Bordetella bronchiseptica infections in patients with HIV/AIDS

A case report and review of the literature

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Abstract

Rationale: Bordetella bronchiseptica is a common cause of upper respiratory tract infections in domesticated dogs and cats and a rare zoonotic pathogen in immunocompromised humans. With increasing numbers of people acquiring pets and spending time with them in confined spaces due to COVID-19 lockdowns, it is important to be aware of adverse health consequences brought about by this interaction. We present a case of B bronchiseptica pneumonia in a patient with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and review key characteristics of an additional 30 cases of B bronchiseptica infections in 29 patients with HIV/AIDS that were identified by literature review.

Patient concerns: A 61-year-old male with HIV/AIDS who was not on antiretroviral therapy and had advanced immunosuppression with a CD4+ T-lymphocyte count of 3 cells/µL sought medical attention for multiple somatic issues including subjective fevers, shortness of breath, and intermittent chest pain.

Diagnosis: Computed tomography of the chest identified bilateral nodular opacities in the lower lobes with scattered areas of ground glass opacities. B bronchiseptica was identified in sputum culture by mass spectrometry followed by supplementary biochemical testing.

Interventions: Empiric broad-spectrum antibiotics were initiated and changed to levofloxacin after susceptibility testing was completed.

Outcomes: The patient was discharged after symptomatic improvement with levofloxacin.

Lessons: Pneumonia with interstitial infiltrates in the setting of advanced CD4 lymphocyte depletion is the most common clinical syndrome caused by B bronchiseptica in patients with HIV/AIDS, and may be accompanied by sepsis. Advanced immune suppression, as well as chronic medical conditions, for example, alcoholism, diabetes, and renal failure that compromise host defenses are also commonly found in cases of B bronchiseptica infection in patients who do not have HIV infection. Reported animal contact among patients was not universal. Isolates were susceptible to aminoglycosides, carbapenems, fluoroquinolones, but typically resistant to most cephalosporins.

Abbreviations: AIDS = acquired immunodeficiency syndrome, HIV = human immunodeficiency virus, TMP/SMX = trimethoprim/sulfamethoxazole.

Keywords: Bordetella bronchiseptica, human immunodeficiency virus/acquired immunodeficiency syndrome, pneumonia, respiratory pathogens, zoonotic infections
1. Introduction

*Bordetella bronchiseptica* is a gram negative coccobacillus that frequently causes respiratory tract infections in domesticated mammals and is a rare cause of zoonotic infections in humans. It is most commonly associated with canine infectious tracheobronchitis known as “kennel cough”, and contributes to atrophic rhinitis in swine.¹⁻³ In these animals manifestations range from asymptomatic carriage to pneumonia with ensuing death. Domestic cats are also susceptible to *B bronchiseptica*, particularly those in crowded environments or multi-cat households.¹⁻²,⁴ Key bacterial virulence factors include adhesions required for tracheal colonization, autotransporters, and a type 3 secretion system to inject toxins including adenylate cyclase, dermonecrotic toxin, and tracheal cytotoxin into host cells.²⁻⁵,⁶ *B bronchiseptica* can invade and survive within phagocytic and nonphagocytic cells and cell lines, including tracheal epithelial cells, but lacks the ability to replicate intracellularly.⁷ Host defenses against *B bronchiseptica* depend on IFN-γ stimulation of host cells and antibodies.⁸⁻¹⁰

*B bronchiseptica* is shed in nasal and respiratory secretions of infected animals.¹⁻² Thus, spread to humans occurs through direct contact with infected respiratory secretions and presumably also by aerosolized respiratory droplets as shown for *Bordetella pertussis*.³⁻¹¹ Human infection by *B bronchiseptica* is rare with only 5 cases cited in a 1980 review, 25 in 1991, and approximately 90 cases reported in 2009.¹²⁻¹³ Data suggest that most humans infected by *B bronchiseptica* are immunocompromised, with the initial reports of infections in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) occurring in 1991.¹⁻³,¹³ Interestingly, *B bronchiseptica* is not included among diseases that can spread between humans and animals on the Centers for Disease Control and Prevention website (https://www.cdc.gov/healthypets/diseases/index.html). Nonetheless, the SARS-2-CoV pandemic spurred an increase in pet adoption suggesting that higher numbers of vulnerable people could come into contact with this bacterium.¹⁴ Here, we describe a case of *B bronchiseptica* in a patient with HIV/AIDS and reviewed the literature for similar cases to identify key epidemiologic, clinical, radiographic, and microbiologic features of this unusual zoonosis. Such a series has not been reported in the past 20 years despite changes in diagnostic techniques and antimicrobial usage. These results will be useful for guiding clinicians who care for immunocompromised patients.

