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Case Report

Ceftaroline Fosamil Use in 2 Pediatric Patients With Invasive Methicillin-Resistant *Staphylococcus aureus* Infections

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Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is one of the most common pathogens causing pediatric infections including skin and soft tissue infections, pyogenic arthritis, osteomyelitis, and septic shock. For decades, patients were treated with antibiotics such as vancomycin and clindamycin, but there is an increasing incidence of resistance to these traditional therapies. We describe 2 cases of patients with CA-MRSA invasive infections with bacteremia who experienced vancomycin therapy failure but who were successfully treated with ceftaroline fosamil. Case 1 involves an 8-year-old Hispanic male who was diagnosed with CA-MRSA bacteremia, thigh abscess, and osteomyelitis. The patient was admitted to the pediatric intensive care unit in septic shock. Case 2 involves an 8-year-old Caucasian male who was diagnosed with CA-MRSA sepsis, right arm abscess, and osteomyelitis. We were able to successfully treat both patients with CA-MRSA sepsis and invasive infection—who failed vancomycin therapy—with ceftaroline fosamil with no adverse effects. Despite the positive outcome in both pediatric patients, clinical trials with ceftaroline fosamil are needed to further support its use in pediatric patients.

INDEX TERMS: ceftaroline fosamil, child, methicillin-resistant *Staphylococcus aureus*, osteomyelitis, pediatrics

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INTRODUCTION

Despite an increasing incidence of infections caused by multidrug resistant organisms, few antimicrobial agents to treat these infections are in the pipeline.[1] Methicillin-resistant *Staphylococcus aureus* (MRSA) is known to cause an array of infectious processes ranging from skin and soft tissue infections (SSTIs) to bacteremia and septic shock. Population-based surveillance data have documented an increase in the incidence of community-acquired MRSA (CA-MRSA) infections among children.[2] In light of this increasing incidence of resistant infections, therapeutic alternatives to commonly used therapies are necessary.

In October 2010, the US Food and Drug Administration (FDA) approved the first beta-lactam with activity against MRSA.[3] Ceftaroline (Teflaro, Forest Pharmaceuticals, St Louis, MO) is an active metabolite of the parent product ceftaroline fosamil that has bactericidal activity against a wide range of organisms including *S aureus* (including vancomycin-intermediate isolates), *Streptococcus pneumoniae, Haemophilus influenzae, Klebisella pneumoniae,* and *Escherichia coli*; however, it lacks activity against *Pseudomonas aeruginosa, Acinetobacter* species, and Gram-negative bacteria producing extended-spectrum beta-lactamases.[4] Like other beta-lactams, ceftaroline works by binding to penicillin-binding proteins, especially PBP2a (MRSA) and PBP2x (resistant *S pneumoniae*).[3] Currently, ceftaroline use is only FDA approved for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections caused by susceptible bacteria in adults 18 years of age and older.[5] No data are currently available regarding its clinical use in pediatric patients. This case series describes the management of CA-MRSA infections in 2 pediatric patients who failed vancomycin therapy and were transitioned to ceftaroline fosamil therapy.

CASE 1

An 8-year-old, 46.4-kg Hispanic male with a past medical history of asthma presented to the pediatric emergency department (ED) complaining of 2 days of pain in the left leg secondary to a fall from a trampoline. Upon arrival the patient was disoriented, febrile to 39°C, tachycardic, and hypotensive. His left thigh was tender and swollen with decreased range of motion of the left knee. Ultrasonography revealed a joint effusion tracing from the left knee joint. Laboratory analysis revealed a white blood cell (WBC) count of 12,000 with 70.8% neutrophils, a C-reactive protein (CRP) concentration of 47.9 mg/dL, an erythrocyte sedimentation rate (ESR) of 1 mm/hr, and a creatine kinase concentration of 5514 units/L.

The patient was given ceftriaxone 2000 mg (43 mg/kg) intravenously (IV) every 12 hours in the pediatric ED, which is routinely used in our institution to empirically treat SSTIs. Vancomycin 690 mg (15 mg/kg) IV every 6 hours was added after incision and drainage in the operating room. The patient arrived to the pediatric intensive care unit (PICU) intubated and on dual vasopressor therapy. An initial vancomycin trough concentration drawn before the fourth dose was 6.4 mg/dL (below the goal range of 15-20 mg/dL), requiring a dose increase to 850 mg (18 mg/kg) IV every 6 hours.

