Successful Use of Temocillin as Salvage Therapy for Cervical Osteomyelitis Secondary to Multidrug-Resistant *Burkholderia cepacia*

Marcela Rodriguez,1 Miranda Nelson,2 James E. Kelly,3 Alexis Elward,2 and Sharon Celeste Morley2

1Department of Pediatrics, Southern Illinois University School of Medicine, Springfield; and Departments of 2Pediatrics, and 3Radiology, Washington University School of Medicine, St Louis, Missouri

Corresponding Author: Marcela Rodriguez, MD, Assistant Professor of Clinical Pediatrics, Division of Infectious Diseases, Southern Illinois University School of Medicine, The Pavilion at St John’s, 301 N 8th St, 4A, PO Box 19658, Springfield, IL 62794. E-mail: mrodriguez@siumed.edu.

Received July 5, 2012; accepted October 16, 2012; electronically published January 8, 2013.

Infection with multidrug resistant *Burkholderia cepacia* presents a therapeutic challenge in patients with cystic fibrosis. In this study, we present a case of progressive cervical osteomyelitis secondary to *B cepacia* that failed surgical drainage and extended therapy with meropenem, piperacillin-tazobactam, doxycycline, and aminoglycosides. Temocillin (Negaban) was successfully used to clear the infection.

**Key words.** *Burkholderia cepacia*; cystic fibrosis; multidrug-resistant; vertebral osteomyelitis.

*Burkholderia cepacia* is an aerobic, glucose non-fermenting, gram-negative rod that colonizes patients with cystic fibrosis. Colonization or infection with multidrug-resistant *B cepacia* is associated with increased morbidity and mortality in patients with cystic fibrosis [1, 2]. The drug of choice for treatment is trimethoprim-sulfamethoxazole. Second choice agents include piperacillin, meropenem, aminoglycosides, tetracyclines, and fluoroquinolones, either singly or in combination [1]. Unfortunately, *B cepacia* can develop resistance to all of these agents, leaving few therapeutic options.

A patient with cystic fibrosis developed otitis externa due to *B cepacia*. Despite prompt and repeated surgical drainage and intravenous (IV) antimicrobial therapy, his infection progressed to mastoiditis and eventual cervical osteomyelitis with bacteremia. His infection was finally cured with IV administration of temocillin.

**CASE REPORT**

A 20-year-old male with cystic fibrosis and receiving IV meropenem for cervical osteomyelitis secondary to *B cepacia* complex, *Burkholderia multivorans* (hereafter referred to as *B cepacia*), was admitted to the hospital for fever and increased neck pain.

The patient’s past medical history was significant for 2 bilateral lung transplants 3 years before the current admission. The first bilateral lung transplant failed after 3 weeks due to acute rejection. After receiving a second transplant, he developed bronchiolitis obliterans and required significant immunosuppression. In addition, the patient had insulin-dependent diabetes mellitus and was colonized with *B cepacia*.

Six months before this admission, the patient’s illness began with left ear pain, left-sided jaw pain, and low grade fever. Upon initial presentation, his exam was notable for an erythematous left tympanic membrane and swelling posteriorly around the left second molar. Maxillofacial computed tomography CT showed bilateral mastoid and ear fluid. He underwent placement of bilateral tympanostomy tubes, and cultures of the ear fluid grew *B cepacia*. This isolate demonstrated in vitro intermediate sensitivity to meropenem and resistance to trimethoprim-sulfamethoxazole, cefazidime, and ticarcillin-clavulanate. In addition, there were no zones of inhibition around tobramycin, gentamicin, amikacin, ciprofloxacin, levofloxacin, colistin, and cefepime in a disk diffusion assay, severely limiting therapeutic options. Prior isolates of *B cepacia* from cultures of his respiratory secretions had shown in vitro susceptibility to combination therapy with meropenem and doxycycline but were resistant to
doxycycline alone. Subsequent isolates from ear drainage were resistant to tigecycline, aztreonam, minocycline, moxifloxacin, and doripenem. We did not have testing available for fosfomycin, but most isolates of *B. cepacia* appear to be fosfomycin-resistant [3]. Chloramphenicol was not considered at this time because of its potential side effects. Therefore, the patient was treated with meropenem and doxycycline and discharged home.

