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***Bordetella holmesii* Bacteremia Cases in the United States, April 2010–January 2011**

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Abstract

We describe the first report of temporally related cases of *Bordetella holmesii* bacteremia. Demographic and clinical data were collected through chart abstraction and case-patient interviews. Twenty-two cases were identified from 6 states. Symptom onset dates ranged from April 2010 to January 2011. Median age of patients was 17.1 years and 64% had functional or anatomic asplenia. Pulsed-field gel electrophoresis profiles of a sample of isolates were identical. These cases occurred during a peak in pertussis outbreaks with documented cases of *B. holmesii*/*Bordetella pertussis* respiratory coinfection; whether there is a link between *B. holmesii* respiratory and bloodstream infection is unknown.

Keywords

Bordetella holmesii; bacteremia; asplenia; pertussis

Bordetella holmesii is a gram-negative, nonoxidizing, slow-growing organism first identified as a species in 1995 [1]. Relatively little is known about the epidemiology, clinical manifestations, or natural history of *B. holmesii*. Unlike *Bordetella pertussis*, *B. holmesii* has been associated with invasive disease in immunocompromised persons, primarily bacteremia in young adults with sickle-cell anemia [2–6]. Although *B. holmesii* has not been historically associated with a cough illness, more recently the pathogen has been associated with a pertussis-like respiratory syndrome in healthy individuals [7–9]. Prior knowledge about *B. holmesii* bacteremia has come from single case reports or small case series [3–6,

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10]. The largest published series described all *B. holmesii* bacteremia cases (n = 30) identified by the Centers for Disease Control and Prevention (CDC) over a 17-year period (1983–2000) [2].

Between 12 June 2010 and 13 August 2010, the New York City Department of Health and Mental Hygiene (NYC DOHMH) Public Health Laboratory received 4 *Bordetella holmesii* blood isolates submitted for confirmatory testing from 4 New York City hospitals. On 23 August 2010, *B. holmesii* was isolated from a fifth blood specimen at a New York City hospital laboratory. This number of cases was above baseline for that time period based on historic records.

We describe the first reported investigation of temporally related *B. holmesii* bacteremia cases.

METHODS

On 7 and 8 September 2010, NYC DOHMH issued laboratory and clinician alerts requesting the report of all cases of *B. holmesii* isolated from a sterile site or respiratory specimen in the previous 2 years. Additionally, laboratories were asked to report unidentified gram-negative coccobacilli biochemically compatible with *B. holmesii* from patients with invasive or respiratory disease, and clinicians were asked to conduct prospective surveillance for *B. holmesii* in febrile immunocompromised patients (particularly asplenic).

Finally, a nationwide notification was issued by the CDC in collaboration with NYC DOHMH on 16 September 2010 to identify additional cases of invasive *B. holmesii*. The notification was distributed through the EPI-X (CDC's Web-based communications portal for public health professionals) requesting reporting of additional cases of *B. holmesii* identified since 1 January 2010.

For this investigation, cases were defined as patients with *B. holmesii* isolated from a normally sterile site (blood; cerebrospinal, pleural, peritoneal, pericardial, or joint fluid; bone; surgical aspirate; or internal body site [eg, lymph node, brain]) between 1 January 2010 and 1 February 2011. Laboratory-confirmed cases detected as a result of the New York City and national EPI-X alerts were reported to CDC or NYC DOHMH. Patients with *B. holmesii* isolated only from nasopharyngeal specimens were not included in these analyses.

A standardized data collection form was developed and included patient demographic characteristics, clinical signs and symptoms, laboratory results, and diagnosis, treatment, and outcome variables. Data were collected through a combination of chart abstraction and telephone interviews with case patients or case-patient representatives. Data collection forms were distributed to all health departments that reported *B. holmesii* cases to NYC DOHMH or CDC. Completed de-identified forms were sent to CDC. Data were analyzed using Excel 2010. Human subjects review at CDC determined this study to be public health practice, not research; informed consent was not obtained for this study.

