https://doi.org/10.15360/1813-9779-2023-2-2265

Secondary Infections in Patients with Extremely Severe COVID-19 During ECMO Therapy

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For citation: *Sergey S. Andreev, Mikhail V. Ketskalo, Polina O. Narusova, Maryana A. Lysenko.* Secondary Infections in Patients with Extremely Severe COVID-19 During ECMO Therapy. *Obshchaya Reanimatologiya = General Reanimatology.* 2023; 19 (2): 4–13. https://doi.org/10.15360/1813-9779-2023-2-2265 [In Russ. and Engl.]

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Summary

Up to 70% of patients hospitalized with COVID-19 need respiratory support, up to 10% need high–flow oxygen therapy, non-invasive and invasive ventilation. However, standard methods of respiratory support are ineffective in 0.4–0.5% of patients. In case of potentially reversible critical refractory respiratory failure those patients may require ECMO. Management of patients with extremely severe COVID-19 associates with numerous clinical challenges, including critical illness, multiple organ dysfunction, blood coagulation disorders, requiring prolonged ICU stay and care, use of multiple pharmacotherapies including immunosuppressive drugs. Pharmacological suppression of immunity is associated with a significant increase in the risk of secondary bacterial and fungal infections. Currently, data on epidemiology of secondary infections in patients with COVID-19 undergoing ECMO is limited.

Aim. To study the prevalence and etiology of secondary infections associated with positive blood cultures in patients with extremely severe COVID-19 requiring ECMO.

Materials and methods. A single-center retrospective non-interventional epidemiological study including 125 patients with extremely severe COVID-19 treated with ECMO in April 2020 to December 2021.

Results. Out of 700 blood culture tests performed in 125 patients during the study, 250 tests were positive confirming bacteremia/fungemia. Isolated pathogens varied depending on the duration of ECMO: gram-positive bacteria (primarily coagulase-negative staphylococci) dominated from the initiation of ECMO support; increased duration of ECMO associated with an increasing proportion of pathogens common in ICU (*Klebsiella pneumoniae* and/or *Acinetobacter baumannii* with extensively drug resistant and pan-drug resistant phenotypes, and vancomycin-resistant *Enterococcus faecium*). When ECMO lasted more than 7–14 days, opportunistic pathogens (*Candida species, Stenotrophomonas maltophilia, Providencia stuartii*, non-diphtheria corynebacteria, *Burkholderia species* and others) prevailed as etiological agents.

Conclusion. Longer duration of ECMO resulted in increasing rates of infectious complications. In patients undergoing ECMO for more than 14 days, the microbiological landscape becomes extremely diverse, which hampers choosing an empirical antimicrobial therapy. Since potential pathogens causing secondary infections in patients during ECMO are difficult to predict, rapid identification of rare opportunistic pathogens and their sensitivity profile, followed by targeted administration of antimicrobials, seems most beneficial.

Keywords: COVID-19; ECMO; secondary infections; multi-drug resistant pathogens; K. pneumoniae; antimicrobial therapy; opportunistic pathogens

Conflict of interest. The authors have no conflicts of interest to declare that are relevant to the content of this article.

Introduction

In 2019, the first cases of respiratory viral infection caused by a novel coronavirus named SARS-CoV-2 were described in the People's Republic of China [1]. In March 2020, the World Health Organization declared the disease caused by SARS-CoV-2, COVID-19 (COronaVIrus Disease 2019), a pandemic [2, 3]. COVID-19 has become not only a medical problem, but also a major social issue, leading to lockdowns and economic crises. By February 2022, the number of confirmed cases had reached 106 million and the number of deaths had exceeded 2.3 million [4].

According to epidemiologic studies, the severity of COVID-19 varied depending on the strain of SARS-CoV-2 infection. The number of patients with an extremely severe course of COVID-19 (requiring lung ventilation) reached 8.1% of the total number when infected with the «delta» strain B.1.617.2 [5].

