

Brevundimonas spp. infection in immunocompromised children: Two case reports

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Abstract

Introduction *Brevundimonas* spp. are rare and opportunistic pathogens which may cause infections in patients who are immunocompromised or have underlying disease.

Case report Two cases with a microbiological diagnosis of *Brevundimonas aurantiaca* and *Brevundimonas* spp. are presented. Both occurred in immunocompromised patients with post-chemotherapy febrile neutropenia for B-type acute lymphoblastic leukemia and hepatoblastoma. Antibigram findings showed resistance to quinolones, ceftazidime, and intermediate resistance to cefepime, being susceptible to carbapenems and aminoglycosides. The cases responded favorably to the administration of carbapenem.

Conclusions The identification of the species and antimicrobial susceptibility profile favor response to infection, denoting the importance of species identification and the performance of an antibiogram to determine the different susceptibility profiles described in the literature on this emerging pathogen.

Keywords Gram-negative aerobic bacteria, immunocompromised host, child.

Introduction

The species of *Brevundimonas* spp. belong to the Alphaproteobacteria class and the Caulobacteraceae family.^{1,2} The genus *Brevundimonas* was proposed in 1994 with several species that previously belonged to other genera, mainly the *Pseudomonas* genus.² Currently, the genus consists of 37 species,³ the main species are *B. diminuta* and *B. vesicularis*, non-fermenting Gram-negative bacilli, catalase, and oxidase-positive, aerobic, and non-spore-forming, which have a polar flagellum that provides mobility. In

addition, these species have been isolated in multiple environments, mainly in water reservoirs and underwater sediments.^{1,4}

Infection by *Brevundimonas* is usually observed in patients with an underlying disease, especially in immunosuppressed patients.^{1,5} There is little information on the mechanisms of antimicrobial resistance in this genus, although resistance to cotrimoxazole, third-generation cephalosporins, fluoroquinolones, piperacillin/tazobactam, and even colistin has been reported.^{5,6}

There are few reports of *Brevundimonas* in pediatric patients, therefore, we present two cases of *Brevundimonas* infection in immunocompromised pediatric patients diagnosed with acute lymphoblastic leukemia and hepatoblastoma undergoing chemotherapy and surgical treatment, respectively. The patients evolved favorably and achieved microbiological clearance in control blood cultures with the use of carbapenems.

Case reports

Case 1

This case was a 5-year-old female patient from Cajamarca-Peru, with a history of Down syndrome, single kidney, hypothyroidism and type B acute lymphoblastic leukemia, who

Received: 22 November 2022; revised: 22 January 2023; accepted: 16 February 2023.

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Article downloaded from www.germs.ro

Published March 2023

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ISSN 2248 - 2997

ISSN - L = 2248 - 2997

received multiple chemotherapy schemes (induction IA, induction IB, Block I, Block II and reinduction of 5 drugs) which failed, thereby requiring palliative management. During chemotherapy, the patient had episodes of febrile neutropenia and received broad-spectrum antimicrobial treatment. Approximately 5 months after the last cycle of chemotherapy, the patient was hospitalized for febrile neutropenia. Auxiliary examinations revealed a hemogram with leukocytes 8660 cells/ μ L, absolute neutrophil count (ANC) 519 cells/ μ L, blast cells 73%, C-reactive protein (CRP) 199 mg/L, and procalcitonin (PCT) 0.81 ng/mL.

Treatment with piperacillin-tazobactam (320 mg/kg/day) was started, but due to the persistence of fever after 4 days of effective therapy, it was decided to switch to meropenem (60 mg/kg/day), with a favorable response. Blood culture results were positive for *B. vesicularis* and the antibiogram showed susceptibility to amikacin (minimum inhibitory concentration [MIC] $\leq$ 8 mg/L), gentamicin (MIC $\leq$ 2 mg/L), piperacillin/tazobactam (MIC 8/4 mg/L), cotrimoxazole (MIC $\leq$ 0.5/9.5 mg/L) and imipenem (MIC 1 mg/L) and resistance to ceftazidime (MIC $>$ 16 mg/L), ciprofloxacin (MIC $>$ 2 mg/L) and levofloxacin (MIC $>$ 4 mg/L). In addition, intermediate susceptibility to cefepime (MIC 16 mg/L) was reported (no susceptibility test to meropenem). Despite clinical and laboratory improvement, the isolation of microorganisms in the blood culture after more than 5 days of treatment with meropenem led to the decision to change the therapeutic regimen, to piperacillin/tazobactam (320 mg/kg/day) plus amikacin (15 mg/kg/day) based on the antibiogram results. However, after 3 days of therapy, the patient again became febrile with elevated inflammatory markers, and the administration of meropenem was reinitiated (120 mg/kg/day), completing a total of 11 days of therapy with favorable evolution, a reduction in inflammatory markers (PCT: 0.23 ng/mL), and negative blood culture controls. The patient had a Port-A-Cath catheter that was removed due to infection during antimicrobial treatment.

