Clinafloxacin for Treatment of *Burkholderia cenocepacia* Infection in a Cystic Fibrosis Patient

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This journal section presents a real, challenging case involving a multidrug-resistant organism. The case authors present the rationale for their therapeutic strategy and discuss the impact of mechanisms of resistance on clinical outcome. An expert clinician then provides a commentary on the case.


In the cystic fibrosis (CF) patient population, infection with *Burkholderia cepacia* complex (Bcc) is uncommon but important, due to the accelerated decline in lung function and the increased mortality in affected individuals (1). Bcc consists of 18 different genetically related Gram-negative, non-spore-forming species (2). Infection with Bcc leads to a spectrum of clinical manifestations, ranging from asymptomatic carriage in respiratory secretions to necrotizing pneumonia (1, 3, 4). *Burkholderia cenocepacia* isolates are frequently virulent, transmissible, and innately resistant to multiple drug classes (1, 5). No standardized regimens have been developed for treatment of *B. cenocepacia* infection (3). Lung transplantation is seldom an option for CF patients harboring this species, as pretransplant carriage usually portends poor postoperative outcome (6). Unfortunately, the low prevalence of *B. cenocepacia* infection has limited the systematic *in vivo* study of potential therapies. To date, there has been only one randomized controlled trial for Bcc infection (inhaled aztreonam), which unfortunately did not demonstrate efficacy of this agent (7). We herein report the off-label use of clinafloxacin for the treatment of *B. cenocepacia* infection in a CF patient.

**CASE PRESENTATION**

A 30-year-old Caucasian male with CF (genotype F508del/3199del6), complicated by pancreatic insufficiency and diabetes, was admitted with increasing dyspnea. He was chronically infected with *Pseudomonas aeruginosa* and *B. cenocepacia* (identified using *recA* PCR and further characterized as strain PHDC by repetitive-element PCR using the BOX AIR primer, as described previously [8]). The patient experienced progressive clinical worsening, highlighted by a precipitous decline in pulmonary function over the year prior to presentation (his forced expiratory volume in 1 s [FEV1] decreased from 79% to 43% predicted). On hospital admission, he reported shortness of breath and hemoptysis, despite aggressive treatment with standard therapies for CF lung disease, including multiple courses of intravenous antibiotics and chronic suppressive therapy with minocycline. Severe allergies to cephalosporins, aminoglycosides, and carbapenems complicated the selection of antibiotics.

On examination, the patient had a hoarse voice. His vital signs included a heart rate of 119 beats/min, blood pressure of 136/85 mm Hg, a respiratory rate of 16 breaths/min, and oxyhemoglobin saturation of 96% while breathing room air. Diffuse bilateral crackles were auscultated. There was a nonblanching erythematous papular rash over the lower extremities below the knees along with pitting edema.

The patient’s C-reactive protein level was 138.2 mg/liter, compared to 6 mg/liter at the end of hospitalization 2 months earlier, and his white blood cell count was elevated, at 18,400 cells/ml. His serum albumin level was 3.1 g/dl. The patient was diagnosed with a CF pulmonary exacerbation based on the clinical presentation.

**CHALLENGE QUESTION**

*Burkholderia cenocepacia* infections are often difficult to control with standard antimicrobial therapies. Which of the following is NOT a recognized cause of treatment failure of *B. cenocepacia* infection?
A. Organisms may possess inherent resistance to multiple drug classes.

