Archives of Orthopaedic and Trauma Surgery (2023) 143:5515–5526
https://doi.org/10.1007/s00402-023-04848-4

ORTHOPAEDIC SURGERY

Interest in the combination of antimicrobial therapy for orthopaedic device-related infections due to *Enterococcus* spp.

Charles Maurille[1,2] · Jocelyn Michon[1] · Christophe Isnard[2,3] · Goulven Rochcongar[4] · Renaud Verdon[1,2] · Aurélie Baldolli[1]

Received: 29 September 2022 / Accepted: 14 March 2023 / Published online: 29 March 2023

Abstract

Introduction The objective of this study was to evaluate the management of orthopaedic device-related infections (ODRIs) due to *Enterococcus* spp.

Materials and methods We performed a retrospective cohort study in a French tertiary university hospital. Patients with prosthetic joint- or osteosynthesis-associated infections caused by enterococci from 2013 to 2020 were included. Patients who died within 5 days after surgery; who were in palliative care; or who had osteosynthesis of the hand, foot or vertebra were excluded.

Results Thirty-six patients were included, with 24 in the arthroplasty group and 12 in the osteosynthesis material group. Most infections were polymicrobial (63.9%, $n=23$). Debridement, antibiotics and implant retention (DAIR) was performed in 30.6% ($n=11$), withdrawal of material in 16.7% ($n=6$), one-stage exchange in 30.6% ($n=11$) and two-stage exchange in 22.2% of cases ($n=8$). The antibiotic regimen was amoxicillin in 41.6% ($n=15$), rifampicin in 27.8% ($n=10$), linezolid in 25% ($n=9$) and/or fluoroquinolones in 30.6% ($n=11$). Clinical success at 1 year was 67% (18/27). The only variable statistically associated with a decreased risk of clinical failure was a duration of antibiotic therapy of 12 weeks ($p=0.04$). Patients with a lower body mass index and age tended to decrease the risk of clinical failure ($p=0.05$ and 0.06 respectively).

Conclusions The management of enterococcal ODRIs is complex, and ODRI patients are at high risk for relapse. In our small study, a better outcome was not demonstrated for patients with combination therapy and rifampicin use. Further studies are needed to improve the medico-surgical strategy for treating these infections.

Keywords *Enterococcus faecalis* · Outcome · Periprosthetic joint infection · Total hip arthroplasty · Total knee arthroplasty

Introduction

Total knee and hip arthroplasty have become the standard treatment in end-stage osteoarthritis because these methods reduce pain and improve the functionality of the joint and occasionally the quality of life [1]. Prosthetic joint infection (PJI) is one of the most dreaded complications and occurs in 1–2% of operated patients [2]. PJIs are associated with complex management and an increase in morbidity and mortality [3]. The overall cost to treat bone and joint infections was evaluated to €259 millions to the French health care system in 2008, which presents a major economic burden [3].

Enterococci are Gram-positive facultative anaerobic cocci and are commensals of human and animal digestive microbiota. They have been traditionally implicated in bloodstream infections, endocarditis or urinary tract infections. Enterococci are naturally resistant to many antibiotics, including

Presented in part at European Congress of Clinical Microbiology and infectious Diseases 2021 which took place online from 9 to 12 July 2021 and at "Journées Nationales d'Infectiologie" 2021 in Montpellier (France) from August 30 to September 1, 2021.

✉ Charles Maurille
maurille-c@chu-caen.fr

1 Department of Infectious Diseases, Normandie University, UNICAEN, CHU de Caen Normandie, 14000 Caen, France

2 Normandie Univ, UNICAEN, UNIROUEN, Inserm UMR 1311 DynaMicURe, 14000 Caen, France

3 Microbiology Department, Normandie University, UNICAEN, CHU de Caen Normandie, 14000 Caen, France

4 Orthopaedics and Traumatology Department, Normandie University, UNICAEN, CHU de Caen Normandie, 14000 Caen, France

cephalosporins and aminoglycosides [4]. *Enterococcus* spp. account for 3–10% of PJIs [5–8]. *Enterococcus faecalis* is responsible for the vast majority (90%) of enterococci PJI, but it often occurs as part of a polymicrobial infection [6, 9]. The rate of treatment failure was higher in PJI patients infected with *Enterococcus* spp. than in patients infected with other species [10, 11]. The polymicrobial nature of these infections, the formation of biofilms and the increased patient age and number of comorbidities could explain this worse outcome [9, 12–14].

Because of its rarity, the optimal management of PJI due to enterococci remains poorly understood, and guidelines on medico-surgical therapy against these infections are mostly based on the opinions of expert committees [15–17]. Given this lack of data, it becomes necessary to carry out additional studies on the treatment of PJI caused by *Enterococcus* spp. to improve the prognoses of these infected patients.

We therefore conducted a retrospective cohort study and asked the following: (1) Does combination therapy improve outcomes compare to monotherapy in ODRIs due to *Enterococcus* spp.? (2) Does an antibiotic targeting the biofilm, such as rifampicin, improve the prognosis of patients?

Materials and methods

Study design and participants

We performed a retrospective cohort study in the University Hospital of Caen (France), one of the French reference centres for the management of complex Bone and Joint Infections. All patients with PJI or osteosynthesis-associated infections caused by enterococci from January 2013, to July 2020 were included. Patients who died within 5 days after surgery or who were in palliative care were excluded. Because the diagnosis, management and prognosis are different from other osteosynthesis, we also excluded patients who had osteosynthesis of the hand, foot or vertebra. All patients were followed until July 2020. Cases were first defined using microbiology laboratory data (TD Nexlabs, TECHNIDATA, France). This study was performed using the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of the biomedical research institute of Caen (ID 3164, 03/23/2022).

Definition and outcome

The diagnosis of PJI was defined according to the Philadelphia consensus conference guidelines published in the 2018 "Proceedings of the International Consensus Meeting on Orthopaedic Infections", which were (i) two positive growths of the same organism using standard culture methods or (ii) sinus tract with evidence of communication to the joint or visualization of the prosthesis or (iii) a combined score ≥ 6 as assessed based on an increase in serum C-reactive protein (CRP) (2 points) or sedimentation rate (1 point), elevated synovial white blood cell count (WBC) (3 points) or polynuclear neutrophils (2 points), histology in favour of an infection (3 points), single perisample prosthetic positive (2 points) or positive intraoperative purulence (3 points) [18]. Because of the absence of consensus regarding the definition of osteosynthesis-associated infection, we used similar criteria to those of the PJI definition for the diagnosis of osteosynthesis material infection. Osteoarticular infection was distributed according to the Tsukayama classification: early postoperative infection (<4 weeks), late postoperative infection (>4 weeks) or haematogenous origin [19]. Patients with early postoperative infection or haematogenous infection were planned to receive debridement, antibiotics and implant retention (DAIR) procedure via open arthrotomy, with exchange of mobile components if available, followed by antibiotic treatment. Those with late postoperative infection underwent whether 1-stage exchange consisting of infected implant removal and reimplantation of a material followed by antibiotic treatment, or 2-stage exchange procedure consisting of infected implant removal and antibiotic-loaded spacer placement followed by an antibiotic treatment course prior to prosthetic implant replacement. Decision between 1-stage or 2-stage exchange depended on many factors including joint age, pathogens resistance, medical comorbidities, quality of the periprosthetic soft tissue and patient's preference. Same approach was applied for osteosynthesis associated infection: debridement with implant retention for acute infection, 1-stage exchange or implant removal for chronic infection. Six to 12 weeks of postoperative pathogen-specific antimicrobial therapy following the Philadelphia consensus conference and IDSA guidelines [17, 18] was given. The other factors influencing the choice of treatment were: the chronicity of the infection, pathogens antimicrobial resistance, surgery protocol or patient's comorbidities. For each patient, the management of PJI or osteosynthesis-associated infection was chosen during a multidisciplinary staff with infectious disease specialists, orthopaedic surgeons and microbiologists. The follow-up period was calculated from the date of infection surgery. During the follow-up, patients underwent routine clinical, biological and radiological evaluations. Clinical success was defined by the absence of clinical failure, and was analyzed at 6 months, 1 year and 2 years. Relapse due to enterococci or other microorganisms, unplanned surgery or death related to PJI or osteosynthesis-associated infection were considered clinical failure. Relapse was defined according to the Philadelphia consensus criteria [18].

