

Research Paper

Daptomycin Plus Fosfomycin as Salvage Therapy in a Difficult-to-Treat Total Femoral Replacement Infection

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Received: 2018.06.11; Accepted: 2018.07.12; Published: 2018.10.04

Abstract

The highly active anti-biofilm combination of daptomycin plus fosfomycin was successfully used in a difficult-to-treat infection of a total femoral replacement caused by multi-drug resistant *Staphylococcus epidermidis* in a 79-year-old woman. There was no need to remove the orthopedic hardware, and the patient is currently pain free and able to walk.

Key words: prosthetic joint infection, biofilm, Staphylococcus, bone and joint infection

Introduction

Indications for total femoral replacement (TFR) usually regard oncological surgery and sometimes revision arthroplasty in cases of massive bone loss. Infection of TFR is not infrequent and a challenging complication, with remarkable technical problems for removing and replacing such a complex device [1]. The use of highly active anti-biofilm antimicrobial regimes is of paramount importance in this setting, especially when facing multi-drug resistant (MDR) microorganisms. We present the case of an elderly woman with a TFR infection caused by MDR coagulase-negative staphylococci which was successfully treated by debridement, implant retention, and treatment with the novel combination of daptomycin plus fosfomycin.

Case Report

A 79-year-old woman with an unremarkable medical history other than hypertension and a

total-hip prosthesis underwent revision surgery, and a TFR was implanted (Megasystem-C, cemented polar-cup dome) due to lack of bone stock. She presented with early post-surgical polymicrobial infection of the TFR (*Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Morganella morganii*). In spite of surgical management with debridement, antibiotics and implant retention, the enterococcal infection relapsed.

Four years later a two-step exchange procedure was decided. The TFR was removed, and the patient received IV ampicillin plus ceftriaxone for 21 days, followed by oral amoxicillin for 22 more days. Second-stage surgery was performed three months later, and a silver-coated TFR was implanted (Figure 1). *E. faecalis* was again isolated in intraoperative cultures (one culture out of six), besides *Staphylococcus epidermidis* (six out of six cultures).



Figure 1. X-ray of the patient's total femoral prosthesis.

Vancomycin was prescribed since surgery. However, the patient suffered prosthesis dislocation some days after, so she underwent a single-step surgical exchange of the acetabular component. Again, *S. epidermidis* with the same antimicrobial susceptibility profile was isolated in intraoperative cultures.

During the following weeks, the patient underwent several antimicrobial regimes (Table 1) and two plastic surgeries due to poor evolution of the skin and soft tissues surrounding the orthopedic hardware. *S. epidermidis* was recovered from intraoperative cultures of both surgeries; it showed resistance to all previous oral antibiotics received (Table 1). At this point, limb amputation was considered, but the patient refused.

Four months after the placement of the new TFR, a final surgical attempt including debridement followed by a complex plastic surgery was done. This consisted of a muscle-cutaneous *Latissimus Dorsi* flap, anastomosed to a neo-vessel done with an arteriovenous loop from saphenous vein. Intraoperative cultures confirmed *S. epidermidis* persistence. The patient was then treated with daptomycin (700 mg qd \approx 10 mg/kg qd) plus intravenous fosfomycin (2g qid) for 42 days. The wounds healed successfully, and a progressive decrease of inflammatory signs and acute-phase reactants were observed. The tolerance to the antibiotic treatment was good, with no development of edemas, electrolytic disturbances or increase of the CPK value. After intravenous antibiotic treatment, the patient continued with chronic suppressive oral amoxicillin (1g bid), targeting the previous isolated enterococci.

Since then, the patient has been closely followed in the outpatient clinic (Figure 2). Two years after her last prosthetic surgery she is able to walk with 2 crutches, hip range of motion is 85° flexion, 0° extension, 30° internal rotation, 40° external rotation, 40° abduction and 20° adduction; the knee prosthesis range motion is 80° flexion and 0° extension. She has improved her Enneking functional score by sixteen points compared to her previous TFR. She has shown no clinical signs of infection relapse, and the C-reactive protein value is 1.18 mg/dL.

Discussion

This is, to the best of our knowledge, the first report on the successful use of the combination of daptomycin plus fosfomycin for staphylococcal prosthetic joint infection managed with implant retention. Our patient has proved to be infection-free for the last two years, in spite of the staphylococcal multi-drug resistance, the complexity of the orthopedic device and the need of a technically challenging plastic surgery.

Table 1. Antimicrobial susceptibility profile over time of *Staphylococcus epidermidis*

Surgical procedure	*	Reimplantation 27 th Jan (day 0)	*	Luxation - Acetabular exchange (day 8)	*	Gastrocnemius flap (day 48)	*	Muscular flap removal (day 106)	*	New muscular flap (day 119)	
Penicillin	Ampicillin, Ceftriaxone, Amoxicillin	R	Vancomycin	R	Rifampin, Fusidic acid, Amoxicillin	R	Linezolid, Amoxicillin	R	Vancomycin	R	Daptomycin plus fosfomycin
Oxacillin		R		R		R		R		R	
Erythromycin		R		R		R		R		R	
Clindamycin		R		R		R		R		R	
Levofloxacin		R		R		R		R		R	
Co-trimoxazole		R		R		R		R		R	
Vancomycin		S		S		S		S		S	
Daptomycin†		S		S		S		S		S	
Linezolid		S		S		S		S		R	
Rifampin		S		S		S		-		R	
Fusidic acid	S	-	-	-	R						
Fosfomycin‡	S	S	S	S	S						

Text in vertical columns (*) refers to antimicrobial treatment received between surgical procedures. Squared boxes (italic font) point out the acquisition of resistance. R: resistant; S: susceptible. The antimicrobial susceptibility testing was performed by MicroScan WalkAway® system (Siemens Healthcare Diagnostics, Deerfield, IL, USA), and isolates were categorized according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints. The hyphen (-) denotes that the antimicrobial susceptibility was not tested. †Daptomycin MIC was 0.5 mg/L. ‡Fosfomycin MIC was ≤32 mg.



