Case Report: Treatment of Chronic Osteomyelitis

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Presented is a case of chronic methicillin-resistant *Staphylococcus aureus* osteomyelitis, which was unsuccessfully treated with multiple courses of debridement and potent antibiotic therapies. Amputation of the patient’s lower limb was believed to be the only option remaining. A compassionate access program, with approval from the US Food and Drug Administration and the institutional review board, enabled the patient to undergo a course of treatment with oral fusidic acid (CEM-102). The patient tolerated the drug well, with no significant toxicities noted to date. His infection improved rapidly, his flap healed, he has returned to work part-time, and he continues to take daily suppressive doses of oral CEM-102.

Reported is a case of chronic methicillin-resistant *Staphylococcus aureus* (MRSA) femoral osteomyelitis. Despite multiple debridements and failed curative antibiotic courses, the use of suppressive fusidic acid (CEM-102) resulted in the sparing of the lower limb and resolution of acute infective symptoms. Although presently not registered in the United States, fusidic acid offers an attractive alternative for difficult-to-treat cases of MRSA infection as a well-tolerated, oral agent. It has been used widely since the 1960s and is currently available in Europe, Australia, New Zealand, and Israel, where it is available in oral and topical form. Increasing drug resistance, noted especially in staphylococcal isolates, has lead to revitalized interest in its use in countries where it is currently unavailable, such as the United States [1], as well as cautious attempts at restriction in places where it is widely used [2].

CASE REPORT

In 2008, a 49-year-old man presented with a myxoid/round cell liposarcoma (T2b, N0, and M0), emanating from the lateral head of the gastrocnemius, posterior to the left knee. He had a past medical history notable for smoking, coronary artery disease status after coronary artery stent placement, insulin-requiring diabetes mellitus, and hypertension. After 36 days of neoadjuvant external beam radiotherapy, the patient underwent a wide local excision, neuroplasty of the peritoneal and sciatic nerves, and complex exploration and repair of the popliteal artery. He required subperiosteal dissection to free the tumor capsule. He has been clinically and radiologically free of tumor for >48 months.

He was readmitted to the hospital 4 weeks after the operation with increasing pain, decreased range of movement, fever, and serosanguinous drainage from the wound. During 4 sequential operative joint washouts, he was noted to have copious deep purulence extending into the posterior compartments of the knee joint. Two of 2 blood cultures and numerous operative cultures grew MRSA. Minimum inhibitory concentration data for the MRSA isolate are presented in Table 1. His subsequent treatment consisted of intravenous vancomycin, achieving plasma drug levels approximating 20 μg/mL. This treatment was extended for 8 weeks, given the clinical concern for possible osteomyelitis in an area with impaired vascular supply after radiotherapy and popliteal artery damage. Treatment was complicated by significant tinnitus and a decline in hearing.

The patient experienced relapse with recurrent septic arthritis 2 months later; MRSA was again isolated. On this occasion, he was treated with 6 weeks of intravenous daptomycin (6 mg/kg per day), followed by oral trimethoprim-sulfamethoxazole suppressive therapy. Oral
therapy was complicated by the development of persistent fever and a diffuse allergic rash; oral antibiotics were discontinued. The patient then remained well for almost 5 months, with improving mobility and decreasing pain, although his wound was healing slowly. Of note, his Erythrocyte Sedimentation Rate had decreased from a peak of 107 mm/h to 26 mm/h. Unfortunately, the patient experienced clinically relapse once more, with MRSA again isolated from purulence found in deep radiation-affected tissues and bone. After repeated debridements, a pedicle lateral gastrocnemius muscle flap with split-thickness skin graft was applied in an attempt to improve the local vascular flow and close an increasing skin defect (see Figure 1). He was treated again with 6 weeks of intravenous daptomycin (6 mg/kg per day), followed by attempted suppression with both rifampicin and doxycycline, to allow tissues to heal; however, intractable nausea and vomiting occurred while the patient was receiving these 2 drugs, both in combination and independently. Despite the flap, a fourth relapse occurred 2 months later. After additional femoral debridement, the patient was given daptomycin (10 mg/kg/day for 10 weeks), during which time he also underwent daily hyperbaric oxygen therapy.

When a fifth clinical failure occurred, a final attempt at curative treatment was constructed with intravenous telavancin (10 mg/kg per day) and implantable vancomycin beads in the femoral shaft after debridement and sequestrectomy. Three days into the course of telavancin, the patient experienced a precipitous decline in renal function, with his serum creatinine level increasing from 1.0 to 2.3 mg/dL. The medication was discontinued, and although the patient’s renal function stabilized, no additional curative antibiotic treatments were deemed appropriate. The patient was informed amputation would be necessary. Two chronic sinuses had formed adjacent to his flap, his range of movement at the knee was restricted to 10 degrees of flexion, he had become wheelchair-bound, and he required a combination of analgesic therapies. Ultimate failure to cure was attributed to a combination of inadequate debridement and poor vascular supply (ie, irradiated, scarred tissue, with restricted popliteal artery flow, in a patient with preexisting peripheral vascular disease).

