Clinical features and outcome of bone and joint infections with streptococcal involvement: 5-year experience of interregional reference centres in the south of France

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Abstract

Streptococcal bone and joint infections are less common than staphylococcal cases. Few studies have reported the cases with well-identified Streptococcus species. Their clinical features and prognosis are not clearly known to date. Moreover, no treatment regimen has yet been clarified. We reviewed the streptococcal bone and joint infection cases managed in our centres from January 2009 to December 2013. We described the epidemiology, clinical and microbiologic characteristics, treatment approach and outcome. Among the 93 cases, 83% of patients were men with a median age of 60 years, and 90% of patients had comorbidities or risk factors. Bacteraemia occurred in 14% of cases. Serious complications occurred in six patients, including severe sepsis (two cases) and infective endocarditis (two cases). Orthopaedic device infections were observed in 35% of cases, including 17 patients with internal osteosynthesis device infection, 14 with prosthetic joint infection and three with vertebral osteosynthesis device infection. The median time between orthopaedic device implantation and onset of infection was 447 days. Fourteen species of Streptococcus were identified, including 97 isolates using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and three isolates using molecular identification. The five most represented species included S. agalactiae (37%), S. dysgalactiae (12%), S. anginosus (11%), S. constellatus (10%) and S. pneumoniae (9%). Streptococci isolates were susceptible to amoxicillin, with the exception of one S. mitis isolate. Remission 1 year after the end of treatment was recorded in 83%. One patient died of infection; eight patients had infections that failed to respond to treatment; and seven patients experienced relapse. Twenty patients (22%) had an unfavourable functional outcome, including 19 amputations and one arthrodesis. Five significant prognostic factors associated with an unfavourable clinical outcome were identified, including peripheral neuropathy (p 0.009), peripheral arterial disease (p 0.019), diabetes mellitus (p 0.031), location in the femur (p 0.0036), location in the foot (p 0.0475), osteitis without an orthopaedic device (p 0.041) and infection caused by S. dysgalactiae (p 0.020). The rate of poor outcomes remains high despite the low number of Streptococcus isolates resistant to antibiotics. Some prognostic factors, such as the presence of S. dysgalactiae, are associated with an unfavourable clinical outcome. Antibiotic regimens of streptococcal bone and joint infections are not standardized and need to be further investigated.

Keywords: Arthritis, bacterial infection, bone and joint infection, human, MALDI-TOF MS, osteitis, osteomyelitis, prosthetic joint infection, streptococci, Streptococcus

Original Submission: 5 February 2016; Revised Submission: 24 March 2016; Accepted: 25 March 2016

Article published online: 13 April 2016

Introduction

Although streptococcal bone and joint infections such as arthritis and osteomyelitis are less common than infections due to staphylococci, their role as causative agents of bone and joint infections
Infections with streptococcal involvement

Materials and Methods

Study population

This study was approved by the institutional research ethics board, and written informed consent was provided by each patient. We retrospectively reviewed 93 cases of streptococcal bone and joint infection in 3931 patients (inpatients and outpatients aged >18 years) managed in our referral centre for the treatment of bone and joint infections.

Specimen collection and microbiologic analysis

For all patients, deep samples were obtained by surgical procedures, i.e. joint fluid, crushed tissue or bone biopsy samples inoculated on 5% sheep’s blood, chocolate, Mueller-Hinton, trypticase soy and MacConkey agar plates (bioMérieux, Marcy l’Etoile, France) and incubated at 37°C in a 5% CO₂ atmosphere and in an anaerobic atmosphere for 10 days. Pure bacterial cultures, obtained by picking isolated colonies, were identified with MALDI-TOF MS and molecular methods, as previously described [22,30]. The antibiotic susceptibilities of Streptococcus sp. isolates were determined and interpreted according to the recommendations of the French Society for Microbiology and the European Committee on Antimicrobial Susceptibility Testing (CA-SFM/EUCAST, available at http://www.sfm-microbiologie.org/UserFiles/files/casfm/CASFM_EUCAST_V1_0_2014.pdf).