On postoperative day (POD) 2, the infectious disease specialist was consulted. Because of suspicion of vancomycin failure, and a family history of MRSA SSTI with vancomycin failure in the patient's brother, the antibiotics were changed. Taking into consideration the severity of the infection and the critical condition of the patient, clindamycin 500 mg (13 mg/kg) IV every 6 hours and linezolid 500 mg (13 mg/kg) IV every 6 hours were initiated, and vancomycin and ceftriaxone were discontinued. Magnetic resonance imaging (MRI) at this time revealed findings consistent with an abscess surrounding the distal femoral diaphysis of the left femur with no evidence to suggest osteomyelitis, and a small volume joint effusion of the left knee. Blood and sputum cultures collected on POD 3 and POD 4 also demonstrated growth of MRSA.

The WBC count continued to rise to a peak of 35,960 on POD 5 and the finalized report of cultures from the blood, left knee swab, left thigh swab, and sputum collected on the day of admission demonstrated the growth of MRSA with documented susceptibility to clindamycin with no inducible resistance, daptomycin, linezolid, and vancomycin and resistance to erythromycin. The vancomycin minimum inhibitory concentration (MIC) was 2 mg/L. An MRSA MIC of ≥2 mg/L to vancomycin is reported in less than 15% of the MRSA isolates in our institution. This prompted the addition of daptomycin 350 mg (7.5 mg/kg) IV every 24 hours and the discontinuation of clindamycin. The first negative blood culture was collected on POD 5. Antibiotic therapy was changed secondary to lung involvement to ceftaroline fosamil 600 mg (13 mg/kg) IV every 8 hours on POD 6 after ceftaroline fosamil susceptibility was documented via the Kirby Bauer method (disk diffusion zone diameter ≥ 24 mm). Additionally, the patient was extubated and weaned off all vasoactive medications. Repeated blood cultures drawn before discharge remained negative and no further surgical intervention was required. The patient defervesced on POD 15, and a normal WBC count was documented on POD 16. The patient was discharged home on POD 16 to complete 4 weeks of ceftaroline fosamil therapy. Repeated ESR and CRP at discharge were 100 mm/hr and 3.8 mg/dL, respectively; however, repeated values upon completion of therapy were lower at 34 mm/hr and 0.6 mg/dL, respectively. Complete blood count, liver function test, renal function, CRP, and ESR were monitored daily during hospitalization and weekly after discharge until the completion of treatment. No adverse effects of ceftaroline fosamil were reported. On 6-month follow-up, neither recurrence of infection nor side effect of treatment was reported.

CASE 2

An 8-year-old Caucasian male with no significant past medical history presented to the pediatric ED complaining of 5 days of fever, body pain, and migratory joint swelling. Associated symptoms included decrease in appetite, vomiting, and abdominal pain. Per family report, the patient attended a football camp 5 days before presentation.

On presentation, the patient was tachycardic, afebrile with oxygen saturation of 94% to 95% on room air, and weighed 28.7 kg. Physical examination revealed a moderately swollen erythematous

right elbow and tenderness to palpation on all 4 extremities. Chest x-ray demonstrated lower airway disease. Right humerus x-ray was unimpressive; however, MRI revealed muscle edema concerning for myositis. Laboratory analysis demonstrated a WBC count of 13,050 with 77% neutrophils, a CRP concentration of 14.5 mg/dL, an ESR of greater than 80 mm/hr, and a low sodium concentration of 125 mEq/L. Cerebrospinal fluid studies were all within normal limits. Antimicrobial therapy was initiated with ceftriaxone 2000 mg (70 mg/kg) IV and vancomycin 430 mg (15 mg/kg) IV in the pediatric ED.

