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# Bloodstream Infection caused by *Corynebacterium striatum* in COVID-19 patient: a Case Report with Literature Review

## Infekcija krvotoka uzrokovana *Corynebacterium striatum* kod pacijenta oboljelog od COVID-19: prikaz bolesnika i pregled literature

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### Abstract

**Objectives:** Recent research recognized coryneform bacteria as emerging opportunistic pathogens. *Corynebacterium striatum* appears as a significant pathogen in immunocompromised and immunocompetent patients.

**Methods:** In this paper, we report a case of an adult COVID-19 patient with *C. striatum* bloodstream infection. In addition, we reviewed clinical cases of bloodstream infection caused by *Corynebacterium* spp, mainly *C. striatum*.

**Results:** We present a 43-year-old patient hospitalized due to bilateral pneumonia caused by a SARS-CoV-2 infection. During hospitalization, the patient was connected to a veno-venous extracorporeal membrane oxygenation (ECMO) circuit. *C. striatum* was isolated in seven sets of blood cultures sampled over seven consecutive days. Based on identification done by MALDI- ToF, empirical therapy with vancomycin was initiated. Identification was confirmed by 16S ribosomal RNA gene sequencing. Although central venous catheter was replaced, *C. striatum* was persistently isolated in blood cultures in the following days. Although replacement of the ECMO cannula would be recommended, the procedure was not performed due to the severe patient's condition. Fosfomycin was added to vancomycin as salvage therapy in order to reorganize the structure of the biofilm and enable better penetration and efficacy of vancomycin which resulted in sterile blood cultures in the following days.

**Conclusion:** During the last decades, there have been many examples of bloodstream infections caused by skin contaminants. Although the central venous catheter is most commonly described as a route of entry of the skin microbiota in the bloodstream, other catheters such as pleural catheter and ECMO system, should not be neglected. It is well known that bacterial cells often form a biofilm on the surface of different medical devices such as central venous catheters, endoscopes, and urinary catheters.

Fosfomycin has the potential to penetrate the biofilm, transform the biofilm structure and potentially increase the concentration of other antimicrobial agents in the biofilm.

### Sažetak

**Cilj:** Nedavna istraživanja prezentirala su korinebakterije kao uzročnike oportunističkih infekcija. *Corynebacterium striatum* pojavljuje se kao značajan uzročnik kod imunokompromitiranih i imunokompetentnih bolesnika.

**Metode:** U ovom radu je prikazan slučaj odraslog pacijenta oboljelog od COVID-19 bolesti s infekcijom krvotoka uzrokovanom *C. striatum*. Uz to, predstavljeni su klinički slučajevi infekcija krvotoka uzrokovanih *Corynebacterium* spp., uglavnom *C. striatum*.

**Rezultati:** Prikazujemo 43-godišnjeg pacijenta hospitaliziranog zbog bilateralne pneumonije uzrokovane virusom SARS-CoV-2. Tijekom liječenja primijenjen je postupak izvantjelesne membranske oksigenacije (engl. extracorporeal membrane oxygenation, ECMO). *C. striatum* izoliran je u sedam setova hemokultura uzorkovanih tijekom sedam uzastopnih dana. Na temelju identifikacije pomoću MALDI-ToF-a, započeta je empirijska terapija vankomicinom. Identifikacija je potvrđena sekvenciranjem gena 16S ribosomske RNA. Centralni venski kateter je zamijenjen, ali je *C. striatum* kontinuirano izoliran u hemokulturama sljedećih dana. Iako je preporučena zamjena ECMO kanile, postupak nije izveden zbog teškog stanja pacijenta. Vankomicinu je dodan fosfomicin kao „terapija spasa" kako bi se reorganizirala struktura biofilma te omogućila bolja penetracija i učinkovitost vankomicina što je rezultiralo sterilnim hemokulturama u narednim danima.