COVID-19 is characterized by multi-organ involvement and leads to several complications, including respiratory failure, immune response hyperactivation syndrome («cytokine storm»), and coagulopathy [6]. Another concern is drug toxicity and drug interactions, especially in the setting of

polypharmacy in the ICU [7–9]. Patients with milder COVID-19 rarely have co-infections and secondary infectious complications. Routine administration of antibiotics to patients with viral infections, including COVID-19, does not reduce the risk of secondary infections or the likelihood of progression of viral lung injury [10, 11]. In patients with severe and extremely severe COVID-19, secondary infections (bacterial, fungal) may play a critical role in poor outcome [12].

To date, the WHO and national societies of different countries have adopted protocols for the management of patients with COVID-19 [6, 13, 14]. Some issues, especially in drug therapy, remain controversial, but most recommendations outline the main directions of management of patients with novel coronavirus infection: 1) antiviral therapy; 2) respiratory support; 3) anticoagulation and coagulation control; 4) immunosuppressive therapy to control the «cytokine storm»; 5) prevention and treatment of complications [15–17].

Despite a wide range of approved drugs with antiviral activity against SARS-CoV-2 (remdesivir, molnupiravir, nirmatrelvir/ritonavir, viral neutralizing monoclonal antibodies), none of them is intended to treat patients with extremely severe respiratory failure (requiring mechanical ventilation and/or extracorporeal membrane oxygenation) [6, 18]. Anticoagulant therapy is indicated in all patients with severe COVID-19 unless there are absolute contraindications [19]. Immunosuppressive therapy, including systemic steroids, genetically engineered biological agents that block effects of the key proinflammatory cytokine IL-6 (tocilizumab, sarilumab, levilimab), and extracorporeal therapies (plasmapheresis, therapeutic plasma exchange), is used in most patients with severe/extremely severe COVID-19 [6].

Respiratory therapy is the mainstay of severe and extremely severe COVID-19 treatment. Up to 70% of hospitalized patients require respiratory support, up to 10% require high flow oxygen therapy, non-invasive and invasive ventilation, and in 0.4–0.5% of patients conventional respiratory support proves ineffective. Extracorporeal membrane oxygenation (ECMO) is suggested for potentially reversible critical and refractory respiratory failure.

According to international consensus, it is not recommended to open new ECMO centers during a pandemic because of the high cost of material, human and organizational resources [20]. Nevertheless, ECMO often remains the only way to help patients with COVID-19 with critical respiratory failure (PaO_2/FiO_2 index reduction below 80 for more than 6 hours on protective parameters of respiratory support) [21, 22].

The management of patients in the ECMO center is associated with numerous clinical challenges, including critical illness, extremely severe damage to the lungs, other organs and systems, coagulation disorders, the need for prolonged stay in the intensive care unit, concomitant immunosuppressive and antimicrobial therapy. Antiviral therapy is irrelevant for patients in ECMO centers both because of the lack of sufficient scientific evidence (patients with COVID-19 requiring mechanical ventilation and/or ECMO are excluded from clinical trials) and because of the duration of the disease (acute respiratory distress syndrome develops 7–8 days after the onset of the disease, when there is no rationale for the use of antivirals). The main methods of COVID-19 drug therapy during ECMO remain anticoagulant and immunosuppressive, including systemic steroids and genetically engineered biological drugs (blockers of IL-6 receptors, IL-6 and IL-1) [6, 22]. However, medical immunosuppression is also associated with a significant increase in the risk of secondary infectious complications, primarily bacterial and fungal [24, 25].

Pathogens characterized by XDR (extensively drug resistant, meaning resistance to almost all but one or two classes of antibiotics) and PDR (pan-drug-resistant, meaning resistance to all classes of antimicrobials studied) phenotypes are typical of critically ill patients who stay in the ICU for long periods of time [26–28].

Study aim was to examine the prevalence and etiology of secondary blood-borne pathogen infections in patients with severe COVID-19 requiring ECMO.