B. Organisms may acquire resistance through plasmid-based gene transfer.

C. Organisms may be sequestered in the intracellular compartment.

D. Organisms may use some antimicrobial agents as nutritional substrates.

E. Upon exposure to antimicrobial agents, organisms enter a spore phase.

TREATMENT AND OUTCOME

Symptoms worsened, despite ongoing treatment with a variety of broad-spectrum intravenous antibiotics for more than 3 months, including amikacin, cefepime, ciprofloxacin, minocycline, chloramphenicol, and tobramycin (see Fig. S1 in the supplemental material). B. cenocepacia isolated on earlier sputum cultures was resistant to ceftazidime, levofloxacin, and meropenem. Spirometry showed an FEV₁ of 1.29 liters (34% predicted), compared to 1.57 liters (43%) 2 months earlier. Chest computed tomography (CT) showed saccular bronchiectasis with areas of mucus plugging, scattered ground glass opacities, and nodular consolidation (Fig. 1). The patient was felt to have “cepacia syndrome,” characterized by persistently elevated inflammatory markers, leukocytosis, intermittent fevers, and recurrent petechial skin eruption (shown to be leukocytoclastic vasculitis on skin biopsy), although his blood cultures did not become positive until a later date. This condition, well described in published case series, is recognized to be uniformly fatal (1, 9). Thus, a sense of urgency developed.

Reports of lower in vitro MICs of clinafloxacin for Burkholderia spp. led us to pursue compassionate use of the medication for our patient. Investigational drug approval from our institutional review board and the Food and Drug Administration (FDA) was obtained for single-patient administration. The drug was procured from a foreign vendor and verified by our pharmacy. Informed consent for drug administration was obtained from the patient. Dosing, adapted from previous reports (10), was started at 200 mg intravenously every 12 h. Initially, the drug was infused in the intensive care unit accompanied by continuous telemetry, and the steady-state pharmacokinetic (PK) profile was determined. There were no prescribed changes in the patient’s chronic regimen during the administration of clinafloxacin. Eight blood samples were obtained over the dosing interval, and serum concentrations were determined using a validated high-performance liquid chromatography assay. Serum concentration data (Fig. 2) were fit to a one-compartment model to provide the following PK estimates: area under the concentration-time curve (0 to 12 h), 15.2 mg·h/liter; maximum concentration, 2.4 mg/liter; volume of distribution, 95.3 liters; clearance, 13.1 liters/h; and half-life, 5.0 h. Although the pharmacodynamic relationship between fluoroquinolones (FQ) and Burkholderia cepacia complex has not been fully elucidated, an AUC₂₄/MIC ratio of >125 has been described between ciprofloxacin and P. aeruginosa (11). Thus, we approached the dose and frequency of clinafloxacin to target this pharmacodynamic parameter in our patient. The patient received two courses of clinafloxacin. After the initial 1-week course to establish safety, he received an extended 3-week course 5 weeks later. He tolerated the starting dose, so it was increased on day 3 to 250 mg every 12 h. During the last 2 weeks of therapy, clinafloxacin was increased to 400 mg twice daily, with the expectation of a

FIG 1 Chest CT images. (A) A representative image prior to clinafloxacin therapy shows regions of nodular consolidation (an arrow denotes one pronounced area in the right upper lobe). (B) Improvement in consolidation during clinafloxacin therapy. (C) Sustained improvement 7 months after clinafloxacin therapy. (D) Diffuse areas of nodular opacities with cavitition 8 months after clinafloxacin therapy.
Flux proteins are believed to drive the frequent emergence of FQ, though little description of the clinical course is provided (12). Patients for treatment of *Pseudomonas cepacia* are generally susceptible to FQ, although multidrug efflux proteins have been postulated as an explanation for increased efficacy (14). Ciprofloxacin has been used as an investigational drug in a wide array of life-threatening infections, such as endocarditis (8). Unfortunately, it was withdrawn from the market due to adverse events, including phototoxicity and drug-induced hypoglycemia (10). In our patient, there was no evidence of the aforementioned adverse effects. Clinical improvement, albeit temporary, was demonstrated on several fronts, including clearing of radiographic infiltrates, improvement in airflow obstruction, resolution of skin lesions, and reduction in C-reactive protein. We speculate that therapy may have been more effective if we had initiated treatment earlier in the patient’s disease course.

Alterations in the pharmacodynamics and PK of various medications in CF patients are well described, although FQ are usually affected to a lesser extent (11). Data from our patient mirrors that reported in healthy volunteers, suggesting that pharmacokinetics of ciprofloxacin is not altered by CF (5). It should be emphasized that this drug is not currently approved for human use by the FDA. Data from appropriately designed clinical trials are needed before ciprofloxacin could be generally recommended for use in patients.

