The Brief Case: A Traveler’s Tale—*Burkholderia pseudomallei* Infection in a Cystic Fibrosis Patient

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**CASE**

Our patient is a 26-year-old female with cystic fibrosis (CF) (DF508/1898 + 1G>T), diagnosed at 2 weeks of age, who subsequently developed pancreatic insufficiency, impaired glucose tolerance, and osteopenia as a consequence of her CF. She was colonized with *Staphylococcus aureus*, with intermittent colonization of *Pseudomonas aeruginosa* since the age of 18 years. Her regular medication included pancreatic enzymes, nebulized hypertonic saline, salbutamol, and steroid inhalers. She could not tolerate flucloxacillin prophylaxis due to gastrointestinal side effects and found it difficult to accommodate regular antipseudomonal antibiotics.

She presented to the CF clinic in July 2017 with a short history of cough producing yellow sputum, which improved with a 2-week course of amoxicillin-clavulanic acid. Her chest was clear and her forced expiratory volume in 1 s (FEV₁) was stable at 3.15 liters (95% predicted). Her sputum sample grew a *Burkholderia* species in addition to *Staphylococcus aureus* and *Aspergillus fumigatus*.

Initially, the travel history of the patient was not known, and a select agent was not suspected; therefore, the organism was prepared for identification by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Inc, Billerica, MA, USA; database, *in vitro* diagnostic, version 4.2) using full ethanol extraction. The *Burkholderia* species was provisionally identified as *Burkholderia thailandensis* with a log value of 1.84 (low confidence score) at the local microbiology laboratory (1). Due to the similarity between *B. thailandensis* and *Burkholderia pseudomallei*, the isolate was sent to the Public Health England UK antimicrobial resistance and health care-associated infections reference unit, opportunistic pathogens section, Colindale, London, and they identified the organism as *Burkholderia pseudomallei* using a species-specific PCR assay (2, 3). Antimicrobial susceptibility testing was performed at the referred public health laboratory by broth microdilution and indicated the following MICs: amoxicillin-clavulanic acid, MIC of 4 mg/liter; ceftazidime, MIC of 2 mg/liter; imipenem, MIC of 0.2 mg/liter; trimethoprim-sulfamethoxazole, MIC of 0.5 mg/liter; doxycycline, MIC of 0.5 mg/liter; tetracycline, MIC of 2 mg/liter.

Following the isolation of *B. pseudomallei* from the patient’s sputum, a detailed travel history was obtained and revealed extensive travel to Southeast Asia in the preceding 5 years. The patient had lived and worked in Cambodia 18 months prior to attending the clinic. This included working in a bar and undertaking land development. During this time, she recalled a trip where she returned to the United Kingdom via Beijing, where she experienced an influenza-like illness with fever, nausea, and vomiting, which was self-limiting.

Following this, repeat sputum samples were sent and grew the same organism. The patient was admitted to hospital to receive 2 weeks of ceftazidime 3 g three times a day intravenously and tobramycin 500 mg once daily intravenously. The tobramycin (which...
is inactive against *B. pseudomallei* was included to provide additional cover for *Pseudomonas aeruginosa*, which the patient was intermittently colonized with. Her initial C-reactive protein (CRP) was 40, white cell count was normal, and FEV\(_1\) was 2.83 liters (81% predicted). Her chest radiograph revealed radiological evidence of bronchiectasis which was longstanding, but no cavitations were present.

During her inpatient stay, the patient was isolated in a side room on a separate ward away from the local CF unit. She received dedicated equipment and was advised to wear a mask when she left her isolation cubicle. Ward staff were advised to wear standard personal protective equipment and undertake respiratory precautions (gloves, gowns, and masks for patient contact).

Having completed the 14-day course of intravenous ceftazidime and tobramycin, her CRP was 4 and she achieved her best recorded lung function (FEV\(_1\), 110% predicted). She was prescribed an initial 3-month course of oral trimethoprim-sulfamethoxazole 960 mg twice daily, and sputum samples after completing this course of antibiotics appeared to initially clear the organism. However, repeat sputum from November 2017 regrew *B. pseudomallei*, and oral trimethoprim-sulfamethoxazole was recommenced for a further 5 months. Six sputum samples in the past 13 months have only grown the organisms she is colonized with (*Staphylococcus aureus* and *Pseudomonas aeruginosa* on one occasion), and she remains well.

