Catheter-related Infections in Pediatric Patients Due to a Rare Pathogen

Herbaspirillum huttiense

Seval Özen, MD, Saliha Kanik Yüksek, MD,* Bedia Dinç, MD,† Fatih Üçkardeş, PhD,‡ Hatice Kübra Konca, MD,* Tuğba Erat, MD,* Ahmet Yasin Güney, MD,* Ömer Güneş, MD,* Zehra Nihan Coşkun, MD,* Belgin Gülhan, MD,* Gülsüm İclal Bayhan, MD,* Nilay Çöplü, MD,† Aslı Nur Özkaya Parlakay, MD,* and Namık Yaşar Özbek, MD§*

Downloaded from http://journals.lww.com/pidj by GC6LOAQkBctlV1dhYAHlqCRP415WxR+ZZmL01PrrVFIHWT9QPD8AbOdczkHg3zvv3TsVzEfOmW8pzhOIwvVoXdN4tlJA4Zg1uxIlDqvqf4izJFCvP2pqLA2xK9UAAa5bBn2dgyn+E= on 12/27/20 24

Background: *Herbaspirillum species* are nonfermenting, aerobic, helical or curved, Gram-negative bacteria belonging to the class Betaproteobacteria, order Burkholderiales. To date, only a few studies have reported on the epidemiology, clinical symptoms, antibiotic susceptibility profiles, treatment and outcomes of *Herbaspirillum huttiense*-related infections in pediatric patients.

Methods: The aim of this study was to present 3 years of *H.huntiense* data, antibiotic susceptibility profiles, systemic antibiotics and antibiotic lock therapy (ALT) options and clinical outcomes.

Results: Fourteen episodes of infection in 12 patients were included in this retrospective study. The patients had a male/female ratio of 1:1 and a median age of 160.5 months (range, 3–198 months). Catheter-related bloodstream infection (CRBSI) was detected in 11 patients. Only 1 patient developed catheter-related infective endocarditis. The patient's catheter was removed, and she was successfully treated with systemic antibiotics for 4 weeks. Systemic antibiotics were used in all infections related to *H. huttiense*. In septic, critically ill patients, the catheter was removed, and systemic antibiotics were started. Port catheters were removed in 5 patients. ALT was performed in clinically stable patients. ALT using amikacin was administered to 6 patients through the port catheter. Two patients had a 2nd attack. After the 2nd ALT treatment, 1 patient cured, and the catheter of the other patient was removed due to persistent microbial growth in cultures. Antimicrobial susceptibility testing of the reported isolates showed susceptibility to meropenem (90%), ceftazidime (87%) and piperacillin/tazobactam (65%), with 92% resistance to colistin.

Conclusion: *H. huttiense* is an emerging pathogen in CRBSI. Piperacillin/tazobactam, ceftazidime and meropenem appear to be good therapeutic options for the treatment of *H. huttiense* infections. ALT and systemic antibiotics can be used in *H. huttiense*-CRBSI to sterilize and preserve the central venous catheter.

Key Words: catheter lock therapy, catheter-related bloodstream infection, *Herbaspirillum huttiense*, pediatric

(*Pediatr Infect Dis J* 2024;43:e231–e234)

Accepted for publication March 11, 2024

From the *Department of Pediatric Infectious Diseases; †Department of Medical Microbiology, Ankara Bilkent City Hospital, Ankara, Turkey; ‡Department of Biostatistics and Medical Informatics, Adıyaman University, Adıyaman, Turkey; §Department of Pediatric Hematology/Oncology and Pediatric Bone Marrow Transplantation Unit, Ankara Bilkent City Hospital, Ankara, Turkey.

The authors have no funding or conflicts of interest to disclose.