Statistical analysis

Data analyses were performed by SPSS 20.0 (IBM SPSS, Chicago, IL, USA). We conducted a descriptive analysis of our data.
population (chi-square test), then analysed the relapse prognostic factors after medicosurgical treatment. Univariate analysis was performed first to identify prognostic variables strongly associated (p < 0.2) with risk of relapse (proportional hazard assumptions verified on the representation of Schönefeld residuals); then multivariate analysis was performed to assess the predictions specifically for Streptococcus species after adjusting for significant variables in the univariate analysis and/or risk factors such as those reported in the literature including diabetes mellitus, location in the foot and polymicrobial infection [3,4,6,31–33]. A p value of <0.05 was considered statistically significant. Kaplan-Meier curves were used for graphical illustration. The median follow-up reverse Kaplan-Meier method was observed: chronic wound, peripheral arterial disease, peripheral neuropathy. The following risk factors were the most important and frequently identified: diabetes mellitus and tobacco use were respectively 34 (37%) and 28 cases (30%). A history of malignancy was observed in 15 patients (16%), including solid cancer in 11 cases (12%) and haematologic malignancy in four cases (4%). Nine patients (10%) were immunocompromised involving corticosteroid treatment in four cases (4%), asplenia in two cases (2%) and HIV infection in two cases (2%). The following risk factors were the most important and frequently observed: chronic wound, peripheral arterial disease, peripheral neuropathy and closed fracture (Table 1).

Local inflammation, which occurred in 64 patients (69%), was the most frequent clinical symptom, followed by purulent discharge inside the wound in 57 patients (61%), fever in 40 (43%) and erysipelas in 13 (14%). Bacteraemia occurred in 13 patients (14%). Serious complications occurred in six patients, including two cases of severe sepsis and two cases of infectious endocarditis. One case of septic shock was recorded (Table 1).

**Results**

Demographics and clinical characteristics

Of the 93 patients with streptococcal bone and joint infection, 77 patients (83%) were men, yielding a male/female ratio of 4.81; median patient age was 60 years (±17 years; range, 22–92 years). Ninety percent of our patients had comorbidities and/or risk factors. Diabetes mellitus and tobacco use were respectively identified in 34 (37%) and 28 cases (30%). A history of malignancy was observed in 15 patients (16%), including solid cancer in 11 cases (12%) and haematologic malignancy in four cases (4%). Nine patients (10%) were immunocompromised involving corticosteroid treatment in four cases (4%), asplenia in two cases (2%) and HIV infection in two cases (2%). The following risk factors were the most important and frequently observed: chronic wound, peripheral arterial disease, peripheral neuropathy and closed fracture (Table 1).

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Streptococcal bone and joint infections without an orthopaedic device were observed in 60 patients (65%), including 42 (45%) with osteitis, 12 (13%) with arthritis and nine (10%) with vertebral osteomyelitis. Of the 42 cases of streptococcal osteitis, 27 were located in the foot, including 17 cases of diabetic foot infection and seven cases of nondiabetic foot infection (four cases of peripheral neuropathy and three cases of peripheral arterial disease). Another 15 cases of streptococcal osteitis were located in the tibia (six cases), knee (two cases), ankle (two cases), femur (two cases), hib (one case), pelvis (one case) and hand (one case). Three cases of vertebral osteomyelitis without an orthopaedic device were associated with osteitis in one case and with arthritis in two cases.

Streptococcal orthopaedic implant infections were observed in 33 patients (35%), including 17 cases (18%) of orthopaedic

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**Table 1. Clinical relevance of 93 cases of osteoarticular infections due to Streptococcus species**

| Characteristic                  | Total (n = 93), n (%) | Monomicrobial infection (n = 34), n (%) | Polymicrobial infection (n = 59), n (%) |
|--------------------------------|-----------------------|----------------------------------------|----------------------------------------|
| **Sex**                        |                       |                                        |                                        |
| Female                         | 16 (17)               | 6 (18)                                 | 10 (17)                                |
| Male                           | 77 (83)               | 28 (82)                                | 49 (83)                                |
| **Comorbidities and risk factors** |                       |                                        |                                        |
| Diabetes mellitus              | 34 (37)               | 10 (29)                                | 24 (41)                                |
| Tobacco use                    | 28 (30)               | 10 (29)                                | 18 (31)                                |
| Peripheral arterial disease    | 27 (29)               | 6 (18)                                 | 21 (36)                                |
| Peripheral neuropathy          | 21 (23)               | 1 (3)                                  | 20 (34)                                |
| Malignancy                     | 15 (16)               | 6 (18)                                 | 9 (15)                                 |
| Haematologic malignancy        | 4 (4)                 | 3 (9)                                  | 1 (2)                                  |
| **Solid cancer**               | 11 (12)               | 3 (9)                                  | 8 (14)                                 |
| **Chronic liver disease**      | 10 (11)               | 1 (3)                                  | 9 (15)                                 |
| **Immunodeficiency**           | 9 (10)                | 5 (15)                                 | 4 (7)                                  |
| Corticosteroid treatment       | 4 (4)                 | 1 (3)                                  | 3 (5)                                  |
| Asplenia                       | 2 (2)                 | 2 (6)                                  | 0                                      |
| HIV infection                  | 2 (2)                 | 0                                      | 2 (3)                                  |
| Alcoholism                     | 7 (8)                 | 0                                      | 7 (12)                                 |
| Inflammatory rheumatism        | 5 (5)                 | 2 (6)                                  | 3 (5)                                  |
| Pneumonia                      | 3 (3)                 | 1 (3)                                  | 2 (3)                                  |
| Intraavenous drug use           | 2 (2)                 | 1 (3)                                  | 1 (2)                                  |
| Chronic wound                  | 42 (45)               | 1 (3)                                  | 41 (69)                                |
| Closed fracture                | 22 (24)               | 4 (12)                                 | 18 (31)                                |
| Open fracture                  | 8 (9)                 | 3 (9)                                  | 5 (8)                                  |