2. Case report

A 61-year-old male diagnosed with HIV for greater than 15 years with inconsistent antiretroviral use sought medical attention for subjective fevers, shortness of breath, intermittent chest pain, odynophagia, and weight loss. On presentation, the patient was afibrile, vitally stable, with an oxygen saturation greater than 94% on room air. Physical exam revealed normal respiratory sounds and oral candidiasis. The WBC was 1130 cells/µL (reference: 4000–10,000 cells/µL) with an absolute neutrophil count of 620 cells/µL (reference: 1600–8600 cells/µL). The CD4 count was 3 cells/µL (reference: 200–3390 cells/µL) and the HIV RNA was 109,000 copies/mL (reference: not detected) Computed tomography of the chest revealed nodular opacities in both lower lobes with scattered areas of ground glass opacities consistent with pneumonia (Fig. 1). The patient was admitted and started on empiric, broad-spectrum antibiotics including trimethoprim/sulfamethoxazole (TMP/SMX). Gram stain of induced sputum showed 2 to 5 WBCs/field with moderate Gram positive rods, few Gram positive cocci in clusters, and few Gram negative rods. Culture yielded normal oral flora along with *Staphylococcus aureus* and small white colonies of *Gram* negative rods on sheep blood agar. Identification by matrix assisted laser desorption ionization time of flight (Bruker, Billerica, MA) mass spectrometer resulted as *Bordetella* group to include *B pertussis/B bronchiseptica/Bordetella parapertussis* (log score 2.66). Supplementary testing differentiated between the 3 species; the isolate was motile and positive for both oxidase and urease which led to identification as *B bronchiseptica*. *B pertussis*, and *B parapertussis* are both nonmotile; *B parapertussis* is oxidase negative and *B pertussis* is urease negative.¹¹⁵ After susceptibility testing (Trek Sensititre, ThermoFisher Scientific, Waltham, MA), antibiotics were changed to levofloxacin 500 mg daily and the patient was discharged home after improvement to complete 14 days of antibiotics. Notably, the patient denied recent animal exposure.

After discharge blood cultures turned positive for *Mycobacterium avium*. However, the patient did not keep follow up appointments in the Infectious Diseases clinic and did not return phone calls post-discharge or during the writing of this report. Informed consent was waived as the Institutional Review Board (IRB) of the Office of Human Research Participant Protection at the University of Oklahoma Health Sciences Center, Oklahoma City, OK was consulted and determined that this case report did not meet the definition of human subject’s research.

3. Results of literature review

A Medline search was done to identify cases of *B bronchiseptica* in patients with HIV/AIDS. Search terms included “*Bordetella bronchiseptica*”, “HIV”, and “AIDS”. Articles in languages other than English were excluded. The search identified an...
additional 30 cases in 29 patients since 1991, the characteristics of which are shown in Table 1. Most cases were reported in the 1990s (19/31, 61%) with a median age of 35 (range 21–61) and 73% (22/30) were male. CD4 lymphocyte counts were reported for 24/30 (80%) patients showing a median of 32.5 CD4 cells/μL (range 0–212) with only 2 cases in patients with CD4 counts ≥ 200 cells/μL. Animal exposure history was given for 73% (22/30) of patients with 55% (12/22) patients reporting animal contact. Of these, 7/12 (58%) reported contact with dogs and 3/12 (25%) reported contacts with only cats. One patient reported contact with both cats and dogs, and 1 reported contact with multiple species as he was a kennel worker.

Nearly all clinical episodes (30/31, 97%) involved respiratory tract infections, the most common being pneumonia (24/31, 77%) (Table 1). Less common syndromes included sinusitis (3/31, 10%), bronchitis (2/31, 6%), bacteremia (2/31, 6%), and pleural effusion (1/31, 3%), often accompanied by pneumonia. Table 1 details radiographic findings and shows interstitial infiltrates alone are the most common finding and less frequently appear with consolidation or cavitation. Outcomes data was available for 20 of 31 episodes and shows a case fatality rate of 10% (2/20) (Table 1). One patient was reported as recovered but with persistent symptoms.

