A recurrent prosthetic joint infection caused by Erysipelothrix rhusiopathiae: case report and literature review

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Sarrah Boukthir[1], Harold Common[2,3], Cédric Arvieux[2,4], Vincent Cattoir[1,2,5], Solène Patrat-Delon[2,4], Anne Jolivet-Gougeon[1,2,6*]

[1] Bacteriology and Hygiene Department, Teaching Hospital of Rennes, 2 rue Henri-Le-Guilloux, 35033 Rennes, France.

[2] CRIOGO Great West Reference centers for Complex Bone and Joint Infections (CRIOGO), France

[3] Teaching Hospital of Rennes, Department of Orthopedic Surgery and Traumatology, 2, rue Henri-Le-Guilloux, 35033 Rennes, France.

[4] Teaching Hospital of Rennes, Department of Infectious Diseases and Intensive Care Medicine, Rennes University Hospital, 2, rue Henri-Le-Guilloux, 35033 Rennes, France.

[5] Inserm U1230 BMR, University of Rennes 1, Rennes, France.

[6]Univ Rennes, INSERM, INRAE, CHU Rennes, Institut NUMECAN (Nutrition Metabolisms and Cancer), U1241, Microbiology, F-35000 Rennes, France

***Corresponding author**

Anne Jolivet-Gougeon, INSERM UMR1241, Institut NuMeCan, Université de Rennes 1, 2, avenue du Professeur Léon Bernard, 35043 Rennes, France

Phone: (33) 2 23 23 49 05 – Fax: (33) 2 23 23 49 13

E-mail: anne.gougeon@univ-rennes1.fr

Abstract

Prosthetic knee joint infection caused by *Erysipelothrix rhusiopathiae* is uncommon and only one case of recurrent infection has previously been described. Here, we describe the case of a 77-year-old male patient who was admitted to the teaching hospital of Rennes (France) with bilateral and nocturnal gonalgia evolving for one month. He had bilateral knee prosthesis 10 years ago, and a history of large B-cell lymphoma in remission. The diagnosis of infective endocarditis, with prosthetic knee infection, was performed, with positive cultures of synovial fluids and blood; colonies of *E. rhusiopathiae* were properly identified by MALDI-TOF mass spectrometry. Initial treatment involved debridement, implant retention surgery and intravenous amoxicillin (12g/day) for 6 weeks with gentamicin 3 mg/kg/day added for the first four days. One year later, a second episode of *E. rhusiopathiae* infection occurred, suggesting a recurrence or reinfection due to the same bacterial species. Patient was finally cured after a two-stage exchange with a cemented articulated spacer and a 3-month course of amoxicillin (12g/day, IV). Different characteristics of *E. rhusiopathiae* infection were discussed, with a review of all cases of prosthetic joint infections caused by *Erysipelothrix* spp. It highlights the need for a long-term survey of patients, and a good knowledge of their environment to avoid any risk of reinfection.

Keywords: *E. rhusiopathiae;* prosthetic; knee; endocarditis; infection

Introduction

Erysipelothrix rhusiopathiae, a thin, pleomorphic, nonsporulating, Gram-positive rod, is considered a pathogen of butchers, fishermen and veterinarians because of their exposure to a wide variety of animals [1]. *E. rhusiopathiae* most commonly causes localized (erysipeloid) or diffuse cutaneous disease, which can disseminate, resulting in invasive infections, such as infective endocarditis (IE) or device-related infections [2]. Cases of suppurative arthritis, osteoarthritis or prosthetic joint infections caused by *E. rhusiopathiae* have been reported, as the result of direct inoculation during trauma, surgery, or the presence of a foreign body [3]. This bacterium has virulence factors that promote its adhesion, such as adhesins [4,5], which can therefore allow binding and survival on prostheses and thus induce chronic infections [6]. This hypothesis has been supported by infection in animal models [7]. Compared to other Gram-positive bacteria, the structure and/or composition of the cell wall of *E. rhusiopathiae* is atypical; it lacks many orthologous genes for the biosynthesis of wall teichoic acids, lipoteichoic acids, and the *dltABCD* operon. EpsG, a putative glycosyltransferase, could be involved in the biosynthesis of the unusual peptidoglycan of the organism [8].

