Successful Outpatient Treatment of Severe Diabetic-Foot Myositis and Osteomyelitis Caused by Extensively Drug-Resistant Enterococcus faecalis with Teicoplanin plus Rifampicin: A Case Report

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Patient: Male, 76-year-old
Final Diagnosis: Extensively drug-resistant Enterococcus faecalis diabetic-foot myositis and osteomyelitis
Symptoms: Fever, pain to his left lower foot and altered level of consciousness
Clinical Procedure: Surgical debridement combined with the administration of teicoplanin plus rifampicin in the outpatient setting, completing in-total a twelve-week course of antibiotic therapy
Specialty: Endocrinology and Metabolic • Infectious Diseases • General and Internal Medicine

Objective: Rare disease
Background: Foot ulcers are high-morbidity and debilitating complications of diabetes mellitus, and carry significantly increased rates of associated major amputations. They contribute to significantly worse quality of life. Osteomyelitis is a frequent complication of diabetic foot ulcers, since bacteria can contiguously spread from soft tissues to the bone, involving the cortex first and then the bone marrow. Unfortunately, clinically unsuspected osteomyelitis is frequent in persisting diabetic foot ulcers. It is associated with limb amputations and increased mortality.
Case Report: We describe a 76-year-old man with long-standing insulin-treated type 2 diabetes, who experienced extensively drug-resistant Enterococcus faecalis diabetic foot myositis and osteomyelitis associated with sepsis. He was successfully treated with surgical debridement combined with the administration of teicoplanin plus rifampicin in the outpatient setting, completing, in total, a twelve-week course of antibiotic therapy.
Conclusions: Clinically unsuspected osteomyelitis in patients with persisting diabetic foot ulcers has been associated with infections from highly resistant bacteria. Early and accurate diagnosis of diabetic foot osteomyelitis, as well as proper therapeutic approach (antimicrobial and surgical), is of great importance to reduce the risk of minor and major amputations, septic shock leading to multiple organ failure, and overall mortality.

Keywords: Case Reports • Diabetic Foot • Enterococcus faecalis • Osteomyelitis • Teicoplanin

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Background

Diabetic foot ulcer (DFU) is defined as a localised skin injury and/or an injury to the underlying tissue, below the ankle, in patients with diabetes mellitus [1]. Unfortunately, most longitudinal epidemiological studies suggest that a considerable number of diabetic patients will experience DFUs during their lives [2]. The International Diabetes Federation emphasizes that approximately 9.1-26.1 million patients with diabetes mellitus will develop DFUs every year, while the lifetime risk of patients with both type 1 and type 2 diabetes (T2D) is as high as 34% [2,3]. Several risk factors have been closely associated with the evolution of DFUs and other foot lesions (lower extremity infections, necrotizing fasciitis, and gangrene) such as: (i) trauma; (ii) inadequate glycaemic control; (iii) peripheral arterial disease (PAD) of the lower extremities; (iv) peripheral neuropathy and subsequent loss of protective sensation; (v) inadequate foot care; (vi) foot deformities such as Charcot neuroosteoarthropathy; and (vii) diabetes-associated suppressed immune function [4].

Diabetic foot osteomyelitis (DFO) is a high-morbidity and debilitating complication that carries significantly increased rates of associated major amputations and mortality; it contributes to significantly worse quality of life to the affected population [2-4]. It is a frequent complication of DFUs, since bacteria can contiguously spread from the soft tissues to the bone, involving the cortex first and then the bone marrow [2,5]. The forefoot is more frequently affected (90%), followed by the midfoot (5%), and finally the hindfoot (5%), while the amputation risk above the ankle is significantly higher for hindfoot infections (50%) rather than midfoot (18.5%) or forefoot (0.33%) infections [1,2,5,6]. We report a case of a 76-year-old man with long-standing insulin-treated T2D, who experienced severe, extensively drug-resistant (XDR) Enterococcus faecalis diabetic foot myositis and osteomyelitis associated with sepsis. He was successfully treated with surgical debridement, combined with the administration of teicoplanin plus rifampicin in the outpatient setting, completing, in total, a twelve-week course of antibiotic therapy.