Materials and Methods

We conducted a single-center, retrospective, noninterventional epidemiologic study including 125 patients with extremely severe COVID-19 treated at the ECMO Center of the Moscow City Clinical Hospital 52 of the Department of Healthcare from April 2020 to December 2021, who required extracorporeal membrane oxygenation (ECMO). The mean age of the patients was 48.7±10 years (18 to 72 years), 91 (72.8%) of them were men. 109 patients (87.2%) underwent veno-venous (VV) ECMO, 2 patients (1.6%) veno-arterial ECMO, and 14 patients (11.2%) had other ECMO circuit variations (including veno-veno-venous, veno-arterio-venous). The mean duration of ECMO was 18.5 days (ranging from 1 to 141 days).

Baseline patient characteristics were similar to those of the European ECMO Registry, but the proportion of patients with VV ECMO was significantly higher in the EuroELSO Registry patient cohort (92.5% vs. 87.2%, Fisher's exact test $P= 0.038$). Outcomes such as weaning from ECMO (χ^2 test $P<0.001$) and discharge from hospital (χ^2 test $P<0.001$) were significantly better in patients from the EuroELSO registry (Table) [22]. In the cohort of

Table. Characteristics of patients from the ECMO Center and the EuroELSO Registry (completed cases as of October, 3 2022).

Parameters	Registry	
	ECMO Center Registry (Hospital 52)	EuroELSO Registry
Number of patients	125	6.112
Mean age, years	48.7±10 [18;72]	51.6* [16; 84]
Men, %	72.8	72.6
Women, %	27.2	27.4
ECMO circuit type, %	87.2 — veno-venous 12.8 — other	92.5 — veno-venous 7.5 — other
Mean duration, days	18.5	26.3
Successful ECMO-weaning, *n* (%)	22 (17.6)	3,440 (56.3)
Discharged from the hospital, *n* (%)	12 (9.8)	3,259 (53.3)

Note. * — EuroELSO registry does not provide data on the standard deviation of age.

patients from the ECMO Center of Hospital 52, twenty-two patients (17.6%) were successfully weaned from ECMO and 12 patients (9.6%) were discharged from the hospital. In our opinion, one of the factors negatively influencing ECMO weaning and hospital mortality could be secondary infections, including those associated with bacteremia.

During hospitalization, 82.4% (103) of patients received renal replacement therapy. Drug therapy was administered according to the current version of the provisional «Guidelines of the Russian Ministry of Health for Prevention, Diagnosis and Treatment of Novel Coronavirus Infections (COVID-19)». All patients received IL-6 antagonists (tocilizumab, sarilumab, levilimab, olokizumab), while 79 patients (63.2%) received systemic steroids.

Blood cultures were obtained when a bacteremia-associated or fungemia-associated infection was suspected by the treating physician or as recommended by the clinical pharmacologist. Pathogen identification was performed by matrix-associated laser desorption/ionization time-of-flight mass spectrometry MALDI-TOF MS (Bruker), antibacterial susceptibility testing was performed by the Phoenix 100 automated system (BD), and beta-lactamase genes were detected by real-time PCR using the BacResist GLA reagent kit or the GeneXpert analyzer (Cepheid).

Statistical analysis of data. No prespecified power calculation was performed. All patients treated at the center during the study period were included in the study. Means and standard deviations were used for descriptive statistics. Data were analyzed using the IBM SPSS STATISTICS V22.0 statistical software package.

Results

A total of 700 blood tests were performed in 125 patients, of which bacteremia/fungemia was detected in 250 cases. The frequency of positive blood cultures increased significantly with the duration of ECMO: from 18.4% (in 23 of 125 patients) in the first 48 hours after the start of the procedure to 68.4% (in 39 of 57 patients) 14 days or more after the start of ECMO (fig. 1).

We observed a change in the pattern of pathogens isolated from blood culture as a function of time after ECMO initiation: initially, Gram-positive pathogens (primarily coagulase-negative staphylococci) were predominant. When the duration of ECMO exceeded 7 days, the most common pathogens were those typical of intensive care units (*Klebsiella pneumoniae, Acinetobacter baumannii* with XDR/PDR phenotype, vancomycin-resistant Enterococcus faecium) and opportunistic agents (*Candida species, Stenotrophomonas maltophilia, Providencia stuartii*, non-diphtherial *Corynebacterium species*, *Burkholderia species*, and others).