Address for correspondence: Seval Özen, MD, Department of Pediatric Infectious Diseases, Ankara Bilkent City Hospital, Ankara, Turkey. E-mail: drsevalcevik@hotmail.com.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0891-3668/24/437-e231e234
DOI: 10.1097/INF.0000000000004350

Herbaspirillum species (spp.) are nonfermenting, aerobic, helical or curved, Gram-negative bacilli of the Betaproteobacteria class found in various environmental habitats, including soil, groundwater and drinking water distribution systems.[1] *Herbaspirillum* spp. were first described in 1986 by Baldani,[2] this species were reclassified as *Herbaspirillum huttiense* in 2004 by Ding and Yokota.[3] Subsequently, isolated cases as well as case series were reported in immunosuppressed and immunocompetent individuals.[4–7] It is mostly associated with bacteremia in patients with underlying conditions such as cancer, cirrhosis or immunosuppression.[1,6] The identification of this agent is clinically important. Conventional identification methods fail to detect *Herbaspirillum* spp. and may confuse *Herbaspirillum* with other microorganisms such as *Cupriavidus pauculus*, *Burkholderia cepacia* complex, *Ralstonia* spp. or *Ochrobactrum anthropi*.[4,8–10] Advanced bacterial diagnostic methods [e.g., matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) and/or molecular techniques] that can reveal the protein structure or nucleic acids of microorganisms are expected to enable accurate identification of this microorganism. MALDI-TOF MS is a spectroscopic method that requires a reliable and complete database. The rapid identification and high discriminative power of MALDI-TOF MS have made it a useful tool in identifying rare bacteria that are difficult to identify. Implementation of the bioMérieux MS scientific research database improved the detection probability of rare bacteria.[1,9–11]

Most patients require long-term use of central venous catheters (CVC) for procedures such as administration of intravenous drugs, blood transfusions, parenteral feeding, and laboratory tests. Different types of intravascular catheters are currently being used, leading to a myriad of infectious complications. In patients with CVC, catheter-related bloodstream infections (CRBSI) can cause significant morbidity and mortality if not treated quickly and effectively.[12] Antibiotic therapy for catheter-related infection is often initiated empirically. In the treatment of CRBSI, antibiotic lock therapy (ALT) can be used together with systemic antimicrobial therapy. ALT, with or without heparin, is the retention of antibiotics at high concentrations and for certain periods of time in the catheter to sterilize the catheter lumen. Indicated in patients with CRBSI involving long-term catheters with no signs of exit site or tunnel infection where catheter salvage is the goal.[13]

There are only a few studies that examined the epidemiology, clinical findings, antibiotic susceptibility profiles, treatment and outcomes of *H. huttiense*-related infections in pediatric patients. The aim of this study was to present 3 years of *H.huntiense* data, antibiotic susceptibility profiles, systemic antibiotics and ALT options and clinical outcomes.

PATIENTS AND METHODS

In this retrospective, single-center study, 14 infection episodes in 12 patients with positive *H. huttiense* cultures at Ankara

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Bilkent Children's Hospital between August 2019 and December 2022 were included.

Patients with underlying conditions included those with hematologic or oncologic malignancy, ventriculoperitoneal shunt and hematopoietic stem cell transplant recipients.

Demographic and clinical data of the patients were retrieved from the hospital's electronic medical records. Age, sex, underlying diseases, the presence of CVC, antibiotics, regimen, antibiotic susceptibility profile, the presence of fever, total white blood cell count, neutrophil and lymphocyte counts, catheter removal status, discharge and mortality data were reviewed.

The diagnosis of CRBSI was considered if at least one of the following findings: (1) the occurrence of chills accompanied by fever (>38 °C) within 1 hour after catheter manipulation or flushing, (2) isolation of the same pathogen from both catheter and peripheral blood cultures, and (3) isolation of the same pathogen from the catheter tip and blood.[14]

In patients with a diagnosis of CRBSI, ALT was administered with a concentration of 2 mg/ml amikacin without the use of heparin, considering the susceptibility pattern of the isolate, with the goal of catheter salvage in mind. The antibiotic solution was changed at 24-hour intervals.[15] The treatment of the patients whose fever decreased after 72 hours and whose blood culture was negative was completed for 10–14 days with ALT and systemic antibiotics. Treatment of patients whose catheters were removed continued with systemic antibiotics for 10–14 days.

Isolates were identified with VITEK MS v3.2.0 (bioMérieux), a system that uses MALDI-TOF technology. Antibiotic susceptibility testing of the isolates was performed using the ETEST method (bioMerieux, France), and evaluated according to pharmacokinetic pharmacodynamic breakpoints of the European Committee on Antimicrobial Susceptibility Testing.

Statistical Analysis

Statistical analyses were performed using the SPSS software, version 25.0 (IBM Inc., Armonk, NY) and GraphPad software, version 8.0.2. Kolmogorov–Smirnov test was used to determine whether the data was distributed normally. Sex distribution was analyzed using the Mann–Whitney *U* test. The results were reported as median (min-max). A P value of <0.05 was considered statistically significant.