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**Zaključak:** Tijekom posljednjih desetljeća u literaturi je opisano mnogo primjera infekcija krvotoka uzrokovanih kontaminantima kože. Iako se centralni venski kateter najčešće opisuje kao put ulaska mikrobiote kože u krvotok, ne smiju se zanemariti ni drugi kateteri, poput pleuralnog katetera i ECMO sustava. Poznato je kako bakterijske stanice često stvaraju biofilm na površini različitih medicinskih uređaja, kao što su središnji venski kateteri, endoskopi i urinarni kateteri.

Fosfomicin ima potencijal prodrijeti u biofilm, transformirati strukturu biofilma i potencijalno povećati koncentraciju drugih antimikrobnih sredstava u biofilmu.

## Introduction

During the past decades, many clinical studies and case reports have presented coryneform bacteria as opportunistic pathogens in immunocompromised patients[1]. In the present case, we report a bloodstream infection caused by *Corynebacterium striatum* in an adult COVID-19 patient supported with the ECMO system. Although the central venous catheter was not proven as a source of infection, continuous bacteremia with *C. striatum* was confirmed during seven days in a patient on the ECMO support with clinical and microbiological signs of bloodstream infection.

## Methods

A 43-year-old patient underwent diagnostic and treatment procedures at the Intensive Care Unit (ICU) at the University Hospital for Infectious Diseases in Zagreb, Croatia.

The PubMed database was searched for the literature review. The terms used in literature search were: („*Corynebacterium* spp." OR „*C.striatum*") AND („bloodstream infection AND „catheter infection"). The searched data presented clinical cases with confirmed *Corynebacterium* spp. bloodstream infection. These infections had different sources but were mostly catheter-related (central venous catheters, pleural catheters, ECMO). Since catheters are part of the standard ICU treatment procedures, the formation of the biofilm on these devices is considered one of the main causes of treatment failure. Recent studies provide new information on fosfomycin as adjuvant therapy for the treatment of biofilm-related infections in patients with different catheters. So far, fosfomycin treatment of the bloodstream infections caused by *Corynebacterium* spp was not described[2].

## Results

### Case report

A 43-year-old patient without known comorbidities was referred by a family physician to the General Hospital „Dr. Ivo Pedišić" in Sisak due to SARS-CoV-2 pneumonia. Due to the deterioration of the clinical condition, the patient was transferred to the Intensive Care Unit (ICU) of the University Hospital for Infectious Diseases „Dr. Fran Mihaljević" in Zagreb. His condition required the insertion of a central venous line and connection to mechanical ventilation. Worsening of the clinical status soon followed with an increase of the inflammatory parameters and empirical therapy with colistin, ceftazidime/avibactam, and linezolid was introduced. Empirical therapy was based on the current epidemiological situation in the ICU targeting multidrug-resistant *Klebsiella pneumoniae, Staphylococcus aureus* (MRSA), *Acinetobacter baumannii,* and *Pseudomonas aeruginosa*. Due to further deterioration in gas exchange, the patient was connected to the veno-venous ECMO circuit. In the third week of hospital treatment, *A. baumannii* was isolated from clinically significant samples: the blood, endotracheal aspirate, and urine. Due to the patient`s deteriorated general condition and a significant increase in the inflammatory parameters, combined therapy of colistin and ampicillin/sulbactam was started. In the fifth week of hospitalization, Gram-positive rods were isolated in two sets of blood cultures from the peripheral blood. The isolated pathogen was identified as *C. striatum* using matrix-assisted laser desorption/ionization-time of flight (MALDI-ToF) and confirmed by 16S ribosomal RNA gene sequencing. Comparison of obtained sequences to NR/NT (non-redundant protein, non-redundant nucleotide) database using Nucleotide Basic Local Alignment Search Tool (BLASTn) (https://blast.ncbi.nlm.nih.gov/Blast.cgi) revealed a match to *C. striatum* (the most significant alignment with accession number: MT225764.1, percent identity 99.42%, 0.0 E-value). The antimicrobial susceptibility was tested by the disk diffusion method, and the results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables for interpretation of MICs and zone diameters from 2021[3]. The bacterial isolate was sensitive to vancomycin and linezolid while penicillin, ciprofloxacin, clindamycin, and rifampicin were resistant. Intravenous vancomycin therapy was added to the current antimicrobial therapy, colistin, and ampicillin/sulbactam. Over the next seven days, in daily blood culture samples, the same bacterium was isolated and central venous catheter was removed. Semiquantitative