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*One vertebral infections without osteomyelitis were associated with osteitis and arthritis in one and two, respectively.*

*Three vertebral infections with osteomyelitis were associated with osteitis and arthritis in two cases.*

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device infection, 14 cases (15%) of prosthesis joint infection and three cases (3%) of vertebral orthopaedic device infection. One case of vertebral orthopaedic device infection was associated with orthopaedic device infection in the tibia. Most cases of orthopaedic device infection (88%) were chronic infections occurring more than 1 month after implantation (Table 1). The median time delay between orthopaedic device implantation and infection onset was 447 days. In total, the foot represented the main location of osteitis (33%), followed by the knee (15%) and tibia (15%). Six patients (5%) had multiple sites of streptococcal bone and joint infection (Table 1).

**Microbiologic characteristics**

Fourteen species of *Streptococcus* from 100 streptococcal isolates were identified, of which 97 strains (97%) were identified by MALDI-TOF MS and three (3%) by molecular biology. The five most represented species were *S. agalactiae* in 37 cases (37%), *S. dysgalactiae* in 12 cases (12%), *S. anginosus* in 11 cases (11%), *S. constellatus* in ten cases (10%) and *S. pneumoniae* in nine cases (9%) (Fig. 1).

The two most frequent streptococcal species of the 12 cases of streptococcal arthritis were *S. agalactiae* (42%) and *S. pneumoniae* (33%). The four main streptococcal species involved in the 42 cases of osteitis without an orthopaedic device were *S. agalactiae* (36%), *S. anginosus* (17%), *S. dysgalactiae* (17%) and *S. constellatus* (14%). The three main species of the 17 cases of osteitis with internal orthopaedic device infection were *S. agalactiae* (41%), *S. dysgalactiae* (18%) and *S. mitis* (18%). The two most frequent species involved in the 14 cases of joint prosthesis infection were *S. agalactiae* (36%) and *S. pneumoniae* (29%). *S. agalactiae* was the main streptococcal species (47%) involved in the 12 cases of vertebral osteomyelitis with and without an orthopaedic device. The three main streptococcal species involved in the 31 bone and joint infections located in the foot were *S. agalactiae* (39%), *S. dysgalactiae* (26%) and *S. anginosus* (19%); these species were identified in the 18 cases of diabetic foot, at 39%, 33% and 17%, respectively (Fig. 2).

Among the species of streptococci involved in bone and joint infection, *S. agalactiae* was associated with haematologic malignancy (p 0.023), *S. constellatus* with solid cancer (p 0.016), *S. dysgalactiae* with peripheral neuropathy and the foot (p 0.004 and 0.018). *S. anginosus* with a closed fracture (p 0.019) and *S. pneumoniae* with arthritis, joint prosthesis infection and in the hip (p 0.015, 0.027 and 0.004).

Thirty-four cases (37%) of streptococcal bone and joint infections were monomicrobial infections; 59 cases (63%) were associated with another bacteria species. The bone and joint infections caused by *S. agalactiae* and *S. pneumoniae* were usually monomicrobial infections (p 0.027 and 0.011). Arthritis and vertebral infections without an orthopaedic device were frequently monomicrobial infections (p 0.027 and 0.011). Among the 59 cases of polymicrobial infection, *Staphylococcus aureus* and coagulase-negative staphylococci were the main bacterial species (Fig. 1). Polymicrobial infections were
commonly observed in cases involving peripheral arterial disease, peripheral neuropathy, alcoholism, closed fractures, chronic wounds, location in the foot, and bone and joint infection caused by *S. anginosus* \((p < 0.001, 0.001, 0.045, 0.046, 0.0001, 0.001, 0.006, \text{ respectively})\).