Here, we report a case of *E. rhusiopathiae* prosthetic knee infection (with IE) in a 77-year-old man. An infectious recurrence or reinfection, without endocarditis, was observed one year after the end of antimicrobial therapy.

Case report

A 77-year-old male patient, with a five-year history of large B-cell lymphoma in remission, was admitted to the emergency department of the tertiary-care hospital of Rennes in July 2018 for faintness, in a context of bilateral and nocturnal gonalgia evolving for one

month. He had had bilateral knee prostheses for 10 years. He had been complaining of fever associated with complete functional disability for 24 hours. The clinical examination was as follows: fever (38.5°C), swelling and inflammatory knees (without cellulitis/erythema) and pain at knee mobilization, predominant on the left knee. A known aortic systolic murmur was present. Physical examination showed no adenopathy and no hemodynamic disorder. The patient was a farmer (in contact with cows, rabbits and chickens), hunter of small game and freshwater fisherman consequently involved in preparation of fish and game.

There was a significant biological inflammatory syndrome with neutrophil polynucleosis (white blood cells: 27.1G/L, neutrophils: 24.5 G/L) and high C-reactive protein (CRP) (131.5 mg/L). On admission, the knee X-ray showed bipolar osteolysis on both knees, predominantly in the femur suggesting an onset of bipolar loosening. In this context, joint aspirations were performed bringing a purulent liquid from the left knee and a citrus-like liquid from the right knee; two pairs of blood cultures were also collected. Empiric antibiotic therapy was started with amoxicillin-clavulanic acid (200 mg/kg/day, IV). The next day, debridement was performed on both knees (with implants retention), without exchange of removable components of the prostheses. During the operation, the prostheses were not unsealed, contrary to X-ray findings.

The two joint fluids collected in the emergency room had a direct examination with many leukocytes (left: 11,000 red cells/mm^3, 62,000 white cells/mm^3 including 85% neutrophils; right: 48,000 red cells/mm^3, 11,000 white cells/mm^3 including 83% neutrophils) and many small nonsporulating Gram-positive bacilli [9]. After one-day incubation, growth subcultures of both knees onto chocolate agar revealed small, flat, greyish and round colonies and subcultures onto sheep blood agar revealed small, convex, α-hemolytic and smooth

colonies. Blood cultures were positive after an average of 15 hours of incubation, the direct examination found the same Gram-positive bacilli. *E. rhusiopathiae* was identified by MALDI-TOF mass spectrometry (Mixcroflex; Brucker Daltonics, Bremen, Germany). The MIC of amoxicillin was determined by Etest (bioMérieux, Marcy-l'Etoile, France) and was at 0.032 mg/L. According to bacteriological findings, antibiotic therapy was switched two days after the patient's admission to the combination of intravenous amoxicillin 12 g/day, with gentamicin 3 mg/kg/day added for the first four days. The cultures were all positive for the left knee (4/4 samples) and all negative for the contralateral joint (4/4), despite the positive culture of the right joint aspiration two days earlier, potentially due to poor sample quantity.

Because of patient's bacteremia and the presence of an aortic-stenosis murmur, a trans-thoracic cardiac ultrasound was performed and diagnosed aortic endocarditis on aortic stenosis, without abscess. A subsequent good clinical (apyrexia, decreased gonalgia) and biological (decrease of inflammatory syndrome) outcome was observed, blood cultures collected one week after treatment initiation were negative. Amoxicillin was resumed for 6 weeks with optimal amoxicillin blood levels (range: 30 - 57 mg/L). Clinical and biological outcome was favorable at 3 and 6 months despite persistent mild pain in the left knee.

In August 2019, the patient was again admitted to the emergency room for chills, left gonalgia associated with edema and functional disability. The clinical examination found: fever, a knee effusion and painful joint mobilization of the left knee, non-inflammatory and non-exuding scars, known aortic systolic murmur and lower limb excoriations. A biological inflammatory syndrome was present (neutrophil cells: 24 G/L and CRP: 103.6 mg/L). The joint aspiration of the left knee brought back purulent fluid, blood cultures were collected before starting intravenous cloxacillin (12 g/day) antibiotic therapy. Direct examination of the joint

fluid of the left knee found Gram-positive bacilli and cultures grew with *E. rhusiopathiae*. Six days after initiation of cloxacillin, a puncture of the right knee was performed and was negative for culture, but 16S rRNA gene amplification was positive for *E. rhusiopathiae.* This species was also found in a pair of initial blood cultures. Antibiotic therapy was changed to intravenous amoxicillin 12 g/day for a total of three months, while the MIC of amoxicillin was still at 0.03 mg/L; amoxicillin blood levels were in the range of 24 to 56 mg/L. Cardiac ultrasound by trans-thoracic and trans-esophageal pathways found no argument for a recurrence of infectious endocarditis. X-rays and scans of both knees showed a bipolar loosening of the two prostheses.