RESULTS

The patients had a male/female ratio of 1:1 and a median age of 160.5 months (range, 3–198 months). At the time of diagnosis, the patients had a median white blood cell count of 3190 (200–11,620) cells/μL, absolute neutrophil count of 2625 (10–6,030) cells/μL and absolute lymphocyte count (ALC) of 500 (30–48,420) cells/μL.

The clinical characteristics of the patients diagnosed with *H. huttiense* infection are presented in Table 1. CRBSI associated with implanted devices (port) was detected in 11 immunocompromised patients. All patients (100%) had fever symptoms.

Systemic antibiotics were used in all infections related to *H. huttiense*. In septic, critically ill patients, the catheter was removed and systemic antibiotics were started. Port catheters were removed in 5 patients. ALT was performed in clinically stable patients. ALT was administered to 6 patients through the port catheter. However, *H. huttiense*-CRBSI was detected again in 2 patients. In the other patient, a CRBSI episode developed 3 months later. Due to technical difficulties, we learned antibiotic susceptibility late. *H.huntiense* was resistant to amikacin. The catheter was removed due to persistent microbial growth in cultures (case 5 and case 7 in Table 1).

TABLE 1. Clinical Characteristics of the Cases Described

No	Sex/Age	Underlying Disease	Diagnosis	Catheter Removal Status	Systemic Treatment	Antibiotic Lock Therapy	Complication	*Herbaspirillum Huttiense*-Related Mortality
1	M/15 years	ALL	CRBSI	Yes	Piperacillin-tazobactam plus amikacin	No	No	No
2	M/12 years	ALL	CRBSI	Yes	Piperacillin-tazobactam plus amikacin	No	No	No
3	F/14 years	ALL	CRBSI	Yes	Ceftazidime plus amikacin	No	No	No
4	F/3 monthly	Hydrocephalus	VP shunt infection	Yes	Meropenem	No	No	No
5	F/2 years	Medulloblastoma	CRBSI	No	Ceftazidime plus amikacin	Yes	No	No
6	M/13 years	Osteosarcoma	CRBSI	No	Piperacillin-tazobactam plus amikacin	Yes	No	No
7	M/13 years	Osteosarcoma	CRBSI	No	Cefoperazone sulbactam	Yes	No	No
8	M/2 years	Embryonal rhabdomyosarcoma	CRBSI	No	Cefepime plus amikacin	Yes	No	No
9	F/14 years	ALL≫HSCT	CRBSI	No	Meropenem plus amikacin	Yes	No	No
10	M/15 years	Ewing sarcoma	CRBSI	No	Meropenem plus amikacin	Yes	No	No
11	F/16 years	Embryonal rhabdomyosarcoma	CRBSI	Yes	Meropenem	No	No	No
12	F/11 years	Osteosarcoma	CRBSI	Yes	Piperacillin-tazobactam >meropenem plus amikacin	No	Endocarditis	No

ALL indicates acute lymphoblastic leukemia; CRBSI, catheter-related bloodstream infection; F, female; HSCT, hematopoietic stem cell transplant; M, male; VP, Ventriculoperitoneal.

Downloaded from http://journals.lww.com/pidj by GC6LOAQkBctiIV1dhYAHlqCRP415WxR+ZZmL01PrvFIHWT9QPD8AbOdczkHg3zvv3TsVzEfOmW8pzhOlwvVoXdN4tlJA4Zg1uxIlDqvqf4izjFCvP2pqLA2xK9UAAa5bBn2dgyn+E= on 12/27/20 24

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/pidj by GC6LOAQkBctIlV1dhYAHlqCRP415WxR+ZZmL01PrrVFIHWT9QPD8AbOdczkHg3zvv3TsVzEfOmW8pzhOlwvVoXdN4tlJA4Zg1uxIlDqvqf4izlFCvP2pqLA2xK9UAAaSbBnZdgyn+E= on 12/27/2024