Gram-positive pathogens. The percentage of gram-positive pathogens was maximal in the first 48 hours after ECMO initiation: they were isolated in 17 of 125 patients (13.6%) (Fig. 1).

The pathogen profile changed over time (Fig. 2). Coagulase-negative staphylococci (CoNS), including oxacillin-resistant, were dominant, accounting for 14 of 28 (50%) of all positive blood cultures in the first 2 days of ECMO. With increasing duration of

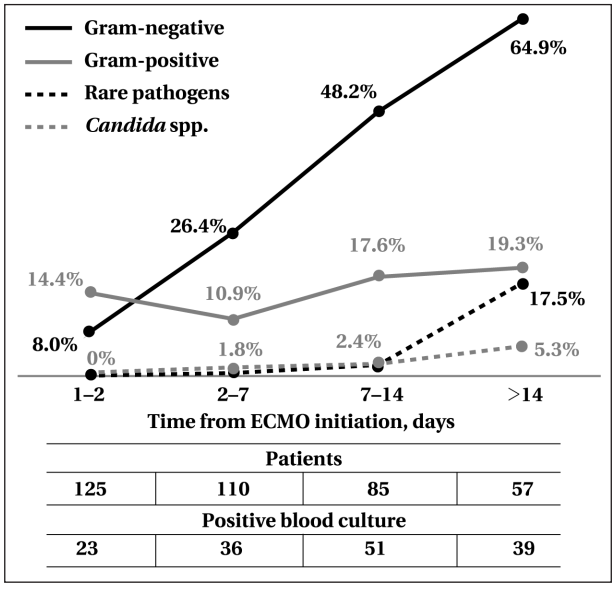

Fig. 1. Frequency of pathogen isolation from blood culture in patients during ECMO.

ECMO, the percentage of bacteremia due to *E. faecium*, including vancomycin-resistant, increased from 6.5% (1 of 14) in the first 2 days of ECMO to 12.8% (in 5 of 39 blood cultures) after 14 or more days of ECMO. *S. aureus* was not isolated in patients during ECMO.

Gram-negative pathogens. The proportion of gram-negative pathogens increased with increasing duration of ECMO: from 8.8% (in 11 of 125 patients) during the first 48 hours to 64.9% (in 37 of 57 patients) when ECMO was performed for more than 14 days (Fig. 3).

The most common pathogen was *K. pneumoniae* with XDR phenotype and resistance to carbapenems in 100% and PDR phenotype in 9 cases. The incidence of *K. pneumoniae* bacteremia during ECMO increased from 4% (5 cases in 125 patients) at day 2 to 37.6–41.2% (in 32 of 85 and 24 of 57 patients receiving ECMO for 7–14 and more than 14 days, respectively). Other *Enterobacterales* were less common and were mostly isolated during prolonged ECMO. *Escherichia coli, Proteus mirabilis,* and *Serratia marcescens* were isolated from blood cultures in some patients.

Acinetobacter baumannii was isolated in patients from the first 48 hours of ECMO initiation. The incidence of *A.baumannii* bacteremia increased from 5 cases (4% of all patients) in the early period to 8.8% (in 5 of 57 patients) with long duration of ECMO. All isolated strains were characterized by the XDR phenotype and remained susceptible only to polymyxins.

Pseudomonas aeruginosa was isolated from blood cultures in 2 patients after 7 days of ECMO and in 4 patients with ECMO duration longer than 14 days. All *P. aeruginosa* strains isolated were resistant to carbapenems.

