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CLINICAL CASE

Recurrent *Cupriavidus pauculus* catheter-related bacteremia

Bacteriemia recurrente relacionada con catéter por *Cupriavidus pauculus*

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What do we know about the subject matter of this study?

Cupriavidus spp. infections are rare, especially in children, causing infections in immunocompromised or intravascular device carriers.

What does this study contribute to what is already known?

This work discusses possible therapeutic options for this rare infection, with little evidence about its optimal treatment, especially in relation to the need or not for central venous catheter (CVC) removal.

Abstract

Catheter-related bacteriemia by *Cupriavidus* spp. is a rare condition with very few cases reported in the literature. Most of them occurred in immunocompromised patients. **Objective:** To report a case of recurrent catheter-related bacteriemia by *Cupriavidus pauculus* in an immunocompromised infant in order to analyze possible therapeutic options, especially in relation to the need or not for central venous catheter (CVC) removal. **Clinical Case:** 22-month-old infant with B-cell acute lymphoblastic leukemia (ALL) in reinduction phase, CVC carrier. He presented to the Emergency Room with fever without focus on examination. Blood tests were performed (without increase of acute phase reactants) and differential blood cultures (peripheral and CVC). He was hospitalized and empirical antibiotic therapy was started with intravenous fourth-generation cephalosporin (cefepime). After 24 hours, blood cultures were positive for *Cupriavidus pauculus*, growing first in the CVC culture. We maintained cefepime, adding catheter lock therapy with ciprofloxacin. Afterward, the infection was resolved, allowing us to keep the CVC. Seven months later, in the context of fever, *Cupriavidus pauculus* was again identified in CVC blood culture. We decided this time to remove the catheter, in addition to the administration of intravenous cefepime. The patient has not presented new episodes nine months after de removal of the CVC. **Conclusion:** Catheter-related bacteremia by *Cupriavidus* is a rare condition in children that usually occurs in immunocompromised patients. Catheter lock therapy associated with systemic antibiotics could be a safe option in patients with difficult CVC removal. However, if persistent colonization of the CVC is suspected, it may be necessary to remove it.

Keywords:
Catheter-related bacteremia;
Cupriavidus;
Immunocompromised;
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Introduction

Cupriavidus spp. infections are rare, especially in children. They generally occur in immunocompromised patients or patients with central venous catheters (CVC) or other devices, and cases of bacteremia, meningitis, pneumonia-related to mechanical ventilation, and abscesses have been described in different locations[1,2]. The genus *Cupriavidus*, which currently includes other former genera such as *Wautersia* and some species of *Ralstonia*,[3] is a Gram-negative bacteria with flagellated, aerobic, non-glucose-fermenting bacilli morphology. They are environmental bacteria that are generally found in soils, water contaminated with heavy metals, or contaminated plants[1] and have been described as the cause of some nosocomial outbreaks, mostly due to contamination of water supply systems[4,5,6]. There are 17 species, of which 3 have been associated with human infection: *C. pauculus*, *C. gilardii*, and *C. metallidurans*[7]. *C. pauculus* (previously known as CDC group IV c-2) is catalase and oxidase positive[8,9].

Given the rarity of these infections, there is little evidence on their optimal treatment, especially in children, and on the need or not to remove the CVC in cases of CVC-related bacteremia. The objective of this work is to present a case of recurrent CVC-related bacteremia due to *Cupriavidus pauculus* in a pediatric patient, in order to analyze possible therapeutic options, especially in relation to the need or not for CVC removal.

Clinical Case

A 22-month-old infant with intermediate-risk ALL type B in the reinduction phase, carrier of a CVC with reservoir, presented to the emergency department with a 1-hour history of 38.4ºC fever, without other associated symptoms. A few hours earlier, the patient had received treatment with cytarabine, an antimetabolite pyrimidine analog chemotherapy drug that inhibits the synthesis of deoxyribonucleic acid, used in some childhood tumors.

On the physical examination, the patient presented good general condition, with no infectious focus. Given the presence of fever in an immunosuppressed patient, laboratory samples were collected, which showed no neutropenia (4,100 leukocytes/uL with 2,700 neutrophils/uL) and no elevation of acute phase reactants (CRP < 0.1 mg/dL), and the rest of the hemogram, coagulation, and biochemistry presented no alterations. Differential blood cultures (peripheral blood cultures as well as CVC) and urine cultures were also collected, and a chest X-ray was performed with no pathological findings. Given the history of recent chemotherapy treatment, the patient was admitted with empirical antibiotic therapy with intravenous cefepime (4th generation cephalosporin), at 150mg/kg/day, according to the protocol of the Children's Oncohematology unit for neutropenic patients or those who had received chemotherapy in the previous 7 days.