(The answer to the challenge question is “E: Upon exposure to antimicrobial agents, organisms enter a spore phase.” This statement is incorrect, as *Burkholderia cenocepacia* is a non-spore-forming organism.)

**COMMENTARY**

Pulmonary infection with *Burkholderia cenocepacia*, a species within the *Burkholderia cepacia* complex, raises concerns for both CF clinicians and patients alike, given its association with increased lung function decline and earlier mortality (1, 15–17). *B. cenocepacia* is perhaps best known as the most frequent cause of “cepacia syndrome,” a necrotizing pneumonia with sepsis resulting in rapid clinical decline and, frequently, death (4). CF patients infected with *B. cenocepacia* who undergo lung transplant are also at greater risk of death during the early postoperative period (6,18, 19). Due to several intrinsic mechanisms that confer resistance to many classes of antimicrobial agents, *B. cenocepacia* infections are notoriously difficult to treat (20).

In the clinical case described above, Balwan et al. report a case of a 30-year-old male with CF infected with *B. cenocepacia* who presents with a pulmonary exacerbation and is treated with the investigational drug ciprofloxacin. As with many such patients, he was infected with a multidrug-resistant *B. cenocepacia*, had very low lung function, and had been treated repeatedly with multiple broad-spectrum antibiotics with little improvement. Elevated inflammatory markers, leukocytosis, intermittent fevers, and a persistent skin rash suggested systemic involvement of the infection, which was confirmed to be cepacia syndrome when blood cultures were positive for *B. cenocepacia*. Following 3 weeks of ciprofloxacin treatment, the patient appeared to stabilize, with improvement in symptoms, an increase in FEV₁ from 34% to 41% predicted, and a normalization of his C-reactive protein (CRP). However, the lack of control subjects and measures of microbiological efficacy, such as sputum bacterial density counts, makes it difficult to directly attribute this improvement to a specific intervention. Despite this initial response, however, the patient ultimately succumbed to this infection, reflecting the high mortality associated with this condition.
This case report highlights the dire need for more effective antimicrobial treatments for B. cepacia complex infections in individuals with CF. There are currently no chronic suppressive antibiotics for B. cepacia complex-infected patients, who represent only approximately 3% to 5% of the CF population (21, 22). A recent double-blind, placebo-controlled trial, the only one done in this patient population, of continuous inhaled aztreonam in B. cepacia complex-infected CF patients demonstrated no significant differences in microbiological or lung function outcomes between treatment arms (7). Although clinafloxacin was withdrawn from the market due primarily to concerns regarding phototoxicity (23, 24), this case represents a reasonable attempt to use an in vitro active agent to treat an infection caused by a multidrug-resistant organism. Laboratory-based studies have demonstrated that clinafloxacin, an extended-spectrum fluoroquinolone, has activity against a wide range of Gram-positive, Gram-negative, and anaerobic organisms (25). Specifically, in comparison to a number of other fluoroquinolones, clinafloxacin was noted to be the most active against efflux-mediated multidrug-resistant Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Burkholderia cepacia, all recognized pathogens in CF patients (14). This is particularly relevant in the treatment of CF pulmonary infections that are characterized by biofilms, or matrix-encased communities of bacterial cells (26). Efflux pumps play a significant role in biofilm-specific resistance to multiple classes of antibiotics, including fluoroquinolones, in bacteria such as B. cenocepacia (27, 28). Although clinafloxacin is no longer available as a treatment option, phase III trials of inhaled levofloxacin in CF patients with chronic P. aeruginosa infection have recently been completed and demonstrate safety and FEV1 increases comparable to those for patients treated with inhaled tobramycin solution (29). It is not known whether aerosolized levofloxacin treatment of B. cepacia complex infections in CF patients can lead to similar improvements in lung function and whether these improvements can be sustained over multiple treatment cycles, given the known rapid emergence of antimicrobial resistance to fluoroquinolones. However, with the poor outcomes related to these infections, as illustrated by this case report, identification of effective antimicrobial treatments for this patient population needs to be a research priority.

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