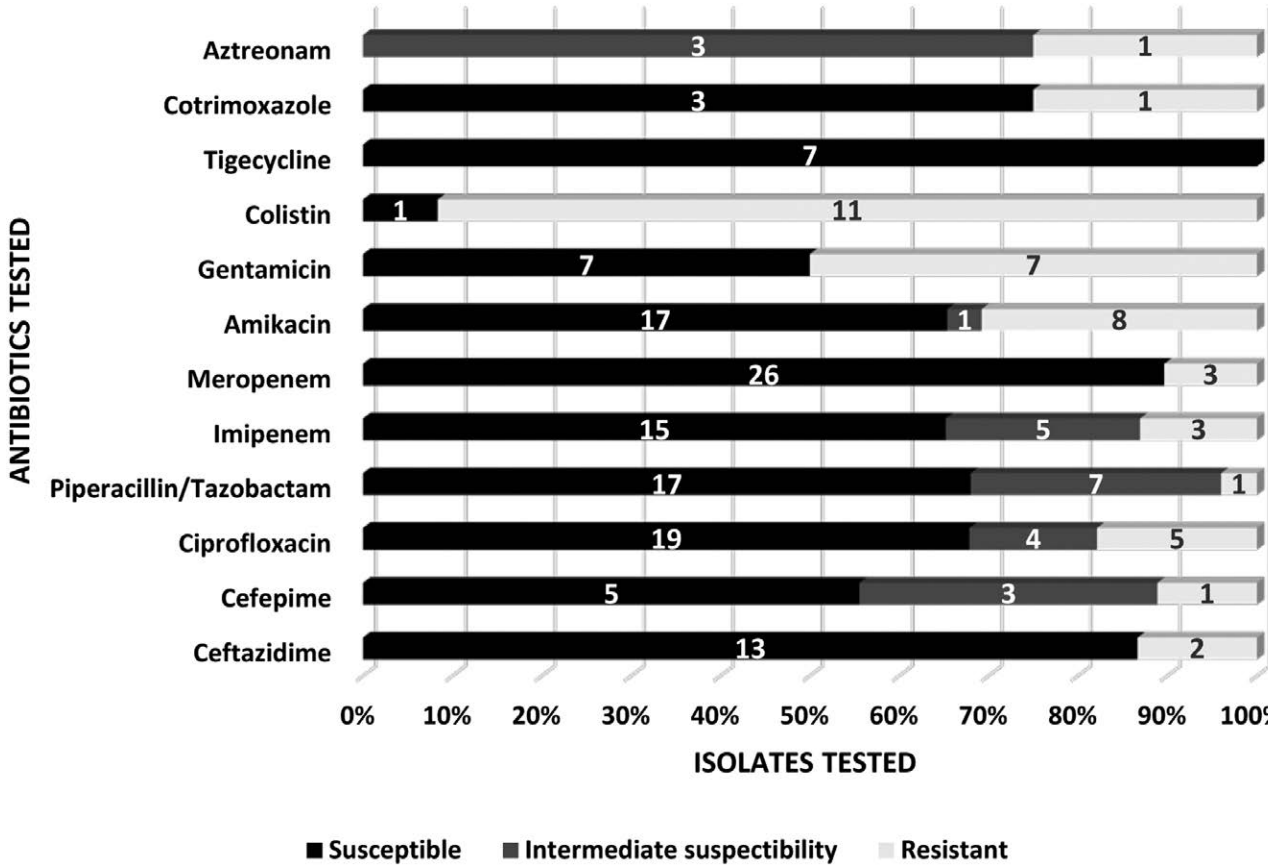


FIGURE 1. Antimicrobial susceptibility of the isolates.

One patient (an 11-year-old girl) developed a complication of catheter-related infective endocarditis. A transthoracic echocardiogram of this patient revealed hyperechogenic 2 × 3.5 cm vegetation at the inferior vena cava and right atrium junction. Cardiac magnetic resonance imaging showed impaired left ventricular systolic function (57%), hypointense foci in the right atrium and right ventricle and decreased right ventricular systolic function. The patient's catheter was removed and she was successfully treated with meropenem and amikacin for 4 weeks.[16]

Antimicrobial susceptibility results of the reported isolates are displayed in Figure 1. Almost 92% of the isolates were resistant to colistin, followed by gentamicin (50%) and amikacin (31%). The minimum inhibitory concentration (MIC) values of amikacin ranged between 8 and 64 μg/mL for the isolates tested for MIC. The MIC values were 8–24 μg/mL for gentamicin. Colistin showed a high MIC value of ≥256 μg/mL. Meropenem (90%), ceftazidime (87%) and piper–acillin/tazobactam (65%) were susceptible. Of the quinolones, 68% of the isolates were susceptible, 14% were intermediately susceptible and 18% were resistant to ciprofloxacin.

