


Staphylococcus lugdunensis: a neglected pathogen of infections involving fracture-fixation devices

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Abstract

Purpose Cases of fracture-fixation device infection involving *Staphylococcus lugdunensis* are not frequent. The clinical characteristics and the choice of treatment strategies of these infections are not obviously known to date.

Methods We performed a review of fracture-fixation device infection involving *S. lugdunensis* managed by our centres.

Results Among the 38 cases of fracture-fixation device infection involving *S. lugdunensis*, 53% were located in the tibia. Most of our cases (87%) were chronic infections. Purulent discharge, which occurred in 79% of cases, was the most frequent clinical symptom, followed by pain in 63%, local inflammation in 55%, and fever in 37%. Bacteremia and severe sepsis occurred in 10% and 18% of cases, respectively. Four cases (10%) were treated exclusively with antimicrobial treatment alone. Thirty-four cases (89%) were treated with a combination of surgery with antimicrobial therapy including surgical debridement, antibiotics and osteosynthesis device retention in six cases (16%), and

osteosynthesis device removal in 27 cases (71%). The mean length of antibiotic treatment was 119 days. The relapse rate was high that was not related to selection of resistant strains. Polymicrobial infection had no impact on clinical outcome. A combination of surgery with antimicrobial therapy was identified as a significant prognostic factor associated with remission ($p = 0.042$).

Conclusions *S. lugdunensis* is probably involved in more infections than has been reported. Using appropriate microbiological methods laboratories should routinely identify the species of all coagulase-negative Staphylococci isolates involved in fracture-fixation device infection to better achieve the treatment strategies of fracture-fixation device infection involving *S. lugdunensis*.

Keywords *Staphylococcus lugdunensis* · Fracture-fixation devices · Internal fixation · Osteosynthesis · Osteomyelitis · Bone and joint infection · Infection · Bacteria · Human

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Introduction

Unlike other coagulase-negative staphylococci that is usually involved in a subacute or chronic infection, *Staphylococcus lugdunensis* is an aggressive pathogen that shares major virulence factors with *S. aureus* [1]. Cases of *S. lugdunensis* infections are often under reported due to its lack of detection in clinical laboratories using conventional phenotypic identification including biochemical assays like the Api-Staph test (Biomérieux, Marcy l'Etoile, France) and automated phenotypic identification systems including MicroScan (Dade Behring, West Sacramento, CA, USA), Vitek 2 (BioMérieux, Marcy l'Etoile, France), and Crystal GP (Becton Dickinson, Sparks, MD, USA) [2]. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry and molecular techniques have improved the identification of *S. lugdunensis* strains [2].

S. lugdunensis is a virulent coagulase-negative staphylococcus that emerges in several human infections such as infectious endocarditis, vascular infections and blood stream infections [3]. *S. lugdunensis* has been reported as a pathogen able to form biofilms that seems to play a determinant role in orthopaedic device infection particularly in prosthetic joint infection [2, 4, 5]. Only a few reports of osteoarticular infection caused by *S. lugdunensis* have been published [6–16]. However, we believe that the organisms may still be under-recognized as a pathogen in osteoarticular infections. In this study, we review the clinical features and outcomes of the cases of infection associated with fracture-fixation devices caused by *S. lugdunensis* treated by our referral centre for the treatment of bone and joint infection and in collaborating centres in southern France.

Material and methods

All the cases of infection associated with fracture-fixation devices caused by *S. lugdunensis* were managed in our centre and in collaborating centres between January 2002 and December 2014, and were diagnosed based on medical history with clinical evidence of infection using biological and/or radiological compliant data, with positive culture of *S. lugdunensis* identified from ≥ 2 surgical biopsies. The cases of osteomyelitis without orthopaedic devices and prosthetic joint infection involved *S. lugdunensis* were not included in this study. Infections involving fracture-fixation devices were classified according to the time of onset after implantation: early infection when infection is diagnosed within < 3 weeks after implantation of the orthopaedic device, delayed infections when infection develops between three and ten weeks, and late infections occur more than ten weeks after implantation. [17, 18].