Piperacillin-tazobactam 3.375 g (100 mg/kg piperacillin component) IV every 8 hours and vancomycin 430 mg (15 mg/kg) IV every 6 hours were initiated upon admission to the PICU. Doxycycline 60 mg (2.1 mg/kg) IV every 12 hours was also initiated on the day of admission secondary to initial concern for tick-borne illnesses. Vancomycin trough was optimized to 14.4 mg/dL by day 3 of admission on a dose of vancomycin 600 mg (21 mg/kg) IV every 6 hours. Blood collected in the pediatric ED demonstrated growth of *S aureus* in less than 24 hours. Susceptibility testing revealed methicillin resistance and a vancomycin MIC of 2 mg/L, and the patient continued spiking fevers in excess of 38.8°C. Therefore, rifampin 300 mg (10.5 mg/kg) orally every 12 hours was initiated on hospital day 3, and piperacillin-tazobactam and doxycycline were discontinued. On hospital day 4 an infectious disease consult was obtained to assist with antibiotic management.

Further review of chest radiographs unveiled concern for septic emboli versus possible acute respiratory distress syndrome. The infectious disease physician recommended a transition from vancomycin and rifampin to ceftaroline fosamil 600 mg (21 mg/kg) IV every 12 hours on hospital day 4. Ceftaroline fosamil susceptibility was determined via the Kirby Bauer method. Repeated MRI revealed osteomyelitis of the right proximal arm, left radius, and left ulna with each location associated with an adjacent abscess. On hospital day 6 the ceftaroline fosamil dose was modified to 450 mg (15 mg/kg) IV every 8 hours to reflect pediatric studies currently in progress that use 15 mg/kg/dose every 8 hours, and the patient was taken to the operating room for incision and drainage of all 3 sites. As anticipated, surgical specimens and a sputum specimen demonstrated growth of MRSA with a vancomycin MIC of 2 mg/L. Unfortunately, a blood culture collected from the freshly placed peripherally inserted central line (PICC) on the day of placement also grew MRSA. A transthoracic echocardiogram performed on the same day showed no vegetations. The first day of negative cultures was documented on day 8 of hospital admission. The patient continued to improve and was transferred to the general pediatrics floor. His last fever was documented on hospital day 9. The ESR collected on hospital day 11 was 64 mm/hr and WBC count was 9860. The PICC line was changed on hospital day 14, and the patient was discharged home to complete 4 weeks of intravenous ceftaroline fosamil therapy.

The patient returned to the pediatric ED 11 days after discharge with complaints of 24 hours of fever to 102°F, chills, and emesis. The patient's father stated that when he finished the most recent ceftaroline fosamil infusion the patient began to shiver and shake. The ESR was again elevated to greater than 80 mm/hr; however, WBC count remained normal at 5720 with a neutrophil predominance at 82.4%. Cultures drawn from the PICC grew *Enterobacter cloacae* organisms that were ceftaroline fosamil–resistant via Kirby Bauer method (disk diffusion zone diameter ≤ 19 mm). The patient was transitioned to cefepime 1500 mg (52 mg/kg) IV every 12 hours and linezolid 300 mg (10.5 mg/kg) IV every 8 hours and discharged home after PICC line change. Peripheral blood cultures and catheter tip cultures failed to demonstrate bacterial growth. After 10 days of therapy all symptoms had resolved, and the patient was switched back to ceftaroline fosamil IV to complete the remainder of the 4-week regimen. The ESR and CRP values at the completion of therapy were 10 mm/hr and 0.4 mg/dL, respectively. No adverse effects of ceftaroline fosamil were reported while monitoring with daily complete blood count, liver function test, serum creatinine, CRP, and ESR during hospitalization and weekly after discharge until the completion of treatment. The patient was followed up in clinic for up to 6 months with no reported recurrence of the infection or side effects to therapy.