DISCUSSION

H. huttiense infections have often been associated with risk factors such as pneumonia, hematologic disorders and cardiovascular diseases. Hickman and port catheters are increasingly used in patients with malignancy due to the ease of establishing continuous venous access. In patients with central venous catheter, CRBSI can lead to severe morbidity and mortality if not treated quickly and effectively.[17] In a case series reported by Bloise et al.,[6] CRBSI was detected in 1 patient and was successfully treated with systemic piperacillin-tazobactam. Ziga et al.[9] presented a case of CRBSI caused by *H. huttiense* in a 2-year-old patient with ALL, which resolved with meropenem. In our study, systemic antibiotics were used in all infections associated with *H. huttiense*. We employed ALT to 6 patients. However, 2 of these patients developed a second CRBSI episode 3 and 6 months later, respectively. ALT was repeated for both patients but was successful in one of them. In the patient in whom ALT failed, we learned antibiotic susceptibility late due to technical difficulties. *H. huntiense* was resistant to amikacin.

Li et al.[1] reported that *H. huttiense* is susceptible to imipenem, meropenem, piperacillin-tazobactam and levofloxacin, while Hernández et al.[5] reported that *H. huttiense* is susceptible to levofloxacin, ceftazidime, trimethoprim-sulfamethoxazole, minocycline and meropenem and resistant to amikacin and colistin. Consistently, we observed that *H. huttiense* was susceptible to meropenem, ceftazidime, piperacillin-tazobactam and resistant to colistin. In our study, antibiotic susceptibility tests differed for each isolate. The antibiotic discs available in our laboratory at that time could be used. Published studies show that meropenem and piperacillin-tazobactam are the most used drugs with good clinical efficacy. Meropenem and piperacillin-tazobactam were also the most used antibiotics in our study. We think that catheter lock therapy can be used simultaneously with systemic treatment in patients diagnosed with CRBSI for catheter salvage. This is the first study to use catheter lock therapy for CRBSI caused by *H. huttiense* and also the largest case series reported to date.

MALDI-TOF MS enables the identification of bacterial species as well as those reported as rare human pathogens, which

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

can be challenging with conventional phenotypic methods. At our hospital, we use the VITEK MS v3.2.0 (bioMérieux) system and database. *H. huttiense* has a high phenotypic similarity to *Burkholderia cepacia*, which sometimes results in misidentification.[8,10] Phenotypic characterization does not allow differentiation between species. MALDI-TOF MS or molecular methods are required for reliable identification. Fatal cases of *H. huttiense* infection have been reported in a small of number of patients.[6,18] In our study, no death occurred.

Chemaly et. al,[4] reports a hospital-based cluster of Herbaspirillum species infections in cancer patients, as well as subsequent sporadic cases of the hospital- and community-onset infections. The study included facility observations, infection prevention assessments, and environmental sampling to explore potential sources of Herbaspirillum species. Despite all intensive efforts, the source of the bacterium could not be identified. So far, we do not know the source of *H.huttiense* in our cluster.

In conclusion, catheter lock therapy using amikacin can be considered for the treatment of CRBSI caused by *H. huttiense,* an emerging pathogen rarely infecting humans. As for systemic antibiotics, piperacillin-tazobactam, ceftazidime and meropenem appear to be good therapeutic options for this microorganism. Future studies are warranted to obtain further data on the source, transmission, antimicrobial susceptibility pattern, and clinical course of the *H. huttiense* infection.