Microbiologic confirmation of *B. holmesii* isolates was performed by the NYC DOHMH Public Health Laboratory and reporting hospital laboratories. Pulsed-field gel

electrophoresis (PFGE) was performed at the NYC DOHMH Public Health Laboratory and CDC on a sample of available case isolates. At CDC, PFGE with *XbaI* enzyme was performed on 9 isolates using methods previously described [11]. At NYC DOHMH Public Health Laboratory, 8 isolates were characterized by PFGE using *XbaI* and *SpeI* as previously described [7]. Three *B. holmesii* isolates from the NYC DOHMH Public Health Laboratory were sent to CDC for comparison with the 9 isolates, as well as a reference database of 47 *B. holmesii* strains, using BioNumerics software (version 5.0, Applied Maths, Austin, Texas). Of the 47 reference strains, 13 (28%) were isolated from respiratory specimens, 18 (38%) were from blood specimens, and 16 (34%) were of unknown origin.

RESULTS

A total of 22 cases of invasive *B. holmesii* infection were identified from 6 states. *Bordetella holmesii* was isolated from blood specimens in 21 patients and from both blood and synovial fluid specimens in 1 patient. Symptom onset dates ranged from 1 April 2010 to 19 January 2011 (Figure 1). Eleven (50%) cases were clustered between June and August of 2010. Twelve (55%) patients were from New York and of those, 10 (83%) were from New York City. Colorado reported 4 cases, Indiana and Pennsylvania each reported 2 cases, and Connecticut and Delaware each reported 1 case. In New York City, 2 separate hospitals reported 2 cases each. Two cases were reported from the same hospital in Philadelphia. All other cases were single cases identified in separate hospitals. No epidemiologic links between the patients were identified.

Data collection forms were completed or partially completed for 18 (82%) of the patients (New York City = 10, New York State = 2, Indiana = 2, Pennsylvania = 2, Connecticut = 1, Delaware = 1). Some clinical or demographic data were obtained for the 4 remaining patients. Twelve (55%) patients were male, and the median patient age at onset was 17.1 years (range, 1.5–77.3 years) (Table 1). Of 18 patients with data on race/ethnicity, 10 (56%) were black, 5 (28%) were white, and 2 (17%) reported “other” race.

In total, 20 (91%) patients reported at least 1 underlying medical condition. Fourteen (64%) patients had functional or anatomic asplenia, of whom 11 (79%) had sickle cell disease and 3 had splenectomies without reported reasons (Table 1). Reported underlying conditions that could result in immunosuppression included diabetes (14%), history of kidney transplant (9%), cancer (9%), end-stage renal disease (9%), and IgA nephropathy (5%). One patient who did not report an immunocompromising condition had facial hematomphangioma. One patient reported no underlying conditions.

The majority of patients reported fever (89%); among 10 patients with a highest temperature recorded, the median temperature was 39.4°C (range, 38.1°C–40.2°C). The most commonly reported presenting symptoms included headache (44%), joint pain (28%), cough (28%), and difficulty breathing (22%). Among 5 patients reporting cough, none reported paroxysmal cough, whoop, or posttussive vomiting. Three of 11 (27%) patients with chest radiographic results had abnormal findings (2 with possible consolidation, 1 with pleural effusion); of these, 1 reported cough as a presenting symptom. Among the 11 patients with sickle cell disease, 9 (82%) were diagnosed with vasoocclusive crisis on presentation; the

tenth patient reported fever, chills, and abdominal pain, which may also represent vasoocclusive crisis (Table 1). The median white blood cell count ($n = 17$) on presentation was 13 700 cells/ μL (range, 4600–29 600 cells/ μL), and the mean peak lymphocyte percentage ($n = 13$) was 23.3% (range, 7.6%–48.3%).

Of 21 cases with data available, 2 patients had *B. holmesii* identified in cultures obtained on 2 separate days, with a period of 2 and 6 days between collections, respectively. The median time between symptom onset and date of first specimen collection was 1.5 days (range, 0 to 30 days; $n = 16$). No patients had blood cultures identifying a pathogen other than *B. holmesii*. Of 21 patients with data, 18 (86%) were hospitalized for this illness. Data were incomplete for length of stay or antibiotic treatment. There were no reported deaths, and 2 of 10 (20%) patients with data on highest level of care were admitted to the intensive care unit.