Case Report

A 76-year-old man presented to our clinic with fever, pain in his left lower foot, and altered consciousness. His past medical history was significant for: (i) long-standing T2D diagnosed 20 years previously and treated with metformin 1000 mg daily, empagliflozin 10 mg daily, and basal-bolus insulin therapy (insulin glargine 45 units administered subcutaneously daily and insulin glulisine administered subcutaneously before his main meals, the dose of which was adjusted according to the carbohydrate content of his meals, his premeal glucose levels, and his daily physical activity); (ii) coronary artery disease, with coronary artery bypass grafting for symptomatic 3-vessel disease 11 years previously; (iii) PAD of the lower limbs diagnosed by color and pulsed-wave Doppler ultrasound (Fontaine classification: stage I); (iv) diabetic neuropathy of the lower limbs (abnormal 10 g monofilament and biothesiometer); (v) lumbar spine surgery 2 years previously; and (vi) obesity. His body mass index was 32 kg/m².

His wife reported a 15-month history of a DFU in his left lower foot that caused swelling and tenderness. During this time, he received several courses of conservative sharp wound debridement together with the administration of several courses of antibiotics (including levofloxacin, clindamycin, doxycycline, and metronidazole), experiencing intervals of remissions and recurrences. Three months before his presentation, ampicillin-sensitive E. faecalis was isolated from a swab culture that was taken during debridement of his DFU. He was then treated with oral amoxicillin/clavulanic acid (1 g every 12 hours) and ciprofloxacin 500 mg every 12 hours for 4 weeks. He did not report any recent trauma.

His physical examination showed that he experienced all 3 quick sepsis-related organ failure assessment (SOFA) criteria for sepsis: (i) altered mentation (Glasgow Coma Scale score: 10); (ii) respiration rate of 28 breaths/minute; and (iii) systolic
blood pressure of 90 mmHg [7]. His full SOFA score was 4. His body temperature was 39°C and his heart rate was 120 beats/minute. Except for swelling, erythema, local warmth, and tenderness of his left lower foot, due to the presence of a DFU in the area of the fifth metatarsal bone, the rest of the clinical examination was unremarkable (Figure 1). Results of his laboratory investigations showed mild anemia (hemoglobin: 12.2 g/dL) and white blood cell count of 11,550/mm$^3$ (neutrophils: 84%). The erythrocyte sedimentation rate was 95 mm/h, and the C-reactive protein level was 14.3 mg/dL. His glycated hemoglobin (A1C) was 8.6%. All other laboratory values were within normal limits except for renal function markers: serum urea and creatinine levels were 85 mg/dL and 1.6 mg/dL, respectively. Urine analysis disclosed mild microscopic hematuria. The urine culture was negative. Laboratory tests for hepatitis B surface antigen (HBsAg) and sexually transmitted infections were negative. The purified protein derivative skin test was also negative.

His electrocardiogram revealed sinus tachycardia. Chest radiography did not disclose any abnormal findings, while abdominal ultrasound revealed hyperechogenic liver suggesting nonalcoholic fatty liver disease. The transthoracic echocardiogram disclosed global mild reduction of the ejection fraction (EF: 45%). Magnetic resonance imaging (MRI) of the left lower foot was performed (Figure 2). Contrast-enhanced T1-weighted fat saturation MRI in the coronal and axial planes of the foot showed marked contrast enhancement of the distal fifth metatarsal bone and proximal phalanx, with signs of early destruction of the articular surfaces of the metatarso-phalangeal joint space (white arrow). There was also prominent contrast enhancement of the plantar and dorsal muscles of the foot extending from the fifth to the second toe suggestive of extensive myositis. (B) Contrast-enhanced T1-weighted fat saturation MRI in the axial plane of the foot. The axial image showed a sinus tract extending to a subcutaneous abscess adjacent to the base of the fifth metatarsal bone, with an overlying skin ulcer (Figure 2B).

The patient was hemodynamically stabilized. Meropenem 1 g intravenously every 8 h and daptomycin 10 mg/kg/day were started. Two sets of blood cultures, for bacteria (aerobic and anaerobic) and fungi were obtained immediately after admission of the patient and surgical removal of all devitalized and necrotic soft tissues. Cultures were obtained from deep tissues that were removed from the area closest to the bone, as well as from a small bone specimen. The $E$. faecalis that was isolated from all investigated specimens was resistant to ampicillin, amoxicillin/clavulanic acid, nitrofurantoin, doxycycline, fluoroquinolones, aminoglycosides, streptomycin, piperacillin/tazobactam, carbapenems, linezolid, tigecycline, and, as expected, to quinupristin-dalfopristin. Sensitivity was found to glycopeptides (teicoplanin and vancomycin), daptomycin, and rifampicin. Blood cultures did not indicate the presence of any pathogen. Meropenem was stopped and oral rifampicin was initiated (600 mg daily) together with daptomycin.
Metformin and empagliflozin were stopped during his hospitalization. He was treated only with insulin therapy, which was adjusted as needed.