Data collection

Information regarding the demographics (age and gender), underlying conditions (chronic obstructive pulmonary disease (COPD), cirrhosis, diabetes mellitus, immunosuppressive treatment, chronic renal failure, tobacco, rheumatoid arthritis), initial surgery (total knee arthroplasty, total hip arthroplasty, osteosynthesis material), delay between the first surgery and the first symptoms of infection, clinical manifestations (fever, sinus tract, local symptoms, joint pain, endocarditis), biological investigations (CRP, WBC), radiological findings, microbiological data (enterococcus species, antimicrobial susceptibility testing, isolation of other microorganisms) and infection management, type of septic surgery (1-stage, 2-stage exchange, DAIR, removal of material), delay between infection and surgery, antibiotic regimen and outcome were collected using the informatics medical records. Electronic medical records (Usv2-Crossway, McKesson, USA) were prospectively filled in by medical and paramedical staff.

Microbiological analysis

The standard microbiological protocol includes the culture of different samples (between 3 and 5 if possible). Briefly, all samples were inoculated on the following media: blood agar, chocolate agar and Schaedler broth with vitamin K3, all from BioMérieux (Marcy l'Etoile, France) under different atmosphere conditions (*e.g.,* anaerobic and aerobic conditions). Biopsies were mechanically grind before to inoculation. Sonication of the removed implants was not used. All cultures performed in agar media were incubated for 5 days and those in Schaedler broths were incubated for 15 days. Species identification was carried out using a Maldi ToF technology (Microflex®, Brucker, Germany). Antimicrobial Susceptibility profiles were determined using the disk diffusion method, or VITEK® XL (bioMérieux, Marcy l'Etoile, France). Clinical susceptibility profiles were evaluated according to the French committee for antibiogram (CA-SFM/EUCAST) [20].

Statistical analysis

Categorical data are expressed as numbers and percentages, and continuous variables are reported as the means and standard deviations (SDs). Raw characteristics were compared between groups using Fisher's exact test for categorical variables and Mann–Whitney *U* tests for continuous variables. A *p*-value less than 0.05 was considered significant and indicated in bold.; all p-values were two tailed. Statistical analyses were performed using R software (The R Foundation for Statistical Computing).

Results

Population and infection characteristics

A total of 36 patients were included, with 24 in the arthroplasty group and 12 in the osteosynthesis material group (Fig. 1). The demographic data and comorbidities of the patients are reported in Table 1. The mean age (SD) was 69.3 years [17], and 52% were male ($n=19$). The most frequent underlying conditions were chronic renal failure (16.7%, $n=6$), immunosuppressive treatment (13.8%, $n=5$), diabetes mellitus (11.1%, $n=4$) and rheumatoid arthritis (8.3%, $n=3$). The most frequent infections were hip PJI ($n=19$, 52.8%), osteosynthesis-associated infections located on the tibia or fibula ($n=11$, 30.5%) and knee PJI ($n=4$, 11.1%). Twenty-seven patients (75%) had a delayed postoperative infection with a mean delay (SD) of 42.1 months (90.2). Clinical symptoms were pain (71.4%, $n=25$), sinus tract (57.1%, $n=20$), local symptoms (37.1%, $n=13$) and fever (25.7%, $n=9$). The mean CRP (SD) level was 85.7 mg/l (93), the mean WBC (SD) was 8.0 G/l (3.0), and 7/33 patients (21.2%) had radiological signs of implant loosening. One patient (2.7%) had a diagnosis of endocarditis according to the Duke criteria [21]. Patients with osteosynthesis were younger ($p=0.002$), more often smokers ($p=0.03$) and had more local symptoms ($p=0.02$), whereas patients with PJI had a longer delay between the last surgery and infection ($p=0.03$) and more frequent implant loosening on X-ray ($p=0.03$).

Microbiological results

Table 2 shows microbiological data of the cohort. *E. faecalis* was the most common pathogen (30 isolates, 83.3%), while *E. faecium* was found in 13.9% (5 isolates). Isolates were susceptible to ampicillin in 90.6% (29/32), vancomycin in 97% (32/33), linezolid in 100% (27/27), levofloxacin in 87.5% (14/16) and rifampicin in 54.8% (17/31) of cases. Infections were polymicrobial for 23 patients (63.9%) with mostly methicillin-sensitive *Staphylococcus aureus* (MSSA) (56.5%, 13/23) or enterobacteria (52.2%, 12/23). Osteosynthesis-associated infections were more often polymicrobial than PJIs ($p=0.002$) and were mostly associated with fermenting Gram-negative bacilli ($p=0.03$).

Medico-surgical treatment and outcome

Medico-surgical management and outcomes of the 36 patients are described in Table 3. DAIR was performed in 11 cases (30.6%), withdrawal of material in 6 cases (16.7%), 1-stage exchange in 11 cases (30.6%) and 2-stage exchange in 8 cases (22.2%). Antibiotic treatment directed against

