cultures cannot be strongly recommended in this group because of concerns about inappropriate treatment for contamination and increased risk of anti-microbial resistance.

A balanced approach of routine cultures, and on demand cultures, keeping risk factors in mind, maybe reasonable to pick up true infection. This, however, needs to be explored

further. Culture independent rapid diagnostic test also need to be studied in this population.[7,10]

TREATMENT

Documented infection in ECMO patients should be treated on the same principles as for other ICU patients who are not on ECMO support. Despite best efforts microbiological diagnosis may not be reached in about one-third of patients. Antibiotic therapy for nosocomial pneumonia and BSI should empirically be broad spectrum, which should be more focused once positive cultures are obtained. It is essential to be aware of institutional microbiological pattern, and prevalent anti-microbial resistance, to decide an appropriate initial therapy.

Antibiotics stewardship practices should be strictly adhered to, as for all critically ill patients. It should include appropriate empirical therapy, periodic reviews, and descalation based on culture reports. Empirical antibiotics regimes are listed in [Table 1].

ANTIBIOTICS IN ECMO

Interaction of antibiotics on ECMO has been found to be complex and may actually result in a suboptimal plasma level of antibiotics. ECMO may affect plasma levels of antibiotics by virtue of increased volume of distribution (VD) and circuit sequestration. Antibiotic strategies not accounting for these factors may lead to underdosing and subsequent treatment failures.

Circuit parameters which may alter pharmacokinetics are biofilm formation and circuit type. In addition, ECMO circuit comprises of large surface area, which may sequestrate antibiotics resulting in subtherapeutic plasma level of antibiotics. This particular effect is more pronounced in lipophilic drugs such as fluoroquinolones, macrolides, lincosamides, tigecycline, triazoles, and echinocandins. Despite being hydrophilic in nature, b lactam antibiotics such as meropenem, cefepime, and piperacillin-tazobactam are lost in significant proportion through the ECMO circuit leading to low plasma levels. In addition, there may be altered drug clearance, due to presence of renal and hepatic hypoperfusion and hypoxia. There is also increased VD secondary to hemodilution from priming solution, leaky capillaries, and altered protein binding. Patients should receive antibiotics directly through the intravenous catheter rather than in the ECMO circuit.[7,11-13]

Table 1: Antibiotics for hospital acquired infections.

Infection	Antibiotic regimen
VAP	Antipseudomonal cephalosporin OR carbapenem OR B-lactam/lactamase inhibitor PLUS antipseudomonal fluoroquinolone OR aminoglycosides PLUS vancomycin OR linezolid
CRBSI	Vancomycin PLUS carbapenem OR piperacillin-tazobactam PLUS fluconazole
CAUTI	Carbapenems OR BL/BLI combination±fluoroquinolone

VAP: Ventilator-associated pneumonia, CRBSI: Central line-related blood stream infections, CAUTI: Catheter-associated urinary tract infection

EFFECTIVENESS OF ANTIBIOTIC THERAPY IN ECMO PATIENTS

There are no randomized and controlled trials studying the success rates between patients receiving similar antibiotic regimen on mechanical ventilation versus patients on ECMO. However, several case reports have demonstrated that ECMO as a technology did not interfere which successful treatment with antibiotics. This aspect needs further analysis because theoretically it is convincing that antibiotic loss would be happening. However, we need a robust study design to address this issue. The clinical outcomes may not have been affected in these studies for two reasons: One that adsorption would decrease over a period of time due to saturation of the circuit, and second that the bactericidal drugs may still be remaining in the bacteriostatic range long enough to show a clinical response. However, it definitely needs more studies.[7]

ANTIMICROBIAL DOSING CONSIDERATIONS

Optimal dosing correlates with improved patient outcomes and sub-optimal antibiotic dosing would lead to treatment failure and rise in bacterial resistance. It has been suggested to keep the antibiotic doses on the higher end of the medications dosing range [Table 2].[7,13-15]

FUNGAL INFECTIONS IN ECMO

Patients requiring ECMO are not more predisposed to developing fungal colonization or infection as compared to routine critically sick patients. Candida bloodstream infection-related mortality has been observed to be higher as compared to other critically sick patients. *Aspergillus* infection typically has been observed in VV-ECMO for respiratory support and influenza patients.[7,16]

PREVENTION

A study carried out in cardiac surgery patients showed higher prevalence of infection in the ECMO group despite adhering to the similar standard of care with various bundles used in other critically sick patients. This may actually point toward a need for something more for infection prevention in ECMO patients. Another before and after study found extensive chlorhexidine disinfection of exposed ECMO

Table 2: Antibiotic dosing in ECMO.