(This case report was presented as an oral presentation at the All Wales Cystic Fibrosis Club Meeting on 11 October 2017.)

**DISCUSSION**

Melioidosis is caused by the Gram-negative bacterium *Burkholderia pseudomallei*, which is classically found in regions of endemicity of Southeast Asia and Northern Australia (4, 5). Infection is acquired through direct inoculation, inhalation, or ingestion of contaminated soil or water with an incubation period of 1 to 21 days (4–10). The typical presentation with melioidosis in adults is pneumonia, which ranges from mild disease to subacute pulmonary disease mimicking tuberculosis to fulminant septic shock (4–10). Extrapulmonary presentations such as cutaneous infections, septic arthritis, genitourinary infections, and encephalitis have been reported (4–10). Children tend to present more frequently with skin lesions following an inoculating event (4). Common risk factors for the disease include diabetes, renal disease, alcohol excess, and chronic lung disease (4–9). *B. pseudomallei* is increasingly being recognized as a pathogen in CF as a result of improved life expectancy with CF and increasing global travel (4–9, 11, 12). Person-to-person transmission has been reported in CF (9).

Unlike in the general population where the acquisition of *B. pseudomallei* often results in acute severe infection, in CF, the organism tends to cause chronic disease (4–9). A study evaluating melioidosis in 24 CF patients found that in 79% of their cohort (19 patients), initial infection was followed by chronic infection (1 to 11 years) (7). Of these patients, 14 went on to have an accelerated decline in lung function. In 10 patients in this study, *B. pseudomallei* was an incidental finding on routine sputum culture, which raises the possibility of latency and reactivation of this organism.

Diagnosis of melioidosis requires culture of the organism from any site, with all positive cultures deemed significant, as this organism is not part of the commensal microbiota in humans (5, 10). *B. pseudomallei* is a small Gram-negative bacillus that can exhibit bipolar staining. It is a motile organism that is oxidase positive and indole negative and is intrinsically resistant to aminoglycosides and polymyxins (5, 13). Its susceptibility to amoxicillin-clavulanic acid can aid in confirming the identification of this organism (13). On sheep blood agar, colonies are typically small and cream and may develop a dry wrinkled appearance upon incubation beyond 24 to 48 h (5, 13). On MacConkey agar, colonies are non-lactose fermenters and colorless and may develop a pinkish rugose appearance after 48 h. *B. mallei*, the etiological agent of glanders, differs from *B. pseudomallei* because it is nonmotile, slower growing, and susceptible to aminoglycosides.

Laboratory safety is an important aspect to consider with this organism, which is a
hazard group 3 pathogen (select agent). If the organism is suspected or confirmed, the laboratory should be notified preemptively and all samples must be labeled as hazardous. As *B. pseudomallei* can be acquired through inhalation, all culture plates for suspected or confirmed cases should be handled by trained personnel with the appropriate personal protective equipment (PPE). Respiratory protection must be used during centrifugation because of the potential to generate aerosols and transmit infection (3, 5, 10, 13–16). Sealed cups should be used in all centrifuges, and these should be opened only in a biologic safety cabinet (5).

The recommendations for handling such samples before the identification of the organism have been confirmed vary between the United Kingdom and the United States. In the United Kingdom, the Control of substances hazardous to health (COSHH) 2002 guidance recommends the processing of all such samples within a biosafety level 3 (BSL3) facility (17). In comparison, U.S. guidance states such samples should be handled in BSL3 laboratories if available, or where purpose-built BSL3 facilities are not available, the work can be performed in a certified class II biosafety cabinet using BSL3 practices and appropriate BSL3 PPE (13). If a select agent cannot be ruled out, then further identification should not be attempted and the isolate should be referred to a Public Health reference laboratory to confirm or exclude this pathogen and to perform susceptibility testing.