A two-stage revision surgery procedure was chosen for the left knee. During the surgery, tibial loosening was observed. A mobile antibiotic-impregnated (gentamicin) cement spacer was implanted. The surgical samples taken during the 1st stage were culture negative after 17 days of antibiotic therapy. One month after amoxicillin completion, the patient underwent the 2nd stage of reimplantation of the prothesis. Four intraoperative samples of the left knee cultures and 16S rRNA gene amplification remained negative. A tibial reconstruction with trabecular metal was performed with a NexGen LCCK (Legacy Constrained Condylar Knee, ZIMMER). There was no bone loss at the femur. In order to rule out an infection of the contralateral prosthesis, two joint fluids of the right knee were collected and both remained negative. Amoxicillin was restarted after the 2nd stage surgery and stopped at day 7 with the negative results of culture. At one month, there was clinical improvement with an afebrile and pain-free patient but a swollen left knee without inflammatory sign. The CRP dropped to 13.4 mg/L. At six months, the patient remained clinically well from an orthopedic point of view, without pain or functional disability on both knees; CRP level decreased to 10 mg/L, and blood

culture remained negative. Because of the known and symptomatic aortic stenosis, he underwent a transcatheter aortic valve implantation in June 2020, with secondary heart block necessitating a pacemaker insertion in November 2020, without any infectious complication.

In December 2020, the patient remained without sign of infection but presented right mechanical gonalgia; the left knee was without pain or functional disability. Blood culture remained negative.

Review search strategy

We conducted a systematic review of the literature about prosthetic joint infections caused by *Erysipelothrix* spp. Our protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA—ScR) [10]. We performed an online search of the Medline/PubMed database of all international publications containing "*Erysipelothrix"* published between the period of their first indexation, 1936/09 and 2022/02/02 (n=1825). The word *Erysipelothrix"* was crossed with "prosthesis" (n=19) and the references including the word "*endocarditis*" were excluded (n=4). The selected publications were entered into an Excel spreadsheet and organized by authors, sex and age of patients, localization of the prosthesis, debilitating conditions, exposure to animals/ food / water, suspected mechanism causing bacteria to spread/persist to joint, fever/ bacteremia/ associated endocarditis, inflammatory parameters, bacterial diagnosis, clinical features (duration before diagnosis), surgical procedures/ antibiotic therapy (duration), recurrence/ reinfection and outcome.

Discussion

There are very few reports of human *E. rhusiopathiae* bone and joint infections, which often follows environmental exposure to farmed or wild animals, or water sources (Table 1). Seven infections were reported in patients with a prosthesis, mainly of the knee (5/7), risk factors were systematically found (especially immunosuppressive therapies), except for one patient. Four patients had a good clinical outcome during the following year. Two patients presented a recurrence or reinfection episode: one within one month of the first episode [6] and the other later, at one year (the reported case). While a bite can be a mechanism of inoculation [11], some infections have been observed without invasive procedures. Any breach of the cutaneous barrier can be the gateway for a secondary infection [12], as knee or hip prostheses, consecutive to injuries with or without associated endocarditis. In our reported case, the patient was in contact with farm animals, but was also a freshwater fisherman and hunter, involved in preparation of fish and game. Historically erysipeloid of Rosenbach has been more strongly associated with fisheries and butchering than with simple animal husbandry. *E. rhusiopathiae* is able to survive for a long time in marine environments and to grow on the exterior mucoid slime of fish, which could also explain their survival on prosthetic materials. *E. rhusiopathiae* can also synthetize capsular polysaccharides, known as virulence factors [8]. *E. rhusiopathiae* has adhesive surface proteins (RspA and RspB), which share some characteristics with those of *Staphylococcus aureus*[13]. These surface proteins can initiate biofilm formation and explain the persistence of bacterial cells in joints or material, until reactivation. The long-term persistence of this bacteria in different morphologic forms may well account for the chronic course of the infection, as demonstrated by Toshkov et al. [14], in experiments in rats. Other adhesins have been recently described as CbpB [4], SpaA