Eight isolates analyzed by PFGE at the NYC DOHMH Public Health Laboratory had indistinguishable PFGE profiles. Nine isolates (Colorado [4], Delaware [1], New York State [2], and Pennsylvania [2]) analyzed by the CDC laboratory also showed indistinguishable PFGE profiles. These 9 strains were compared with 3 randomly selected isolates from NYC DOHMH Public Health Laboratory using CDC PFGE running conditions and all presented identical profiles. These 12 strains were also indistinguishable by PFGE typing from 37 of the 47 (79%) reference strains maintained at CDC. The remaining 10 reference strains were categorized into 7 different PFGE types.

DISCUSSION

We describe the first reported investigation of temporally related *B. holmesii* bacteremia cases. We are unaware of any widespread changes in diagnostic capacity, contamination concerns, heightened laboratory or clinician suspicion or testing prior to the alert, or increases in populations known to be at risk for *B. holmesii* bacteremia that would have explained the increased number of cases.

The cases we describe occurred in the same time period as the historic peak in US pertussis disease in 2010 [12]. Two pertussis outbreak investigations conducted during the study time period (November 2010–January 2011 in Jefferson County, New York; and May 2010–May 2011 in Franklin County, Ohio) used 4-probe multiplex polymerase chain reaction (PCR) methods to demonstrate that *B. holmesii* was circulating with *B. pertussis* in 12%–16% of samples tested (personal communication, Kimberlee A. Musser, New York State Department of Health Wadsworth Center [13]). These are higher proportions than were seen in a study from Massachusetts in 1999, when *B. holmesii* was isolated from 0.6% of 2508 respiratory specimens [8].

Respiratory infections caused by *B. holmesii* are clinically indistinguishable from those by *B. pertussis* [7, 8]. Whether there is a link between *B. holmesii* respiratory and bloodstream infection is unknown. In our study, respiratory symptoms (cough and difficulty breathing) were reported by one-third and one-fifth of case patients, respectively, but we do not know if these symptoms were caused by *B. holmesii*, and nasopharyngeal specimens were not taken. Given that these cases of *B. holmesii* bacteremia emerged in the same geographic area as

several pertussis outbreaks with documented cases of *B. holmesii* coinfection, the cases may reflect the exposure of susceptible populations, such as those with asplenia and other immunocompromising conditions, to *B. holmesii* circulation. However, because there is no routine surveillance for *B. holmesii* disease, we do not know the true burden of disease in the United States or if these cases represent a true increase in circulation. Although efforts were made to capture all cases during the study period, it is likely that some cases may have been missed. Further work is needed to evaluate the link between *B. holmesii* respiratory and blood infections and to estimate the burden of *B. holmesii* disease in the United States and how it relates to circulation of pertussis disease.

Similar to previous reports, the majority of patients in this investigation were functionally or anatomically asplenic [2, 3, 5, 6]. Asplenia is associated with an increased risk of morbidity and mortality from some bacterial infections, most commonly polysaccharide encapsulated bacteria [14]. While the presence of polysaccharide capsule has not yet been definitively demonstrated in *B. holmesii*, preliminary investigations provide evidence supporting the presence of polysaccharide capsule in other *Bordetella* species [15, 16]. Further studies are needed to confirm the role of encapsulation in the pathogenesis of *B. holmesii* among asplenic patients.

Identification of *B. holmesii*, even in high-risk patients, is difficult. Routine diagnostic tools such as conventional methods using biochemical patterns and automated diagnostic machines for blood specimens are used to identify *B. holmesii*. However, these tests, particularly automated blood specimen microbial identification systems, are not always capable of distinguishing *B. holmesii* from other pathogenic species [10]. In fact, of the 8 isolates sent by hospital laboratories to NYC DOHMH Public Health Laboratory for confirmatory testing, 1 was initially suspicious for *Francisella tularensis*, 1 for *Acinetobacter lwoffii*, and 1 for *Kingella* species based on automated diagnostic machine results [17]. Cellular fatty acid analysis (CFA) performed by NYC DOHMH Public Health Laboratory conclusively identified all 8 isolates as *B. holmesii* [17]. Specialized reference methods such as CFA, 16S ribosomal RNA sequence analysis, multitarget real-time PCR assays, and PFGE are useful for more definitive identification of *B. holmesii* [2, 10, 17, 18]. While these specialized methods are increasingly available at state health department reference laboratories, these techniques are not widely available in hospital diagnostic laboratories. As such, *B. holmesii* may be frequently misidentified by routine clinical laboratories.