Twenty-four hours after admission, the Microbiology Department reported the growth of Gram-negative bacilli in the differential blood cultures, with probable origin in the CVC (growth at 20.66 hours in the CVC blood culture versus 30.69 hours in the peripheral blood culture). The microorganism was identified as *Cupriavidus pauculus* (by MALDI-TOF mass spectrometry and 16s rRNA gene sequencing), being sensitive to ceftazidime, cefepime, piperacillin-tazobactam, imipenem, cotrimoxazole, and quinolones, with resistance to aminoglycosides, cefotaxime, aztreonam, and meropenem. Antimicrobial susceptibility was assessed by automated broth microdilution method (MicroScan, Beckman Coulter, CA, USA) and interpretation of clinical categories of susceptible and resistant was determined following EUCAST recommendations. Systemic antibiotic treatment was continued with cefepime in addition to lock therapy of the CVC with 2 ml of ciprofloxacin lock flush solution (2mg/ml), for 2 hours each day.

The clinical evolution was favorable, with disappearance of fever, without peri-catheter inflammatory signs, and with sterile control blood cultures. The patient completed 2 weeks of antibiotic therapy since the first sterile blood culture. Given the good clinical evolution and the absence of complications, it was decided to keep the CVC, despite the scarce evidence in the literature as to which treatment was the most appropriate for this microorganism.

However, 7 months later, the patient presented another episode of fever without focus, and *Cupriavidus pauculus* was isolated again in the blood culture of the CVC, with the same sensitivity as the previous one. This time, as it was the second episode with suspected persistent colonization, it was decided to remove the CVC. The infant received treatment with cefepime for 7 days, with sterile control blood cultures, and good clinical evolution. Subsequently, 9 months after this second episode, the patient did not present any further incidences related to this infection.

Discussion

Cupriavidus spp. infections are infrequent in pediatric patients and, therefore, there is little evidence on their optimal treatment, especially on the need or not to remove the CVC in cases of CVC-related bacteremia.

Oncological children generally require a CVC for the administration of chemotherapy treatment, presenting an increased risk of infectious complications and the removal of the catheter is not always possible[10]. Therefore, given the scarce evidence on the best therapeutic option for this microorganism, especially in relation to the need or not to remove the CVC, a review of the literature on other cases of infections by this microorganism was carried out.

After searching Medline, between 1985 and 2020, we found 30 publications in the literature related to infections by this microorganism. Of these, only 10 are pediatric cases, including data from 17 patients (table 1)[1,12,13,14,15,16,17,18,19,20]. Five of them had complex heart disease on extracorporeal membrane oxygenation (ECMO), 8 had different pathologies or treatments that produced immunosuppression, and only 3 were healthy children (all under 6 months of age)[11,12,13]. In most cases, the prognosis was favorable with complete recovery, although there were 3 deaths during treatment (one patient with leukemia, another with idiopathic aplastic anemia, and another with severe heart disease)[14,15,16].

There is little evidence available on the antimicrobial susceptibility of *Cupriavidus* bacteria, as well as on the optimal therapy and its duration, especially in severe cases. Most isolates are sensitive to piperacillin-tazobactam, fluoroquinolones, ceftazidime, cefepime, and imipenem, with resistance to aminoglycosides and, occasionally, to meropenem, as in our case (table 1). Therefore, perhaps the most appropriate treatments for infections by this microorganism, especially in immunocompromised children, would be piperacillin-tazobactam or fourth-generation cephalosporin.

Of the pediatric publications, only 7 patients[1,17,18] were CVC-related bacteremias, all of them presenting good evolution, and the catheter was removed in only one of them[18]. In addition, of all the published cases reviewed (both pediatric and adult patients), only one of them, an adult with HIV infection[21], presented recurrent CVC-related bacteremia, as was our case.

In the first episode of CVC-related bacteremia in our patient, given the good clinical evolution, absence of signs of peri-catheter inflammation, and sterile control blood cultures, it was decided to conserve the catheter with antibiotic lock therapy and maintain systemic treatment for two weeks after the first sterile blood culture, with adequate recovery. The use of antibiotic lock therapy had not been described so far for this specific microorganism. In the case of our patient, to preserve the CVC safely, it was decided to perform it, according to the recommendations of the Microbiology Service of our hospital. Ciprofloxacin was used because it is a microorganism resistant to aminoglycosides, which are the most commonly used antibiotics in catheter lock therapy for infections caused by Gram-negative microorganisms. However, after the second episode of CVC-related bacteremia due to the same microorganism, it was finally decided to remove the catheter.

