

CASE REPORT

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# Methicillin-resistant *Staphylococcus epidermidis* knee prosthetic infection treatment with two-stage revision and fosfomycin–rifampin combination therapy: a case report

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## Abstract

**Background** *Staphylococcus epidermidis* is one of the pathogens most commonly involved in prosthetic joint infections, and when methicillin resistant, poses significant challenges in treatment, owing to its virulence and antibiotic resistance. Intravenous fosfomycin disodium is a broad-spectrum antibiotic recently introduced in clinical practice for treating osteoarticular infections caused by Gram-negative and Gram-positive bacteria, including multidrug-resistant pathogens. Continuous infusion administration of fosfomycin, by an elastomeric pump, is feasible thanks to its good stability at room temperature after reconstitution in aqueous solution. This report describes the case of a methicillin-resistant *Staphylococcus epidermidis* knee prosthetic infection successfully treated with a two-stage revision coupled with a combination therapy of oral rifampin plus continuous infusion of fosfomycin administered by an elastomeric pump, filled daily through an outpatient parenteral antimicrobial treatment service.

**Case presentation** A 31-year-old Italian woman presented right knee pain and functional limitation. A previous diagnosis of pigmentous villonodular synovitis led to destructive arthropathy requiring total knee arthroplasty and extensive synovectomy. Three months later, a methicillin-resistant *Staphylococcus epidermidis* prosthetic infection was diagnosed and a two-stage procedure was adopted with spacer cement positioning for 4 months, followed by removal and definitive total knee arthroplasty. The methicillin-resistant *Staphylococcus epidermidis* infection was successfully treated with a combination therapy of oral rifampin plus continuous infusion fosfomycin by an elastomeric pump. At 1-year postoperative follow-up, no complication was detected and the patient was satisfied.

**Conclusion** This case underscores the effectiveness of combining a two-stage revision procedure with continuous infusion fosfomycin and rifampin for managing complex methicillin-resistant *Staphylococcus epidermidis* prosthetic infection.

**Keywords** Elastomeric pump, Fosfomycin, Villonodular pigmentous synovitis, Hinged, Total knee arthroplasty, Infection

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## Background

*Staphylococcus epidermidis* (SE) is one of the pathogens most commonly involved in prosthetic joint infections (PJIs), and when methicillin resistant (MRSE), is even more virulent and difficult to eradicate [1–3].

Intravenous fosfomycin disodium is a broad-spectrum antibiotic recently introduced in clinical practice for treating osteoarticular infections (OIs) caused by Gram-negative and Gram-positive bacteria, including multidrug-resistant (MDR) pathogens [4].

Continuous infusion (CI) administration of fosfomycin by an elastomeric pump is feasible due to its stability at room temperature when reconstituted in aqueous solution [5].

This report describes the case of an MRSE knee prosthetic infection successfully treated with a two-stage revision coupled with a combination therapy of oral rifampin plus CI fosfomycin administered by elastomeric pump, filled daily through an outpatient parenteral antimicrobial treatment (OPAT) service.

## Case presentation

A 31-year-old Italian woman, polyallergic (to latex, parabens, mites, and *Gramineae*, including nickel), suffering from dysmetabolic myopathy, celiac disease, and recurring tonsillitis, was examined at the orthopedic outpatient clinic in late October 2020 because of a persistent gonalgia and functional limitation in the right knee. Her medical history reported a progressive villonodular pigmented synovitis of the right knee (Fig. 1) unsuccessfully treated with immunosuppressive drugs, which led to a destructive degenerative arthropathy needing surgical approach in mid-November 2020 (Fig. 2a, c). This involved the implantation of a cement-retained hypoallergenic hinge-bound total knee arthroplasty (Endomodel Link type) and concomitantly executing an extensive synovectomy, including the inner part of the joint capsule and the collateral ligaments of the knee (Fig. 2b, d).

In late February 2021, she presented to the emergency department with pain, swelling, and limited range of motion (ROM 0–80°) in the operated knee. An arthrocentesis procedure collected 150 cc of serum-ematic joint fluid, which was sent to the laboratory for physicochemical examination and microbiological culture. Joint fluid culture yielded a methicillin-resistant *Staphylococcus epidermidis* (MRSE), so that in early March 2021, she was hospitalized for further investigation. Following collegial evaluation with infectivologists, knee prosthesis removal was planned. Intraoperatively, widespread intracapsular soft tissue inflammation and profuse cloudy joint fluid discharge were found, and multiple bone and soft tissue bioptic samples of the joint chamber were taken. These latter were sent to the laboratory for histologic culture

examination, and for sonication of the explanted prosthetic components. Thorough surgical cleaning coupled with implantation of Palacos-type (Heraeus) articulating antibiotic spacer cement were performed (Fig. 2e, g).