All streptococci isolates were susceptible to amoxicillin, with the exception of one strain of *S. mitis* that demonstrated reduced susceptibility to amoxicillin. Fifty-six streptococci isolates (48%) demonstrated reduced susceptibility to doxycycline, seven strains (8%) to rifampicin and six strains (9%) to gentamicin.

**Medical and surgical treatment**

Eighty-two patients (88%) were treated by a combination of surgery with at least one antibiotic that was active against *Streptococcus* isolates. Eleven patients (12%) received only medical treatment, including five cases (5%) of arthritis, five cases of osteitis without an orthopaedic device, one case of prosthetic joint infection and two cases of vertebral osteomyelitis without an orthopaedic device (Table 2). It should be noted that these two cases were of vertebral osteomyelitis without an orthopaedic device were localized to more than one site, i.e. one case associated with arthritis and one case with osteitis without an orthopaedic device.

Amoxicillin therapy was provided in 55 cases (59%), rifampicin in 34 cases (37%), clindamycin in 23 cases (25%), quinolones in 20 cases (22%), cotrimoxazole in 21 cases (23%) and ceftriaxone in 20 cases (21%). Twenty-one cases (23%) were treated by only one antibiotic; the main antibiotics used were amoxicillin and ceftriaxone in 12 cases and three cases, respectively. The median dose of amoxicillin used was 9 g/day (range, 6–12 g/day).

Antibiotic combinations were recorded in 72 cases (77%). The most frequently used associated antibiotic was amoxicillin–rifampicin in 24 cases (26%), followed by clindamycin–cotrimoxazole in ten cases (11%) (Table 2). Short courses of initial treatment with intravenous antibiotics were provided in 49 cases (53%). The mean time of antibiotic duration was 124 days (±68 days; range, 16–350 days).

Forty-four patients (47%) were treated directly by oral antibiotics. Forty-nine patients (53%) were treated by intravenous antibiotics with a mean time of intravenous antibiotic treatment of 62 days (median, 34 ± 63 days; range, 2–238 days). Thirty-three patients (35%) were changed secondarily to oral antibiotics at a mean time of 28 days (median, 18 ± 27 days; range, 2–103 days); 16 patients were treated by intravenous antibiotics until the end of treatment.

Surgical treatment was performed in 50 cases (83%) of bone and joint infection without an orthopaedic device and in 32 cases (97%) of orthopaedic device–related infection. Ten cases (83%) of streptococcal vertebral osteomyelitis were treated with surgical debridement, including establishment of vertebral osteosynthesis in our cases. Seven cases (58%) of streptococcal arthritis without orthopaedic device infection were treated with surgical debridement and five cases (42%) with antibiotic treatment without surgical debridement. Thirty-seven cases (88%) of streptococcal osteitis without orthopaedic device infection were treated with surgical debridement and five cases (42%) with antibiotic treatment without surgical debridement. Thirty-seven cases (88%) of streptococcal osteitis without orthopaedic device infection were treated with surgical debridement and five cases (42%) with antibiotic treatment without surgical debridement. Thirty-seven cases (88%) of streptococcal osteitis without orthopaedic device infection were treated with surgical debridement and five cases (42%) with antibiotic treatment without surgical debridement. Thirty-seven cases (88%) of streptococcal osteitis without orthopaedic device infection were treated with surgical debridement and five cases (42%) with antibiotic treatment without surgical debridement. Thirty-seven cases (88%) of streptococcal osteitis without orthopaedic device infection were treated with surgical debridement and five cases (42%) with antibiotic treatment without surgical debridement.
Treatment of 93 cases of osteoarticular infections
Clinical outcome of 93 cases of bone and joint infection were treated by surgery, including 15 cases of osteosynthesis removal, one case of surgical debridement without removal and one case of amputation (Table 2).

Follow-up and clinical outcomes
A total of 93 patients were evaluated during an average follow-up time of 22 months (±15 months; range, 1–58 months). Remission at 1 year after the end of treatment was recorded in 76 patients (82%). Sixteen patients (17%) had an unfavourable clinical outcome related to infection, including one death, eight cases (9%) of failure to treat and seven cases (8%) of relapse. The median time to failure to treat was 141 days after starting treatment, and the median time to relapse was 218 days after the end of treatment. The clinical outcome of failure and relapsed cases is detailed in Table 3.