Case 2

A female patient aged 1 year 9 months from Lima-Peru, was hospitalized with a diagnosis of hepatoblastoma with suspected metastasis due to the presence of pulmonary nodules. The patient was administered Block A chemotherapy schemes with cisplatin and doxorubicin; and Block B with carboplatin and doxorubicin, showing partial response. Approximately 7 days after the last chemotherapy scheme, the patient presented febrile neutropenia without a focus. Physical examination revealed a palpable abdominal mass located in the hypochondrium and right flank. Auxiliary tests showed a leukocyte count of 1460 cells/ μ L, ANC: 160 cells/ μ L, PCT: 0.1 ng/mL and CRP: 4.1 mg/L. The result of the peripheral blood culture test was positive for *Brevundimonas* spp. with an antibiogram showing susceptibility to amikacin (MIC $\leq$ 8 mg/L), gentamicin (MIC $\leq$ 2 mg/L), and imipenem (MIC 2 mg/L), and resistance to ceftazidime (MIC $>$ 16 mg/L), ciprofloxacin (MIC $>$ 2 mg/L), levofloxacin (MIC $>$ 4 mg/L), cotrimoxazole (MIC $>$ 2/38 mg/L), and intermediate susceptibility to cefepime (MIC 16 mg/L) and piperacillin/tazobactam (MIC 32/4 mg/L).

Empirical antimicrobial treatment was started with piperacillin/tazobactam (320 mg/kg/day), received for 3 days. However, as the febrile episodes persisted and the results of blood cultures became available, the antimicrobial therapy was changed to meropenem (60 mg/kg/day) completing a total of 14 days of therapy with favorable clinical evolution and negative control blood cultures. The patient had a Port-A-Cath catheter that was not removed due to infection. Subsequently, primary tumor resection surgery and hepatectomy was performed.

Microbiological identification

The initial microbiological identification and antibiogram were performed at the Instituto Nacional de Salud del Niño San Borja, Lima-Peru, using the Phoenix automated system, reporting *B. vesicularis* in both cases. The susceptibility profile is shown in Table 1. The microbiological sample of case 1 was sent to the Laboratory of the Universidad Científica del Sur,

Table 1. Susceptibility report of the isolates reported in the National Institute of Children's Health San Borja – Peru.

Antibiotic	<i>Brevundimonas</i> spp.		<i>Brevundimonas aurantiaca</i>	
	MIC (mg/L)	S/I/R	MIC (mg/L)	S/I/R
Amikacin	≤8	S	≤8	S
Cefepime	16	I	16	I
Ceftazidime	>16	R	>16	R
Ciprofloxacin	>2	R	>2	R
Gentamicin	≤2	S	≤2	S
Imipenem	2	S	1	S
Levofloxacin	>4	R	>4	R
Piperacillin/tazobactam	32/4	I	8/4	S
Cotrimoxazole	>2/38	R	0.5/9.5	S

S – sensitive; R – resistant; I – intermediate; MIC – minimum inhibitory concentration.

Lima-Peru, for molecular typing. A fragment of the 16S rRNA gene was amplified by polymerase chain reaction (PCR) using primers 8F (5'-AGAGTTTGATCCTGGCTCAG-3') and 1510R (5'-GGTTACCTTTGTTACGACTT -3') under conditions previously described.⁷ The amplified product was resolved on a 1.5% agarose gel stained with 5% GreenSafe DNA Gel Stain, (Canvax Biotech, Spain), excised and purified using the E.Z.N.A. Gel extraction kit (Omega Bio-Tek, GA) following the manufacturer's instructions. The purified product was sent to Macrogen (South Korea) for sequencing. The presence of a member of the genus *Brevundimonas* was confirmed by comparison of the fragment in BLAST (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) matching the 16S rRNA of *B. aurantiaca* (strain CB-RT = ATCC 15266T = DSM 4731T - GenBank access: AJ227787) with 100% identity. In case 2, molecular identification was not performed.