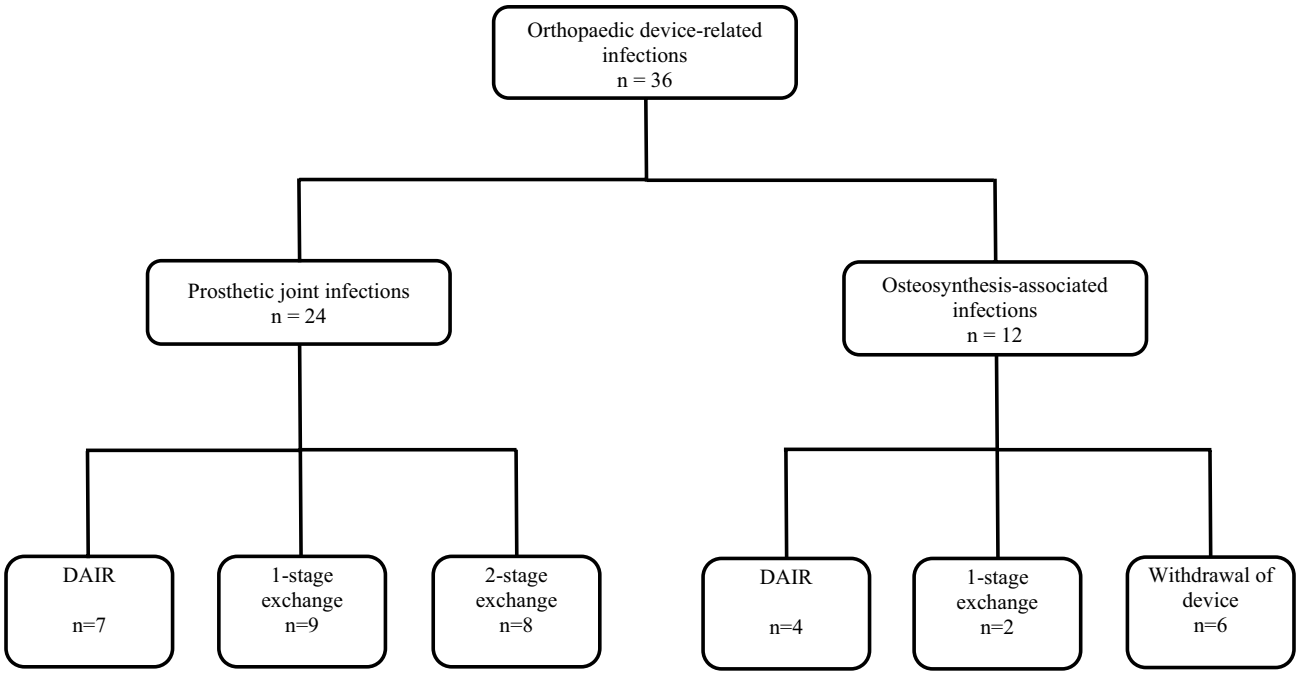

Fig. 1 Flowchart of the study

enterococci included amoxicillin (41.6%, $n=15$), fluoroquinolones (30.6%, $n=11$), rifampicin (27.8%, $n=10$), and/or linezolid (25.0%, $n=9$). The duration of antimicrobial therapy was 6 weeks for 14 patients (38.9%) and 12 weeks for 19 patients (52.8%). Combination therapy was prescribed in 60.8% of polymicrobial (14/23) and in 38.5% of monomicrobial infections (5/13), mostly with amoxicillin and rifampicin (13.9%, 5/36) (Table 4). The mean follow-up (SD) was 33.8 months (28). The clinical success rates at 6 months, 1 year and 2 years were 76% (22/29), 67% (18/27) and 59% (13/22), respectively. No relapse due to enterococci was identified. Among 12 patients with osteosynthesis infection, 8 were recovering, 2 were amputated (4 and 18 months after septic surgery) and 2 were in pseudarthrosis and needed new surgery. Two-stage exchanges were more often performed in patients with PJI ($p=0.03$), while device removal was more often performed in patients with osteosynthesis-associated infection ($p=0.0005$).

Univariate analysis of factors associated with clinical failure

An univariate analysis of factors associated with clinical failure is presented in Table 5 and was carried out after excluding 3 patients who died of other causes, 3 who were lost to follow-up and 3 with a postoperative follow-up of less than 1 year. In this analysis, the only variable statistically associated with a reduced risk of clinical failure was a duration of antibiotic therapy of 12 weeks, with a p-value of 0.04. Lower BMI and lower age tended to decrease the risk of clinical failure but the difference was not statistically significant ($p=0.05$ and 0.06 respectively). Combination therapy and the use of rifampicin were not associated with a decreased risk of clinical failure.

Subgroup analysis

We performed an univariate analysis in the group of PJI and the group of osteosynthesis associated infection. We found that lower age ($p=0.02$) and 12 weeks of antimicrobial therapy ($p=0.03$) were factors significantly associated with clinical success in the PJI group while only lower age was statistically significant ($p=0.009$) in the osteosynthesis associated infection group (Tables 6 and 7). The results are, therefore, consistent with the pooled analysis.

Discussion

In our retrospective cohort, patients with ODRI due to enterococci had poor clinical success, and the combination of antimicrobial therapy did not impact the outcome. To the best of our knowledge, this is the first study to include osteosynthesis-associated infections caused by enterococci.

Enterococcus spp. is an opportunistic pathogen that is able to adapt its lifestyle to its environment and modulate the host's immune response to silently persist in multiple niches, such as in bones and joints [22]. Despite frequent

Table 1 Demographics, comorbidities and infection characteristics of 36 patients with enterococci PJI and osteosynthesis-associated infection

Variable	Prosthetic joint infection $n=24$ (%)	Osteosynthesis associated infection $n=12$ (%)	p*	All episodes $n=36$ (%)
Mean (SD) age—years	77.5 (6.9)	52.8 (19.7)	**0.0002**	69.3 (17)
Male sex	14 (58.3)	5 (41.6)	0.48	19 (52)
Mean (SD) BMI—kg/m^2	29.5 (6.1)	28.5 (5.7)	0.66	28.1 (5.9)
Chronic renal disease	6 (25)	0 (0)	0.07	6 (16.7)
Diabetes mellitus	3 (12.5)	1 (8.3)	1	4 (11.1)
COPD	1 (4.1)	1 (8.3)	1	2 (5.5)
Liver cirrhosis	0 (0)	1 (8.3)	0.33	1 (2.7)
Rheumatoid polyarthritis	3 (12.5)	0 (0)	0.53	3 (8.3)
Active tobacco smoking	0 (0)	3 (25)	**0.03**	3 (8.3)
Immunosuppressive treatment	3 (12.5)	2 (16.6)	1	5 (13.8)
Affected joint/bone				
Knee	5 (20.8)	0 (0)	NA	5 (13.9)
Hip	19 (79.1)	0 (0)	NA	19 (52.8)
Femur	0 (0)	1 (8.3)	NA	1 (2.8)
Tibia/fibula	0 (0)	11 (91.6)	NA	11 (30.5)
Type of infection according to the time after last surgery				
Early postoperative (< 4 weeks)	4 (16.7)	3 (25)	0.66	7 (19.4)
Delayed postoperative (> 4 weeks)	18 (75)	9 (75)	1	27 (75)
Haematogenous origin	2 (8.3)	0 (0)	0.54	2 (5.6)
Mean delay from last surgery to diagnosis of infection (SD)—months	60.3 (93.7)	5.75 (13.0)	**0.03**	42.1 (90.2)
Open fracture	0 (0)	2 (16.6)	NA	2 (5.5)
Clinical presentation				
Fever	7/23 (30.4)	2 (16.6)	0.44	9/35 (25.7)
Pain	18/23 (78.2)	7 (58.3)	0.25	25/35 (71.4)
Local symptoms	5/23 (21.7)	8 (66)	**0.02**	13/35 (37.1)
Sinus tract	11/23 (47.8)	9 (75)	0.16	20/35 (57.1)
Endocarditis	1 (4.1)	0 (0)	1	1 (2.7)
Laboratory results at the diagnosis				
Mean (SD) serum C-reactive protein—mg/l	99.2 (100)	61.1 (77)	0.12	85.7 (93)
Mean (SD) white blood cell count—G/l	7.8 (3.2)	8.4 (2.8)	0.43	8.0 (3.0)
Mean (SD) polynuclear neutrophils—G/L	5.8 (2.9)	5.9 (3.0)	0.83	5.9 (2.9)
Implant loosening in X-ray	7/21 (33.3)	0 (0)	**0.03**	7/33 (21.2)

Data are no. (%) of episodes, unless otherwise indicated. Where the denominator is shown, data were not available for all patients

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *NA* not applicable, *SD* standard deviation

*Fisher's exact test for categorical variables and Mann–Whitney U tests for continuous variables

Values in bold correspond to statistically significant values

coinfections, the clinical manifestations of our patients are reminiscent of infections with slow-growing bacteria such as coagulase-negative staphylococci or corynebacteria [23]. Infections were most often chronic with significant local symptoms contrasting with few systemic signs.

