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Bordetella holmesii Bacteremia in Sickle Cell Disease

Timothy L. McCavit, MD[1,2,*], **Steve Grube, MD**[2,3], **Paula Revell, PhD**[2], and **Charles T. Quinn, MD, MS**[1,2]

[1]Division of Hematology-Oncology, Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

[2]Children's Medical Center Dallas, Dallas, Texas

[3]Division of Infectious Diseases, Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

Abstract

Patients with sickle cell disease (SCD) have an increased risk of invasive bacterial infection because of hyposplenism. *Bordetella holmesii* is a recently described Gram-negative coccobacillus with an apparent predilection for asplenic hosts. We report two patients with SCD and *B. holmesii* bacteremia. Fastidious growth in culture and a typically uncomplicated clinical course distinguish *B. holmesii* infection from other invasive bacterial infections in SCD. Providers for patients with SCD should be aware of this pathogen and ensure that their microbiology laboratories are capable of isolating and identifying this organism.

Keywords

asplenia; bacteremia; *Bordetella holmesii*; sickle cell disease

Introduction

Prophylactic penicillin and immunization against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b have markedly decreased the incidence of invasive bacterial infections in children with sickle cell disease (SCD) [1–3]. Selective pressure from antibiotic prophylaxis and immunizations may have created an environment for other organisms to emerge as pathogens. No comprehensive studies of the changing microbiology of invasive bacterial infections in SCD have been published in the past decade to address this possibility.

Bordetella holmesii is a small, fastidious Gram-negative coccobacillus that was first described in 1995 [4]. *B. holmesii* can cause endocarditis, community acquired pneumonia, cellulitis, suppurative arthritis, and pyelonephritis [5,6]. However, the most common clinical

*Correspondence to: Tim McCavit, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9063, tim.mccavit@childrens.com.

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manifestations are fever and bacteremia in asplenic patients [5]. In 2004, the Centers for Disease Control (CDC) reported a series of 26 patients with *B. holmesii* bacteremia [5]. Twenty-two (85%) of these patients were asplenic, and ten had SCD. Clinical details were not provided. Besides the 2004 CDC report, only two other manuscripts describe *B. holmesii* in SCD, both of which focused on the microbiology of *B. holmesii* [4,7]. To further characterize this new infectious complication, we report two children with SCD who had *B. holmesii* bacteremia within a two-month period in the spring of 2007.

Patients

Case 1

A 14-year-old female with sickle-hemoglobin C disease presented to the emergency department (ED) with a fever of 38.9°C, shaking chills, mild headache, nasal congestion, and cough (Table I). Her other vital signs and oxygen saturation were unremarkable. Physical examination revealed no obvious focus of infection. A blood culture was obtained, and she was given clindamycin IV because of a suspected ceftriaxone allergy. After brief observation, she was discharged without outpatient antibacterial therapy because she was non-toxic, her blood counts were near baseline, and follow-up was arranged.

Her fever and other symptoms resolved one day after the first ED visit. After 56 hr of incubation, Gram-negative bacilli (GNB) were detected in her blood culture. She returned to the ED for re-evaluation; a repeat blood culture was obtained; and ceftriaxone IV was given (the suspected allergy to ceftriaxone was incorrect). She was again discharged without outpatient antibacterial therapy appearing clinically well. After 61 hr of incubation, the second blood culture grew GNB. A third blood culture was obtained, and the patient was hospitalized for ceftriaxone therapy. Upon admission, a history of a fall with a mild ankle sprain on the first day of her fever was elicited. Mild edema and warmth were now apparent in the soft tissues over her right distal tibia and the dorsum of her foot. Roentgenograms of the ankle and foot were normal. Magnetic resonance imaging (MRI) showed soft tissue edema of the anterior ankle and foot suspicious for cellulitis, but not osteomyelitis. Four doses of daily ceftriaxone IV were completed before discharge when the physical signs of cellulitis had resolved. She received oral cefixime for three additional days at home. Her final blood culture remained sterile. She was asymptomatic at a follow-up visit 3 weeks after discharge.

Case 2

An unrelated 10-year-old female with sickle cell anemia on hydroxyurea presented to the ED for evaluation of a reported temperature of 40.2°C (Table I). The patient had frontal headaches and bilateral low back pain of 4 days' duration. Her temperature was 38.4°C, but physical examination identified no obvious focus of infection. Her peripheral smear was significant for Howell-Jolly bodies. A blood culture was obtained, 75 mg/kg of ceftriaxone was given IV, and the patient was hospitalized. The next day her fever, back pain, and headaches resolved, so she was discharged without another dose of ceftriaxone.