Before amputation, oral fusidic acid (CEM-102) was made available through an expanded-access program, with the approval of the hospital institutional review board. The investigational drug (CEM-102) was supplied by Cempra Pharmaceuticals. A loading dose of 1500 mg twice per day of CEM-102 was given for 24 h, followed by 900 mg twice per day thereafter. During the first week of therapy, fusidic acid was combined with oral linezolid (600 mg twice per day) to reduce the microbiologic burden. The patient tolerated the medication well, although during the first week, he developed moderate anemia requiring transfusion (nadir hemoglobin concentration, 6.8 g/dL; hematocrit, 0.22 L/L) that was believed to be secondary to chronic inflammation and linezolid.

At last clinical review, the patient has now been receiving CEM-102 for almost 9 months without clinical relapse. His anemia has steadily resolved (the most recent hemoglobin

### Table 1. Susceptibility Testing for Final *Staphylococcus aureus* Isolate

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC, µg/mL</th>
<th>Interpretive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEM-102</td>
<td>0.12</td>
<td>S</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>&lt;0.5</td>
<td>S</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>&gt;2</td>
<td>R</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt;8</td>
<td>R</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt;8</td>
<td>R</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt;8</td>
<td>R</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.25</td>
<td>S</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>&lt;1</td>
<td>S</td>
</tr>
</tbody>
</table>

**NOTE.** Isolates were tested at JMI Laboratories, and with exception of CEM-102, which was verified at my institution. Criteria were based on CLSI interpretive guidelines. MIC, minimum inhibitory concentration; R, resistant; S, susceptible.

![Figure 1. Large skin defect after multiple courses of antibiotic therapy.](cid2011-52-s539-f1.jpg)
concentration was 12.1g/dL), his mobility has improved such that he is able to mobilize with a single-point stick, and his analgesic requirement has been reduced. Both of his draining sinuses have closed, and his Erythrocyte Sedimentation Rate has once again decreased from 120 to 15 mm/hr (see Figure 2). He returned to part-time work for the first time in >2 years.

**DISCUSSION**

Chronic adult-onset staphylococcal osteomyelitis is an illness with significant morbidity, and often the only cure is through amputation. Our patient was prepared to explore multiple suppressive options, given that he had already survived limb-sparing surgery for his original liposarcoma. By the end of 2 long years, he was intolerant to vancomycin, telavancin, trimethoprim-sulfamethoxazole, linezolid, doxycycline, and rifampicin, and high-dose, prolonged daptomycin infusions had failed twice. Fusidic acid (CEM-102) provided a well-tolerated oral alternative for long-term suppression, without any significant toxicities to date.

*S. aureus* is the leading cause of osteomyelitis; not only does it adhere to bone, but it resists immune-modulated clearance and destruction through biofilm production and other microbiologic mechanisms [3]. Successful eradication therefore requires ample—and indeed, aggressive—surgical debridement to remove the bacterial load and devitalized bone. Removal of dead space, restoration of blood flow, and adequate soft-tissue coverage are also important, although as our case demonstrated, this can often be difficult to achieve. Furthermore, a prolonged course of antibiotics is usually recommended, with most clinicians favoring 4–6 weeks of treatment, depending on the organism involved, the adequacy of debridement, and the location [3, 4]. The use of long-term suppressive antibiotic therapy is more controversial, although such treatments are often used when a cure cannot be attained.

For MRSA in particular, antibiotic options are limited. Intravenous vancomycin remains the most common first-line agent, although clinicians might expect more failures of osteomyelitis treatment, as have been seen in bacteremia, as minimum inhibitory concentrations increase to >2 [5]. Both hearing loss and renal impairment can result from longer courses of therapy, although both are uncommon [6]. Other agents have been used, although comparative trials are generally lacking [7], and attempted meta-analyses of studies have been hampered by the frequent use of concomitant antibiotics, small sample sizes, limited patient demographic characteristics, and disease characteristics [8]. Daptomycin is an intravenous agent available for the treatment of osteomyelitis, and both quinupristin-dalfopristin and tigecycline are additional options, although toxicity significantly limits the use of these agents [9–11]. Outside of North America, teicoplanin is an available alternative. Linezolid can be used for *Staphylococcus* isolates, although neurotoxicity and bone marrow suppression become more common as the duration of treatment increases, making it an unsuitable long-term option for osteomyelitis. Oral doxycycline, rifampicin, clindamycin, and trimethoprim-sulfamethoxazole all have variable in vitro activity against MRSA isolates and, therefore, lack the activity to be used as monotherapy in the curative intent treatment of osteomyelitis. Fusidic acid, in comparison, has a favorable adverse effect profile and excellent oral bioavailability, as described elsewhere in this supplement. In countries where it is available, clinicians should consider its use for suppression in cases of difficult-to-treat osteomyelitis.

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References