Discussion

Brevundimonas spp. is not frequently implicated in human infections, and in previous reports, it was observed in patients with underlying diseases. Most cases are attributed to nosocomial sources, although some community-acquired cases have been reported. It is usually mainly found in blood samples.^{6,8-10} However, the isolation of *Brevundimonas* species has been reported in other samples such as urine, joint

fluid, ascitic fluid, respiratory secretions, and vaginal secretions.¹¹⁻¹⁶

A search was made in the PubMed and Google Scholar databases on isolates of *Brevundimonas* spp. in pediatric patients, and the summary of the cases is presented in Table 2. A total of 24 cases reported in pediatric patients were found, including the 2 cases presented in the present article.^{6,8-14,16-21} Of these, 19 cases corresponded to infections by *B. vesicularis*, 3 to *B. diminuta*, one case to *Brevundimonas* spp., and one case to *B. aurantiaca*, the latter being identified in the present report by molecular methods. To date, only one case of human infection by *B. aurantiaca* has been previously reported.²² Likewise, infection by *Brevundimonas* species in children was more frequently observed in patients under 1 year of age in 60% of the cases.

The cases occur mainly in patients with an underlying disease such as chronic kidney disease on hemodialysis, sickle cell anemia, acute leukemia, myelodysplastic syndromes, diabetes mellitus, congenital heart disease, systemic lupus erythematosus, glomerulopathy, and cystic fibrosis, due to the immunological defect, and thus, *Brevundimonas* can be considered an opportunistic pathogen.^{1,5,6} However, some cases have also been reported in apparently immunocompetent patients.^{8,12,17} Table 2 shows that the reports of pediatric patients were more

Table 2. Characteristics of pediatric patients diagnosed with infection by *Brevundimonas* spp.^{6,8-14,16-21}

Case no.	Age/ gender	Country	Source of infection	Comorbidity	<i>Brevundimonas</i> species	Susceptibility profile	Treatment	Result
1	17y/F	United States	Cervicitis	ND	<i>B. vesicularis</i>	S: ampicillin, gentamicin, kanamycin, streptomycin R: colistin	ND	ND
2	1y/F	India	Bacteremia	Immunocompetent	<i>B. vesicularis</i>	S: ND R: ceftazidime, ceftazidime, cotrimoxazole, tobramycin	Cefotaxime	Favorable
3	5y/M	United States	Bacteremia	Sickle cell anemia	<i>B. vesicularis</i>	S: ceftazidime, gentamicin, ciprofloxacin, ceftriaxone, piperacillin R: ND	Ceftriaxone + gentamicin	Favorable
4	1y 3m/F	Israel	Septic arthritis	Immunocompetent	<i>B. vesicularis</i>	S: aminoglycosides, aminopenicillins, piperacillin, 1 st , 2 nd and 3 rd generation cephalosporins, quinolones, and cotrimoxazole R: ND	Cefuroxime	Favorable
5	3y/M	Taiwan	Bacteremia	Immunocompetent	<i>B. vesicularis</i>	S: ND R: ND	Cefazolin	Favorable
6	7y/F	Taiwan	Bacteremia	Immunocompetent	<i>B. vesicularis</i>	S: ND R: ND	Cefalexin	Favorable
7	Newborn/M	Turkey	Bacteremia	Prematurity	<i>B. vesicularis</i>	S: gentamicin, imipenem, ceftriaxone, amikacin, cotrimoxazole R: piperacillin/ tazobactam, ceftazidime, aztreonam	Meropenem + ciprofloxacin	Favorable
8	Newborn/F	Turkey	Meningitis	Congenital heart disease, CNS malformations	<i>B. vesicularis</i>	S: cefotaxime, gentamicin, amikacin, imipenem R: piperacillin/ tazobactam, ceftazidime, aztreonam	Ampicillin + cefotaxime + meropenem	Unfavorable
9	Newborn/M	Turkey	Lymphadenitis	Congenital heart disease	<i>B. vesicularis</i>	S: ceftriaxone, tobramycin, amikacin, cotrimoxazole, imipenem, ciprofloxacin, polymyxin B R: piperacillin/ tazobactam, ceftazidime, aztreonam, colistin	Meropenem	Favorable
10	Newborn/M	Turkey	Bacteremia	Congenital heart disease	<i>B. vesicularis</i>	S: cefotaxime, gentamicin, amikacin, imipenem, ciprofloxacin, cotrimoxazole R: piperacillin/tazobactam, ceftazidime, aztreonam	Ampicillin + cefotaxime	Favorable
11	Newborn/M	Turkey	Bacteremia	Immunocompetent	<i>B. vesicularis</i>	S: ceftriaxone, gentamicin, tobramycin, amikacin, cotrimoxazole, imipenem, ciprofloxacin, polymyxin B R: piperacillin/tazobactam, ceftazidime, aztreonam, colistin	Cefotaxime + meropenem	Favorable