Cultures, including sonication of the explanted prosthetic components, identified an MRSE strain resistant to fluoroquinolones, tetracycline, and teicoplanin. Histologic examination showed chronic inflammation.

In the meantime, the patient reported a medical history of several infectious episodes, including a thoracic *Staphylococcus* sp. infection involving the right breast and recurrent episodes of genital infections not mentioned in the medical history.

After first stage surgery, empirical broad-spectrum antibiotic therapy with CI fosfomycin and oral rifampin was started. During therapy, ALT levels increased to more than eight times the upper normal limit. One week after, as soon as the culture results became available, targeted oral therapy was switched to rifampin and cotrimoxazole, serum transaminases normalized, and the patient was discharged. As per orthopedic indications at discharge, she was allowed to deambulate with graded load (with the aid of antibrachials) wearing a knee brace locked in extension. She was advised to perform passive mobilization exercises of the operated limb with Kinetec, 3 times daily for 30 min starting from 0 to 40° of flexion, and increasing by 5° a day until reaching a maximum of 75°.

Three weeks after discharge, she developed severe neutropenia ( $0.7 \times 10^9/L$ ) and rash, and so therapy was stopped.

After 2 weeks of washout, neutrophils normalized and antibiotic therapy was restarted and continued for 3 weeks with oral rifampin and CI fosfomycin by elastomeric pump in an OPAT programme. C-reactive protein (CRP) levels remained below the limit of the blood test detection during the follow-up. A labeled leukocyte scintigraphy performed around 1 month after antibiotic discontinuation showed nonspecific uptake on the right knee without specific signs of infection.

She came back for orthopedic follow-up 2 weeks after surgery. Both clinical and laboratory findings improved with a drop in CRP values (to 1.5), and physiotherapy with Kinetec 0–30° of flexion–extension was recommended for an additional week. Three months after surgery, she was revisited in the outpatient clinic: inflammatory biomarkers were negative and scintigraphy showed no uptake signs at the right knee. Therefore, an indication was made for reimplantation of cement-retained hypoallergenic hinge-bound total knee arthroplasty.

In late July 2021, the patient was readmitted to hospital for knee prosthesis reimplantation. After spacer cement removal, tissue sampling for histologic



**Fig. 1** Preoperative magnetic resonance imaging showing a severe synovitis, resulting in degenerative–destructive arthropathy of the knee. T1 sequence in sagittal view showing villonodular synovitis at the posterior knee capsule (**a**). Short tau inversion recovery sequence in coronal projection showing edema and osteonecrosis of the two tibial hemiplates and the lateral femoral condyle (**b**). Axial T1 sequence showing signs of severe joint degeneration in the context of widespread villonodular synovitis (**c, d**)

examination, extemporaneous neutrophil count (negative for in progress acute inflammation), and sampling of soft tissue from the joint chamber and bone tissue were collected, and subsequently sent to the laboratory for culture examination and sonication. The patient was re-implanted with a cemented hypoallergenic rotating

hinge constrained monoblock total knee arthroplasty (Endomodel Link type) with 25 mm distal medial and lateral femoral augment to restore the joint line level, as supported by several scientific studies (Fig. 2f, h).

After second-stage surgery, the patient was empirically treated again with CI fosfomycin and rifampin.



**Fig. 2** Preoperative anteroposterior X-ray shows villonodular pigmented synovitis that led to the development of a destructive degenerative arthropathy for which surgery was indicated (**a**). Anteroposterior X-ray on day 1 after cemented hypoallergenic constrained with rotating hinge total knee arthroplasty (Endomodel Link type) (**b**). Additional lateral X-rays are shown in the same order as anteroposterior ones (**c, d**). Anteroposterior X-ray on day 1 after prosthesis explantation and placement of Palacos-type (Heraeus) articulated antibiotic spacer cement (**e**). Anteroposterior X-ray on day 1 after reimplantation with a cemented hypoallergenic constrained with rotating hinge total knee arthroplasty (type Endomodel Link) with 25 mm medial and lateral distal femoral augment to restore the correct level of the joint line (**f**). Additional lateral X-rays are shown in the same order as anteroposterior ones (**g, h**)



**Fig. 2** continued

Histological examination found no inflammation signs and the intraoperative sample cultures were negative. Afterward, antibiotic therapy was discontinued and 1 week after surgery the patient was discharged.

Three months post-surgery, outpatient follow-up confirmed prosthetic stability. The patient reached a ROM of 0–125°, and 1 year later was able to return to sports activity with good satisfaction for the clinical functional result obtained.