Surgical biopsies obtained from all patients, i.e., joint fluid, bone biopsies or tissue samples around fracture-fixation devices were crushed in Eppendorf (Hamburg, Germany) tubes and inoculated on 5% sheep-blood, chocolate, Mueller-Hinton, trypticase soy, and MacConkey agar plates (BioMérieux, France) and incubated at 37 °C in a 5% CO₂ atmosphere and in an anaerobic atmosphere for ten days. Pure bacterial cultures, obtained by picking isolated colonies, were identified with conventional phenotypic identification such as Gram staining (Aerospray Wiescor; Elitech), catalase and oxidase activity tests, automated phenotypic identification systems included the Vitek 2 system (BioMérieux, Marcy l'Etoile, France), MALDI-TOF mass spectrometry or molecular methods, as previously described [19]. The antimicrobial susceptibilities of *S. lugdunensis* isolates to fosfomicin, fusidic acid, clindamycin, benzylpenicillin, rifampicin, quinolones, cotrimoxazole, doxycycline, aminoglycoside, vancomycin, and teicoplanin 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>. Susceptibility to methicillin was screened by agar diffusion using cefoxitin disks (BioRad, Marnes-La-Coquette, France). All of our cases were treated by standard treatment protocol (Supplementary Table S1).

We evaluated treatment success as the remission defined by the absence of infection signs evaluated at least 12 months after the end of the antimicrobial treatment. We used the last follow-up time as the endpoint. Relapse was defined by the occurrence of pain and swelling of the bone or joint, wound drainage, implant site erythema, induration or oedema, joint pain, joint effusion, fever, purulent discharge from the wound, sinus tract drainage and persistent positive culture from deep samples based on surgical procedures after the end of treatment during follow-up examinations at the clinic. Time to relapse was calculated from the date of the end of curative treatment to relapse.

We performed a descriptive analysis of our population using the IBM® SPSS® Statistics software v.20.0. Then, we analyzed the clinical outcome and prognostic factors such as co-morbidities, location of fractures-fixation devices, clinical signs, C-reactive protein levels, polymicrobial infection, and infection cases by *S. lugdunensis* resistant to antimicrobials following medico-surgical treatment strategies including antimicrobial treatment without surgery, surgical debridement, antibiotics and osteosynthesis device retention, and antibiotic with osteosynthesis device removal. First, we analyzed factors for relapse versus non-relapse cases using univariate analysis to identify prognostic variables strongly associated with remission or relapse risk ($p < 0.2$), then multivariate analysis was performed to assess the predictions, after adjusting for significant variables in the univariate analysis and/or risk

factors. A p -value less than 0.05 was considered statistically significant.

Results

Thirty-eight cases of *S. lugdunensis* infection associated with fracture-fixation devices treated by our centre. The mean age was 49 years \pm 16 years (range 28–85 years), yielding a male/female sex ratio of 3.22. Seventy-six percent of our cases had comorbidities and risk factors including diabetes mellitus and a history of open fracture, which were identified in six cases (16%) and 15 cases (39%), respectively (Table 1). The mean of the Charlson comorbidity index [20] (a combined age-

Table 1 Clinical characteristics, treatment options, and outcomes of the 38 cases of *Staphylococcus lugdunensis* infection involving fracture-fixation devices

	Number of cases (%)
Sex	
Male	29 (76)
Female	9 (24)
Co-morbidities & risk factors	
Alcoholism	5 (13)
Tobacco use	12 (32)
Diabetes mellitus	6 (16)
Inflammatory rheumatism	1 (3)
History of open fracture	15 (39)
Location of infections	
Tibia	20 (53)
Ankle	8 (21)
Knee	4 (10)
Femur	2 (5)
Foot	2 (5)
Vertebral	2 (5)
Clinical and biological signs	
Purulent discharge	30 (79)
Local inflammation	21 (55)
Pain	24 (63)
Fever	14 (37)
Bacteremia	4 (10)
Severe sepsis	7 (18)
Elevated C-reactive protein levels	22 (58)
Polymicrobial infections	23 (60)
Antimicrobial treatment alone without surgery	4 (10)
Surgical treatment	34 (89)
Surgical lavage and debridement	6 (16)
Osteosynthesis device removal	27 (71)
Osteosynthesis device replacement	1 (3)
Hyperbaric oxygen therapy	5 (13)

comorbidity score used to estimate relative risk of death from prognostic clinical covariates) was 0.66 ± 2 .

We identified 20 cases (53%) located in the tibia. Another 18 cases were located in the ankle (eight cases), knee (four cases), femur (two cases), foot (two cases), and vertebra (two cases). The mean time delay between orthopaedic device implantation and infection onset was 311 days \pm 285 days (range 5–2237 days). Most of our cases (87%) were delayed and late infections occurring after three weeks of implantation. Only five cases (13%) were early infections that occurred within three weeks of implantation.