The recurrence of bacteremia due to the same microorganism could be related to permanent colonization of the catheter or reinfection. Colonization seems the most likely hypothesis, although the two episodes of CVC-related bacteremia occurred 7 months apart, with the patient remaining clinically stable and without isolation of the microorganism in several blood cultures performed during other episodes of febrile neutropenia. Given that it is an environmental bacterium, it could also be reinfection, although we were unable to find the origin, nor have there been episodes of infection by the same microorganism in any other patient in our hospital, so the existence of contamination in the water systems or any hospital material seems unlikely.

Conclusion

Cupriavidus spp. infections are rare in pediatrics, causing infections in immunosuppressed or intravascular device carriers, requiring broad-spectrum antibiotic therapy. It is an infrequent infection with little evidence in the literature on its optimal treatment, especially in children, as well as on the need or not to remove the CVC in cases of bacteremia.

From the described evolution of our patient and what has been reviewed in the literature, it seems that systemic treatment associated with CVC lock therapy could be a safe option in stable patients. However, in cases of suspected persistent colonization of the catheter, as in our case, it may be necessary to remove the CVC.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Table 1. Pediatric cases reported in the literature of bacteremia caused by *Cupriavidus* spp.

Author, year	Age	Underlying disease	Diagnosis	Species	Treatment	Antibiogram	Outcome
Ramos[19], 1993	10 y	Leukemia	Bacteremia	*C. pauculus*	Ceftriaxone	Unknown	Recovery
Moissenet[1], 1996	1 m 11 y 3 m 11 y 14 y	Jejunal atresia Carcinoma ID Lymphoma Leukemia	CVC- related bacteremia	*C. pauculus*	3 ceftazidime + amikacin 1 imipenem + amikacin 1 no treatment Preserved catheters	Unknown	Recovery
Noyola[20], 1999	6 m	No	Bacteremia	*C. pauculus*	Cefotaxime	Unknown	Recovery
Thayu[14], 1999	8 y	Leukemia	Secondary bacteremia (pneumonia)	*C. pauculus*	Ampicillin sulbactam + ciprofloxacin + gentamicin	Unknown	Death
Wauters[17], 2001	7 y	Leukemia	CVC-related bacteremia	*C. gilardii*	Ceftriaxone + amikacin + ciprofloxacin Preserved catheter	Unknown	Recovery
Karafin[15], 2010	12 y	Aplasic anemia	Secondary bacteremia (abdominal infection)	*C. gilardii*	Cefepime + amikacin + ciprofloxacin	S: cefepime,cotrimoxazol, ciprofloxacin R: piperacillin-tazobactam, aztreonam, imipenem, meropenem	Death
Stovall[16], 2010	4 m 3 y < 1 m 16 m	Congenital heart disease, in ECMO	Bacteremia	*C. pauculus*	1 piperacillin-tazobactam 1 cefepime + piperacillin-tazobactam 1 cefepime + ciprofloxacin 1 cefepime + gentamicin	Unknown	3 Recovery 1 Death
Aydyn[13], 2012	16 d	No	Secondary bacteremia (pneumonia)	*C. pauculus*	Ceftazidime	S: ceftriaxone, ceftazidime, piperacillin-tazobactam, quinolones, imipenem, cotrimoxazol, aminoglycosides	Recovery
Duggal[12], 2013	6 d	No	Bacteremia and meningitis	*C. pauculus*	Ceftazidime	S: ceftazidime, quinolones, piperacillin-tazobactam, cotrimoxazol, imipenem, meropenem R: ceftriaxone, aztreonam, aminoglycosides	Recovery
Uzodi[18], 2014	15 m	Congenital heart disease, in ECMO	CVC-related bacteremia	*C. pauculus*	Cefepime + catheter removal	S: cefepime, ceftazidime, piperacillin-tazobactam, quinolones, cotrimoxazol R: meropenem, aminoglycosides	Recovery

ID: immunodeficiency. CVC-related bacteremia: central venous catheter- related bacteremia. ECMO: extracorporeal membrane oxygenation. S: sensitivity. R: resistance y: years. m: months.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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References