Twenty patients (22%) had an unfavourable functional outcome, including 19 amputations and one arthrodesis. Amputation was performed in 19 patients (20%), with a median time to amputation from date of infection of 447 days. Diabetic foot was the main type of streptococcal bone and joint infection, leading to amputation in 11 cases, followed by chronic device infection were treated by surgery, including 15 cases of osteosynthesis removal, one case of surgical debridement without removal and one case of amputation (Table 2).

### TABLE 2. Treatment of 93 cases of osteoarticular infections caused by Streptococcus species

| Characteristic | Value |
|----------------|-------|
| Antibiotic     |       |
| Amoxicillin    | 55 (59)|
| Rifampin       | 34 (37)|
| Clindamycin    | 23 (25)|
| Ciprofloxacin  | 21 (23)|
| Fluoroquinolone| 20 (22)|
| Ceftriaxone    | 20 (22)|
| Vancomycin     | 11 (12)|
| Ticarcillin-clavulanate | 11 (12)|
| Aminoglycoside | 9 (10) |
| Piperacillin-tazobactam | 5 (5) |
| Imipenem-cliastatin | 4 (4) |
| Telocplatin    | 5 (5)  |
| Doxycycline    | 2 (2)  |
| Hyperbaric oxygen therapy | 16 (17) |
| Osteoarticular infection without orthopaedic device | 60 (65) |
| Vertebral osteomyelitis | 9 (10) |
| Medical treatment only | 2 (2) |
| Surgical treatment | 7 (8) |
| Surgical debridement | 3 (3) |
| Surgical debridement and establishment of internal osteosynthesis device | 4 (4) |
| Arthritis      | 12 (13) |
| Medical treatment only | 5 (5) |
| Surgical treatment | 7 (8) |
| Surgical debridement | 7 (8) |
| Surgical debridement and establishment of internal osteosynthesis device | 0 |
| Amputation     | 17 (18) |
| Osteitis       | 42 (45) |
| Medical treatment only | 5 (5) |
| Surgical treatment | 37 (40) |
| Surgical debridement | 21 (23) |
| Surgical debridement and establishment of internal osteosynthesis device | 1 (1) |
| Amputation     | 18 (19) |
| Osteoarticular infection with orthopaedic device | 33 (35) |
| Vertebral osteomyelitis | 3 (3) |
| Medical treatment only | 0 |
| Surgical treatment | 3 (3) |
| Surgical debridement without removal | 0 |
| Osteosynthesis removal and implantation of new device | 3 (3) |
| Prosthetic joint | 14 (15) |
| Medical treatment only | 1 (1) |
| Surgical treatment | 13 (14) |
| Surgical debridement without removal | 6 (6) |
| One-stage exchange strategy | 0 (0) |
| Two-stage exchange strategy | 0 (0) |
| Amputation     | 0 |
| Internal osteosynthesis device infection | 17 (18) |
| Medical treatment only | 0 |
| Surgical treatment | 17 (18) |
| Surgical debridement without removal | 1 (1) |
| Osteosynthesis removal | 15 (16) |
| Osteosynthesis removal and implantation of new device | 0 |
| Amputation     | 1 (1)  |