Purulent discharge, which occurred in 30 cases (79%), was the most frequent clinical symptom, followed by pain in 24 cases (63%), local inflammation in 21 cases (55%), and fever in 14 cases (37%). Bacteremia occurred in four cases (10%) and severe sepsis was recorded in seven cases (18%). Twenty-two cases (58%) presented an elevated C-reactive protein level (≥ 40 mg/mL). We did not observe any difference of clinical features between cases of early infections that occurred within three weeks of implantation and delayed and late infections occurring after three weeks of implantation. Cases of *S. lugdunensis* infection associated with fracture-fixation devices were polymicrobial infection in 23 cases (60%). Coagulase negative staphylococci is the most frequent pathogen identified in fracture-fixation devices infection involving *S. lugdunensis* (Supplementary Fig. 1). All *S. lugdunensis* isolates were susceptible to classical anti-staphylococcal drugs used in osteoarticular infection, with the exception of three isolates resistant to fosfomycin, one isolate that was resistant to methicillin, one isolate resistant to fusidic acid, and one isolate resistant to clindamycin. Seventy-three percent of isolates were resistant to benzylpenicillin. No isolate resistant to rifampicin, quinolones, cotrimoxazole, doxycycline, aminoglycoside, vancomycin, and teicoplanin was identified.

Four cases (10%) were treated exclusively with antimicrobial treatment alone, without surgery. Thirty-four cases (89%) were treated with a combination of surgery with antimicrobial therapy including surgical debridement, antibiotics and osteosynthesis device retention in six cases (16%), osteosynthesis device replacement in one case (3%), and osteosynthesis device removal in 27 cases (71%). The mean length of antibiotic treatment was 119 days \pm 72 days (range 10–328). A total of 37 patients were evaluated with an average follow-up time of 30 months including 30 cases that were followed more than 12 months after the end of antimicrobial treatment. Remission was recorded in 32 cases (84%). Relapse was observed in five cases (13%). The mean time to relapse was 243 days \pm 85 days (range 150–365 days) after the end of treatment.

In the univariate analysis, two significant prognostic factors associated with relapse were identified, including history of open fracture ($p = 0.007$) and conservative therapy with antimicrobial alone without surgery ($p = 0.042$). A

combination of surgery with antimicrobial therapy was an independent factor associated with remission of fracture-fixation devices infection caused by *S. lugdunensis* ($p = 0.042$). However, polymicrobial infection was not associated with relapse of fracture-fixation devices infection caused by *S. lugdunensis*. The choice of surgery treatment strategies between osteosynthesis device removal and debridement, antimicrobials with osteosynthesis device retention appeared to have no impact on clinical outcome in our study. From the results of the univariate analysis, six variables including alcoholism, history of open fracture, polymicrobial infections, antimicrobial treatment alone without surgery, surgical treatment, and osteosynthesis device removal were included in the multivariate analysis. We did not identify other specific factors in the multivariate analysis adjusted for diabetes mellitus and polymicrobial infection (Table 2).

Discussion

S. lugdunensis infection is more invasive compared to those caused by other coagulase-negative staphylococci [2]. The relationship between *S. lugdunensis* and osteoarticular infections has been reported in prosthetic joint infection [6–8, 14] and in osteomyelitis without orthopedic device infection including diabetic foot osteomyelitis [16, 21]. More recently, Lourtret-Hascoët et al. reported that the cases of prosthetic joint infection caused by *S. lugdunensis* were usually acute infection and have similar relapse rate to those caused by *S. aureus*.

Cases of infections associated with fracture-fixation devices caused by *S. lugdunensis* currently appear to be under reported. To date, only 13 cases have been reported included three cases of knee fracture-fixation devices [22, 23], two

Table 2 Clinical outcome and prognostic factor of the 37 cases of fracture-fixation devices infection caused by *S. lugdunensis*

	Remission	Relapse	Univariate analysis p=	Multivariate analysis p=
Male	24	4	0.648	
Alcoholism	3	2	0.126	0.062
Tobacco use	10	2	0.530	
Diabetes mellitus	6	0	0.390	
Inflammatory rheumatism	1	0	0.865	
History of open fracture	10	5	0.007	0.037
Location of infections				
Tibia	16	3	0.527	
Ankle	8	0	0.272	
Knee	3	1	0.456	
Femur	2	0	0.745	
Foot	1	1	0.255	
Vertebral	2	0	0.745	
Clinical and biological signs				
Early infection (≤ 3 weeks of implantation)	5	0	0.544	
Delayed or late infection (> 3 weeks of implantation)	28	4	0.544	
Purulent discharge	25	4	0.708	
Local inflammation	17	4	0.266	
Pain	20	3	0.638	
Fever	12	2	0.638	
Bacteremia	4	0	0.544	
Severe sepsis	7	0	0.327	
Elevated C-reactive protein levels	19	2	0.367	
Polymicrobial infections	22	0	0.007	0.004
Antimicrobial treatment alone without surgery	1	2	0.042	0.005
Surgical treatment	31	3	0.042	0.005
Surgical lavage and debridement	5	1	0.610	
Osteosynthesis device removal	25	2	0.110	0.074
Osteosynthesis device replacement	1	0	0.865	
Hyperbaric oxygen therapy	5	0	0.462	

cases of ankle fracture-fixation devices [23], two cases of tibia fracture-fixation devices [23], two cases of toe fracture-fixation devices [23], and four cases of infection associated with vertebral arthrodesis [9, 23, 24]. Nevertheless, 38 cases were identified in our centers and in collaborating centres in the area of Marseille, Nimes, and Toulouse.