[15] or glyceraldehyde-3-phosphate dehydrogenase [16,17] exhibiting binding activity to porcine endothelial cells, and binding to host plasminogen and /or fibronectin. *E. rhusiopathiae* serovars 1a, 1b, 2, 5, 8, 9, 12, 15–17 and 23 possess SpaA; *E. rhusiopathiae* serovars 4, 6, 11, 19 and 21 possess SpaB, and a different species (*Erysipelothrix piscisicarius* sp. nov.) possesses SpaC. Tagushi *et al*. [18] recently isolated a *E. rhusiopathiae* strain from a human spondylodiscis, in a patient with diabetes and hepatitis. They performed molecular characterization of this immunogenic surface protective antigen (Spa B), which plays an important role in endothelial cell adherence.

Identification of *E. rhusiopathiae* in the microbiology laboratory is largely facilitated by MALDI-TOF mass spectrometry technology. Infection with *E. rhusiopathiae* has probably been underestimated so far and its identification may be easier to achieve now [19]. The 16S rRNA sequencing has shown its usefulness in many clinical cases, particularly in cases of blood culture negative endocarditis [20,21]. The use of a specific PCR has been reported in animal samples specially for species serotyping [22] but seems to be of little use in human samples, due to the low prevalence of *Erysipelothrix* infection, therefore the 16S PCR is plainly more relevant [21].

E. rhusiopathiae is typically susceptible to penicillins, cephalosporins, carbapenems, fluoroquinolones, daptomycin but resistant to vancomycin (low level), sulphonamides and aminoglycosides [23]. Zhang et al. determined MICs of 11 antimicrobial agents by the broth microdilution method of 46 *E. rhusiopathiae* isolates from 31 pig farms [24]. Seven/46 strains were highly resistant to tiamulin (MICs 32 µg/ml) and clindamycin (MICs 64 µg/ml), with a positive detection of the *lsa*(E), *spw*, *lnu*(B), *aad*E and *aph*A3 genes in strains with the resistant phenotype [24]. After sequencing of the whole assembled circular genome, a multi-drug

strain, isolated from pig, was found to be resistant to tiamulin [minimum inhibitory concentration (MIC) = 64 mg/L], lincomycin (MIC = 64 mg/L), gentamicin (MIC = 64 mg/L), streptomycin (MIC = 512 mg/L), kanamycin (MIC = 256 mg/L), erythromycin (MIC = 8 mg/L) and tetracycline (MIC = 32 mg/L) [25]. Similar resistance data were reported in human strains [23,26,27].

For this patient, recurrence is likely: 6 weeks of antibiotics might be too short in the debridement, antibiotics and implant retention (DAIR) procedure, especially when there is no exchange of the removable parts of the prosthesis [28]. After DAIR, the risk of relapse is not the same, depending on causative bacteria, indeed a higher risk has been reported for *Staphylococcus aureus* compared to *Streptococcus* sp. [29]. The presence of minimal loosening could have prompted discussion for prosthesis exchange, with a higher cure rate. Reinfection of the same joint with this very rare pathogen can almost be ruled out, although gene-sequencing was not performed, either on initial sample or on the relapse one.

Conclusion

The patient recovered after being treated with a combination of prolonged high doses intravenous amoxicillin with optimal surgical management. This observation and the review of the literature highlight the need of a systematic long-term survey of patients, and a good knowledge of their environment to avoid any risk of reinfection. As the right knee showed few symptoms, complete support was possible without pain. After two years of post-surgical follow-up, the patient does not wish for prosthetic revision, in view of the only radiographic aspect of non-evolutionary loosening.

Acknowledgement

We thank Adina Pascu and Pascale Ollivier for helping us edit the manuscript.

Funding information

This work received no specific grant from any funding agency.

Conflict of interest

The authors have no conflict of interest to declare

Consent to publish

A statement, saying a consent to publish, has been obtained.

