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REVIEW

ECLS-associated infections in adults: what we know and what we don't yet know

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Abstract

Extracorporeal life support (ECLS) is increasingly used in the management of patients with severe cardiopulmonary disease. Infections are frequently the etiologies underlying the respiratory, and occasionally cardiac, failure that necessitates ECLS. Just as importantly, infections are among the most commonly reported adverse events during ECLS. Infections in this setting may be the sequelae of prolonged critical illness or of underlying immune dysregulation; they may be hospital-acquired infections, and they may or may not be attributable to the presence of ECLS itself, the latter being an aspect that can be difficult to determine. Current registry data and evidence from the literature offer some insights, but also leave open many questions regarding the nature and significance of infections reported both before and during ECLS, including the question of any causal link between ECLS and the development of infections. An ongoing lack of consistency in the identification, diagnosis, management, and prevention of infections during ECLS is limiting our ability to interpret literature data and thus highlighting the need for more rigorous investigation and standardization of definitions. This review aims to characterize the current understanding of infections associated with the use of ECLS, taking into account data from the updated Extracorporeal Life Support Organization Registry, which provides important context for understanding the epidemiology and outcomes of these patients.

Keywords: ECLS, ECMO, Infections, Complications, Nosocomial, ELSO registry

Introduction

The term extracorporeal life support (ECLS) refers to the use of mechanical support devices that provide gas exchange with or without hemodynamic support through an extracorporeal circuit. Blood is drained through a cannula situated in a central vessel (typically a vein), pumped through a membrane, where oxygen is delivered to the blood and carbon dioxide is removed, and then reinfused back through a cannula into a central vessel (vein or artery, depending on the circuit configuration and indication) [1]. Venovenous ECLS is the preferred configuration when there is severe gas exchange impairment, whereas venoarterial ECLS is the appropriate configuration for severe cardiac dysfunction, with or without concomitant respiratory failure [2, 3].

Severe forms of acute respiratory distress syndrome (ARDS) are the most common indication for venovenous ECLS, and presumed or proven infectious etiologies typically account for a large proportion of ARDS cases [4–6]. Cardiogenic shock, a condition resulting from a heterogeneous group of diseases, is the most common indication for venoarterial ECLS [1]; again, the underlying etiology may be related to an infectious trigger (e.g., sepsis-associated cardiomyopathy, acute myocarditis, infective endocarditis). A clear understanding of the epidemiology and outcomes associated with the various infectious etiologies of cardiopulmonary failure is essential in order to select the patients most likely to benefit from ECLS. Equally important is the ability to recognize and manage the infectious complications that can arise during ECLS, which may or may not be attributable to the

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device itself, and which may adversely impact outcomes. Administering ECLS involves the placement of intravascular catheters, which introduces a risk of both catheter site infections and catheter-associated blood stream infections [7]. The concomitant use of invasive mechanical ventilation in many of these patients exposes them to the risk of developing ventilator-associated pneumonia (VAP) [7, 8]. The ECLS population may be particularly susceptible to additional nosocomial infections as a result of concomitant critical illness and associated prolonged hospitalization, which often coincides with the use of other indwelling catheters (e.g., non-ECLS central venous catheters, urinary catheters, etc.) and devices (e.g., continuous renal replacement therapies, intra-aortic balloon pumps, percutaneous ventricular assist devices) [9]. Furthermore, underlying comorbidities, critical illness, or perhaps even the extracorporeal circuit itself, may cause immune dysregulation, potentially leading to a higher rate of infectious complications. The management of infections during ECLS is made even more challenging by alterations in the pharmacokinetics and pharmacodynamics of antimicrobial agents in the presence of both critical illness and extracorporeal circuitry [10, 11]. This narrative review aims to characterize the current understanding of infections associated with ECLS, discuss the challenges in identifying and treating these infections, and highlight areas where more data are needed to better understand the susceptibility to and impact of infections in patients managed with ECLS.

Infections prior to the initiation of ECLS

Both bacterial and viral pneumonia, when leading to severe acute respiratory failure, are common indications for venovenous ECLS [4–6, 12]. With regard to specific infectious organisms, one of the most widely reported indications for ECLS in ARDS is influenza A (H1N1), partly as a result of the rapid increase in the use of ECLS during the 2009 H1N1 pandemic. Data from several large observational studies suggest, overall, that there is a probable benefit to be derived from the use of ECLS in H1N1-associated severe ARDS refractory to conventional therapy [13–15]. Whereas no specific infectious etiology has been identified as a contraindication to the use of ECLS, co-infections in the context of influenza-associated ARDS, including infections with *S. aureus*, multidrug-resistant Gram-negative bacteria and *Aspergillus*, may correlate with lower survival compared with influenza alone [16–19]. Likewise, concomitant non-pulmonary infections at the time of initiation of ECLS for ARDS may predict worse outcomes and this factor has been incorporated into a validated prognostic scoring system [20].