Case no.	Age/ gender	Country	Source of infection	Comorbidity	<i>Brevundimonas</i> species	Susceptibility profile	Treatment	Result
12	Newborn/F	Turkey	Bacteremia	Immunocompetent	<i>B. vesicularis</i>	S: gentamicin, amikacin, cotrimoxazole, imipenem, ciprofloxacin, polymyxin B R: piperacillin/ tazobactam, ceftazidime, aztreonam, colistin	Meropenem	Favorable
13	Newborn/M	Turkey	Bacteremia	Prematurity	<i>B. vesicularis</i>	S: ceftriaxone, gentamicin, amikacin, cotrimoxazole, imipenem R: ampicillin, cefotaxime, piperacillin/tazobactam, ceftazidime, tobramycin, aztreonam, ciprofloxacin	Meropenem + ciprofloxacin	Favorable
14	Newborn/M	Turkey	Bacteremia, meningitis	Congenital heart disease	<i>B. vesicularis</i>	S: ceftriaxone, gentamicin, amikacin, cotrimoxazole, imipenem, ciprofloxacin, polymyxin B R: piperacillin/tazobactam, ceftazidime, aztreonam, colistin	Meropenem	Favorable
15	8m/ND	India	Bacteremia, meningitis	Immunocompetent	<i>B. vesicularis</i>	S: levofloxacin, amikacin, piperacillin/tazobactam, cefoperazone R: ceftazidime, amoxicillin/clavulanic acid	Cefoperazone + levofloxacin	Favorable
16	Newborn/F	India	Bacteremia	Thrombocytopenia	<i>B. vesicularis</i>	S: meropenem, ceftazidime, cefepime, ampicillin/sulbactam, piperacillin/tazobactam, levofloxacin, ciprofloxacin, ceftazidime, tobramycin, gentamicin R: cotrimoxazole, nalidixic acid	Meropenem + ciprofloxacin	Favorable
17	9m/F	Tunisia	Bacteremia, empyema	Pompe's disease	<i>B. vesicularis</i>	S: cefotaxime, ceftazidime, imipenem, aztreonam, piperacillin/ tazobactam, gentamicin, amikacin, ofloxacin, ciprofloxacin R: piperacillin, ticarcillin	Ceftazidime + amikacin	Favorable
18	Newborn/M	Turkey	Bacteremia	Prematurity	<i>B. vesicularis</i>	S: gentamicin, amikacin, ceftriaxone, imipenem R: ampicillin, 3 rd generation cephalosporins, piperacillin/tazobactam	Meropenem + ciprofloxacin	Favorable
19	Newborn/M	India	Bacteremia	Immunocompetent	<i>B. vesicularis</i>	S: cefotaxime, ciprofloxacin, ofloxacin, gentamicin, amikacin, meropenem, piperacillin/tazobactam. R: ND	Cefotaxime + amikacin	Favorable