To our knowledge, seven other cohort studies focused on enterococcal PJI with a range of patients included from 31 to 203 [9, 11, 12, 23–26]. As previously described in bone and joint infections, enterococcal were often polymicrobial, and the most frequent copathogens identified were staphylococci or *Enterobacteriales* members. Interaction between enterococci and others microorganisms in polymicrobial infections is well known [27]. First, it appears that immune suppression mediated by *E. faecalis* may promote the virulence of co-infecting organisms during polymicrobial infection. Indeed, it was found that *E. faecalis* can limit phagocytosis and intracellular killing of other pathogens in a peritonitis model [28] and can suppress cytokine production of the host in an urinary tract infections model [29], allowing to promote colonization of copathogens such as

Table 2 Microbiological data of 36 patients with enterococci PJI and osteosynthesis-associated infection

Variable	Prosthetic joint infection $n=24$ (%)	Osteosynthesis associated infection $n=12$ (%)	p*	All episodes $n=36$ (%)
Enterococcus spp.				
E. faecalis	21 (87.5)	9 (75)	0.37	30 (83.3)
E. faecium	3 (12.5)	2 (16.6)	1	5 (13.9)
E. avium	0 (0)	1 (8.3)	0.33	1 (2.7)
E. gallinarum	0 (0)	1 (8.3)	0.33	1 (2.7)
Polymicrobial infection	11 (45.8)	12 (100)	**0.002**	23 (63.9)
Coinfecting pathogens				
MSSA	5/11 (45.4)	8 (66.6)	0.41	13/23 (56.5)
MRSA	1/11 (9.1)	0 (0)	0.47	1/23 (4.3)
MSCoNS	0/11 (0)	1 (8.3)	1	1/23 (4.3)
MRCoNS	5/11 (45.4)	1 (8.3)	0.06	6/23 (26.0)
Streptococcus	3/11 (27.2)	1 (8.3)	0.31	4/23 (17.4)
Fermenting Gram-negative bacilli	3/11 (27.2)	9 (75)	**0.03**	12/23 (52.2)
Nonfermenting Gram-negative bacilli	1/11 (9.1)	2 (16.6)	1	3/23 (13.0)
Susceptibility of enterococcus to:				
Ampicillin	17/20 (85)	12 (100)	0.27	29/32 (90.6)
Vancomycin	21/21 (100)	11 (91.7)	1	32/33 (97.0)
Linezolid	19/19 (100)	8/8 (100)	1	27/27 (100)
Levofloxacin	11/13 (84.6)	3/3 (100)	1	14/16 (87.5)
Rifampicin	12/19 (63.1)	5/12 (41.6)	0.28	17/31 (54.8)

Data are no. (%) of episodes, unless otherwise indicated. Where the denominator is shown, data were not available for all patients

MSSA methicillin sensitive *Staphylococcus aureus*, *MRSA* methicillin resistant *Staphylococcus aureus*, *MSCoNS* methicillin sensitive coagulase negative staphylococci, *MRCoNS* methicillin resistant coagulase negative staphylococci

*Fisher's exact test for categorical variables

Values in bold correspond to statistically significant values

Escherichia coli. Second, inter-species interactions between *E. faecalis* and *S. aureus* or *P. aeruginosa* lead to augmented biofilms biomass in vitro and may also explain the frequent co-occurrence of these microbes in PJI [30, 31]. Third, enterococcal biofilm can serve as gene reservoirs for antibiotic resistance transmission between species by horizontal gene transfer, as demonstrated by the transmission of *vanA* from *E. faecium* to *S. aureus* in a polymicrobial wound biofilm [32]. In clinical practice, polymicrobial PJI are complicated to manage by the need to target pathogens with different susceptibilities at the same time, such as Gram-negative and Gram-positive bacteria.

Enterococci PJIs are considered difficult to treat, as are infections caused by *Candida* spp. or *Staphylococcus aureus*. In our study, overall clinical success was only 67% at 1 year. Among the other 7 studies on enterococcal PJI, the overall success rate ranged from 51.7 to 83.7% [24, 25]. This high failure rate should be put into perspective with the definitions of failure. Renz et al. [24] found microbiological success (eradication of *Enterococcus* spp.) in 83.7% but clinical success (without new surgery for septic or aseptic goals) in only 67.5%. This gap was explained by infections with other microorganisms or with reintervention without documented infection. Among our 9 patients with clinical failures, 4 with new microorganisms were documented, and 5 were culture negative or without microbiological findings. Therefore, no cases of relapse with *Enterococcus* spp. were found. This high rate of clinical failure contrasting with a low rate of microbiological failure could be linked to co-founding factors such as comorbidities or copathogens.

Two-stage exchange is recommended by the IDSA for difficult-to-treat organisms such as methicillin resistant, *Staphylococcus aureus*, *Candida* spp. or enterococci [17]. This strategy involves the removal of prosthetic components and the debridement of infected tissue followed, within 2 weeks to several months after the first stage, by reimplantation of a new prosthesis in a second stage. This approach offers better clinical success but at the cost of multiple surgeries and a possible poorer functional outcome [17]. Among others studies focused on enterococcal PJI, overall success rate was ranged from 45.5 to 83.3% for 1-stage exchange and from 43.8 to 100% for 2-stage exchange [11, 12, 25]. In our study, only 6 patients benefited from 1-stage exchange, with a success rate of 100%

Table 3 Medico-surgical treatment and outcome of 36 patients with enterococci PJI and osteosynthesis-associated infection