*B. bronchiseptica* was most commonly isolated from respiratory secretions including bronchoalveolar lavage specimens (16/31, 52%), and sputum (14/31, 45%) (Table 1). It was occasionally cultured from blood (2/31, 7%), bone marrow (1/31, 3%), and pleural fluid (1/31, 3%). Results of antimicrobial susceptibility testing are reported in Table 3. Carbapenems and fluoroquinolones were uniformly active. Aminoglycosides and various beta-lactam/beta-lactamase inhibitor combinations in 15/18 (83%) were also highly active. In contrast, TMP/SMX was active against 8/16 (50%) of isolates and first and 2nd generation cephalosporins were not active against any isolates whereas of the 3rd and 4th generation cephalosporins, only ceftazidime showed activity (7/12, 58%). These results are similar to a compilation of antimicrobial susceptibility testing results showing reliable activity of aminoglycosides, imipenem, ciprofloxacin, and antipseudomonal penicillins (without beta-lactamase inhibitors), whereas cephalosporins currently in use, for example, cefazolin, cefuroxime, ceftriaxone,

| Year of report | Age | Sex | # CD4 (cells/μL) | Animal exposure | Clinical syndrome(s) | Culture source | Definitive treatment | Outcome | Citation |
|---------------|-----|-----|-----------------|-----------------|---------------------|----------------|---------------------|---------|---------|
| 1991          | 61  | Male| 200             | No              | Pneumonia           | BAL            | Ciprofloxacin       | Death   | Amador et al |
| 1991          | 38  | Male| n/a             | New puppy       | Pneumonia           | BAL            | Ceftriaxone ciprofloxacin | Recovered | Decker et al |
| 1992          | 43  | Male| n/a             | n/a             | Pneumonia           | BAL            | Erythromycin ciprofloxacin | Recovered, persistent symptoms | Ng et al |
| 1992          | 33  | Male| n/a             | Cat             | Bacteremia          | Blood          | Imipenem            | Recovered | Qureshi et al |
| 1993          | 32  | Female| 56          | No              | Pneumonia           | Sputum          | Amoxicillin         | n/a        | Mesnard et al |
| 1994          | 28  | Male| 73              | Dogs cats       | Pneumonia           | Sputum          | Ciprofloxacin       | Recovered | de la Fuente et al |
| 1995          | 29  | Male| 46              | No              | Pneumonia           | Sputum          | Clarithromycin      | Recovered | Libanore et al |
| 1995          | 28  | Male| n/a             | Kennel worker   | Pneumonia           | Sputum          | Ceftazidime         | Recovered | Woodard et al |
| 1998          | 33  | Female| 100         | no              | Pneumonia           | Sputum, BAL     | Tobramycin Davycycline | Recovered | Garcia San Miguel et al |
| 1999          | 28  | Male| 7               | n/a             | Sepsis              | Bone marrow     | n/a                 | n/a        | Dworkin et al |
| 1999          | 24  | Male| n/a             | Pneumonia       | Sputum, BAL         | n/a             | n/a                 | n/a        | Dworkin et al |
| 1999          | 37  | Male| 22              | n/a             | Pneumonia           | BAL             | n/a                 | n/a        | Dworkin et al |
| 1999          | 28  | Female| 35           | n/a             | Sinusitis           | Nasal           | n/a                 | n/a        | Dworkin et al |
| 1999          | 26  | Female| 7             | Cats            | Sinusitis           | Nasal           | n/a                 | n/a        | Dworkin et al |
| 1999          | 34  | Male| 10              | Sinusitis, pneumonia | Sputum, BAL     | BAL             | n/a                 | n/a        | Dworkin et al |
| 1999          | 33  | Male| 8               | Dog             | Bronchitis          | Sputum          | n/a                 | n/a        | Dworkin et al |
| 1999          | 36  | Female| 1             | No              | Pneumonia           | Sputum          | n/a                 | n/a        | Dworkin et al |
| 1999          | 35  | Male| 153             | Dog             | Pneumonia           | BAL             | n/a                 | n/a        | Dworkin et al |
| 2002          | 34  | Female| 25           | Dog             | Pneumonia           | Sputum, BAL     | Ofloxacin           | Recovered | Lorenzo-Pajuelo et al |
| 2002          | 26  | Male| 97              | No              | Pneumonia           | Sputum, BAL     | Vancomycin rifampin ciprofloxacin | Recovered | Lorenzo-Pajuelo et al |
| 2002          | 38  | Male| 39              | No              | Pleural effusion, pneumonia | Pleural fluid | Ceftazidime         | Recovered | Viejo et al |
| 2009          | 44  | Male| 93              | Cat             | Pneumonia           | Blood, BAL      | Ciprofloxacin gentamicin | Recovered | Muzumder et al |
| 2009          | 42  | Male| 20              | Dog             | Pneumonia           | Sputum          | Levofloxacin        | Recovered | Galezio et al |
| 2011          | 42  | Female| n/a          | n/a             | Pneumonia           | BAL             | Levofloxacin, TMP/SMX | Recovered | Wernli et al |
| 2016          | 43  | Male| 212             | n/a             | Pneumonia           | Sputum          | Levofloxacin        | Recovered | Rampello et al |
| 2016          | 49  | Male| 60              | Dogs            | Pneumonia, sepsis  | Sputum          | Ceftazidime, meropenem | Death   | Rampello et al |
| 2019          | 24  | Male| 0               | Dog             | Pneumonia           | Sputum          | Moxifloxacin        | Recovered | Sameed et al |
| 2019          | 52  | Female| 30            | No              | Pneumonia           | BAL             | Levofloxacin        | Recovered | Gupta et al |
| 2021          | 61  | Male| 7               | No              | Pneumonia           | Sputum          | Levofloxacin        | Recovered | This report |