### TABLE 3. Clinical outcome of 93 cases of bone and joint infection due to Streptococcus species

| Characteristic | Value |
|----------------|-------|
| Remission after 1 year after end of treatment | 76 (82) |
| Death | 7 (8) |
| During treatment period | 3 (3) |
| After end of treatment | 4 (4) |
| Causes of death | 3 (3) |
| Death by infection | 1 (1) |
| Death by cancer | 3 (3) |
| Death by acute respiratory distress syndrome | 2 (2) |
| Death by suicide | 1 (1) |
| Unfavourable clinical outcomes | 16 (17) |
| Death by infection | 1 (1) |
| Failure during treatment | 8 (9) |
| Median time to failure after further treatment | 141 days |
| Evolution | 4 (4) |
| Remission after further ATB | 1 (1) |
| Failure after further treatment | 4 (4) |
| Wound care only | 2 (2) |
| Wound care with suppressive antibiotic therapy | 2 (2) |
| Remission after osteoartesis | 1 (1) |
| removal and antibiotic therapy | 1 (1) |
| Amputation | 2 (2) |
| Relapse | 1 (1) |
| Median time to relapse (after end of treatment) | 218 days |
| Evolution (after further treatment) | 2 (2) |
| Remission | 5 (5) |
| Amputation | 19 (20) |
| Median time to amputation (from date of infection) | 447 days |
| Type of infection | 12 (12) |
| Diabetic foot | 11 (11) |
| Ischemic foot | 1 (1) |
| Chronic wound of foot | 1 (1) |
| Chronic osteitis | 5 (5) |
| Joint prosthesis infection | 1 (1) |
| Delay of amputation | 3 (3) |
| Before starting antibiotic treatment | 2 (2) |
| Diabetic foot | 3 (3) |
| During antibiotic treatment | 10 (11) |
| Neoplastic transformation | 1 (1) |
| Ischemic foot | 1 (1) |
| Diabetic foot | 5 (5) |
| Chronic osteitis | 2 (2) |
| Joint prosthesis infection | 1 (1) |
| Treatment failure | 1 (1) |
| After end of antibiotic treatment | 7 (8) |
| Neoplastic transformation | 0 |
| Ischemic foot | 0 |
| Diabetic foot | 4 (4) |
| Chronic osteitis | 3 (3) |
| Joint prosthesis infection | 0 (0) |
| Failure to treatment | 2 (2) |
| Relapse | 5 (5) |
| Reason for amputation | 2 (2) |
| Treatment failure | 1 (1) |
| Relapse | 6 (6) |
| Other | 12 (12) |
| Neoplastic transformation of foot osteitis | 1 (1) |
| Ischemic foot | 1 (1) |
| Diabetic foot | 6 (6) |
| Chronic osteitis | 2 (2) |
| Joint prosthesis infection | 1 (1) |

*Unfavourable clinical outcome was included in cases of treatment failure and relapse. Data are presented as n (%) unless otherwise indicated.*

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ostitis in five cases, ischemic foot in one case, a chronic foot wound in one case and joint prosthesis infection in one case.

Three amputations were performed before initiating antibiotic treatment; all were diabetic foot infections. Ten amputations were performed during antibiotic treatment involving diabetic foot infection in five cases, chronic ostitis in two cases, neoplastic transformation in one case, ischemic foot in one case and prosthesis joint infection in one case. Seven amputations were performed after the end of antibiotic treatment involving relapses in six cases, diabetic foot infection in four cases, chronic ostitis in three cases and failure to treat in two cases. One patient had two amputations: one before treatment and one after the end of antibiotic treatment for relapse (Table 3).

Seven patients (8%) died, including four during the treatment period and three after the end of treatment. One patient died of infection; two died of acute respiratory distress syndrome related to severe pneumonia; three deaths were related to cancer; and there was one case of suicide.

In the univariate analysis (Table 4), five significant prognostic factors associated with an unfavourable clinical outcome were identified, including peripheral neuropathy (odds ratio (95% confidence interval): 5.25 (1.56–17.71) p 0.009), peripheral arterial disease (4.55 (1.39–14.93) p 0.019), diabetes mellitus (4.07 (1.23–13.49) p 0.031), location in the femur (relative risk 2.10 (1.01–4.00) p 0.0475), osteitis without an orthopaedic device (1.85 (1.02–3.40) p 0.0387), and osteitis associated with pacemaker infection (1.70 (1.01–2.86) p 0.043). We did not identify any specific factors in the multivariate analysis adjusted for diabetes mellitus, location in the foot and polymicrobial bone and joint infection. The Kaplan-Meier curve showed that bone and joint infections caused by *S. dysgalactiae* have worse clinical outcomes than other streptococcal species (Fig. 3).

### Discussion

Here we report a large series of streptococcal bone and joint infections identified at the species levels, representing 2.4% of the bone and joint infections followed up in our reference centres over the past 5 years. Streptococcal bone and joint infections, which are less common than staphylococci, were reported to be approximately 2% to 15.4% in the literature [1,2,34–36]. As for the cases of *S. dysgalactiae*, strategy and treatment approaches have improved the management over the last 20 years. There are now specific treatment protocols dedicated to specific staphylococcal species [37]. However, no similar approaches exist for streptococcal bone and joint infections.