Take-home message

Infections commonly precede and are frequently identified during ECLS. The current paucity of knowledge about the epidemiology and outcomes of ECLS-associated infections highlights the need for standardized definitions, consistent detection strategies, and more data, which might allow meaningful conclusions to be drawn regarding the clinical significance of these infections, and inform best practices for their prevention and management.

While infectious etiologies may account for a relatively small proportion of the indications for venoarterial ECLS in cardiac failure, certain subpopulations warrant consideration. Both acute myocarditis, which is often attributable to infection, and sepsis-associated cardiomyopathy are indications that may be associated with favorable survival rates [21–23].

The Extracorporeal Life Support Organization (ELSO) registry is the largest international repository of epidemiological data on ECLS. The results of an ELSO registry search for all infectious organisms identified on culture prior to the initiation of ECLS between January 1, 2012 (correlating with a reformatting of data entry within the registry for more extensive detail on infections) and July 31, 2019 are summarized in Figs. 1 and 3a, and in the Online Resource, with the most common pathogens listed by frequency. These data should be interpreted with caution, as culture positivity may not represent true infection, and the presence of these organisms prior to the initiation of ECLS may or may not have contributed to the cardiopulmonary failure that prompted the use of ECLS. Furthermore, when interpreting infections identified during ECLS, it is important to take into account any pre-ECLS infections; indeed, without a thorough understanding of what was present prior to ECLS, any pre-existing infections may incorrectly be characterized as de novo ones. With regard to the frequency of positive cultures, represented as a percentage of total ECLS runs, it is important to remember that individual patients may be represented by more than one culture. Additionally, registry data is self-reported by ELSO member centers, and may therefore be influenced by variability in data collection and in interpretation of data definitions; furthermore, these data, even if accurate, may not be representative of ECLS practices at non-ELSO-affiliated sites. Albeit subject to these important limitations and caveats, the registry data search revealed 5492 positive cultures prior to the initiation of 17,374 distinct ECLS runs for respiratory failure (31.6%). Positive cultures prior to ECLS appeared to be much more common in the case of ECLS administered for respiratory failure than for cardiac indications (8.8% of cardiac failure runs; 7% of runs for extracorporeal cardiopulmonary resuscitation