Resistance genes were detected in 17 patients (13.6% of all patients included in the study). The isolated bacteria were characterized by a high diversity of beta-lactamase encoding genes: *Enterobacterales* (mainly *K. pneumoniae*) had class A (CTX-M, TEM and SHV; KRS), D (OXA-48-like) and B (NDM) beta-lactamase genes, *A. baumannii* had class D carbapenemases (OXA-23-, OXA-40-, OXA-51-like), while *P. aeruginosa* had class A and B (IMP, NDM and VIM). In one patient, the mechanism of resistance could not be verified in *K. pneumoniae* with the panresistant phenotype (PCR did not identify the genes encoding the most common class A, B and D beta-lactamases).

Invasive candidiasis. Invasive candidiasis with candidemia was detected in 7 patients (5.6% of the total study population). The incidence of candidemia increased with prolonged ECMO duration, from 0% at baseline to 8.8% (in 5 of 57 patients) at 14 days. Different *Candida species* were identified: *C. albicans* — in 5 samples, *C. auris* — in 3 samples,

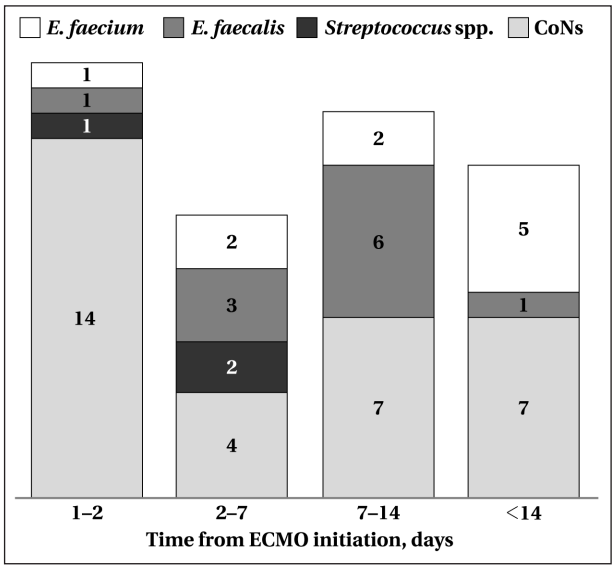

Fig. 2. Isolation of Gram-positive pathogens from blood cultures at different durations of ECMO (absolute number of pathogens isolated).

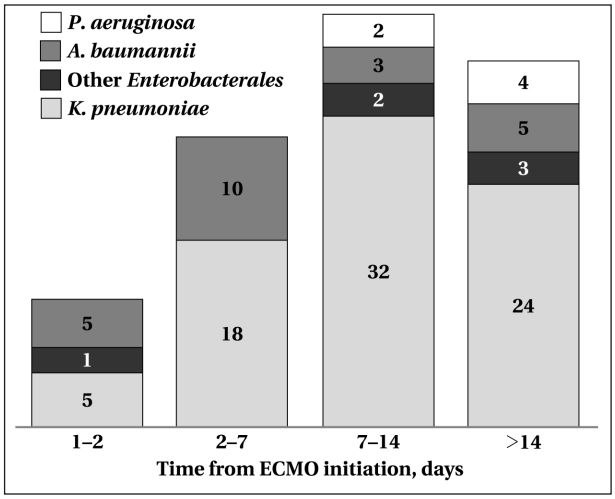

Fig. 3. Isolation of Gram-negative pathogens from blood cultures at different durations of ECMO. Absolute number of pathogens isolated shown.

C. parapsilosis — in 1 case. In one patient with *C. auris* candidemia, the pathogen was isolated three times and blood culture sterility could not be achieved.

Infections caused by rare opportunistic pathogens. During prolonged ECMO, a large number of non-ICU pathogens were isolated from patients' blood cultures: in 3 of 85 patients (3.5%) after 7 days of ECMO and in 8 of 57 (14%) when ECMO lasted longer than 14 days. The spectrum of pathogens included gram-negative (*Providencia stuartii, Stenotrophomonas maltophilia, Burkholderia cepacia* and *B. multivorans, Delftia acidovorans, Achromobacter xylosoxidans*) and Gram-positive

bacteria (*Corynebacterium striatum* and other non-diphtheria *Corynebacterium species*).