The blood culture obtained in the ED grew GNB at 60 hr of incubation. She was then re-hospitalized for treatment of bacteremia with ceftriaxone. She was afebrile, and again, no

obvious focus of infection was identified. A repeat blood culture obtained at the time of re-admission grew GNB at 55 hr of incubation. She remained asymptomatic and was discharged after 36 hr to complete empiric antibacterial treatment with oral levofloxacin. A final blood culture obtained 1 week after discharge was negative.

Identification of the Organism

The blood cultures were incubated in the BacT/Alert 3D continuously monitored blood culture system (bioMerieux, Marcy-l'Etoile, France). Gram-stained smears of the positive cultures showed small GNB. Growth on subculture was slow, requiring 48 hr of incubation to visualize small colonies on blood and chocolate agar. At 72 hr a zone of browning was observed around the colonies. The organisms had no oxidase or catalase activity. Commercially available identification systems, including the Dade Microscan Walk away Gram negative ID card, the Remel rapid ID NH, and the API NE, failed to identify the organism. Therefore, the 16s rRNA gene (1283 nucleotides) was sequenced, and the results showed 100% nucleic acid sequence identity to published *B. holmesii* 16s rRNA gene sequences (GenBank accession numbers: DQ409136.1, AF469002.1, AJ239044.1) [6,8,9].

Discussion

Hyposplenic patients are at increased risk for infection with the emerging pathogen, *B. holmesii*. It has been reported from geographically distinct areas of the world, but in only 10 patients with SCD [4,5,7]. We report two new patients with SCD and *B. holmesii* bacteremia. Both had fever and non-specific constitutional symptoms without marked leukocytosis, a left shift, or hyper-hemolysis. One patient had suspected cellulitis; the other had no apparent focus of infection. Neither patient had an indwelling catheter. We identified no epidemiologic link between these patients except that both had SCD, which is associated with hyposplenism. No formal testing of splenic function was performed in either patient. However, case 2 clearly had hyposplenism despite the hydroxyurea therapy, given the Howell-Jolly bodies on her peripheral blood film. Case 1 had Pappenheimer bodies, which are also normally removed by the spleen.

The unusual microbiology of *B. holmesii* distinguishes it from other bacterial pathogens in SCD. Consistently prolonged time to detection (50–60 hr of incubation) in standard culture systems is uncommon for bacterial pathogens in patients with SCD [10] and in the general population [11]. The uncomplicated clinical course of *B. holmesii* bacteremia [5] distinguishes it from other Gram-negative organisms, like *Salmonella* and *E. coli*, which can cause significant morbidity or mortality. The optimal treatment for *B. holmesii* bacteremia has not been established because so few infections have been reported. The average minimal inhibitory concentration (MIC) of isolates from the CDC was high for the penicillins, cephalosporins, and macrolides, which might preclude their clinical use. The MICs of the fluoroquinolones and the carbapenems were lower, so they could be considered for serious infections [5]. Only 80% of the patients in the CDC report received antimicrobials of any kind [5], so it is possible that *B. holmesii* bacteremia is self-limited in some patients. Our patients may have recovered despite antibacterial therapy.

B. holmesii is a newly identified bacterial pathogen in patients with SCD. The relatively benign clinical course and unusual bacteriology of *B. holmesii* distinguish it from other bacterial pathogens in SCD. Proper identification of this organism might permit a limited course of parenteral antibacterial therapy and prevent prolonged hospitalizations for patients with *B. holmesii* bacteremia. Therefore, physicians who manage patients with SCD need to be aware of this bacterium and ensure that their microbiology laboratories can properly identify it.

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TABLE I

Clinical Features of Cases

	Steady-state values			Presenting values				
Presenting symptoms	**Leukocytes (/mm^3)**	**Hgb (g/dl)**	**Retics (%)**	**Leukocyte (/mm^3)**	**Hgb (g/dl)**	**Retics (%)**	**Time to growth in blood culture (hr)**	**Treatment**
Case 1								
Fever, chills, cough	11,100; 71% segs; 0% bands	8.6	5.9	16,600; 80% segs; 7% bands	9.0	7.6	56, 61;N = 2	IV ceftriaxone, then oral cefixime
Case 2								
Fever, headache, back pain	9,300; 46% segs; 0% bands	10.0	1.7	7,400; 64% segs; 4% bands	10.5	5.5	60, 55;N = 2	IV ceftriaxone, then oral levofloxacin

Hgb, hemoglobin concentration; Retics, reticulocytes.