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329 **Table 1.**

330 Cases and clinical characteristics of prosthetic joint infections caused by *Erysipelothrix*

331 *rhusiopathiae.*

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Reference	Patient	Sex	Age	Localisation	Debilitating conditions	Exposure to animals/ Food/ Water	Suspected mechanism causing bacteria to spread/persist to joint	Fever/ bacteremia/ associated endocarditis	Inflammatory parameters	Bacterial diagnosis	Clinical features (duration before diagnosis)	Surgical procedures/ antibiotherapy (duration)	Recurence/ reinfection	Outcome
Reported case	1	M	77	Knee	Renal and cardiac insufficiency. Large cell B lymphoma (Rituximab Cyclophosphamide Hydroxy Doxorubicine Vincristine Prednisone)	The patient was a farmer (cows, rabbits and chickens), hunter of small game and freshwater fisherman.	NP	Positive blood cultures. Endocarditis.	CRP= 100 mg/L	**2018** Positive blood cultures (n=6) Positive culture of synovial fluid (n=6)(left knee) Identification by mass spectrometry **2019 (August)** No positive blood culture Positive culture of synovial fluid (left knee) Identification by mass spectrometry 16S rRNA sequencing (right knee) : negative PCR **2019 (December)** No positive blood culture Culture of peroperative samples (left knee) and 16S rRNA sequencing : negative Puncture of the painful right knee: negative culture	Bilateral prosthetic knee infection + endocarditis	Amoxicillin (12g/day) for 12 weeks	Yes: one year after antibiotic therapy	Clinically well two years after the last surgery

Groeschel et al. 2019 (20)	2	F	69	Knee	Obesity, hypertension, gastroesophageal reflux disease Total arthroplasty of the right knee with a *Brucella suis* PJI (12 years prior)	Exposure to multiple wild host species in the Canadian Arctic	Consumption of raw caribou, muskox, seal and fish?	No fever Negative blood cultures Echocardiogram not performed	CRP=171.4 mg/L No leukocytosis or neutrophilia in blood	Positive 16S rRNA sequecing on the pre-operative knee aspirate. Positive cultures of intra-operative tissues (5/5)		After intra-operative tissue specimen collection: 2 g of cefazolin IV Intravenous ceftriaxone 1 g daily was switched to intravenous penicillin G and completed 6 weeks of intravenous antibiotic therapy and an additional 6 weeks of oral amoxicillin 1 g three times daily.	No	Clinically well 1 year after the last surgery
Gazeau et al. 2018 (6)	3	M	82	Knee	No medical history	NP	NP	NP	Hihg CRP level	Positive synovial fluid (n=4/5)	Four arthroplasties and loosening, local pains, and hematoma	High doses of IV amoxicillin Ceftriaxone (2 g daily) for three months Knee prosthesis removal surgery and replacement with a gentamicin-loaded spacer Ceftriaxone (2 g) and levofloxacin (500 mg) twice a day for a total duration of 12 weeks. Re-implantation of a hinged knee prosthesis	Yes: one month after antibiotic therapy completion, the patient presented with a new episode of arthritis.	After two years, no new infectious or surgical problem
Troelsen et al. 2010 (11); Hocqueloux et al. 2010 (3)	4	F	73	Hip	Chronic wound on the heel Total teeth extraction.	Exposure to a healthy dog, which is used for hunting No visits to farms or contact with birds or fish. No remembrance of wounds or cuts on the hands being infected.	Carrying wild animals in the dog's mouth	NP	CRP = 167 nmol/L)	Negative culture of the preoperative aspiration Positive culture of intraoperative tissue samples (n=5/5) and from the sonicated sample of the prosthetic material.	Persistent groin pain and lateral thigh pain after hip arthroplasty	Debridement, implant evacuation, and extensive lavage. Antibiotic loaded (Gentamicin and Clindamycin) cement spacer. Dicloxacillin IV was changed to benzylpenicillin 3 weeks, followed by oral administration of Amoxicillin for another 2 months	No	16 weeks postoperatively, there were no signs of recurring infection and no pain