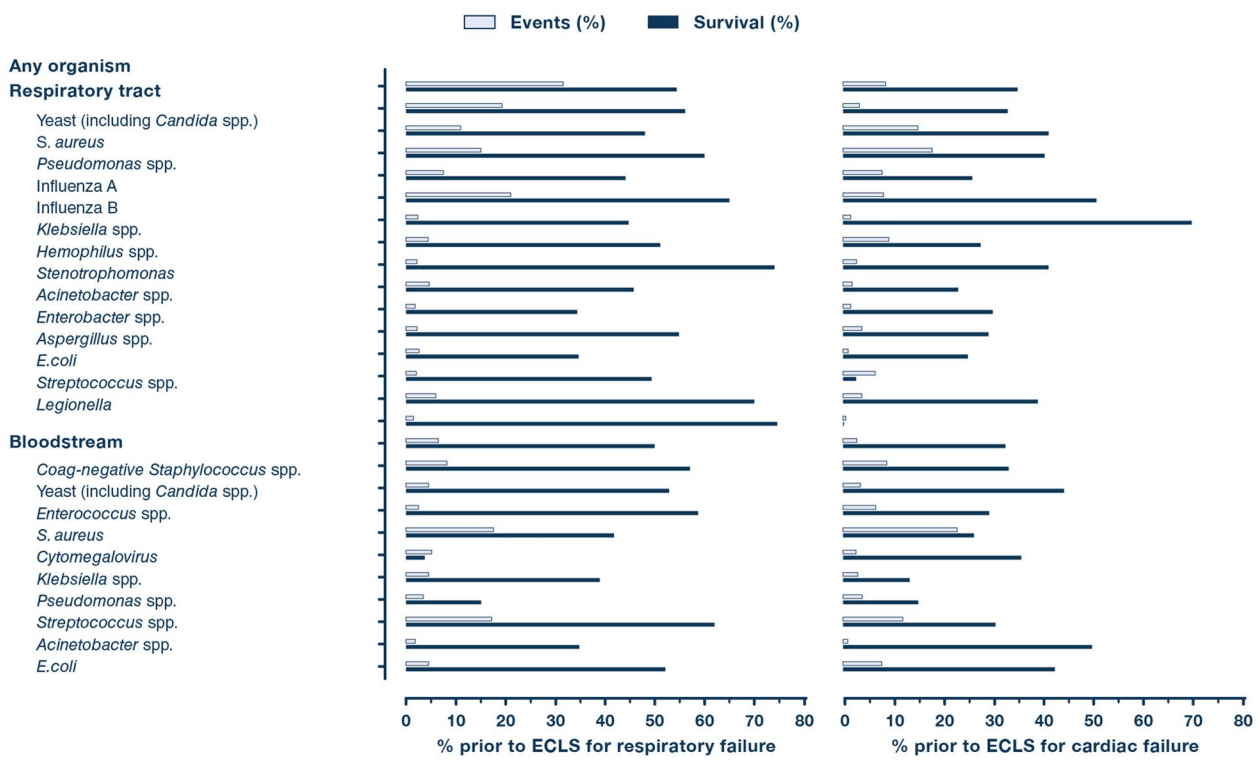

Fig. 1 Most common organisms identified on culture prior to initiation of ECLS for respiratory and cardiac failure. Based on a total of 17,374 ECLS runs for respiratory failure and a total of 18,514 total ECLS runs for cardiac failure from January 2012 through July 2019. Event rate represents the number of positive cultures for a given organism divided by the total number of ECLS runs. *ECLS* extracorporeal life support

(ECPR)), with the respiratory tract being the most frequent site throughout.

Regardless of ECLS indication, *S. aureus* and yeast were consistently among the most common respiratory tract pathogens reported. Notably, Influenza A was the most commonly identified organism in the respiratory tract in patients receiving ECLS for respiratory failure, accounting for 12.7% of all organisms identified. *Staphylococcus* and *Streptococcus* were the most common isolates in the bloodstream across all indications. Yeast, *E. coli*, and *Enterococcus* were common pathogens in the urine.

Infections during ECLS

Reported rates of hospital-acquired infections during ECLS have varied substantially across case series and registries; these data have inherent limitations due to variations in definitions, reporting methods, and surveillance practices. Patients receiving ECLS may be at risk of developing typical ICU-related nosocomial infections (e.g., VAP, bloodstream infections, urinary tract infections), in addition to ECLS-specific infections, such as localized infections at peripheral cannulation insertion sites or mediastinitis in the setting of central cannulation [7, 24]. Bizzarro et al. [25] reported a 21% prevalence rate of nosocomial infections among adults recorded in the ELSO registry from 1998–2008, whereas previous case series estimated nosocomial infection rates of between 9 and 65% during ECLS [7, 26–29].

Figures 2 and 3b and the Online Resource summarize the ELSO registry data documenting positive cultures during ECLS administered for respiratory failure, cardiac failure, and cardiac arrest. ECLS for respiratory failure showed the highest rate of positive cultures during ECLS (64.9%), whereas ECPR showed the lowest rate (22%). The distribution of pathogens during ECLS was found to be similar to the pre-ECLS pattern. Yeast and *S. aureus* were the most common organisms in the respiratory tract during ECLS across all three groups, whereas *Staphylococcus*, yeast, and *Enterococcus* were among the organisms isolated most frequently from blood cultures. The survival rates of individuals with positive cultures during ECLS administered for respiratory failure or cardiac failure were lower than the overall survival rates of all ECLS recipients over a similar timeframe (54.3% vs 61.1% and 38.0% vs 44.2%) [12], 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%) [12]. Although