Variable	Prosthetic joint infection $n=24$ (%)	Osteosynthesis associated infection $n=12$ (%)	p*	All episodes $n=36$ (%)
Type of surgical therapy				
DAIR	7 (29.2)	4 (33.3)	1	11 (30.6)
1-stage exchange	9 (37.5)	2 (16.7)	0.27	11 (30.6)
2-stage exchange	8 (33.3)	0 (0)	**0.03**	8 (22.2)
Withdrawal of device	0 (0)	6 (50)	**0.0005**	6 (16.7)
Antimicrobial therapy				
Amoxicillin	10 (41.6)	5 (41.6)	1	15 (41.6)
Rifampicin	8 (34.7)	2 (16.6)	0.44	10 (27.8)
Levofloxacin	4 (17.3)	5 (41.6)	0.12	9 (25)
Ofloxacin	0 (0)	1 (8.3)	0.33	1 (2.7)
Ciprofloxacin	0 (0)	1 (8.3)	0.33	1 (2.7)
Linezolid	5 (21.7)	4 (33.3)	0.44	9 (25)
Vancomycin	2 (8.6)	0 (0)	0.54	2 (5.6)
Teicoplanin	2 (8.6)	0 (0)	0.54	2 (5.6)
Daptomycin	2 (8.6)	0 (0)	0.54	2 (5.6)
Imipenem–cilastatin	2 (8.6)	1 (8.3)	1	3 (8.3)
Ceftriaxone	1 (4.3)	1 (8.3)	1	2 (5.6)
Piperacillin–tazobactam	1 (4.3)	1 (8.3)	1	2 (5.6)
Combination therapy	11 (45.8)	8 (66.6)	0.3	19 (52.8)
Duration of antimicrobial therapy				
6 weeks	9 (37.5)	5 (41.6)	1	14 (38.9)
12 weeks	13 (54.1)	6 (50)	1	19 (52.8)
Mean (SD) follow-up in month	29.7 (26)	41.8 (31)	0.2	33.8 (28)
Clinical success at 6 months	14/18 (77.8)	8/11 (72.7)	1	22/29 (75.9)
Clinical success at 1 year	12/17 (70.6)	6/10 (60.0)	0.68	18/27 (66.7)
Clinical success at 2 years	7/12 (58.3)	6/10 (60.0)	1	13/22 (59.1)
Clinical failure	5/21 (23.8)	4/10 (40.0)	0.42	9/31 (29.0)
Relapse with *Enterococcus* spp.	0/5 (0)	0/4 (0)	1	0/9 (0)
Relapse with other genus	2/5 (40.0)	2/4 (50.0)	1	4/9 (44.4)
Unknown	3/5 (60.0)	2/4 (50.0)	1	5/9 (55.6)
Lost to follow-up	2 (8.3)	1 (8.3)	1	3/36 (8.3)

Data are no. (%) of episodes, unless otherwise indicated. Where the denominator is shown, data were not available for all patients

DAIR debridement, antibiotics, and implant retention, *SD* standard deviation

*Fisher's exact test for categorical variables and Mann–Whitney *U* tests for continuous variables

Values in bold correspond to statistically significant values

($p=0.07$). Due to our small cohort of patients, we cannot draw any conclusions but believe that we must take into account not only microbiological findings in the choice of surgery but also other factors, such as age and stability of the prosthesis, quality of the periprosthetic soft tissues, patient comorbidities and preferences [17]. DAIR was the least effective strategy used in our study, with only 50.0% clinical success at 1 year. These results are consistent with those of other studies that report success rates ranging from 26 to 66% [11, 33]. Only the study by Renz et al. [24] found a success rate of 100% with DAIR, which can be explained by a drastic selection of patients with uncomplicated acute infections. This high failure rate with DAIR can be explained by a therapeutic delay during haematogenous infections and by a lack of knowledge about antibiofilm antibiotics targeting enterococci, which is an essential treatment when the implant remains in place. Further studies are needed to assess the possibility of DAIR and 1-stage exchange in enterococcal PJI.

Although our study was underpowered to detect differences, notably due to the heterogeneity of antimicrobial therapy, a better outcome was not demonstrated for patients with combination therapy and rifampicin in our study. For PJI caused by enterococci, the appropriate antimicrobial

Table 4 Antibiotic treatment and outcome of 36 patients with enterococci PJI and osteosynthesis-associated infection according to the mono or polymicrobial character

Variable	Monomicrobial $n=13$	Polymicrobial $n=23$	p*
Monotherapy	8 (61.5)	9 (39.1)	
Amoxicillin	3 (23.1)	0 (0)	0.04
Linezolid	2 (15.4)	2 (8.7)	0.6
Vancomycin	1 (7.7)	1 (4.3)	1
Teicoplanin	1 (7.7)	1 (4.3)	1
Daptomycin	1 (7.7)	1 (4.3)	1
Imipenem–cilastatin	0 (0)	2 (8.7)	0.52
Piperacillin–tazobactam	0 (0)	2 (8.7)	0.52
Combination therapy	5 (38.5)	14 (60.8)	0.29
Amoxicillin/rifampicin	3 (23.1)	2 (8.7)	0.32
Amoxicillin/rifampicin/levofloxacin	0 (0)	1 (4.3)	1
Amoxicillin/levofloxacin	1 (7.7)	2 (8.7)	1
Amoxicillin/ceftriaxone	1 (7.7)	1 (4.3)	1
Amoxicillin/ciprofloxacin	0 (0)	1 (4.3)	1
Linezolid/levofloxacin	0 (0)	3 (13)	0.29
Linezolid/rifampicin	0 (0)	2 (8.7)	1
Ofloxacin/rifampicin	0 (0)	1 (4.3)	1
Levofloxacin/rifampicin	0 (0)	1 (4.3)	1
Duration of antimicrobial therapy			
6 weeks	3 (23.1)	11 (47.8)	0.17
12 weeks	9 (69.2)	10 (43.5)	0.17
Clinical success at 6 month	6/9 (66.7)	16/20 (80.0)	0.64
Clinical success at 1 year	5/8 (62.5)	13/19 (68.4)	1
Clinical success at 2 years	2/3 (66.7)	11/17 (64.7)	1

Data are no. (%) of episodes, unless otherwise indicated. Where the denominator is shown, data was not available for all patients

*Fisher's exact test for categorical variable

therapy remains unclear in the literature. One of the treatments of choice is amoxicillin in monotherapy as recommended by several Infectious Diseases Societies [15–17]. Although *E. faecalis* is susceptible to ampicillin, the low bactericidal activity of antibiotics targeting the cell wall, such as β-lactams, and the high rate of treatment failure have led to the emergence of antibiotic combination therapy [34]. Combination treatments with amoxicillin and gentamicin or ceftriaxone are based on experimental studies showing synergistic activity and are modelled on the management of enterococcal endocarditis [21, 35]. Because rifampicin is a key treatment for staphylococcal PJI notably due to it anti-biofilm activity [17, 36, 37], amoxicillin and rifampicin association is proposed by the French and Spanish Infectious Diseases committees for enterococcal PJI management [15, 16, 38]. In a retrospective cohort study that included 50 episodes of PJI due to enterococci, El Hellou et al. [23] did not find any difference in the outcome between those treated with monotherapy and those receiving combination therapy. Two studies, including the one with the largest case series to date, found better outcomes with rifampicin use [9, 12]. Indeed, Tornero et al. [9] showed in a multicentric cohort study that the use of rifampicin was significantly associated with early infections and increase in the cure rate (60%, $p=0.04$). Thompson et al. [12] reported in a study of 49 patients with enterococcal PJI that there was better clinical success in patients receiving rifampicin in combination with another antibiotic (100%, $p=0.04$). Other combinations of antibiotics, especially with daptomycin, fosfomycin or linezolid, are emerging treatments for enterococcal bloodstream infections and endocarditis but require further evaluation in PJI [34].