In the month after initial presentation, the patient was readmitted twice for recurrent fevers and ear pain, undergoing repeat mastoidectomies and continuing to demonstrate growth of *B. cepacia* from intraoperative cultures. Because 1 isolate demonstrated a zone of inhibition of 24 mm around piperacillin-tazobactam in a disk diffusion assay, piperacillin-tazobactam was added to his antimicrobial regimen. His fever and ear pain resolved, and the patient then completed a standard course of therapy for mastoiditis: 21 days of parenteral doxycycline and IV meropenem and piperacillin-tazobactam. Shortly after discontinuation of these antibiotics, the patient was readmitted with *B. cepacia* bacteremia. He was treated with meropenem, doxycycline, and piperacillin-tazobactam, and after 4 days his blood cultures became negative. A temporal bone CT did not show new bony destruction to suggest ongoing osteomyelitis. He completed another 3 weeks of IV antibiotic therapy for gram-negative bactemiation. Duration of therapy was determined by clinical improvement in the patient's symptoms and by clearance of blood cultures; inflammatory markers such as C-reactive protein level (CRP) and erythrocyte sedimentation rate (ESR) were difficult to interpret in a patient with underlying chronic lung disease and immunosuppression.

Three days after discontinuation of antibiotics, and 2 months before the current admission, he again presented to the hospital with neck pain and swelling associated with left ear drainage. Cultures of blood and ear drainage were positive for *B. cepacia*. Antimicrobial therapy was initiated with meropenem, piperacillin-tazobactam, and tobramycin. Magnetic resonance imaging (MRI) revealed a rim-enhancing fluid collection extending from the left mastoid process under the occipital bone to the left occipital condyle and bone marrow edema, consistent with osteomyelitis. Enhancement of the left atlanto-occipital joint was consistent with septic arthritis. These fluid collections were surgically drained and were culture-positive for abundant *B. cepacia*. He remained bacteremic despite IV antibiotics and surgical drainage. By this time, numerous isolates of *B. cepacia* had been obtained from this patient. Although some isolates demonstrated in vitro sensitivity to meropenem, other isolates were only intermittently sensitive. Because the infection was progressing on standard doses of meropenem, the dose was increased from 20 mg/kg per dose to 40 mg/kg per dose every 8 hours, and the infusion time extended to 3 hours instead of 15 minutes to maximize time above the minimum inhibitory concentration (MIC) to overcome possible meropenem-resistant organisms [4]. With extended dosing of meropenem, his blood cultures became negative. His neck pain improved, and he was discharged to continue therapy with extended dosing of meropenem, IV piperacillin-tazobactam, and oral doxycycline.

Four weeks later, while on the above antibiotic regimen, the patient presented for the current admission. He complained of fever, headache, photo- and phonophobia, increased neck pain and rigidity, nausea, and anorexia. His cervical spine was significantly tender to palpation on exam. His CRP had increased from 7.9 mg/L to 45.2 mg/L. An MRI showed worsening osteomyelitis with epidural extension (Figure 1A), despite 7 weeks of therapy and initial improvement with extended dosing of meropenem. Because infection with *B. cepacia* was progressing on meropenem, we considered the use of temocillin. Although used in Europe, temocillin is not approved for general use by the US Federal Drug Administration (FDA); temocillin E-test demonstrated an MIC of 12 µg/mL for the isolate of *B. cepacia*. Per the manufacturer, an isolate is considered sensitive if the E-test reveals an MIC of less than or equal to 16 µg/mL, whereas resistance is indicated by an MIC of greater than or equal to 32 µg/mL. Therefore, approval was obtained from Eumedica, the Washington University Human Research Protection Office (HRPO), and the FDA for compassionate use under an emergency single use Investigational New Drug. Intravenous temocillin was started, and IV meropenem and piperacillin-tazobactam were discontinued. He remained on oral doxycycline.