| Patient characteristic | Odds ratio | 95% confidence interval |
|------------------------|------------|------------------------|
| Male sex               | 3.25       | —                      |
| Comorbidities and risk factors | — | — |
| Tobacco use            | 0.62       | —                      |
| Alcoholism             | 2.96       | —                      |
| Chronic liver disease  | 2.65       | —                      |
| Peripheral neuropathy  | 5.25       | 1.56–17.71             |
| Peripheral arterial disease | 4.55 | 1.39–14.93         |
| Diabetes mellitus      | 4.07       | 1.23–13.49             |
| Malignancy             | 0.40       | —                      |
| Immunodeficiency       | 0.64       | —                      |
| Inflammatory rheumatism| 1.36       | —                      |
| Pneumonia              | 5.69       | —                      |
| Chronic wound          | 2.55       | —                      |
| Open fracture          | 0.75       | —                      |
| Closed fracture        | 1.36       | —                      |
| Orthopaedic device     | 1.01       | —                      |
| Prosthetic joint infection | — | — |
| Type of infection      |            |                        |
| Arthritis              | —          | —                      |
| Osteitis without       | 3.75       | 1.08–13.06             |
| Orthopaedic device     | —          | —                      |
| Vertebral osteomyelitis| 0.88       | —                      |
| Prosthetic joint infection | — | — |
| Osteosynthesis         | 1.19       | —                      |
| device infection       | —          | —                      |
| Vertebral osteosynthesis| — | — |
| device infection       | —          | —                      |
| Localization of infection | — | — |
| Starmoetricar         | —          | —                      |
| Shoulder              | —          | —                      |
| Wrist                | —          | —                      |
| Hand                | —          | —                      |
| Vertebral            | 0.56       | —                      |
| Pelvis               | —          | —                      |
| Hip                | 0.64       | —                      |
| Femur               | —          | —                      |
| Knee                | —          | —                      |
| Tibia               | 2.60       | —                      |
| Ankle              | 0.75       | —                      |
| Foot                | 1.70       | —                      |
| Multiple localization | —          | —                      |
| Streptococcal species |            |                        |
| *oculomisimus*         | —          | —                      |
| *agelaci*             | 1.12       | —                      |
| *angliss*             | —          | —                      |
| *constellatus*         | 1.62       | —                      |
| *dysgalactiae*        | 5.40       | 1.41–20.65             |
| *equus*               | —          | —                      |
| *intermedus*          | —          | —                      |
| *massalens*           | —          | —                      |
| *mixis*               | 0.88       | —                      |
| *oralis*              | 1.85       | —                      |
| *pneumoniae*          | —          | —                      |
| *pyogenes*            | —          | —                      |
| *salinis*             | —          | —                      |
| *sanginis*            | —          | —                      |
| Polymicrobial infection | 2.44   | 0.23–12.83           |
| Antibiotic            |            |                        |
| Amoxicillin           | 0.84       | —                      |
| Third-generation      | 1.01       | —                      |
| Cephalosporin         | —          | —                      |
| Ticarcillin–clavulanate| 0.50 | — |
| Piperacillin–tazobactam| 0.73 | — |
| Imipenem–cilastatin   | —          | —                      |
| Rifampicin            | 0.99       | —                      |
| Dicloxacillin         | 5.69       | —                      |
| Amoxicillin          | 0.64       | —                      |
| Clindamycin           | 2.76       | —                      |
| Fluoroquinolones      | 2.05       | —                      |
| Cotrimoxazole         | 2.42       | —                      |
| Vancocin and teicoplanin | — | — |
| Hyperbaric oxygen therapy | 0.73  | — |
| Surgical treatment    | —          | —                      |

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Streptococcal bone and joint infections have been reported to be frequent in women (56–62%) [6,15], which contrasts with our finding that only 17% of the cases in our study involved women. Men were affected more often than women, and therefore the demographic characteristics of streptococcal bone and joint infection in our patients were similar to those found in bone and joint infection caused by staphylococci or anaerobic bacterial bone and joint infection [26,38].

Numerous risk factors have previously been associated with bone and joint infections, including malignancy, immunodeficiency, diabetes mellitus, age over 65 years, chronic alcoholism, inflammatory rheumatism [3,4,6,31], diabetic foot and decubitus ulcers, especially for osteomyelitis [31]. Most cases of streptococcal bone and joint infection in our study presented a comorbidity or a risk factor at a rate higher than in previous studies (36–38%) [6,15]. This finding could explain the significant rate of amputation (20%), death (8%) and unfavourable clinical outcomes (17%). Beyond the well-known comorbidity and risk factors for streptococcal bone and joint infection, we observed a significant association between haematologic malignancy and infection with *S. agalactiae* (p 0.023) and solid cancer and infection with *S. constellatus* (p 0.016). This observation has been poorly reported in previous studies. We have also identified three main comorbidities that were significantly associated with unfavourable clinical outcomes: peripheral neuropathy (p 0.009), peripheral arterial disease (p 0.019) and diabetes mellitus (p 0.031).