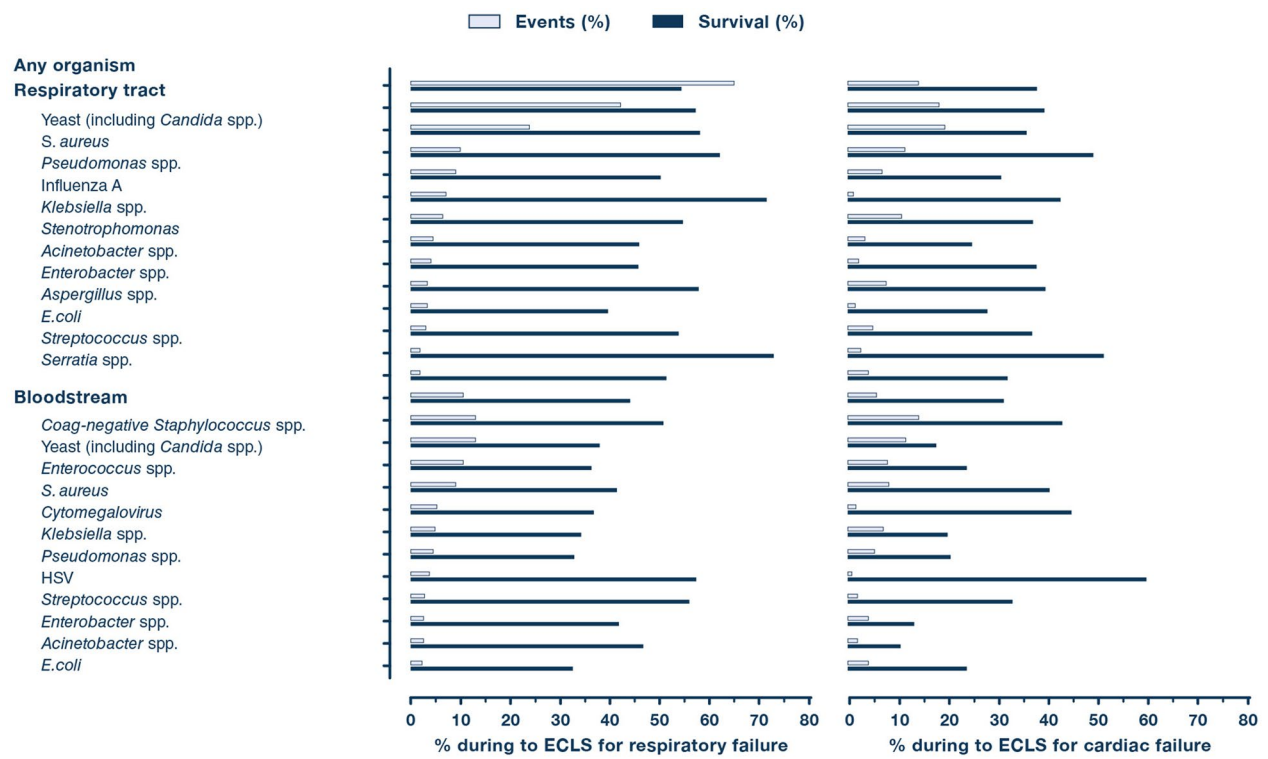

Fig. 2 Most common organisms identified on culture during ECLS for respiratory and cardiac failure. Based on a total of 17,374 total ECLS runs for respiratory failure and a total of 18,514 total ECLS runs for cardiac failure from January 2012 through July 2019. Event rate represents the number of positive cultures for a given organism divided by the total number of ECLS runs. *ECLS* extracorporeal life support

these data seem to suggest a correlation between acquisition of nosocomial infections and increased mortality, in the absence of further information regarding underlying diagnoses, comorbid conditions, and other factors that undoubtedly confound this association, only tentative conclusions can be drawn.

It is important to reiterate that these data refer only to organisms identified on culture and are not necessarily indicative of active infections. Some of these organisms may represent colonizations without pathological significance (e.g., the detection of *Candida* in the respiratory tract). Similarly, cultures obtained during ECLS may show the persistence of an organism already present before ECLS initiation (as in the case, for example, of a patient with *S. aureus* in the bloodstream before ECLS initiation who remains bacteremic during ECLS) rather than necessarily being indicative of newly identified organisms or a new infection. That said, the ELSO registry continues to provide the most comprehensive and detailed body of data available on the prevalence of infections during ECLS.

Beyond registry data, the value of primary investigational data from individual sites is often limited by methodology and generalizability issues. Having said that, a recent single-center observational study of 92 patients receiving ECLS (87% venovenous ECLS), in whom infections were systematically and prospectively identified through application of well-established clinical practice guidelines [30, 31], reported high rates of nosocomial infections (55%), with VAP and multidrug-resistant organisms found to be common [24]. Those who acquired nosocomial infections had higher overall mortality, longer durations of mechanical ventilation and ECLS, and spent longer in the ICU.