In conclusion, these cases of *B. holmesii* bacteremia occurred in the same time period as pertussis outbreaks in which *B. holmesii* was isolated in >10% of suspected cases. While the transmission route and true disease burden of *B. holmesii* is not definitively known, there may have been increased circulation when this series of cases appeared. Routine use of diagnostic tests that can differentiate *B. pertussis* and *B. holmesii* in nasopharyngeal specimens—such as the multitarget PCR protocol developed by CDC—would allow for a better understanding of *B. holmesii* transmission and epidemiology [18]. While the CDC PCR protocol is currently in use by some state health departments, it generally is not used by commercial or hospital clinical diagnostic laboratories. Furthermore, improving automated identification algorithms that distinguish *B. holmesii* from *Francisella tularensis*,

Acinetobacter lwoffii, or *Kingella* species would limit misclassification. Finally, physicians treating immunocompromised or asplenic patients should be aware of this pathogen and consider it as a possible cause of bacteremia. These diagnostic improvements will have the potential to enhance future studies of *B. holmesii* epidemiology, including the role of respiratory transmission in invasive disease, risk factors for colonization and disease, and opportunities for prevention.

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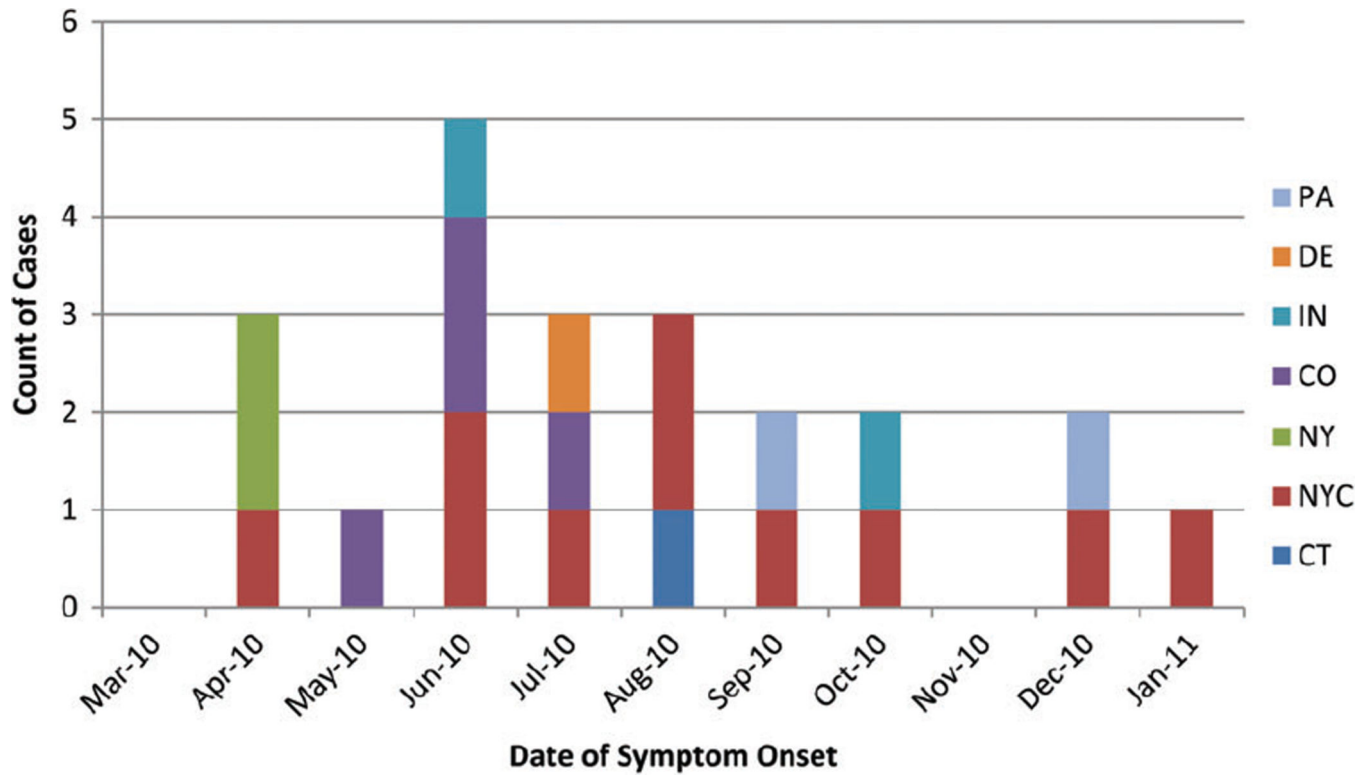