Figure 2. Patient's limb during the follow-up.

Current treatment recommendations of PJI caused by coagulase-negative staphylococci are extrapolated from clinical and experimental studies on *Staphylococcus aureus*. In this setting, it is accepted that rifampin-based combinations are the treatment of choice [2]. The second drug preferred is usually a fluoroquinolone, but it may also be fusidic acid, linezolid, cotrimoxazole, clindamycin, or others [3].

Resistance or intolerance to rifampin may preclude its use. The maintenance of a high inoculum, the wound dehiscence, and the low antibiotic concentration that may reach the femoral mega prosthesis may account for the development of resistance observed in our case [4]. Clinical experience of staphylococcal PJI managed with implant retention without rifampin is scarce and usually retrospective. Most of our knowledge

comes from experimental animal models. In this setting, daptomycin-based combinations have shown promising results. Daptomycin is a cationic peptide with good diffusion in the biofilm and good activity against biofilm-embedded bacteria. Its concentration-dependant bactericidal activity and the risk of resistance emergence from hetero-resistant subpopulation have led current recommendations to advocate for its administration at high doses, in combination with a second antibiotic [5]. The second drug, which also enhances daptomycin's antibiofilm activity, may be rifampin, cloxacillin or fosfomycin, among others [6]. Fosfomycin has a good anti-staphylococcal activity and very good tissue diffusion, but it needs to be administered in combination with a second drug in order to avoid the development of resistance [6].

In the experimental animal model, the efficacy daptomycin plus fosfomycin has been shown to be comparable to rifampin-based combinations [6]. However, more clinical studies are needed in order to assess its clinical efficiency. Potential rhabdomyolysis must be monitored throughout treatment [5]. Also, the use of fosfomycin carries a significant load of sodium, which may lead to the development of edemas or hydropic descompensation in patients with cirrhosis or heart failure. It may also produce severe hypokalemia, which must be strictly monitored. In the case presented, the antimicrobial combination could be safely administered for 6 weeks without significant adverse events, it being the only antimicrobial treatment capable of eradicating the infection.

Infection is indeed a dreaded complication after prosthetic joint replacement. While its frequency is 1-2% in primary prosthesis, it may be as high as 35% for tumoral prostheses and TFR [1, 2]. When considering this complication, this case emphasizes the need for an individualized approach of each patient with PJI, planned by a multidisciplinary medical team of specialists who are able to deal with the complex interplay of surgical and microbiological aspects, and also the patient's choice and expectations.

This case is also illustrative of several controversial aspects of PJI. First, it highlights the bad prognosis of enterococcal PJI [7]. Addition of rifampin [7] or ceftriaxone [8] to treatment with ampicillin has been suggested to ameliorate the prognosis, but still enterococci remain as a difficult-to-treat pathogen. Actually, *E. faecalis* was still recovered from samples at the time of prosthesis second stage surgery. Although it was never isolated afterwards, suppressive therapy with amoxicillin was prescribed, without side effects.

S. epidermidis was also isolated during the second stage of surgery. The rationale for exchanging infected prosthesis in a 2-step procedure is to place the new device in a sterile surgical site. However, this may not be accomplished in 6-20% of cases [9], and this may happen more often when the spectrum of the antimicrobial regime prescribed does not include all staphylococci, as in our case [10].

The use of TFR is rare in settings other than oncologic surgery. Lack of bone stock in selected patients submitted to several revisions over a period of years may be one of these indications. This scenario may be more frequent in the future, due to the aging of the population. Silver-coated implants are believed to reduce the rate of infection [11], which our patient developed anyway.

Surgery is an essential step in prosthetic joint infection (PJI) treatment [2]. It is very important that the final condition of the skin and soft tissues have good results. Some patients may need to undergo complex plastic surgical procedures in order to achieve enough coverage for orthopedic implants. The success of these procedures depends on the surgeon's experience, the type and complexity of the flap, and also on the patient. Elderly patients with cardiovascular risk factors are at increased risk of flap failure due to local vascularization problems [12].

Bearing these thoughts in mind, and even before considering the occurrence of infection, this case represents an orthopedic and plastic surgical challenge. The micro-surgical transfer of flaps is nowadays a highly standardized technique in the reconstructive area of the lower limb. The problem arises when there are no viable vessels in the limb or they are injured by previous conditions. In this setting, arteriovenous loops are technically complex but effective resources [12]. In the case of our 79-year old patient this was particularly challenging, since the creation of these arteriovenous shunts significantly lengthens the time of surgery, and it may imply a significant overload on the cardiac system.

In summary, we have presented a difficult-to-treat case of TFR with an early post-surgical infection by a multi-drug resistant *S. epidermidis*, managed with implant retention and plastic surgery, and successfully treated with the combination of daptomycin plus fosfomycin. This antimicrobial therapy must be considered in selected scenarios, especially when no rifampin is available.

Acknowledgment

We are thankful to the patient depicted in this Report (identity classified due to ethical issues). We are also indebted to Talithia Richards for reviewing the English manuscript. This study has been supported by a grant from the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC).

Competing Interests

The authors have declared that no competing interest exists.

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