Risk factors for the development of infections during ECLS

The etiology of nosocomial infections during ECLS has not been systematically compared with (although it likely parallels) that of infections acquired in the course of critical illness in the absence of ECLS; however it remains to be established whether certain characteristics unique to patients receiving ECLS confer an increased risk of infection. This can only be speculated upon from the existing data (Table 1). 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,

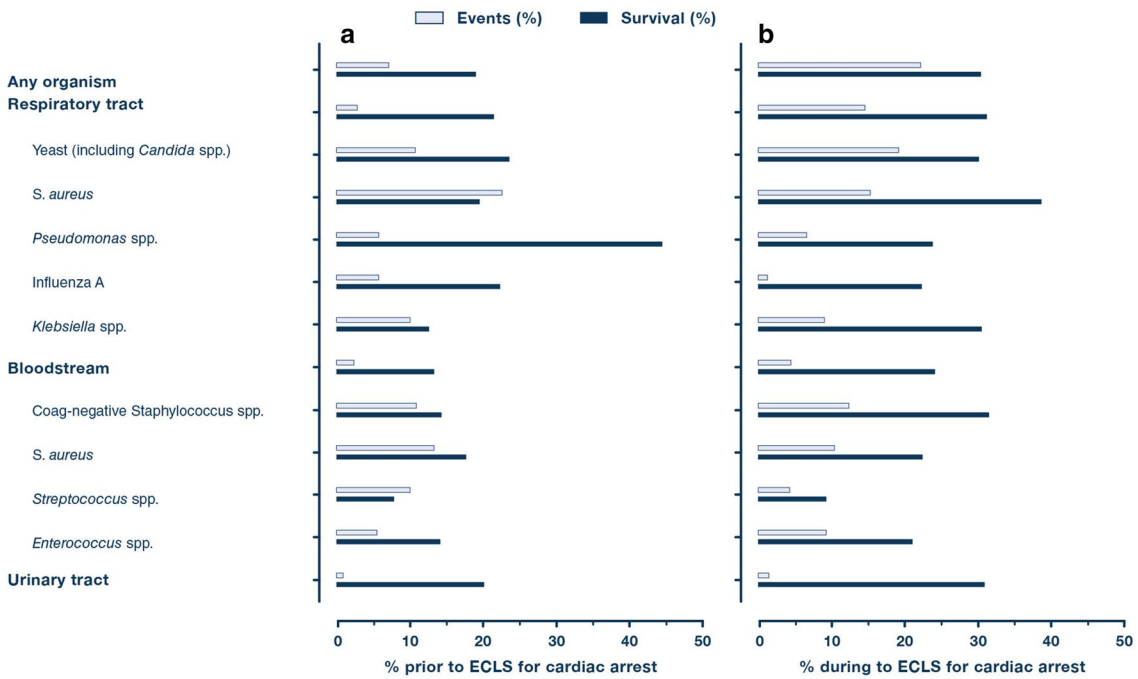

Fig. 3 Most common organisms identified on culture prior to initiation of ECLS (**a**) and during ECLS (**b**) for cardiac arrest. Based on a total of 5979 ECLS runs for cardiac arrest from January 2012 through July 2019. Event rate represents the number of positive cultures for a given organism divided by the total number of ECLS runs. *ECLS* extracorporeal life support

Table 1 Potential risk factors for infections during ECLS

Immunocompromised status (including potential immune dysregulation from the presence of ECLS itself)
Prolonged duration of ECLS[a]
Older age[a]
Higher pre-ECLS severity of illness[a]
Underlying autoimmune disorder
Central cannulation (vs peripheral cannulation)
Surgical cannulation approach (vs percutaneous approach)

ECLS extracorporeal life support

[a] There are no specific cutoffs, per se, but the longer the duration of ECLS, the older the age, and the higher the pre-ECLS severity of illness, the higher the presumed risk

activation of the contact system, coagulation cascade, neutrophils and platelets with consequent release of pro-inflammatory mediators) [32], and that the resulting immune system impairment might explain why ECLS may increase susceptibility to infection [33]. In contrast to this supposed hyperinflammatory response to ECLS, there exist equally compelling data suggesting that ECLS promotes an anti-inflammatory state through improvements in end-organ perfusion and gas exchange in patients with severe cardiopulmonary failure and reductions in pro-inflammatory injury (e.g., ventilator-induced lung injury) [34, 35]. A prospective observational study of 262 adult patients with severe ARDS reported a rapid decline in IL-6 and IL-8 levels within 24 h of the start of venovenous ECLS. Higher cytokine levels were associated with extra-pulmonary causes of ARDS, more aggressive ventilation before ECLS, and mortality [36]. The overall balance between pro- and anti-inflammatory effects (i.e., whether end-organ protective strategies outweigh the injurious effects of ECLS) likely determine the impact on the immune response and the consequent risk of infection. Whether these alterations pose an increased risk of infection after decannulation from ECLS is an area that warrants further investigation [37].