The patient improved and became afebrile 96 hours after his admission. He gradually regained his normal state of consciousness and mobility. All renal function markers eventually became normal (serum urea and creatinine levels were 35 mg/dL and 0.9 mg/dL, respectively, 2 days before he left the hospital). He was then discharged and treated in the outpatient setting with intravenous teicoplanin in a daily dose of 10 mg/kg plus oral rifampicin. He was advised to restart metformin and empagliflozin and intensify his insulin treatment. He experienced regular cautious sharp debridement to remove slough and non-viable necrotic tissues. He was advised to use offloading footwear, to reduce his weight-bearing activity and increase non-weight-bearing activity (mainly moderate intensity stationary cycling). After 6 weeks of treatment, CRP and procalcitonin levels declined to normal levels. His renal status remained within normal limits and urine analysis was also normal. Erythrocyte sedimentation rate, a marker that has been associated with remission or cure of DFO, was normalized after 8 weeks of therapy [8]. The progress of wound healing of his DFU is shown in Figure 3. He eventually completed, in total, a 12-week course of antibiotic therapy. A1C at the end of his antimicrobial therapy dropped to 7.4%. No recurrence was found 2 years after the end of his antimicrobial therapy. Lack of cooperation from the patient was the only reason for not repeating MRI of his left foot.

**Discussion**

DFO is a serious complication of DFUs. Unfortunately, clinically unsuspected DFO is frequent in persisting DFUs. As was the case with our patient, DFO has been associated with suboptimal and inappropriate antibiotic administration, as well as with infections from highly resistant pathogens and life-threatening complications. In contrast to our patient, most of the infections in other cases of DFO are polymicrobial [2,6,9]. The most common pathogens isolated are: *Staphylococcus aureus* (approximately 50% of DFO cases), *Streptococci* species, and *Enterobacteriaceae* (*Escherichia coli*, *Proteus* spp. and *Klebsiella pneumoniae* were the most commonly isolated bacteria, followed by *Pseudomonas aeruginosa*) [2,6,10,11]. Anaerobes are infrequently isolated as likely pathogens; they are more often found in infections with ischemic or necrotic tissues [6,12]. The most common multidrug-resistant organisms isolated in DFUs are non-fermenting gram-negative rods, methicillin-resistant coagulase-negative staphylococci, and methicillin-resistant *S. aureus* (MRSAs) [13,14]. DFO has also been associated with hematogenous spread of several virulent pathogens and the evolution of serious and potentially lethal complications [6,11,15].

*Enterococcus* spp. are isolated in approximately 5-45% of patients with diabetic foot infections [6,11,16,17]. Their natural ability to translocate from the gastrointestinal system to several tissues and organs, as well as their virulence and antibiotic resistance (they exert remarkable ability to achieve new resistance mechanisms), makes their eradication challenging [16,18,19]. *E. faecalis* is one of the most common bacteria cultured from all types of wounds and the third most common pathogen isolated from surgical site infections [18,19]. A retrospective study, which explored the distribution of pathogenic bacteria and drug susceptibility in 101 patients with DFUs complicated by necrotizing fasciitis, reported that *E. faecalis* was isolated from 18.5% of the total population enrolled and from 30% of all gram-positive bacteria [20]. All isolated strains were susceptible to nitrofurantoin, linezolid, daptomycin, teicoplanin, tigecycline, vancomycin and daptomycin. Almost all strains were sensitive to ampicillin (94.4%), while quinolone sensitivity reached 90%.

Magiorakos et al defined XDR *Enterococcus* spp. as the isolates that are non-susceptible to at least one agent in all but 2 or fewer of the following antimicrobial categories: (i) aminoglycosides; (ii) streptogramin; (iii) carbapenems; (iv) fluoroquinolones; (v) glycopeptides; (vi) glycylcyclines (tigecycline); (vii) lipopeptides (daptomycin); (viii) oxazolidinones (linezolid); (ix) penicillins; and (x) tetracyclines [21]. Severe multidrug-resistant (MDR) or XDR *E. faecalis* diabetic foot myositis and osteomyelitis, associated with sepsis, has been rarely reported in the current literature [22]. Although the strain we isolated was sensitive to daptomycin, we administered teicoplanin in the outpatient setting mainly because of the high cost of daptomycin, given the fact that outpatient parenteral antibiotic therapy (OPAT) is not covered by the national health system of our country. Indeed, the cost of daptomycin therapy (10 mg/kg) for our patient was 190 euros daily, while the corresponding cost for teicoplanin (10 mg/kg) was 25 euros daily. The total cost of teicoplanin administration was 12,210 euros less than that of daptomycin, for our patient.