Discussion

Patients in ECMO centers are characterized by a combination of risk factors for secondary infections, including those caused by extremely resistant Gram-positive (oxacillin-resistant *Staphylococcus*, vancomycin-resistant *Enterococcus*), Gram-negative (carbapenem-resistant *Enterobacterales* and non-fermenting Gram-negative bacteria), and opportunistic pathogens (fungi, rare pathogens). Several risk factors for an infection directly relate to ECMO: cannulae that cannot be removed if a bloodstream infection develops, changes in the pharmacokinetics of antimicrobial drugs that prevent them from reaching adequate concentrations at the site of infection. Other infection promoting factors do not relate to ECMO: critical illness, prolonged ICU stay, massive lung tissue injury, prolonged lung ventilation, leukopenia, lymphocytopenia, secondary hypogammaglobulinemia, concomitant drug therapy and drug interactions, renal replacement therapy, need for repeated blood component transfusions [26, 29]. According to epidemiologic studies, the SARS-CoV-2 virus itself serves as a risk factor for the development of some secondary infections in patients with severe COVID-19, mainly mycoses [30, 31].

The results of the study (successful weaning from ECMO, discharge from hospital) were worse than those presented in the European and global ECMO registry [22], with a higher frequency of secondary infections complicated by bacteremia, which in our opinion contributed significantly to the attributable mortality of the patients.

The spectrum of isolated Gram-negative pathogens was consistent with data from regional and local microbiological studies, but there was an early development of severe secondary infections complicated by bacteremia on days 2–5 of ECMO [32, 33]. This was probably due to both the initial severity of the patients' illness and the combination of infection risk factors in patients with critical lung injury. With a relatively high frequency of Co-NS isolation, a low frequency of bacteremia due to *Staphylococcus aureus*, both MSSA and MRSA, was observed, although this pathogen was isolated in 8 patients from other sites (respiratory tract, pleural fluid, urine).

The widespread use of polymyxins as the only effective antimicrobial therapy for infections caused by XDR Gram-negative pathogens has led to the selection of pathogens naturally resistant to colistin and an increase in bacteremia caused by Gram-positive bacteria, fungi, *Enterobacterales* (*Proteus mirabilis, Serratia marcescens*), non-fermenting Gram-negative bacteria (*Providencia stuartii, Burkholderia cepacia*).

Based on the results of this study, a modification of the perioperative prophylaxis and empirical antimicrobial therapy regimen in the first 48 hours after ECMO initiation is recommended: the spectrum of antimicrobial agents should cover Gram-positive pathogens, primarily coagulase-negative staphylococci, with separate consideration of MR-CoNS risk factors.

When prescribing empirical antimicrobial therapy for prolonged ECMO, the microbiologic profile of the patient's ward and previous medications are considered. The predominant pathogens are *K. pneumoniae* and *A. baumannii*, which are carbapenem-resistant and produce a wide range of class A, D, and B beta-lactamases. Due to the prolonged stay of ECMO cannulas and the impossibility of their removal, the prescribed drugs must be active against pathogens with a high potential for biofilm formation (e.g. *Burkholderia cepacia, Candida species*).

Predicting which pathogen will cause a «new wave» of infection in a patient on ECMO for more than 7 days and receiving broad-spectrum and extra-broad-spectrum antimicrobial therapy is challenging. A significant increase in both typical pathogens characterized by extreme and pan-resistance (e. g., Gram-negative bacteria with high frequency of clinical and/or microbiological resistance to polymyxins, high frequency of infections caused by vancomycin-resistant *E. faecium*) has been observed. During prolonged ECMO, a large number of atypical ICU pathogens have been isolated from blood cultures. Rare pathogens with natural resistance to most antibiotics (non-fermenting Gram-negative bacteria, non-diphtheria *Corynebacterium*) were isolated in 17.5% of patients 14 days after the start of ECMO. Most of the isolated pathogens have been described as extremely rare infectious agents in immunocompromised patients. They are characterized by multiple drug resistance and the ability to cause nosocomial infections of the bloodstream, respiratory tract, and urinary tract [34–36].