Hocqueloux et al. 2010 (3)	5	F	68	Knee	Alcoholism, gout, systemic steroids against skin lesions	Feeding pigs	Percutaneous penetration through abrased skin	Afebrile No sign of endocarditis	Peripheral white blood cell count = 6,100 cells/mm3 CRP =74 mg/liter	All Gram staining tests were negative Blood cultures remained sterile Positive culture of peroperative samples (n=4/11) Identification by API-Ana and sequencing of the 16S rRNA-encoding gene *rrs*.	Severe internal condyle osteonecrosis extending to femur, tibia, and patella	Tricompartmental posterior stabilized cemented knee arthroplasty, containing gentamicin Amoxicillin-clavulanate Twelve months after right knee arthroplasty: surgical arthrotomy Prosthesis was removed and replaced by a vancomycin- and gentamicin-impregnated spacer Rifampin and vancomycin IV treatment Imipenem and ofloxacin IV for 2 weeks, followed by oral clindamycin and ofloxacin (total duration = 6 months)	No	32 months after knee arthrodesis: no problems
Traer et al. 2008 (12); Hocqueloux et al. 2010 (3)	6	M	76	Knee	Rheumatoid arthritis Lupus Interstitial nephritis Long-term steroid treatment	Exposure to hides of pigs, cows, deer, kangaroos, and penguins	Worker in a tanning factory with frequent cuts and abrasions	NP	Normal white cell count CRP level = 27 mg/L Histology: capsule and synovial membrane with fibrosis, extensive fibrinoid necrosis, and signs of chronic inflammation.	Negative direct Gram staining Histology: 4 and 8 neutrophil polymorphonuclear leukocytes per high-power field Positive fluid and synovium (n=4/9)	Pain with infection 14 months after a total knee arthroplasty	Washout, debridement, and complete synovectomy Two chains of 30 gentamycin-loaded beads were placed in the tibial cavity. Temporary articulating polymethylmethacrylate knee spacer (+1.7 g of gentamycin) A 3-week course of high dose IV benzyl penicillin and levofloxacin, followed by 7 weeks of oral clindamycin and levofloxacin. Vancomycin and levofloxacin	No	12 months after second-stage surgery, the patient was clinically well, with a pain free knee

Mahon et al. 2021 (19)	7	M	65	right-sided hip	Seronegative rheumatoid arthritis diagnosed 10 years previously. Treatments: methotrexate, baricitinib, for 5 months, tocilizumab, for 6 months, anti–tumor necrosis factor-alpha monoclonal antibody certolizumab pegol for 7 years.	Gardener, who regularly handles chicken manure pellets without gloves	Erythema affecting his hands and fingers consistent with localized cutaneous *E. rhusiopathiae* infection	The patient was febrile at presentation, but initial blood cultures produced no growth	White cell count: 15.9 x 109/L (normal range 4.5-11 · 109/L); CRP 389 mg/L (normal range 0-5 mg/L); erythrocyte sedimentation rate (ESR) 101 mm/hours (normal range 0-20 mm/hours).	**Initially** Joint aspirate: *E. rhusiopathiae* identified by MALDI-TOF Pus: 2/6 were positive to *E. rhusiopathiae* **Revision surgery 5 months after presentation** 3/4 positive peroperative samples **Follow-up arthrocentesis performed before restarting immunosuppressive therapy 1 year postoperatively** Sterile	A 3-month history of right-sided hip pain and swelling with difficulty in weight-bearing and a 2-week history of intermittent febrile episodes was reported by the patient.	Washout, debridement, and implant retention of the right THR 4 days after presentation. Empiric intravenous (IV) vancomycin was commenced after arthrocentesis, and changed by benzylpenicillin and gentamicin IV (after microbiological results). Metronidazole IV was then added for anaerobic coverage (after specialist infectious disease consultation). Patient was discharged on ciprofloxacin monotherapy, because the associated-amoxicillin was discontinued (urticarial skin reaction). First-stage complex revision surgery was performed through posterior approach 5 months after presentation. During second stage revision, a spacer containing 2% gentamicin sulfate and 1% benzoyl peroxide, and impregnated with 3 grams of vancomycin intraoperatively was implanted.		No further signs of infection and a clinically successful outcome after first-stage revision surgery. The patient continues a suppressive regimen of ciprofloxacin 500 mg once daily, and ambulates with a stick at present. He has declined second stage revision surgery, but remains under orthopedic follow up. He complains of ongoing pain and stiffness because of his inflammatory arthritis (immunomodulatory drugs have been restarted).

Abbreviations: M, male; F, female; IV intraveinous; NP information not provided; CRP C-reactive protein; MALDI_TOF, Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

Table 1: Cases and clinical characteristics of prosthetic joint infections caused by *Erysipelothrix rhusiopathiae*.