Whether or not the presence of ECLS leads to additional immune system impairment, immunocompromised patients appear to have worse outcomes than immunocompetent patients. In a multicenter observational study of 203 immunocompromised patients receiving ECLS for severe ARDS, nosocomial infections were common, with VAP diagnosed in 50% of patients and cannula-associated infections (defined as local signs of infection at a cannula site with positive culture from subcutaneous needle aspirate) found in 10% of patients [6]. With 6-month survival rates standing at only 30%, particular consideration should be given to preventive practices and close surveillance of infections during ECLS in

this vulnerable patient population. Of note, the acquisition of nosocomial infections was not an independent predictor of mortality in multivariable analysis.

While ECLS duration has frequently been associated with the development of nosocomial infections [7, 26–29], no existing analyses are able to determine whether longer duration of support is a risk factor for or a consequence of acquired infections. Prolonged use of ECLS will increase the opportunity to acquire infections, and infections are likely to contribute to, and increase the duration of, critical illness. Any relationship found between nosocomial infections and duration of ECLS should be interpreted with particular caution, as patients who acquire and die from infections early in their hospitalization would obviously have had shorter ECLS durations.

Older age, higher pre-ECLS severity of illness, underlying autoimmune disorders, circuit configurations, and performance of procedures during ECLS have all been implicated as risk factors for infections during ECLS [24, 27–29, 38, 39]. However, given the predominantly single-center, retrospective nature of the cited studies, the possibility of determining the true incremental risk, if any, deriving from these factors is limited and warrants more systematic investigation. Of note, Grasselli et al. identified younger, not older, age as being independently associated with higher risk of nosocomial infections, with VAP and multidrug-resistant organisms associated with higher mortality [24].

Whether the site and number of ECLS cannulae is associated with increased infection risk has yet to be thoroughly investigated. There is weak evidence suggesting an increased risk of infection with central cannulation and a decreased risk with single-site, dual-lumen cannulae [7, 38]. In a recent single-center propensity score-matched analysis of 814 patients undergoing venoarterial ECLS, cannula site infections were significantly more common with a surgical approach than a percutaneous approach (27.8% vs 16.5%, $p < 0.001$) [40]. Historical data suggest an increased incidence of bloodstream infections in ECLS patients compared with non-ECLS critically ill patients [41], although this has not been corroborated in the era of modern ECLS technology and practices. Cannulae and membranes are both potential surfaces for microbial colonization, as demonstrated by several studies [42–44]. Whether these surfaces represent primary or secondary sites of infection is not currently known.

Challenges in the detection, treatment, and prevention of infections during ECLS

Efforts to detect infections during ECLS come up against particular difficulties that could impede their prompt recognition and treatment, as well as the assessment of response to antimicrobial therapy. Passive or active cooling or heating of the blood as it passes through the membrane may mask fever or hypothermia [11]. The presence of infiltrates on chest radiographs, used to help identify VAP [31], may be difficult to interpret when extreme lung-protective ventilatory strategies are employed, as these result in extensive airspace opacification in the absence of a new infection [13], or in cases of severe cardiogenic pulmonary edema. The potential for ECLS to affect serological tests used in the detection of infections, much in the way cellulose membranes may elevate 1,3-β-D-glucan levels [45], is an important consideration that warrants further investigation. The difficulty in detecting infection by conventional means may influence surveillance practices, as highlighted by a high reported rate of daily blood cultures performed as routine surveillance in a survey of ELSO-affiliated ECLS centers [46].

The pharmacokinetics and pharmacodynamics of antimicrobial agents used to treat infections during ECLS may be affected by several factors associated with both critical illness and the ECLS circuit itself, including clearance abnormalities in the setting of organ failures, potential for sequestration within the circuit, and increases in the volume of distribution (Vd) [10, 11, 47]. The lipophilicity and protein binding characteristics of a given drug play an important role in its interaction with the circuit [11]. Several antibiotics have been studied in the context of ECLS, and shown varying susceptibility to subtherapeutic levels due to sequestration or increased Vd; the results have been summarized elsewhere [10, 11]. When available, therapeutic drug monitoring should be performed to ensure adequate dosing of medications during ECLS.

Despite a lack of data demonstrating benefits, and in spite of ELSO Infectious Disease Task Force recommendations against the practice, antibiotic prophylaxis is commonly used at ECLS centers, according to surveys of ELSO member sites [46, 48, 49]. Whether or not antibiotic, or antifungal, prophylaxis is warranted or affects the incidence of nosocomial infections may become moot if most patients are already receiving antimicrobial agents at the time of initiation of ECLS. For example, 97% of patients in the previously mentioned cohort of immunocompromised patients were receiving antibiotics before ECLS, despite in many cases not having an infectious etiology for their respiratory failure [6]. Other infection prevention practices, including cannula maintenance strategies, vary across centers [46, 50]. Many of the recommendations put forth by ELSO, such as the use of sterile techniques, adherence to VAP prevention guidelines, and avoidance or removal of unnecessary invasive devices, mirror general infection prevention practices followed in critically ill patients (Fig. 4) [26, 49]. One