REFERENCES

1. Li X, Bao X, Qiao G, et al. First study of bacteremia caused by Herbaspirillum huttiense in China: a brief research report and literature review. *Front Cell Infect Microbiol*. 2022;12:882–827.
2. Baldani JI, Baldani VLD, Seldin L et.al. Characterization of Herbaspirillum seropedicae gen. nov., sp. nov., a root-associated nitrogen-fixing bacterium. *International Journal of Systematic and Evolutionary Microbiology*. 1986;36(1):86–93.
3. Ding L, Yokota A. Proposals of Curvibacter gracilis gen. nov., sp. nov. and Herbaspirillum putei sp. nov. for bacterial strains isolated from well water and reclassification of [Pseudomonas] huttiensis, [Pseudomonas] lanceolata, [Aquaspirillum] delicatum and [Aquaspirillum] autotrophicum as Herbaspirillum huttiense comb. nov., Curvibacter lanceolatus comb. nov., Curvibacter delicatus comb. nov. and Herbaspirillum autotrophicum comb. nov. *Int J Syst Evol Microbiol*. 2004;54:2223–2230.
4. Chemaly RF, Dantes R, Shah DP, et al. Cluster and sporadic cases of Herbaspirillum species infections in patients with cancer. *Clin Infect Dis*. 2015;60:48–54.
5. Liras Hernández MG, Girón de Velasco Sada P, Falces Romero I, et al. Bacteremia caused by Herbaspirillum huttiense in a newborn. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2019;37:491.
6. Bloise I, Guedez-López GV, Tejedor-Rodríguez M, et al. Bloodstream infection due to Herbaspirillum sp.: case series and review of literature. *Eur J Clin Microbiol Infect Dis*. 2021;40:779–785.
7. Liu C, Kwon MJ, Kim M, et al. Septicemia caused by Herbaspirillum huttiense secondary to pneumonia. *Ann Lab Med*. 2019;39:340–342.
8. Regunath H, Kimball J, Smith LP, et al. Severe community-acquired pneumonia with bacteremia caused by Herbaspirillum aquaticum or Herbaspirillum huttiense in a Inmune-competent adult. *J Clin Microbiol*. 2015;53:3086–3088.
9. Ziga ED, Druley T, Burnham C-AD. Herbaspirillum species bacteremia in a pediatric oncology patient. *J Clin Microbiol*. 2010;48:4320–4321.
10. Spilker T, Uluer AZ, Marty FM, et al. Recovery of Herbaspirillum species from persons with cystic fibrosis. *J Clin Microbiol*. 2008;46:2774–2777.
11. Abreu-Di Berardino M, Rodríguez-Czaplicki E, Sánchez-Hellín V. Herbaspirillum huttiense pneumonia in a patient with essential thrombocythaemia. *Rev Esp Quimioter*. 2019;32:83–84.
12. Adler A, Yaniv I, Solter E, et al. Catheter-associated bloodstream infections in pediatric hematology-oncology patients: factors associated with catheter removal and recurrence. *J Pediatr Hematol Oncol*. 2006;28:23–28.
13. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. *Clin Infect Dis*. 2009;49:1–45.
14. Viscoli C, Castagnola E, Giacchino M, et al. Bloodstream infections in children with cancer: a multicentre surveillance study of the Italian association of paediatric haematology and oncology. supportive therapy group-infectious diseases section. *Eur J Cancer*. 1999;35:770–774.
15. Chaves F, Garnacho-Montero J, Del Pozo JL, et al. Diagnosis and treatment of catheter-related bloodstream infection: clinical guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology and (SEIMC) and the Spanish Society of Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC). *Med Intensiva (Engl Ed)*. 2018;42:5–36.
16. Güngör AA, Demirdağ TB, Dinç B, et al. A case of infective endocarditis due to Herbaspirillum Huttiense in a pediatric oncology patient. *J Infect Dev Ctries*. 2020;14:1349–1351.
17. Mert D, Ceken S, Iskender G, et al. Epidemiology and mortality in bacterial bloodstream infections in patients with hematologic malignancies. *J Infect Dev Ctries*. 2019;13:727–735.
18. Suwantarat N, Adams LL, Romagnoli M, et al. Fatal case of Herbaspirillum seropedicae bacteremia secondary to pneumonia in an end-stage renal disease patient with multiple myeloma. *Diagn Microbiol Infect Dis*. 2015;82:331–333.

Downloaded from http://journals.lww.com/pidj by GC6LOAQkBctIlV1dhYAHlqCRP415WxR+ZZmL01PrrVFIHWT9QPD8AbOdczkHg3zvv3TsVzEfOmW8pzhOlwvVoXdN4tlJA4Zg1uxIlDqvqf4izJFCvP2pqLA2xK9UAAaSbBn2dgyn+E= on 12/27/2024

© 2024 Wolters Kluwer Health, Inc. All rights reserved

Copyright © 2024 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.