microbiological analysis of the catheter grew <15 CFU of *Candida non-albicans* while quantitative cultivation was finished as sterile. The isolated pathogen was interpreted as contamination and clinically irrelevant based fungemia was not proven in blood cultures**.** Although administering antibiotic therapy and replacing the central venous catheter did not result in clinical improvement and sterile blood culture(s), other therapeutic procedures were considered. The exchange of an ECMO cannula was not possible because the procedure could cause serious deterioration with a fatal outcome. The adjuvant fosfomycin therapy was initiated based on available research results describing fosfomycin activity in biofilm. The blood cultures remained sterile for the next two weeks when the inflammatory parameters increased due to a new episode of proven bacteremia with *P. aeruginosa*. On the same day, the patient died of refractory shock.

## Literature review

Martin M et al. first described the sepsis caused by *C. striatum* confirmed by molecular method (ribotyping and randomly amplified polymorphic DNA) in 2002 in Spain. *C. striatum* isolated from the skin and the blood culture in a 69-year-old man with cellulitis of the right leg, belonged to the same clone lineage[4].

A Japanese retrospective study analysed 63 adult patients with *Corynebacterium* spp. isolated in blood culture from January 2014 until December 2016. According to the study criteria, bacteremia was confirmed in 28 patients (44%) while in 35 patients (56%) positive blood cultures were interpreted as contamination. A better clinical outcome was observed in patients in whom catheters were removed within seven days of the status deterioration[5].

Catheter-related bloodstream infection was reported in Taiwan in an 83-year-old patient with acute renal failure. The clinical condition worsened on the 25th day of hospitalization accompanied by leukocytosis. *C. striatum* was isolated in two sets of blood cultures, one taken from the peripheral line and the other from the central line catheter. The identical lineage of these two *C. striatum* isolates was confirmed by a randomly amplified polymorphic DNA mhod[1].

Although the central venous catheter is most often mentioned in the literature, other catheters should be considered as a possible route of entry for the skin microbiota. In metastatic breast cancer patients, the pleural catheters were inserted due to pleural effusion and worsening dyspnea. *C. striatum* was identified from the tip of the pleural catheter, a pleural effusion sample, and two sets of blood cultures[6].

ECMO is used as medical treatment in patients with severe acute respiratory failure or cardiac failure[7]. Nowadays, as the education of medical professionals has much improved, ECMO is more often used in treatment. However, there are still many challenges and possible complications during ECMO treatment and the high mortality rate is mainly due to nosocomial infections[8, 9]. Bloodstream infections exhibit the highest prevalence rates, varying from 32.6% to 89.4% across different studies. Respiratory and urinary tract infections come next in terms of occurrence, while surgical site infections are notably infrequent. The duration of ECMO support was the most important risk factor for acquiring nosocomial infection presenting a high correlation with the death rate[10-12]. Our patient acquired a bloodstream infection on the 18th day of the ECMO circuit.

A Korean group of authors analysed data collected from 259 patients connected to the ECMO device over five years. The incidence of ECMO-related nosocomial infections was 43.3 cases per 1000 ECMO days. These included nine cases of bloodstream infection and nine cases of respiratory tract infection. Although Gram-negative pathogens predominated in both groups, one clinically significant bacteremia with *C. striatum* was reported. Acquired nosocomial infections prolong the need for ECMO support. The higher incidence of nosocomial infection was related to the length of the ECMO circuit (>3.7 days)[13].

Souza et al. analysed the *C. striatum* biofilm production (multidrug-resistant and multidrug-susceptible isolates) on the abiotic surfaces and confirmed the formation of extensively adherent biofilm based on *in vitro* catheter model[14].

Besides medical devices (central venous catheter, ECMO cannula) damaged skin can be a possible source of *C. striatum* entry. An example is a case report of recurrent bacteremia in a patient with a chronic right leg ulcer[15].