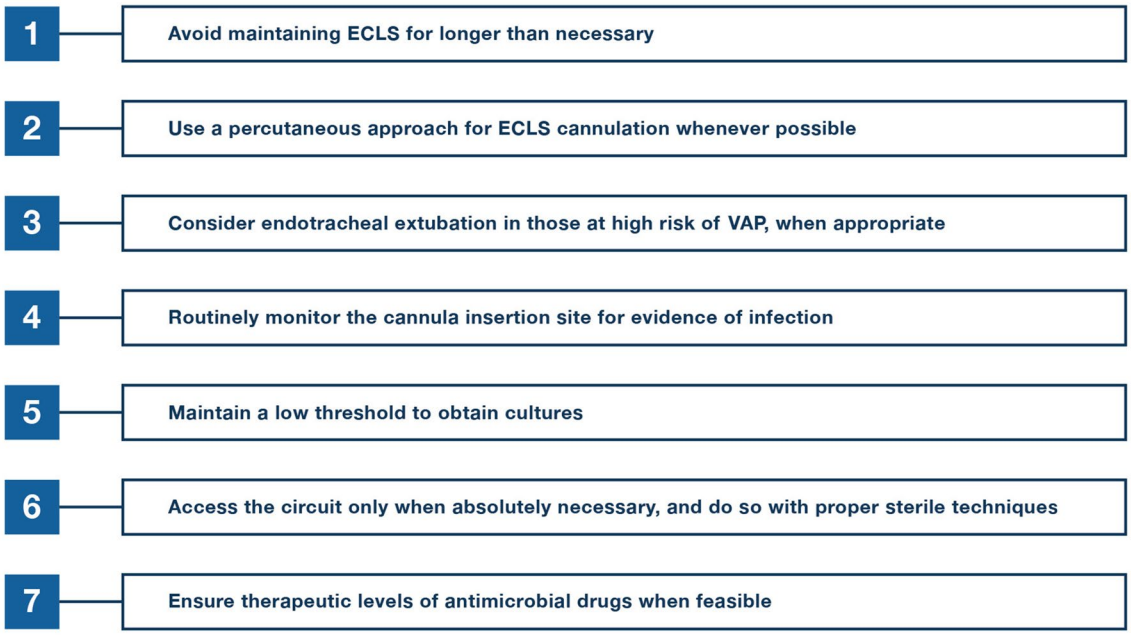

Fig. 4 Potential strategies to reduce infections during ECLS. *ECLS* extracorporeal life support, *VAP* ventilator-associated pneumonia

emerging VAP prevention strategy that may be used in selected ECLS patients is endotracheal extubation with removal of invasive mechanical ventilation. Patients with primarily cardiac failure, who have relatively preserved gas exchange, patients with predominantly hypercapnic respiratory failure, or those in whom early mobilization is of greater importance to their ultimate recovery, such as patients receiving ECLS as a bridge to transplantation, may be particularly suitable for such a strategy [51]. The roles of other infection prevention strategies that have been explored in general critical care populations, such as selective digestive decontamination, remain uncertain in ECLS patients.

Future research directions

The paucity of high-quality data on ECLS-associated infections highlights the need for a more systematic evaluation of their incidence, outcomes and risk factors, and of appropriate prevention approaches and treatment strategies (Fig. 5). Without consistent definitions of ECLS-associated infections (including infections attributed to the device itself) and standardized reporting of these events, it remains impossible to quantify the true incidence of infections both before and after the initiation of ECLS, including infections acquired after ECLS removal. A better understanding of infection susceptibility during ECLS would help to clarify whether antimicrobial prophylaxis or routine surveillance cultures might be warranted in certain patient populations, or perhaps whether ECLS should be avoided altogether in the presence of infections with universally poor outcomes.

A systematic review has previously characterized inconsistencies existing in the definition and reporting of infectious complications in venoarterial ECLS [52], highlighting the need for methodologically rigorous development of consensus opinions regarding infectious complications and associated outcomes in order to obtain accurate and clinically meaningful epidemiological data [53]. The ELSO registry is currently undergoing a redesign that may allow for more granularity regarding infectious indications and complications [54].