## Discussion and conclusion

This case aligns with evidence supporting two-stage revision procedures for PJIs, particularly those involving multidrug-resistant organisms. A British systematic review highlighted improvements in clinical–functional outcomes and pain reduction after total knee arthroplasty (TKA) in patients with pigmented villonodular synovitis (PVNS). However, the review also reported higher complication rates, including postoperative stiffness (6.8%), prosthetic infection (2.9%), recurrent symptoms (7.1%, characterized by swelling, worsening pain, and range of motion deterioration), and revisions due to infection, periprosthetic fractures, or instability. In addition, implant survival rates were lower (82%) after a 25-year follow-up compared with TKA performed for primary osteoarthritis. Therefore, constrained total knee arthroplasty for end-stage PVNS appears to be effective in relieving pain and improving function, despite these higher complication rates and lower survival outcomes [6].

Similarly, a 2022 case report on a 79-year-old patient with high-grade destructive arthropathy caused by villonodular pigment synovitis emphasized the need for extensive synovectomy and concomitant implantation of constrained total knee arthroplasty. The report concluded that this surgical approach yielded satisfactory results, with favorable outcomes in patients with PVNS associated with advanced osteoarthritis [7].

Building on the clinical case previously presented, which highlighted the importance of restoring the joint line, a British case–control study involving 114 patients demonstrated that both the Bristol Knee Score and functional outcomes at a 5-year follow-up were significantly better in patients whose joint line was restored compared with those whose joint line remained elevated by more than 5 mm. In cases of bone loss and joint line modification, the study showed that in revision TKA, the thickness of distal femoral wedges plays a critical role in restoring both bone defects and the joint line [8]. Moreover, a study from Istituto Ortopedico Rizzoli of Bologna, Italy, highlighted the importance of the adductor tubercle of the femur as a landmark for determining the joint line level during TKA. The ratio between the distance from the adductor tubercle to the joint line, and the femoral width at the epicondyles, was found to be comparable both radiographically and intraoperatively, providing a reliable method for measuring the joint line, particularly in complex revision surgeries [9].

Although rifampin is widely used in combination therapy for treating methicillin-resistant (MR) staphylococcal osteoarticular infections (OIs) [10], to the best of our knowledge, this is the first reported case of methicillin-resistant *Staphylococcus epidermidis* (MRSE)

prosthetic joint infection (PJI) treated with a combination therapy of rifampin and fosfomycin. Fosfomycin is a broad-spectrum, time-dependent bactericidal antibiotic with notable activity against MR staphylococci, and also exhibits good bone penetration [4]. Pre-clinical studies have shown that fosfomycin synergizes with various anti-staphylococcal antibiotics, including rifampin [10, 11], and rifampin demonstrates sustained efficacy against biofilm-producing pathogens, highlighting its value in combination regimens.

In conclusion, our case demonstrates that an MRSE prosthetic knee infection was successfully treated by coupling a two-stage procedure, consisting of 4 months of spacer cement placement followed by removal and definitive TKA, with a combination therapy of rifampin and continuous infusion (CI) fosfomycin. This treatment strategy aligns with the broader findings of clinical studies that support the efficacy of this approach in improving outcomes, despite the inherent challenges posed by complex cases such as PVNS and MRSE infections.

### Abbreviations

SE	<i>Staphylococcus epidermidis</i>
PJIs	Prosthetic joint infections
MRSE	Methicillin-resistant <i>Staphylococcus epidermidis</i>
OIs	Osteoarticular infections
MDR	Multidrug-resistant
CI	Continuous infusion
OPAT	Outpatient parenteral antimicrobial treatment
ALT	Alanine aminotransferase
CRP	C-reactive protein

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Not applicable.

### Author contributions

All authors have contributed to the development of the work and manuscript design. GMMM and EZ identified the topic of the manuscript and indicated the method of work development. AF and AG drafted the manuscript. GMMM, SZ, EZ, PV, and FP revised it. All authors reviewed and approved the manuscript.

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### Availability of data and materials

The data used for development of this manuscript are available from the corresponding author.

### Declarations

#### Ethics approval and consent to participate

The presented case report was conducted in accordance with the Declaration of Helsinki in its most updated version (Fortaleza, October 2013), as well as with all national and international regulations applicable to clinical research. Informed consensus was obtained in advance to the use of patient clinical data who is the subject of the case report, and for their publication for scientific purposes only, guaranteeing the patient's anonymity.

#### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**

Giulio Maria Marcheggiani Muccioli: LINK. Stefano Zaffagnini DePuy: S&N.

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