A consistent finding of our study was the association between lower age and clinical success. This result was not found in other studies on enterococcal PJI [9, 11, 12, 23–26] but higher risk of adverse outcome has been reported

Table 5 Outcome of 27 patients with enterococci PJI and osteosynthesis-associated infection; univariate analysis

Variable	Clinical success at 1 year $n=18$ (%)	Clinical failure at 1 year $n=9$ (%)	p*
Mean (SD) age years	64.4 (18.3)	77.4 (9.5)	0.06
Male sex	9 (50.0)	5 (55.6)	1
Mean (SD) BMI in kg/m^2	28.6 (4.9)	32.6 (4.6)	0.05
Polymicrobial infection	13 (72.2)	6 (66.7)	1
Type of surgical therapy			
DAIR	5 (27.8)	5 (55.6)	0.22
1-stage exchange	6 (33.3)	0 (0)	0.07
2-stage exchange	4 (22.2)	3 (33.3)	0.65
Withdrawal of device	3 (16.7)	1 (11.1)	1
Antimicrobial therapy			
Amoxicillin	10 (55.6)	2 (22.2)	0.22
Levofloxacin	5 (27.8)	2 (22.2)	1
Rifampicin	6 (33.3)	1 (11.1)	0.36
Linezolid	4 (22.2)	2 (22.2)	1
Combination therapy	11 (61.1)	3 (33.3)	0.24
Duration of antibiotic therapy			
6 weeks	5 (27.8)	6 (66.7)	0.10
12 weeks	12 (66.7)	2 (22.2)	**0.04**

Data are no. (%) of episodes, unless otherwise indicated

BMI body mass index, *SD* standard deviation

*Fisher's exact test for categorical variables and Mann–Whitney U tests for continuous variables

Values in bold correspond to statistically significant values

Table 6 Outcome of 17 patients with enterococci PJI; univariate analysis

Variable	Clinical success at 1 year $n=12$ (%)	Clinical failure at 1 year $n=5$ (%)	p*
Mean (SD) age years	75.4 (7.5)	84.2 (2.6)	**0.02**
Male sex	7 (58.3)	3 (60.0)	1
Mean (SD) BMI in kg/m^2	28.7 (5.6)	32.8 (3.8)	0.13
Polymicrobial infection	7 (58.3)	3 (60.0)	1
Type of surgical therapy			
DAIR	4 (33.3)	2 (40.0)	1
1-stage exchange	4 (33.3)	0	0.26
2-stage exchange	4 (33.3)	3 (60.0)	0.59
Antimicrobial therapy			
Amoxicillin	6 (50.0)	0	0.10
Levofloxacin	2 (16.7)	0	1
Rifampicin	5 (41.7)	0	0.24
Linezolid	3 (25.0)	1 (20.0)	1
Vancomycin	0	2 (40.0)	0.07
Teicoplanin	0	1 (20.0)	0.29
Imipenem–cilastatin	1 (8.3)	1 (20.0)	0.39
Piperacillin–tazobactam	1 (8.3)	0	1
Daptomycin	2 (16.7)	0	1
Combination therapy	6 (50.0)	0	0.10
Duration of antibiotic therapy			
6 weeks	4 (33.3)	3 (60.0)	0.59
12 weeks	8 (66.7)	0	**0.03**

Data are no. (%) of episodes, unless otherwise indicated

BMI body mass index, *SD* standard deviation

*Fisher's exact test for categorical variables and Mann–Whitney U tests for continuous variables

Values in bold correspond to statistically significant values

after total joint arthroplasty revision in older patients [39] as well as an increased mortality rate related to PJI [40]. Many factors could explain this higher success rate. First, immunosenescence, defined as the decline of the immune function during aging, can result in a compromised immune response against pathogens and greater susceptibility to infections [41]. Second, elderly patients may have geriatric comorbidities (such as incontinence, immobility, lower limb ulcers, arteriopathy, osteoporosis and/or malnutrition) which could contribute to clinical failure due to delayed healing, increased bacterial contamination of the scare or/and increased risk of periprosthetic fracture [42].

Our study has several limitations. First, it is a retrospective single-centre study, confounding factors may exist, and the data cannot be extrapolated to other centres. Second, the number of patients included is small, and unfortunately, almost 20% of patients had incomplete follow-up. In a supplementary analysis considering lost to follow-up as failure, no factor was associated with clinical success (Table S1). However, results of a recent randomized controlled trial showed that antibiotic therapy for 6 weeks was not shown to be noninferior to antibiotic therapy for 12 weeks and resulted in a higher percentage of patients with unfavorable outcomes [43]. Therefore, we suggest treating PJI enterococcal infection with 3 months of antimicrobial therapy. Third, one-year period after septic surgery is too short to judge clinical success, and some patients may have relapsed after the duration of the follow-up. Finally, the inclusion of patients with osteosynthesis-associated infection made our cohort more heterogeneous, which may bias the analysis of the results. However, the inclusion of patients with osteosynthesis-associated infection allowed us to increase the size of our

Table 7 Outcome of 10 patients with enterococci osteosynthesis-associated infection; univariate analysis

Variable	Clinical success at 1 year $n=6$ (%)	Clinical failure at 1 year $n=4$ (%)	p*
Mean (SD) age years	42.3 (11.8)	69 (7.8)	**0.009**
Male sex	2 (30.0)	2 (50.0)	1
Mean (SD) BMI in kg/m^2	28.3 (3.8)	32.5 (5.8)	0.28
Polymicrobial infection	6 (100.0)	4 (100.0)	1
Type of surgical therapy			
DAIR	1 (16.7)	3 (75.0)	0.19
1-stage exchange	2 (33.3)	0	0.47
Withdrawal of device	3 (50.0)	1 (25.0)	0.57
Antimicrobial therapy			
Amoxicillin	4 (66.7)	1 (25.0)	0.52
Levofloxacin	3 (50.0)	2 (50.0)	1
Rifampicin	1 (16.7)	1 (25.0)	1
Linezolid	1 (16.7)	1 (25.0)	1
Imipenem–cilastatin	0	1 (25.0)	0.4
Piperacillin–tazobactam	0	1 (25.0)	0.4
Combination therapy	5 (83.3)	2 (50.0)	0.5
Duration of antibiotic therapy			
6 weeks	1 (16.7)	2 (50.0)	0.5
12 weeks	4 (66.7)	2 (50.0)	1

Data are no. (%) of episodes, unless otherwise indicated

BMI body mass index, *SD* standard deviation

*Fisher's exact test for categorical variables and Mann–Whitney *U* tests for continuous variables

Values in bold correspond to statistically significant values

cohort and represent the real life of a complex bone and joint infections centre.

In conclusion, the prognosis of ODRI due to *Enterococcus* spp. is poor, as previously reported. In our small study, patients with combination therapy and rifampicin use did not demonstrate better clinical success. Further studies are needed to improve knowledge of these infections, which are difficult to treat.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00402-023-04848-4.

Acknowledgements The manuscript was edited for proper English language using American Journal Experts services (code 450F-D493-7B8C-2D94-DC9D).

Data availability The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy but are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Each author certifies that there are no funding or commercial associations (consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article related to the author or any immediate family members.

Ethics approval Approval was granted by the ethics committee of the biomedical research institute of Caen (ID 3164, 03/23/2022).