Several reasons could explain the high resistance of the *E. faecalis* strain we isolated to several antimicrobial categories that target *Enterococcus* spp. (i) Our patient experienced several hospitalizations during the years preceding the present visit. Since enterococci have the ability to colonize the gastrointestinal tract of hospitalized patients for remarkable periods of time, they can serve as a reservoir for cycles of transmission and the spread of antibiotic resistance. (ii) In the past, our patient received long-term, inappropriate antibiotic therapy in different combinations. (iii) PAD can reduce the penetration of antimicrobials in DFUs, making it difficult to reach the target site and achieve effective levels. (iv) Finally, DFO was not diagnosed before his admission; thus, the total duration of his antimicrobial therapy was suboptimal [23,24]. Interestingly, DFO has been diagnosed in approximately 44-68% of patients with
Figure 3. Progression of wound healing of the DFU: (A) 4 weeks; (B) 6 weeks; (C) 8 weeks; (D) 10 weeks after the beginning of antimicrobial therapy. DFU – diabetic foot ulcer.
chronic DFUs [3,6,11,25]. An interesting study that included 20 diabetic patients with chronic DFUs (present for more than 8 weeks) suggested that clinically unsuspected osteomyelitis was frequent in persisting DFUs and was a high-risk factor for limb amputations. MRI was the best diagnostic image modality to diagnose this condition [26].

OPAT has several advantages, including earlier discharge from the hospital, reduced length of hospital stay, lower cost, and overall improved patient satisfaction [27]. Teicoplanin, ceftriaxone, and ertapenem are common antibacterial agents used in this setting [28,29]. Teicoplanin was found to be an attractive antimicrobial that can be administered in the OPAT setting, in view of its favorable dosing regimen, low clinical failure rates, and acceptable safety profile [30]. Furthermore, rifampicin is a potent bactericidal drug that is effective against several gram-positive bacteria, and also displays good bone penetration [31]. It is well absorbed when taken orally and has high activity against biofilm-associated organisms. In cases of rapid development of resistance, this old agent is an important candidate for combination therapies [31]. Rifampicin-based combinations with several antimicrobials (including teicoplanin) have highlighted in vitro synergistic effects and provided evidence that this medication is useful against infections with resistant gram-positive strains [11,31,32]. However, combination strategies that include rifampicin are not in routine use for enterococcal infections [32]. An interesting study, which explored data from 6174 patients treated with antibiotics for DFO, without surgery, reported that rifampicin-treated patients experience significantly lower rates of amputation and overall mortality within 2 years of diagnosis versus those not treated with rifampicin; it was suggested that adjunctive rifampicin administration could be a useful antimicrobial strategy in this setting [33]. The Veterans’ Administration INTREPID study (a multicenter randomized placebo-controlled trial of rifampin to reduce pedal amputations for osteomyelitis in veterans with diabetes) has been launched and will explore whether a rifampin-adjunctive antibiotic regimen (600 mg daily) will increase amputation-free survival in patients with DFO [34].

Cultures taken from soft tissues and pus have predominantly polymicrobial flora, while bone cultures are mainly monomicrobial [2,4,11]. A study in 60 consecutive patients with infected DFUs showed that bacteria isolated from soft tissues were different from those in pus and bone in 54% and 57%, respectively, of the population enrolled [35]. However, in our patient, both cultures taken from the deep tissues closest to the bone and from a small specimen of the infected bone suggested *E. faecalis*. Indeed, a well-organized study found that causative pathogen strains, which are isolated in cultures from deep tissues (closest to the bone), were identical with bone cultures in a considerable proportion of patients with DFO (16 of 25 cases, 64%, *P*<0.001) [36]. Although current evidence suggests that 6-week duration of antibiotic treatment may be sufficient for patients with DFO, in whom surgical resection of the infected bone is not planned, prolonged antibiotic therapy could be considered in patients with severe complicated infections or those caused by highly resistant pathogens, as experienced by our patient [6,11,37,38].

Conclusions

Clinically unsuspected DFO is frequent in persisting DFUs. It has been associated with suboptimal and inappropriate antibiotic administration, as well as infections from highly resistant pathogens and life-threatening complications. Early and accurate diagnosis, as well as proper therapeutic approach (antimicrobial and surgical), is of great importance to reduce the risk of minor and major amputations, septic shock leading to multiple organ failure, and overall mortality.

Departments and Institutions Where Work Was Done

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