Bacteria forming biofilm has high adherence activity to many medical devices, such as urinary catheters, endoscopes, central venous, and/or peripheral catheters, presenting significant complications for all patients, especially immunocompromised (16-18). The bacteria forming biofilm can transfer genes horizontally, which could additionally lead to spread of the antibiotic resistance[19, 20].

Fosfomycin has the potential to penetrate the biofilm, transform the biofilm structure and potentially increase the concentration of other antimicrobial agents in the biofilm. Based on current *in vivo* and *in vitro* experimental studies results, its activity on the biofilm can be accomplished in monotherapy or as adjuvant therapy[21-26].

## Discussion

Corynebacteria are recognized as opportunistic pathogens, especially in immunocompromised patients, such as oncology and hematological patients (1, 27-29). Distinguishing bacteremia from the contamination of the blood culture is also very important in terms of antibiotic stewardship and antimicrobial resistance prevention. Unnecessary antibiotic therapy leads to the selection of antibiotic-resistant organisms, prolonged hospitalization, and an increase in treatment costs[30].

In the case presented, the patient was hospitalized in the University Hospital for Infectious Diseases due to bilateral pneumonia caused by a SARS-CoV-2 infection and significant clinical deterioration. On the tenth day of ICU treatment, the patient was connected to the ECMO circuit, which posed a high risk for nosocomial infection and high risk of mortality. Vancomycin therapy was administered following the isolation of *C. striatum* from two sets of blood cultures sampled on the same day, effectively ruling out the possibility of contamination. Continuous bacteremia with *C. striatum* was detected in daily blood culture samples over the next seven days, although vancomycin therapy was continuously administered. The central venous catheter was not proven as a source of infection. In our patient ECMO cannula alteration was problematic due to the patient's severe clinical condition; therefore, the possibility of bacterial entry through the ECMO cannula from the formed biofilm could not be ruled out.

Also, *C. striatum* shows resistance to highly effective disinfectants, and hospital staff should be aware of the possible nosocomial infections caused by this bacterium. Targeted vancomycin therapy did not result in the sterility of blood cultures. Upon administration of fosfomycin, the blood culture became sterile after 48 hours and remained sterile for the next two weeks. Although *C. striatum* is intrinsically resistant to fosfomycin[31], the decision to add this antibiotic was salvage therapy, based on fosfomycin's ability to disintegrate the biofilm structure. We assume that fosfomycin activity on the biofilm enabled bactericidal vancomycin activity and resolved bacteremia.

## Conclusion

Several clinical case reports indicate an increasing number of nosocomial infections caused by *C. striatum* such as osteomyelitis, endocarditis, bacteremia, catheter-related infections, skin and soft tissue infections. In this case, the patient without medical burden was hospitalized due to bilateral pneumonia caused by SARS-CoV-2 infection and significant clinical deterioration.

Isolation of *C. striatum* from primary sterile samples requires careful interpretation of microbiological results, clinical presentation, and inflammatory parameters to distinguish the sample contamination from clinically significant infection. Also, knowing that biofilm formation is common on the surface of the intravenous catheters and other foreign materials, in the patients where its replacement is not possible, resolution of infection will require additional antibiotic(s) with the ability to disrupt the biofilm structure. We assume that targeted vancomycin therapy would result in sterile blood cultures following administration, but blood culture continued to grow *C. striatum* for the subsequent six days. The microbiological analysis ruled out the central venous catheter as the source of infection. The exchange of the ECMO cannula could not be performed due to the patient's critical clinical condition. Although we were aware of *C. striatum* intrinsic resistance to fosfomycin, this therapy was administered as salvage therapy with the aim to disrupt the biofilm structure. Bloodstream infection resolved soon after administration of fosfomycin and clinical improvement followed sterilization of blood culture sets. Unfortunately, the respiratory and circulatory systems in the reported patient could not recover from damage caused by the SARS-CoV-2 infection and two weeks later the patient died due to *P. aeruginosa* sepsis.

This case report and literature review pointed out that skin commensals can form biofilm on various medical devices especially intravenous catheters which can lead to catheter-related bloodstream infections. Treatment of the biofilm-related bloodstream infection with targeted antibiotics and fosfomycin can disintegrate the biofilm formation and resolve bacteremia.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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