The increase in infections due to *E. faecium*, especially vancomycin-resistant (VRE) bacteria, was probably due to the combination of typical risk factors including the prescription of a wide range of antibacterial drugs targeting Gram-negative pathogens and the high frequency of empirical oral vancomycin administration in patients with diarrhea.

The increased incidence of invasive candidiasis was probably related to an «accumulation» of risk factors for opportunistic infections such as critical illness, prolonged mechanical ventilation, prolonged placement of invasive lines (ECMO cannulas, central venous catheters, arterial catheters), renal replacement therapy, critical illness-related and medical immunosuppression, antibiotic therapy, repeated

transfusions of blood components, and prolonged lymphopenia due to viral infection. The choice of antifungal agents for invasive candidiasis in patients on ECMO is limited. This is due to both patient characteristics (changes in drug pharmacokinetics due to critical illness and the presence of an ECMO circuit) and microbial characteristics (high prevalence of non-albicans *Candida species*, including *C. auris*). The inability to completely eradicate the pathogen from the bloodstream in *C. auris* candidemia was probably due to its properties such as high rate of biofilm formation and multiple resistance to antifungal drugs, as well as the impossibility of removing the ECMO cannulae. Significant variability of pharmacokinetics in critical illness, high risk of adverse drug interactions, inability to remove invasive lines (primarily ECMO cannulae), spectrum of pathogens make echinocandins the preferred option of antifungal therapy, while the use of triazoles is ineffective both due to resistance of microfungi and suboptimal pharmacokinetic parameters.

The results suggest that routine administration of many antimicrobial classes, such as third-generation cephalosporins, fluoroquinolones, and fluconazole, is ineffective in patients with extremely severe COVID-19. Most isolated pathogens are resistant to these classes of antimicrobials, and their administration carries a high risk of selection of multidrug-resistant strains (the concept of «collateral damage») and is associated with a high potential for drug toxicity and drug interactions [37, 38].

Study limitations. The study was retrospective and non-comparative and did not take into account the characteristics of different viral strains (patients were studied during «waves» caused by SARS-CoV-2 strains from «alpha» B.1.1.7 to «delta» B.1.617.2). Resistance mechanisms were detected in only a small fraction of Gram-negative bacteria.

The isolation of some bacteria (coagulase-negative staphylococci, rare non-fermenting Gram-negative bacteria such as *Burkholderia* spp., *Delftia acidovorans*, etc.) from blood culture was not considered contamination. The isolation of pathogens from the sterile site (blood) in critically ill patients with systemic inflammatory reaction was always considered clinically significant. These data were confirmed by repeated isolation of these rare and atypical pathogens from blood culture and/or other sites, clinical efficacy of antimicrobial therapy targeting isolated pathogens.

The frequency of invasive candidiasis was lower than that reported by other centers, which may be due to diagnostic problems (clinical inability to collect large daily blood samples for microbiological examination; unavailability of routine determination of serum mannan/antimannan antibody levels).

Conclusion

Patients with severe COVID-19 requiring ECMO are at high risk for secondary infections. The incidence of infectious complications, including those associated with bacteremia/fungemia, increases progressively during ECMO and reaches 68.4% at a duration of more than 14 days. During the first 48 hours, coagulase-negative staphylococci, including those resistant to oxacillin, play a leading role. With increasing duration of ECMO, the incidence of bacteremia caused by Gram-negative bacteria with extreme drug resistance and panresistance phenotypes increases. When the duration of ECMO is longer than 14 days, the patient's microflora becomes extremely diverse, with the most common pathogens being Gram-negative bacteria with XDR and PDR resistance phenotypes, vancomycin-resistant enterococci, *Candida species*, and rare opportunistic agents.

As the spectrum of pathogens causing secondary infections in ECMO patients becomes more diverse and difficult to predict, rapid identification of rare opportunistic pathogens and their susceptibility profile (MALDI-TOF MS, antigenic studies, staining with special methods, PCR, etc.) as well as targeted antimicrobial therapy are crucial.

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Received 25.09.2022
Accepted 06.02.2023