Antibiotic	Standard dosing	ECMO dosing	Remarks
Aminoglycosides			
Amikacin	20 mg/kg OD	30 mg/kg OD	TDM
Gentamicin	4–7mg/kg OD	7–10 mg/kg OD	TDM
Beta lactams			
Meropenem	1 g q 8 H	2 g over 3 h q 8 H	TDM
Piperacillin/tazobactam	4.5 g q 6–8 H	4.5 g over 4 h every 8 h	TDM
Ceftriaxone	1–2 g q 12 H or 2 g q 12 H	Same	
Cefepime	1 g q 6 H or 1–2 g q 8–12 h	2 g over 3 h q 8 H	TDM
Fluoroquinolones			
Levofloxacin	500–1000 mg q 24 H	Same	
Ciprofloxacin	400 mg q 8–12 H	800 mg LD followed by 400–600 mg q 8 H	TDM
Glycopeptides			
Vancomycin	25–30 mg LD f/b 15–20 mg/kg/d q 8–12 H	30 mg/kg LD f/b 20 mg/kg/d q 8–12 H	TDM
Teicoplanin	10–12 mg/kg q 12H for first 3 doses then q 24 H	12 mg/kg i.v. LD every 12 h (for three to five doses) followed by 12 mg/kg every 24 h	TDM
Linezolid	600 mg q 12 H	600 mg q 8–12 H	
Tigecycline	100 mg LD f/b 50 mg q 12 H	Same	
Azithromycin	500 mg q 24 H	Same	
Echinocandins			
Micafungin	100–150 mg q 2h H	200 mg q 24 H	
Caspofungin	70 mg LD f/b 50 mg q 24 H	70 mg q 24 H	
Voriconazole	10–12 mg/kg for 2 doses f/b 8–9 mg/kg q 12 H	10 mg/kg q 12 H	TDM

TDM: Therapeutic drug monitoring, f/b: Followed by, LD: Loading dose, ECMO: Extra corporeal membrane oxygenation

circuits on a daily basis led to decreased colonization of ECMO cannula and subsequent infection. As per ELSO infectious disease task force, standard surgical prophylaxis is to be used for either surgical or percutaneous cannulations. Routine use of prophylactic antibiotics without any microbiological evidence is strongly recommended against.

Antifungal prophylaxis is one subject that needs to be studied in ECMO patients. As per the current guidelines by European Society of clinical microbiology and infectious disease, antifungal prophylaxis should be used for patients who are on mechanical ventilation, in hospital for more than 3 days, receiving antibiotics, and have a central line *in situ*. Candida scores have also been recommended.

It is worthwhile adding an antifungal drug in addition to empirical antibiotics in a suspected case of nosocomial infection in ECMO patient keeping in mind the high morbidity associated with fungal infection.

The ELSO infectious disease task force also recommends early tracheostomy to decrease the risk of VAP in these patients. Early tracheostomy would decrease the need of sedation promoting effective cough and airway clearance. Sometimes, extubation may also be practically possible in these patients. This should be considered whenever feasible.

All other standard VAP, central line related blood stream infections, and catheter-associated urinary tract infection bundles should be strictly adhered to as for other critically sick patients.[7,17]

CONCLUSION

Nosocomial infections in ECMO patients pose a real threat to life. It has been found to increase the mortality and morbidity in these patients. High clinical suspicion and an active look out for nosocomial infection are a must as the diagnosis is not straight forward in ECMO patients. Maximum efforts should be made toward therapeutic drug monitoring as ECMO has great pharmacokinetic implication for antibiotics and antifungals. There is a lack of sufficient knowledge in this particular area. More focused efforts should be made in future to combat nosocomial infection in ECMO patients.

Declaration of patient consent

Patient's consent not required as their identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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