References

1. Pivec R, Johnson AJ, Mears SC, Mont MA (2012) Hip arthroplasty. Lancet 380:1768–1777. https://doi.org/10.1016/s0140-6736(12)60607-2
2. Zimmerli W, Trampuz A, Ochsner PE (2004) Prosthetic-joint infections. N Engl J Med 351:1645–1654. https://doi.org/10.1056/NEJMra040181
3. Grammatico-Guillon L, Baron S, Gettner S, Lecuyer AI, Gaborit C, Rosset P, Rusch E, Bernard L (2012) Bone and joint infections in hospitalized patients in France, 2008: clinical and economic outcomes. J Hosp Infect 82:40–48. https://doi.org/10.1016/j.jhin.2012.04.025
4. Cattoir V, Giard JC (2014) Antibiotic resistance in enterococcus faecium clinical isolates. Expert Rev Anti Infect Ther 12:239–248. https://doi.org/10.1586/14787210.2014.870886
5. Bjerke-Kroll BT, Christ AB, McLawhorn AS, Sculco PK, Jules-Elysée KM, Sculco TP (2014) Periprosthetic joint infections treated with two-stage revision over 14 years: an evolving microbiology profile. J Arthroplasty 29:877–882. https://doi.org/10.1016/j.arth.2013.09.053
6. Benito N, Franco M, Ribera A, Soriano A, Rodriguez-Pardo D, Sorlí L, Fresco G, Fernández-Sampedro M, Dolores Del Toro M, Guío L, Sánchez-Rivas E, Bahamonde A, Riera M, Esteban J, Baraia-Etxaburu JM, Martínez-Alvarez J, Jover-Sáenz A, Dueñas C, Ramos A, Sobrino B, Euba G, Morata L, Pigrau C, Coll P, Mur I, Ariza J (2016) Time trends in the aetiology of prosthetic joint infections: a multicentre cohort study. Clin Microbiol Infect 22(732):e1-8. https://doi.org/10.1016/j.cmi.2016.05.004
7. Segawa H, Tsukayama DT, Kyle RF, Becker DA, Gustilo RB (1999) Infection after total knee arthroplasty. A retrospective study of the treatment of eighty-one infections. J Bone Jt Surg Am. 81:1434–1445. https://doi.org/10.2106/00004623-199910000-00008
8. Marculescu CE, Berbari EF, Hanssen AD, Steckelberg JM, Harmsen SW, Mandrekar JN, Osmon DR (2006) Outcome of prosthetic joint infections treated with debridement and retention of components. Clin Infect Dis 42:471–478. https://doi.org/10.1086/499234
9. Tornero E, Senneville E, Euba G, Petersdorf S, Rodriguez-Pardo D, Lakatos B, Ferrari MC, Pilares M, Bahamonde A, Trebse R, Benito N, Sorli L, del Toro MD, Baraiaetxaburu JM, Ramos A, Riera M, Jover-Sáenz A, Palomino J, Ariza J, Soriano A (2014) Characteristics of prosthetic joint infections due to *Enterococcus* sp. and predictors of failure: a multi-national study. Clin Microbiol Infect 20:1219–1224. https://doi.org/10.1111/1469-0691.12721
10. Senthi S, Munro JT, Pitto RP (2011) Infection in total hip replacement: meta-analysis. Int Orthop 35:253–260. https://doi.org/10.1007/s00264-010-1144-z
11. Rasouli MR, Tripathi MS, Kenyon R, Wetters N, Della Valle CJ, Parvizi J (2012) Low rate of infection control in enterococcal periprosthetic joint infections. Clin Orthop Relat Res 470:2708–2716. https://doi.org/10.1007/s11999-012-2374-8
12. Thompson O, Rasmussen M, Stefánsdóttir A, Christensson B, Åkesson P (2019) A population-based study on the treatment and outcome of enterococcal prosthetic joint infections. A consecutive