Figure 1.

Bacteremic *Bordetella holmesii* cases by month of onset and reporting site (N = 22).

Abbreviations: CO, Colorado; CT, Connecticut; DE, Delaware; IN, Indiana; NY, New York; NYC, New York City; PA, Pennsylvania.

Table 1
Demographic and Clinical Characteristics of Patients With *Bordetella holmesii* Bacteremia—April 2010 to January 2011

Patient No	State or NYC	Age at Onset, y	Sex	Race	Functional/Anatomic Asplenia	Presenting Symptoms	Diagnosis
1	NYC	2	Female	Black	Unknown	Fever, cough	Hemolytic uremic syndrome
2	NYC	5	Male	Black	Sickle cell	Fever, headache, cough, leg/foot pain	Bacteremia
3	NYC	7	Female	Black	No	Chest pain	Bacteremia
4	NYC	13	Female	White	Sickle cell, splenectomy	Fever, bilateral leg pain, throat pain	Vasooocclusive crisis, streptococcal pharyngitis
5	NYC	14	Male	Black	Sickle cell	Fever, knee/back pain	Vasooocclusive crisis
6	NYC	14	Female	Other	No	Fever, unilateral jaw swelling	Infected facial hematomympangioma
7	NYC	16	Female	Black	Sickle cell	Fever, headache	Vasooocclusive crisis, bacteremia
8	NYC	35	Female	Black	Sickle cell	Fever, back/leg pain, cough	Vasooocclusive crisis
9	NYC	74	Female	Other	Sickle cell	Fever, headache	Meningitis, bacteremia
10	NYC	77	Male	White	Splenectomy	Fever	Cellulitis, bacteremia
11	NY	25	Male	Black	Sickle cell	Fever, headache, nausea	Vasooocclusive crisis
12	NY	41	Male	White	No	Fever, unilateral facial numbness	Acute sinusitis
13	CT	62	Male	White	No	Shortness of breath	Pleural effusion
14	PA	6	Female	Black	Sickle cell	Fever, knee pain, dysuria	Bacteremia
15	PA	15	Male	Black	Sickle cell	Fever, headache	Bacteremia
16	DE	14	Male	Black	Sickle cell	Fever, abdominal pain	Bacteremia
17	IN	18	Male	White	Splenectomy	Fever, chest pain	Pneumonia
18	IN	19	Male	Other	Sickle cell, splenectomy	Unknown	Vasooocclusive crisis
19	CO	9	Female	Missing	Unknown	Bump on chest/neck	Bacteremia
20	CO	52	Male	Missing	Splenectomy	Fever, headache, myalgias	Bacteremia
21	CO	61	Female	Missing	Unknown	Weakness, altered mental status	Bacteremia
22	CO	63	Male	Missing	Unknown	Lower extremity pain/ swelling	Cellulitis

Abbreviations: CO, Colorado; CT, Connecticut; DE, Delaware; IN, Indiana; NY, New York; NYC, New York City; PA, Pennsylvania.