In our patient, the initial sputum sample from July 2017 (travel history was unknown at this stage and a select agent was not suspected) was processed under a class I biologic safety cabinet in a BSL3 laboratory, which is the standard operating procedure for processing all sputum samples at the local laboratory (18). All subsequent samples were labeled as hazardous and were again processed in a BSL3 laboratory. Identification of this organism was initially attempted through MALDI-TOF MS (following ethanol extraction), as *B. pseudomallei* was not clinically suspected. MALDI-TOF MS incorrectly identified this organism as *Burkholderia thailandensis* (albeit at a suboptimal rating), which is genetically closely related to *B. pseudomallei* but is nonpathogenic in humans. Misidentification of *B. pseudomallei* by the Bruker MALDI-TOF MS has been well described in the literature (1, 5, 14–16). In this case, the Public Health England UK antimicrobial resistance and health care-associated infections reference unit, opportunistic pathogens section based in Colindale, London, used a species-specific PCR to identify this organism and performed susceptibility testing in a BSL3 facility (2, 3).

In the event of a laboratory exposure incident, postexposure prophylaxis (PEP) with trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid for 3 weeks is recommended, although the data on the efficacy of PEP is limited (5, 10, 16). As *B. pseudomallei* is a select agent, the local health protection team and the Rare and Imported Pathogens Laboratory (RIPL) in Porton Down, UK, were notified. Management of the case, biosafety aspects, and consideration of staff prophylaxis were discussed with a national expert panel, but further actions were deemed unnecessary following a health and safety risk assessment, as all protocols had been followed appropriately.

Treatment for melioidosis consists of a 2-week intensive phase of intravenous ceftazidime or meropenem providing the patient is improving and no deep seated source of infection is present. This is followed by an eradication phase, which consists of 3 to 6 months of oral antimicrobials. Trimethoprim-sulfamethoxazole is the drug of choice for eradication, but amoxicillin-clavulanic acid and doxycycline are alternatives (4–10). Mortality is high in melioidosis associated with sepsis (50% to 90%) despite adequate treatment (10). Relapse and chronic colonization are common in CF and are associated with declining lung function (7, 9). Unlike in patients harboring *Burkholderia cepacia* complex where lung transplantation is contraindicated, in those harboring *B. pseudomallei*, lung transplantation may be considered, although no specific guidance on this organism in the lung transplantation setting is currently available (11). Early posttransplant results have been promising despite *B. pseudomallei* persisting posttransplantation (7).

This case highlights the contrasting presentation of melioidosis in CF to that in the general population, where chronic infection is more prevalent in the former cohort.
international travel increases, obtaining a detailed travel history and giving travel advice have become more important in CF than ever before. The United Kingdom CF Trust (12) now recommends avoiding travel to rural areas in Southeast Asia and Northern Australia, particularly during the rainy season. Laboratory safety is paramount with this organism, which is a select agent. If melioidosis is suspected clinically, discuss these cases with infectious diseases, hospital epidemiology, and clinical microbiology colleagues who can advise on therapy, infection control, and public health requirements and can notify the laboratory to ensure the samples are handled and processed appropriately.

SELF-ASSESSMENT QUESTIONS

1. What is the most common clinical presentation of melioidosis in adults?
   a. Septic arthritis
   b. Meningitis
   c. Pneumonia
   d. Skin abscesses

2. Which of the following is true about *Burkholderia pseudomallei*?
   a. It is a Gram-negative bacillus which is oxidase negative and indole positive.
   b. It is susceptible to gentamicin.
   c. It is a lactose fermenter on MacConkey agar.
   d. Colonies on sheep blood agar at 48 hours appear small, smooth, and cream colored, and the organism is susceptible to amoxicillin-clavulanic acid.

3. What is the first-line treatment of melioidosis in the induction phase?
   a. Clarithromycin
   b. Ceftazidime
   c. Ceftriaxone
   d. Polymyxins

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REFERENCES