Case no.	Age/gender	Country	Source of infection	Comorbidity	<i>Brevundimonas</i> species	Susceptibility profile	Treatment	Result
20	17y/F	France	Bacteremia, meningitis	Cystic fibrosis, type I diabetes mellitus	<i>B. diminuta</i>	S: ceftriaxone, ticarcillin, imipenem, amikacin, tobramycin, gentamicin, rifampicin, piperacillin/tazobactam. R: amoxicillin, amoxicillin/clavulanic acid, ceftazidime, ciprofloxacin, cotrimoxazole, colistin	Imipenem + inhaled tobramycin	Favorable
21	9m/ND	India	Bacteremia	Immunocompetent	<i>B. diminuta</i>	S: amikacin, amoxicillin/clavulanic acid, cefotaxime, cotrimoxazole, cefepime R: ciprofloxacin	Ticarcillin/clavulanic acid	Favorable
22	18y/M	India	Pneumonia	Focal segmental glomerulosclerosis, pulmonary tuberculosis	<i>B. diminuta</i>	S: imipenem, meropenem, amikacin, gentamicin, fluoroquinolones, minocycline, tigecycline, cefoperazone-sulbactam, ceftazidime, cefepime, cotrimoxazole R: colistin	Cefoperazone/sulbactam	Favorable
23. Case 1	5y/F	Peru	Urinary infection	Acute lymphoblastic leukemia, Down syndrome	<i>B. aurantiaca</i>	S: amikacin, gentamicin, piperacillin/tazobactam, cotrimoxazole, imipenem R: ceftazidime, ciprofloxacin, levofloxacin I: cefepime	Meropenem	Favorable
24. Case 2	1y 9m/F	Peru	Bacteremia	Hepatoblastoma	<i>Brevundimonas</i> spp.	S: amikacin, gentamicin, imipenem R: ceftazidime, ciprofloxacin, levofloxacin, cotrimoxazole I: cefepime, piperacillin/tazobactam	Meropenem	Favorable

CNS – central nervous system; F – female; I – intermediate; M – male; S – sensitive; R – resistant; ND – not determined.

frequent in patients with congenital heart disease (4/24), premature newborns (3/24), and in 9/24 no previous underlying diseases were described. There are reports of *Brevundimonas* infection in adult cancer patients, but in children, these are the first two cases reported in the literature.⁵ Only 1 patient had a fatal outcome related to *B. vesicularis* infection.

On the other hand, the antimicrobial regimen of choice for this pathogen is unknown. Antibiotic therapy should be directed according to susceptibility tests because resistance to different antibiotics has been observed; for example, resistance to colistin is a characteristic found in this genus.²³ Of the reports reviewed, we found that 26% (5/19) had resistance to colistin. In addition, resistance to the fluoroquinolone

family has been detected due to mutations in the *gyrA*, *gyrB*, and *parC* genes, mainly in *B. diminuta*.⁵ Susceptibility to colistin was not reported and resistance to fluoroquinolones was observed in both cases. Zhang *et al.*¹⁷ suggested the use of piperacillin/tazobactam and third-generation cephalosporins as therapies; however, of the reports reviewed, 74% (14/19) showed resistance to ceftazidime and 53% (10/19) presented resistance to piperacillin/tazobactam. In both cases reported, piperacillin/tazobactam was started, but the patients did not show a favorable response with this antibiotic, although the case of *B. aurantiaca* was sensitive to piperacillin/tazobactam. It seems that antibiotic therapy with carbapenems has demonstrated greater effectiveness in infections caused by this pathogen. We did not find resistance to carbapenems in the pediatric population, and our cases responded favorably with meropenem. However, Scotta *et al.*²⁴ reported 3 *Brevundimonas* isolates in hospital wastewater carrying the gene encoding the VIM-13 metalloβ-lactamase (MBL) enzyme, indicating that this pathogen could represent a reservoir for the dissemination of MBL genes. A case of a *B. diminuta* carrier of MBL VIM-2 isolated in tissue culture in an adult patient has been reported.²⁵

Conclusions

In conclusion, *Brevundimonas* species are emerging pathogens, of which little is known. The information available is mainly from the adult population, being scarce in the pediatric population. Therefore, it is important to review the clinical manifestations and the most appropriate antimicrobial regimen against this pathogen in immunocompromised children.

Authors' contributions statement: AAB and JMA conceived the article. AAB, CCC, and JWL collected the data and drafted the article. MJP was responsible for the 16S rRNA gene sequencing. All authors were responsible for the critical review of the manuscript and read and approved its final version.

Ethics approval: This study was approved by the institutional ethical committee of the Instituto Nacional de Salud del Niño San Borja (INSN-SB), Lima-Perú (Reference No - AIIMS/IEC/2021/3546).

Consent: Written informed consent was obtained from the parents of the patients for the publication of this case report.

Conflicts of interest: All authors – none to declare.

Funding: Internal funds were obtained from the Universidad Científica del Sur, Lima-Perú, for molecular typing.

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Please cite this article as:

Altamirano-Beltrán A, Chiara-Chilet C, López JW, Pons MJ, Maquera-Afaray J. *Brevundimonas* spp. infection in immunocompromised children: Two case reports. GERMS. 2023;13(1):72-79. doi: 10.18683/germs.2023.1369