n/a = value not available or not reported.
and ceftazidime as well as ampicillin were unreliable. In contrast, this larger review suggested tetracyclines and TMP/SMX are active more frequently than found in our smaller sample.

4. Discussion

The hallmarks of *B bronchiseptica* infections in patients with HIV/AIDS are a respiratory syndrome, most frequently characterized as an atypical pneumonia with persistent cough, in individuals with advanced immune suppression as evidenced by substantial CD4 lymphocyte depletion. Indeed, the CD4 lymphocyte count was less than 100 cells/µL in over 80% of patients whose CD4 lymphocyte count was reported. This finding is consistent with HIV depleting CD4+ T lymphocyte subsets in the lung and the notion that these cells are critical for immunity against *B bronchiseptica.*

Animal contact is another feature that is common, but not invariably found. Our survey found that 55% of patients with *B bronchiseptica* reported animal contact, a proportion within the range of the 48% to 68% of American households reported to own pets. Thus, individuals with HIV/AIDS and animal contact do not seem over-represented among those with infection and lack of animal contact should not exclude the diagnosis as a possibility. Nonetheless, a vaccine for *B bronchiseptica* is available for dogs and cats and immunosuppressed pet owners should be advised to vaccinate their pets.

*B bronchiseptica* in patients with HIV/AIDS typically causes symptoms ranging from mild to moderate upper respiratory symptoms, for example, cough, to pneumonia, fulminant sepsis, and ARDS. Imaging findings are nonspecific, including increased interstitial markings, nodules, ground glass opacities, and cavitary nodules. *B bronchiseptica* is typically diagnosed via culture of respiratory tract secretions and blood as a Gram negative cocccobacillus that will grow on standard media such as sheep blood and chocolate agar. Some authors have suggested bacterial colony counts greater than 10⁴ CFU/mL in bronchoalveolar lavage fluid could differentiate colonization of the respiratory epithelium from infection. However, since *B bronchiseptica* is rarely isolated and clearly has pathogenic potential, this threshold should be used cautiously in immunocompromised patients with compatible clinical syndromes. In our clinical microbiology laboratory, *B pertussis, B parapertussis,* and *B bronchiseptica* are initially identified as a *Bordetella* group by MALDI then supplementary tests such as biochemical and growth characteristics are used to specify *B bronchiseptica.* There is also a risk of it being identified as *B pertussis* by multiplex molecular assay.