The patient responded to temocillin, with reduction of his neck pain and increased mobility within 3 weeks of initiation of therapy. After 4 weeks of therapy with temocillin, his CRP was 1.1 mg/L. His treatment course was complicated by an episode of mild hemolytic anemia that may have been due to temocillin. As his infection was improving, temocillin was continued and the anemia resolved. This complication was reported to Eumedica, Washington University HRPO, and the FDA. Temocillin and doxycycline were discontinued after 4 months of therapy when all symptoms were resolved, CRP remained low, and MRI showed improvement. Magnetic resonance imaging revealed marked interval improvement with minimal residual enhancement within the left C1 lateral mass, left C2 lateral mass, and left occipital condyle (Figure 1B). Mild edema within the left paravertebral
soft tissues had also improved. The patient has been followed for 2 years after completion of therapy with temocillin and the infection with *B. cepacia* has not recurred.

**DISCUSSION**

We present a case of an immunosuppressed patient with cystic fibrosis who developed otitis externa with *B. cepacia*, which progressed to mastoiditis in 1 month and eventual cervical osteomyelitis in 5 months despite aggressive surgical management and extended antimicrobial therapy with meropenem, piperacillin-tazobactam, and doxycycline. This case illustrates the difficulty of clearing multidrug-resistant *Burkholderia* from patients with cystic fibrosis, and the difficulty in determining adequate duration of therapy in a patient with underlying chronic inflammation that renders some markers of therapy, such as ESR, less useful. Temocillin (Negaban) was successfully used to clear the infection.

Temocillin, the 6-α-methoxy derivative of ticarcillin, was generated in the 1980s [5]. Temocillin was never adopted for widespread use, probably because of a fairly narrow spectrum of activity. Although active against many gram-negative rods, temocillin has no activity against gram-positive organisms, anaerobes, or *Pseudomonas aeruginosa*. However, its extreme stability to AmpC and many extended spectrum β-lactamases (ESBLs) make temocillin ideal for treating infections with highly resistant Enterobacteriaceae [5]. A recent case series reports on the successful use of temocillin to treat sepsis associated with biliary or urinary tract infections with AmpC or ESBL-producing Enterobacteriaceae [6]. Temocillin has also been reported to have effectively treated a cervical osteomyelitis and epidural abscess with an ESBL-producing *Klebsiella* [7]. Furthermore, *B. cepacia* is generally more susceptible to temocillin than to many other β-lactams [5]. Although temocillin is not a standard choice of therapy for *B. cepacia* in the United States, our options were limited due to the resistant nature of the isolate. Chloramphenicol could have been considered, but a majority of isolates of *B. cepacia* are resistant to chloramphenicol [8], and the clinical experience in Europe supported the use of temocillin [5].

Infection with *B. cepacia* presents a serious threat to patients with cystic fibrosis. Like *P. aeruginosa*, colonization or lung infection with *B. cepacia* can progressively impair respiratory function. Colonization with *B. cepacia* complex has been considered an absolute contraindication to lung transplantation, and infection with some species may increase post-transplant mortality [2]. *Burkholderia cepacia* syndrome consists of rapidly progressing necrotizing pneumonia and sepsis in patients with cystic fibrosis and is almost universally fatal [9]. In addition to these common presentations of *B. cepacia* infection in patients with cystic fibrosis, *B. cepacia* has been reported to cause a chest wall abscess and pyomyositis [9, 10]. To our knowledge, this is the second case of cervical osteomyelitis due to *B. cepacia* reported in the literature [11], and the only case of osteomyelitis due to *B. cepacia* treated with temocillin.

Although used for years in European centers, temocillin is not yet licensed for use in the United States. We were fortunate to obtain approval for use of temocillin on a compassionate use basis in our patient, and for him this medication was undoubtedly life-saving. Evidence from European centers is accumulating for the efficacy of temocillin in treating *B. cepacia* colonization and infection.
in patients with cystic fibrosis [12]. We would like to encourage investigators and clinicians in the United States to consider the use of temocillin, with appropriate approval, in otherwise challenging situations.

Acknowledgments

Potential conflict of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References