series of 55 cases. J Bone Jt Infect. 4:285–291. https://doi.org/10.7150/jbji.35683
13. Frank KL, Vergidis P, Brinkman CL, Greenwood Quaintance KE, Barnes AM, Mandrekar JN, Schlievert PM, Dunny GM, Patel R (2015) Evaluation of the *Enterococcus faecalis* biofilm-associated virulence factors AhrC and eep in rat foreign body osteomyelitis and in vitro biofilm-associated antimicrobial resistance. PLoS ONE 10:e0130187. https://doi.org/10.1371/journal.pone.0130187
14. Sandoe JA, Wysome J, West AP, Heritage J, Wilcox MH (2006) Measurement of ampicillin, vancomycin, linezolid and gentamicin activity against enterococcal biofilms. J Antimicrob Chemother 57:767–770. https://doi.org/10.1093/jac/dkl013
15. Société de Pathologie Infectieuse de Langue Française (SPILF); Collège des Universitaires de Maladies Infectieuses et Tropicales (CMIT); Groupe de Pathologie Infectieuse Pédiatrique (GPIP); Société Française d'Anesthésie et de Réanimation (SFAR); Société Française de Chirurgie Orthopédique et Traumatologique (SOFCOT); Société Française d'Hygiène Hospitalière (SFHH); Société Française de Médecine Nucléaire (SFMN); Société Française de Médecine Physique et de Réadaptation (SOFMER); Société Française de Microbiologie (SFM); Société Française de Radiologie (SFR-Rad); Société Française de Rhumatologie (SFR-Rhu) (2010) Recommendations for bone and joint prosthetic device infections in clinical practice (prosthesis, implants, osteosynthesis). Société de pathologie infectieuse de langue Française. Med Mal Infect 40:185–211. https://doi.org/10.1016/j.medmal.2009.12.009
16. Ariza J, Cobo J, Baraia-Etxaburu J, Benito N, Bori G, Cabo J, Corona P, Esteban J, Horcajada JP, Lora-Tamayo J, Murillo O, Palomino J, Parra J, Pigrau C, Del Pozo JL, Riera M, Rodríguez D, Sánchez-Somolinos M, Soriano A, Del Toro MD, de la Torre B (2017) Executive summary of management of prosthetic joint infections. Clinical practice guidelines by the Spanish society of infectious diseases and clinical microbiology (SEIMC). Enferm Infecc Microbiol Clin 35:189–195. https://doi.org/10.1016/j.eimc.2016.08.012
17. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR (2013) Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious diseases society of America. Clin Infect Dis 56:e1-25. https://doi.org/10.1093/cid/cis803
18. Amanatullah D, Dennis D, Oltra EG, Marcelino Gomes LS, Goodman SB, Hamlin B, Hansen E, Hashemi-Nejad A, Holst DC, Komnos G, Koutalos A, Malizos K, Martinez Pastor JC, McPherson E, Meermans G, Mooney JA, Mortazavi J, Parsa A, Pécora JR, Pereira GA, Martos MS, Shohat N, Shope AJ, Zullo SS (2019) Hip and knee section, diagnosis, definitions: proceedings of international consensus on orthopedic infections. J Arthroplasty 34:S329–S337. https://doi.org/10.1016/j.arth.2018.09.044
19. Tsukayama DT, Goldberg VM, Kyle R (2003) Diagnosis and management of infection after total knee arthroplasty. J Bone Jt Surg Am. 85-A Suppl 1:S75-80. https://doi.org/10.2106/00004623-200300001-00014
20. EUCAST (2020) Clinical breakpoints and dosing of antibiotics. EUCAST
21. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL (2015) 2015 ESC guidelines for the management of infective endocarditis: The task force for the management of infective endocarditis of the European society of cardiology (ESC). Endorsed by: European association for cardio-thoracic surgery (EACTS), the European association of nuclear medicine (EANM). Eur Heart J 36:3075–3128. https://doi.org/10.1093/eurheartj/ehv319
22. Kao PHN, Kline KA (2019) Dr. Jekyll and Mr. Hide: how *Enterococcus faecalis* subverts the host immune response to cause infection. J Mol Biol 431:2932–2945. https://doi.org/10.1016/j.jmb.2019.05.030
23. El Helou OC, Berbari EF, Marculescu CE, El Atrouni WI, Razonable RR, Steckelberg JM, Hanssen AD, Osmon DR (2008) Outcome of enterococcal prosthetic joint infection: is combination systemic therapy superior to monotherapy? Clin Infect Dis 47:903–909. https://doi.org/10.1086/591536
24. Renz N, Trebse R, Akgün D, Perka C, Trampuz A (2019) Enterococcal periprosthetic joint infection: clinical and microbiological findings from an 8-year retrospective cohort study. BMC Infect Dis 19:1083. https://doi.org/10.1186/s12879-019-4691-y
25. Kheir MM, Tan TL, Higuera C, George J, Della Valle CJ, Shen M, Parvizi J (2017) Periprosthetic joint infections caused by enterococci have poor outcomes. J Arthroplasty 32:933–947. https://doi.org/10.1016/j.arth.2016.09.017
26. Ascione T, Balato G, Mariconda M, Fantoni M, Giovannenze F, Pagliano P (2019) Clinical and prognostic features of prosthetic joint infections caused by *Enterococcus* spp. Eur Rev Med Pharmacol Sci 23:59–64. https://doi.org/10.26355/eurrev_201904_17475
27. Ch'ng JH, Chong KKL, Lam LN, Wong JJ, Kline KA (2019) Biofilm-associated infection by enterococci. Nat Rev Microbiol 17(2):82–94. https://doi.org/10.1038/s41579-018-0107-z
28. Montravers P, Mohler J, Saint Julien L, Carbon C (1997) Evidence of the proinflammatory role of *Enterococcus faecalis* in polymicrobial peritonitis in rats. Infect Immun 65(1):144–149. https://doi.org/10.1128/iai.65.1.144-149.1997
29. Tien BYQ, Goh HMS, Chong KKL, Bhaduri-Tagore S, Holec S, Dress R, Ginhoux F, Ingersoll MA, Williams RBH, Kline KA (2017) *Enterococcus faecalis* promotes innate immune suppression and polymicrobial catheter-associated urinary tract infection. Infect Immun 85:e00378-e417. https://doi.org/10.1128/iai.00378-17
30. Ch'ng JH, Muthu M, Chong KKL, Wong JJ, Tan CAZ, Koh ZJS et al (2022) Heme cross-feeding can augment *Staphylococcus aureus* and *Enterococcus faecalis* dual species biofilms. ISME J 16(8):2015–2026. https://doi.org/10.1038/s41396-022-01248-1
31. Lee K, Lee KM, Kim D, Yoon SS (2017) Molecular determinants of the thickened matrix in a dual-species *Pseudomonas aeruginosa* and *Enterococcus faecalis* Biofilm. Appl Environ Microbiol 83(21):e01182-e1217. https://doi.org/10.1128/aem.01182-17
32. Weigel LM, Donlan RM, Shin DH, Jensen B, Clark NC, McDougal LK et al (2007) High-level vancomycin-resistant *Staphylococcus aureus* isolates associated with a polymicrobial biofilm. Antimicrob Agents Chemother 51(1):231–238. https://doi.org/10.1128/aac.00576-06
33. Duijf SV, Vos FJ, Meis JF, Goosen JH (2015) Debridement, antibiotics and implant retention in early postoperative infection with *Enterococcus* sp. Clin Microbiol Infect 21:e41–e42. https://doi.org/10.1016/j.cmi.2015.01.006
34. Beganovic M, Luther MK, Rice LB, Arias CA, Rybak MJ, LaPlante KL (2018) A review of combination antimicrobial therapy for *Enterococcus faecalis* bloodstream infections and infective endocarditis. Clin Infect Dis 67:303–309. https://doi.org/10.1093/cid/ciy064
35. Mainardi JL, Gutmann L, Acar JF, Goldstein FW (1995) Synergistic effect of amoxicillin and cefotaxime against *Enterococcus faecalis*. Antimicrob Agents Chemother 39:1984–1987. https://doi.org/10.1128/aac.39.9.1984
36. Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, Sánchez-Somolinos M, Baraia-Etxaburu JM, Rico A, Palomino J, Rodríguez-Pardo D, Horcajada JP, Benito N, Bahamonde A, Granados A, del Toro MD, Cobo J, Riera M, Ramos A, Jover-Sáenz A,

Ariza J (2013) A large multicenter study of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* prosthetic joint infections managed with implant retention. Clin Infect Dis 56:182–194. https://doi.org/10.1093/cid/cis746

37. Senneville E, Joulie D, Legout L, Valette M, Dezèque H, Beltrand E, Roselé B, d'Escrivan T, Loïez C, Caillaux M, Yazdanpanah Y, Maynou C, Migaud H (2011) Outcome and predictors of treatment failure in total hip/knee prosthetic joint infections due to *Staphylococcus aureus*. Clin Infect Dis 53:33440. https://doi.org/10.1093/cid/cir402
38. Hoogkamp-Korstanje JA (1997) *In-vitro* activities of ciprofloxacin, levofloxacin, lomefloxacin, ofloxacin, pefloxacin, sparfloxacin and trovafloxacin against gram-positive and gram-negative pathogens from respiratory tract infections. J Antimicrob Chemother 40:427–431. https://doi.org/10.1093/jac/40.3.427
39. Radcliffe GS, Tomichan MC, Andrews M, Stone MH (1999) Revision hip surgery in the elderly: is it worthwhile? J Arthroplasty 14(1):38–44. https://doi.org/10.1016/s0883-5403(99)90200-0
40. Jamakorzyan C, Meyssonnier V, Kerroumi Y, Villain B, Heym B, Lhotellier L et al (2019) Curative treatment of prosthetic joint infection in patients younger than 80 vs. 80 or older. Jt Bone Spine. 86(3):369–372. https://doi.org/10.1016/j.jbspin.2019.01.017
41. Aw D, Silva AB, Palmer DB (2007) Immunosenescence: emerging challenges for an ageing population. Immunology 120(4):435–446. https://doi.org/10.1111/j.1365-2567.2007.02555.x
42. Walter N, Rupp M, Bärtl S, Uecker C, Alt V (2022) The definition of the term 'Orthogeriatric Infection' for periprosthetic joint infections. Geriatr Orthop Surg Rehabil 13:21514593221111650. https://doi.org/10.1177/21514593221111649
43. Bernard L, Arvieux C, Brunschweiler B, Touchais S, Ansart S, Bru JP, Oziol E, Boeri C, Gras G, Druon J, Rosset P, Senneville E, Bentayeb H, Bouhour D, Le Moal G, Michon J, Aumaître H, Forestier E, Laffosse JM, Begué T, Chirouze C, Dauchy FA, Devaud E, Martha B, Burgot D, Boutoille D, Stindel E, Dinh A, Bemer P, Giraudeau B, Issartel B, Caille A (2021) Antibiotic therapy for 6 or 12 weeks for prosthetic joint infection. N Engl J Med 384:1991–2001. https://doi.org/10.1056/NEJMoa2020