Most of our cases of streptococcal orthopaedic device infection (88% of the 33 cases) were chronic infections occurring after 1 month of implantation, as reported in previous studies [8,15]. The identification of streptococcal isolates from blood cultures in our series (14% of cases) was less frequent than that in the literature (27–72%).

We identified 14 species of 100 streptococcal isolates involved in bone and joint infection almost exclusively by MALDI-TOF MS. Only three isolates (*S. agalactiae, S. pneumoniae* and *S. anginosus*) required molecular identification. *S. agalactiae* was the most frequent species (37% of cases) in our study; it was observed in 12% to 75% of cases in previous studies [6,10,12,15,32,33,39]. *S. pneumoniae* is known as a pathogen of arthritis without an orthopaedic device [6] and vertebral osteomyelitis [12]. Nevertheless, we have identified four cases of pneumococcal prosthetic joint infection and one case of orthopaedic device infection; these types of infection are poorly reported in the literature.

**FIG. 3.** Unfavourable clinical outcome according to bone and joint infection caused by *Streptococcus dysgalactiae* vs. other streptococcal species by Kaplan-Meier test.

- **Streptococcus species**
  - *Streptococcus dysgalactiae*
  - Other streptococcal species
  - Censored
  - Censored

Unfavorable clinical outcome vs. time in month.
Among the 14 Streptococcus species involved in bone and joint infection in our study, S. dysgalactiae was the second streptococcal species (12%). Only a few cases of bone and joint infection caused by S. dysgalactiae (formally group C and/or group G streptococci) have been reported [6,10,12,39–41].

The cases of streptococcal osteitis are located mainly in the foot [31]; 64% of our streptococcal osteitis cases (42 cases) were located in the foot, including 17 diabetes mellitus patients (63%). Diabetic foot osteomyelitis infections are polymicrobial in more than 50% of cases [32,33], and these infections frequently occur with Streptococcus species more than with S. aureus [31,33], although coinfection with S. aureus or Pseudomonas aeruginosa has been reported [32,33].

In our study, polymicrobial foot osteomyelitis was identified in 29 of the 59 cases of polymicrobial bone and infections with streptococcal involved. The polymicrobial nature of foot osteomyelitis in diabetic foot infection and the role of streptococci have been clearly demonstrated in a study of the microbiome of diabetic foot osteomyelitis using conventional culture techniques and 16S rRNA sequencing [42]. Besides diabetic foot osteomyelitis, the polymicrobial nature of nondiabetic foot osteomyelitis including foot osteomyelitis in patients with peripheral arterial disease, peripheral neuropathy and chronic wound were poorly reported. We have identified that, except for diabetic foot osteomyelitis with streptococcal involved (seven cases) that were mixed infection, 85% of 13 nondiabetic foot osteomyelitis with streptococcal involved were mixed infection. To confirm these results, further study is required to elucidate the role and significance of streptococci in polymicrobial foot osteomyelitis with streptococcal involvement.

In our study, foot osteitis was associated with polymicrobial infection in 93% of cases and coinfection with S. aureus in 38% of cases. Polymicrobial infections represent a significant risk factor for limb loss [32], especially when associated with S. aureus strains resistant to antibiotics [32]. These infections were identified as a prognostic factor associated with relapse in our study. The rate of unfavourable clinical outcome was high (17%) despite the very low rate of streptococcal isolate—reduced susceptibility to amoxicillin (1%) in our study. We think that antibiotic treatment regimens need to be further investigated in future studies, particularly for each well-defined Streptococcus species.

Conclusion

Streptococcal bone and joint infections are rare and are usually polymicrobial. Most streptococcal orthopaedic device infections were chronic infections. Surprisingly, the proportion of unfavourable clinical outcomes and amputations related to infection was considerable despite of low rate of antimicrobial resistance. Therefore, therapeutic failure compared to staphylococcal infection is not due to multidrug-resistant microbial strains or to the selection of resistant strains during therapy; rather, it seems to depend on the Streptococcus species involved. Our study clearly determined that some prognostic factors, such as S. dysgalactiae, were associated with unfavourable clinical outcomes.

Acknowledgements

The authors thank C. Leautier, Y. Russo and C. Peruffo for their help on clinical data with this study. The results of this study were presented at the Joint 55th Interscience Conference on Antimicrobial Agents and Chemotherapy and 28th International Congress of Chemotherapy meeting in San Diego, CA, USA.

Conflict of Interest

None declared.

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