1. Moissenet D, Tabone MD, Girardet JP, et añ. Nosocomial CDC group IV c-2 bacteremia: Epidemiological investigation by randomly amplified polymorphic DNA analysis. J Clin Microbiol. 1996;34(5):1264-6.
2. Steinberg JP, Lutgring JD, Burd EM. Especies de Ralstonia y Cupriavidus. En Mandell (Ed.) Enfermedades Infecciosas. Principios y práctica. Editorial Elsevier. 9 ed. 2021. ISBN 9788491134992
3. Vandamme P, Coenye T. Taxonomy of the genus Cupriavidus: a tale of lost and found. Int J Syst Evol Microbiol. 2004;54(Pt 6):2285-9.
4. Balada-Llasat JM, Elkins C, Swyers L, et al. Pseudo-Outbreak of *Cupriavidus pauculus* Infection at an Outpatient Clinic Related to Rinsing Culturette Swabs in Tap Water. J Clin Microbiol. 2010;48(7):2645-7.
5. Inkster T, Peters C, Wafer T, et al. Investigation and control of an outbreak due to a contaminated hospital water system, identified following a rare case of Cupriavidus pauculus bacteraemia. J Hosp Infect. 2021;111:53-64.
6. Cherak Z, Loucif L, Ben Khedher M, et al. MCR-5-Producing Colistin-Resistant Cupriavidus gilardii Strain from Well Water in Batna, Algeria. mSphere. 2021;e0057521.
7. Kweon OJ, Lim YK, Kim HR, et al. Isolation of a novel species in the genus Cupriavidus from a patient with sepsis using whole genome sequencing. PLoS One. 2020;15(5):1-11.
8. Yahya R, Mushannen A. Cupriavidus pauculus as an emerging pathogen: a mini-review of reported incidents associated with its infection. EC Pulmonology and Respiratory Medicine 2019:8(9):633-8.
9. Ortega GA, Bernal EA. Bacteriemia asociada a catéter por Cupriavidus pauculus. Infectio. 2011;15(4):289-92.
10. Albert O, Bonnet E, Cassard B, et al. Antibiotic lock therapy for the conservative treatment of long-term intravenous catheter-related infections in adults and children: When and how to proceed? Guidelines for clinical practice 2020. Infect Dis Now 2021;S2666-9919(21)00038-5.
11. Zhang Z, Deng W, Wang S, et al. First case report of infection caused by Cupriavidus giardii in a non-inmunocompromised Chinese patient. ID Cases 2017;10:127-9.
12. Duggal S, Gur R, Nayar R, et al. Cupriavidus pauculus concomitant menigitis and septicemia in a neonate: first case report from India. Indian J Med Microbiol 2013;31(4):405-9.
13. Aydin B, Dilli D, Zenciroglu A, et al. A case of newborn with community acquired pneumonia caused by Cupriavidus pauculus. Tuberk Toraks 2012; 60(2):160-2.
14. Thayu M, Baltimore RS, Sleight BJ, et al. CDC group IV c-2 bacteriemia in a child with recurrent acute monoblastic leukemia. Pediatr Infect Dis J. 1999;18(4):397-8.
15. Karafin M, Romagnoli M, Fink DL, et al. Fatal infection caused by Crupriavidus gilardii in a child with aplastic anemia. J Clin Microbiol 2010;48:1005-7.
16. Stovall SH, Wisdom C, McKamie W, et al. Nosocomial transmission of cupriavidus pauculus during extracorporeal membrane oxygenation. ASAIO Journal 2010;56:486-48.
17. Wauters G, Claeys G, Verschraegen G, et al. Case of catheter sepsis with Ralstonia gilardii in a child with acute lymphoblastic leukemia. J Clin Microbiol. 2001;39(12):4583-4.
18. Uzodi AS, Schears GJ, Neal JR, et al. Cupriavidus pauculus bacteremia in a child on extracorporeal membrane oxygenation. ASAIO J. 2014;60(6):740-1.
19. Ramos JM, Soriano F, Bernacer M, et al. Infection caused by the nonfermentative gran-negative bacillus CDC group IC c-2: case report and literatura review. Eur J Clin Microbiol Infect Dis. 1993;12:456-8.
20. Noyola DE, Edwards MS. Bacteriemia with CDC group IV c-2 in an immunocompetent infant. Clin Infect Dis. 1999;29:1572.
21. Anderson RR, Warnick P, Schreckenberger PC. Recurrent CDC group IVc-2 bacteremia in a human with AIDS. J Clin Microbiol. 1997;35(3):780-2.