DISCUSSION

According to Infectious Disease Society of

America (IDSA) guidelines for the treatment of MRSA infections, vancomycin is recommended for the empirical treatment of hospitalized children with complicated SSTIs including deep soft tissue infections, major abscess, and osteomylitis.[6,7] Although the Clinical and Laboratory Standards Institute's vancomycin breakpoints published in 2006 list a vancomycin MIC of less than or equal to 2 mg/L as susceptible, the pharmacokinetic and pharmacodynamic analysis in addition to clinical studies suggest that MRSA strains having an MIC of 2 mg/L are more likely to fail vancomycin therapy.[8,9] For pediatric patients who are not bacteremic, clindamycin, trimethoprim/sulfamethoxazole, and doxycycline can be used empirically to treat MRSA SSTIs.[6,7] The list of antimicrobials appears short when facing widespread infection and concerns for treatment failure. In children, linezolid is the only other alternative recommended in the IDSA guidelines for SSTIs with bacteremia and sepsis, while linezolid and daptomycin can be used to treat osteomyelitis.[6,7] Daptomycin and telavancin are alternative therapy options to treat SSTIs in adults but are not approved for use in children.[7] In cases where treatment failure is a concern, a change in therapy is necessary. In both of our patients, there were concerns for vancomycin failure and both were bacteremic, so an alternative therapy was pursued. Daptomycin was used in our first case, but concerns of pulmonary involvement made it an unsuitable alternative.

There is a paucity of data detailing the use of ceftaroline fosamil in pediatric patients. One published article describing the activity of ceftaroline fosamil *in vitro* against isolates obtained from pediatric patients is available, but there are no *in vivo* data available to date.[10] We believe these are the first 2 cases reported in the literature describing ceftaroline fosamil use in pediatric patients. To date 2 studies examining the pharmacokinetics of ceftaroline fosamil in the pediatric patient population have been completed; however, the results are yet to be published. Additionally, there are currently 3 enrolling clinical trials evaluating outcomes of ceftaroline fosamil therapy for pediatric patients with complicated skin infections, CABP, and complicated CABP.[11–13]

The protocol from one of the pediatric studies currently underway was used to determine appropriate ceftaroline fosamil doses for the 2 patients discussed above.[11–13] As both of the patients were being treated for invasive, multisite CA-MRSA infections, the most aggressive of the dosing regimens was used. Cerexa, Inc, is currently sponsoring a study evaluating ceftaroline fosamil versus the combination of ceftriaxone and vancomycin for complicated CABP in pediatric patients aged 2 months to 18 years.[10] The ceftaroline fosamil dosing regimen being used in this study is 15 mg/kg (or 600 mg if the patient weighs more than 40 kg) IV every 8 hours for patients 6 months of age and older and 10 mg/kg IV every 8 hours for patients younger than 6 months of age.[10] This dosing is slightly more aggressive than the 12 mg/kg ceftaroline fosamil dosing used in the other 2 pediatric studies currently underway.[12,13]

In one report on the safety of ceftaroline fosamil in clinical studies in adults, 3% of patients discontinued treatment owing to side effects. Common reported side effects included headache (3.4%-5.2%), hypersensitivity reaction (1%-3%), and diarrhea (3%).[7] Additionally, acute renal failure was reported in <1% and liver function test abnormalities occurred in 2.5% of patients.[7] Neither of our 2 reported patients experienced any documented adverse effects from ceftaroline fosamil therapy; each patient was able to successfully complete the prescribed course of therapy.

As this is an initial report of ceftaroline use in pediatric patients, its extrapolation to other patient cases is limited by the small sample size. The antimicrobial therapy selections made were driven by culture data and provider concern for clinically worsening patients and may not distinctly follow evidence-based recommendations. Despite these limitations, this case series provides the first 2 reports of ceftaroline use in pediatric patients. Although data from clinical trials will greatly expand our current knowledge base on this topic, the above-presented cases provide initial evidence that the newest cephalosporin can be safely and effectively used to manage invasive CA-MRSA infections among pediatric patients.

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Abbreviations CABP, community-acquired bacterial pneumonia; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; CRP, C-reactive protein; ED, emergency department; ESR, erythrocyte sedimentation rate; FDA, US Food and Drug Administration; IDSA, Infectious Disease Society of America; IV, intravenously; MIC, minimum inhibitory concentration; MRI, magnetic resonance imaging; MRSA, methicillin-resistant *Staphylococcus aureus*; PICC, peripherally inserted central line; PICU, pediatric intensive care unit; POD, postoperative day; SSTI, skin and soft tissue infection; WBC, white blood cell

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