| Antibiotic Class | Antibiotic | Isolates tested (n) | Susceptible (%) |
|------------------|------------|---------------------|----------------|
| Aminoglycosides  | Amikacin   | 9                   | 100.00         |
|                  | Gentamicin | 8                   | 100.00         |
|                  | Tobramycin | 10                  | 90.00          |
| Carbapenams      | Imipenem   | 6                   | 100.00         |
|                  | Meropenem  | 2                   | 100.00         |
| Cephalosporins (generation) | Cefazolin (1⁹) | 7 | 0.00 |
|                  | Cefotaxime (3⁹) | 8 | 0.00 |
|                  | Ceftriaxone (3⁹) | 7 | 0.00 |
|                  | Cefepime (4⁹) | 3 | 0.00 |
| Fluoroquinolones | Ciprofloxacin | 9 | 100.00 |
|                  | Levofloxacin | 2 | 100.00 |
|                  | Ofloxacin   | 4                   | 100.00         |
| Monobactams      | Aztreonam   | 7                   | 14.29          |
| Penicillin’s +/− beta-lactamase inhibitors | Amoxicillin/clavulanic acid | 4 | 100.00 |
|                  | Ampicillin  | 13                  | 23.08          |
|                  | Ampicillin/subactam | 2 | 0.00 |
|                  | Piperacillin/tazobactam | 6 | 83.33 |
|                  | Ticarcillin/clavulanic acid | 5 | 100.00 |
| Polymyxins       | Colistin    | 2                   | 100.00         |
| Antifolates      | Trimethoprim-sulfamethoxazole | 15 | 100.00 |
| Tetracyclines    | Tetracycline | 4 | 75.00 |

### Table 3

**Radiographic features of pneumonia.**

| Radiographic appearance of pneumonia | Number of cases (n) | Percentage of total (%) |
|--------------------------------------|---------------------|-------------------------|
| Intersitial infiltrates              | 15                  | 62.50                   |
| Intersitial infiltrates and consolidation | 1                  | 4.17                   |
| Intersitial infiltrates and cavitory lesion | 2                  | 8.33                   |
| Cavity lesion only                    | 1                   | 4.17                   |
| Consolidation only                    | 1                   | 4.17                   |
| Unspecified                           | 4                   | 16.67                   |
Key strengths of this paper are the comprehensive nature of the review of *B bronchiseptica* infections in patients with HIV/AIDS, and the high applicability of results in this unique group of patients to those who are immunocompromised by other conditions. We also show that pet exposure is not the strong risk factor previously reported and that some antibiotics commonly used in patients with HIV/AIDS, for example, TMP/SMX, do not have reliably high activity against *B bronchiseptica*. Notable limitations include the retrospective nature of the work and that antimicrobial susceptibility testing was not standardized across all reports such that some antibiotics were tested on few strains.

Collectively this review shows that *B bronchiseptica* infection in patients with HIV/AIDS, as well as others with advanced immune suppression, largely constitutes a respiratory syndrome, most frequently characterized as an atypical pneumonia with persistent cough. It can be misidentified as *B pertussis* and should be positively identified by a combination of techniques, for example, matrix assisted laser desorption ionization time of flight or multiplex molecular assay followed by supplemental biochemical tests. Although treatable, it can lead to sepsis and death. *B bronchiseptica* is reliably susceptible to antipseudomonal penicillins combined with beta-lactamases, carbapenems, and fluoroquinolones whereas cephalosporins, including 3rd and 4th generation drugs are unreliable. These drugs are commonly used as empiric therapy for pneumonia in immunocompromised patients and definitive antibiotic therapy should be guided by susceptibility testing. As with other rare infections, there are no guidelines on duration of treatment. Thus, duration of antibiotics should be determined by the severity of infection, response to initial therapy, and careful follow-up. Most patients identified by this review received approximately 2 weeks of antibiotics.

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Author contributions
VG, participated in clinical care of the patient, performed the literature review, and drafted and edited the manuscript. BA and MM participated in clinical care of the patient and drafting and editing of the manuscript. DS oversaw diagnostic microbiology and edited the manuscript, DD set overall goals and objectives for the manuscript, oversaw and participated in drafting and editing of the manuscript, sought approval from the institutional IRB, and mentored VG in manuscript writing and publication. All authors have read and approved the final manuscript.

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