Ideally, in order to be generalizable to the broader ECLS community, studies evaluating the epidemiology of ECLS-associated infections should be performed across diverse patient populations with varying rates of organism prevalence and antimicrobial resistance, using standardized definitions of infections, and systematically measuring important confounders that may contribute to infections and outcomes. Along such lines, a multicenter, prospective observational study evaluating the prevalence of nosocomial infections and cannula management practices in ECLS across Australia and New Zealand has recently been proposed [55]. Research networks, such as the International ECMO Network (ECMONet; www.internationalecmonetwork.org), provide a forum for performing this type of research in ECLS across centers and regions. In the meantime, we recommend that all centers

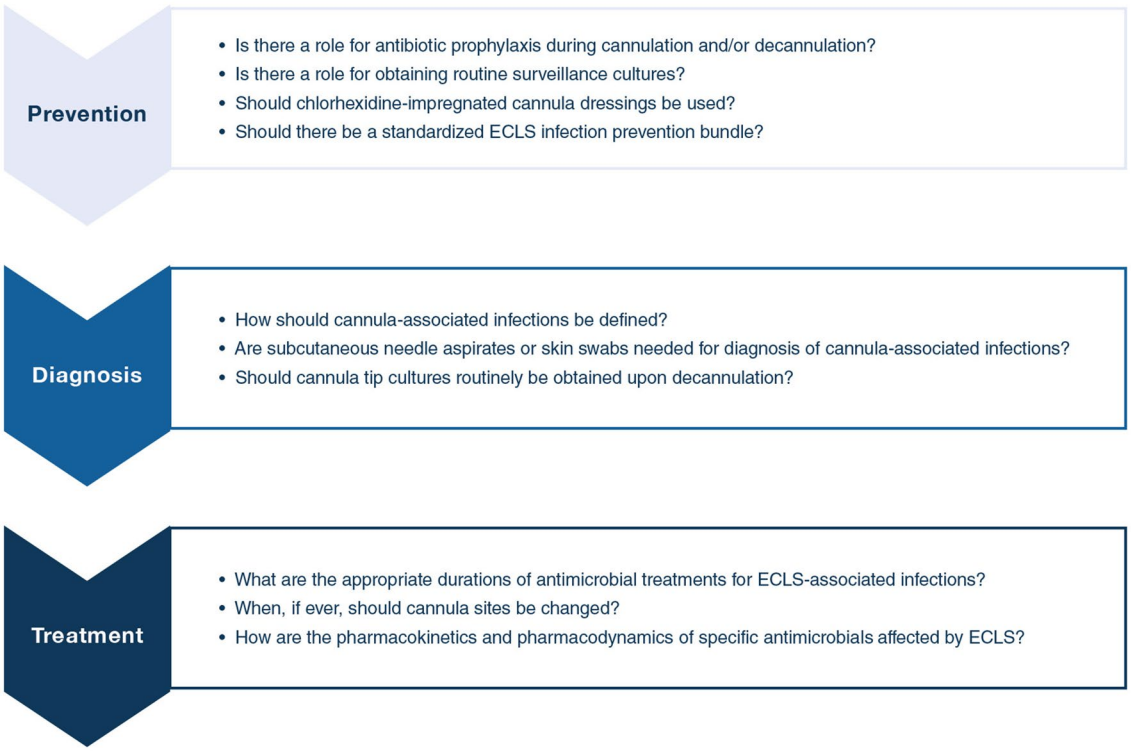

Fig. 5 Research agenda and ongoing uncertainties regarding ECLS-associated infections. *ECLS* extracorporeal life support

performing ECLS enter their data into the ELSO or other equivalent registry.

In addition to epidemiological data, more information is needed regarding antimicrobial pharmacokinetics and pharmacodynamics during ECLS in order to optimize treatment of peri-ECLS infections. The ongoing Analgesia, Sedation, and Antibiotic Pharmacokinetics during Extracorporeal Membrane Oxygenation (ASAP ECMO) study hopes to provide additional insight into the impact of ECLS on the efficacy of antimicrobials [56].

Conclusions

Infections both commonly precede and are frequently identified during ECLS. This review of current knowledge regarding ECLS-associated infections highlights the need for standardized definitions, consistent detection strategies, and more comprehensive descriptions of patient characteristics and outcomes so that meaningful conclusions regarding the clinical significance of these infections can be drawn and inform best practices for their prevention and management.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05847-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
MS has received lectures fees from Getinge, Xenios and Dräger, outside the submitted work. DB reports fees to his university from ALung Technologies, personal fees from Baxter and anticipated fees from BREETHE, an unpaid association with Hemovent, outside the submitted work. GG received payment for lectures from Draeger Medical, Getinge, Fisher and Paykel, Pfizer, and received travel/accommodations/congress registration support from Getinge and Biotest, outside the submitted work.

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