Conventional phenotypic identification tools using morphological and biochemical characteristics fail to identify *S. lugdunensis* [2]. Some automated identification systems have solved part of the problem of *S. lugdunensis* strains identification [2]. The arrival of MALDI-TOF mass spectrometry in clinical microbiology laboratories presents an alternative molecular identification tool for identification of *S. lugdunensis* strains from other coagulase-negative staphylococci [2]. The organisms can still be under-recognized as a pathogen in fracture-fixation device infections that result from improper identification of *S. lugdunensis* [3, 25] or are dismissed as contaminants of normal skin flora in surgical biopsies. In addition, physicians should be aware that a high number of *S. lugdunensis* cases tend to be with another pathogen associated with fracture-fixation device infection. The significant role of *S. lugdunensis* in polymicrobial fracture-fixation device infection should be considered when the organism was isolated from ≥ 2 surgical biopsies.

S. lugdunensis is known as a commensal coagulase-negative staphylococci that usually colonizes the skin in inguinal areas, perineum regions, on the lower extremities, and in the axillae [26]. These localizations may play a role in the potential subcutaneous dissemination of fracture-fixation device infection in patients with a history of open fracture. Among other coagulase-negative staphylococci, *S. lugdunensis* has a distinct position due to its pathogenic capacity, clinical implication that can cause an acute and more severe infection with a higher relapse rate. These clinical characteristics can be explained by the fact that *S. lugdunensis* shares the same virulence factors with *S. aureus* including hemolytic activity, resistance to lysozyme, ability to adhere to host cells by adhesins, and capacity to form biofilm [2].

In comparison to other coagulase-negative staphylococci, *S. lugdunensis* isolates were much more susceptible to narrow-spectrum antimicrobial agents [5, 27]. Despite the low rate of antimicrobial resistant *S. lugdunensis* isolates, we observed a high relapse rate in our study. Lower favourable outcome was observed in patients with *S. lugdunensis* prosthetic joint infection compared to patients with *S. epidermidis* prosthetic joint infection [5]. Surprisingly, relapse was not related to polymicrobial infection in our study. In addition, we found that relapses were associated with a history of open fracture and treatment option with antimicrobial alone without surgery. All five patients with early infection (≤ 3 weeks of implantation) and 87% of patients with delayed or late infection (> 3 weeks of implantation) have favorable outcome. These results were not significant in this population.

Our study suggests that a combination of surgery (i.e., debridement, antibiotics, and osteosynthesis device retention or osteosynthesis device removal) with prolonged antimicrobial therapy (nearly 4 months) were required to control fracture-fixation device infection caused by *S. lugdunensis*. We did not find any difference between cases treated with surgical lavage and debridement and those cases treated with osteosynthesis device removal in our study. Further prospective and randomized trial with a short term (e.g., 6 weeks) versus a long term (e.g., 4 months) of antimicrobial therapy and with surgical lavage and debridement versus osteosynthesis device removal would be required to confirm our findings. A combination of rifampicin and fluoroquinolone were used as a first-line treatment for 71% of patients in this study. Other second-line antimicrobials such as fusidic acid, clindamycin, doxycycline, co-trimoxazole, linezolid, vancomycin, and teicoplanin were used for the treatment of polymicrobial fracture-fixation device infection involving the resistance of coagulase negative staphylococci.

This study is also limited in its retrospective character and the fact that analyzed data derived from only nine hospital centers in two regions in southern France may have biased our finding by local epidemiology. We believe that increasing the description of *S. lugdunensis* in infections associated with fracture-fixation devices should allow for a better understanding of treatment strategies.

Conclusion

Although *S. lugdunensis* infections associated with fracture-fixation devices are rare, the organism should not be dismissed as a contaminant when isolated from surgical biopsies and the diagnosis should be further investigated. This organism is probably involved in more infections than has been reported. Particularly, when a laboratory does not routinely identify the species of all of its coagulase-negative Staphylococci isolates involved in infections associated with fracture-fixation devices. The choice of appropriate microbiological methods such as MALDI-TOF mass spectrometry or molecular methods to correctly identify the organism as *Staphylococcus lugdunensis* should allow clinicians to reach accurate diagnosis of *S. lugdunensis* infections associated with fracture-fixation devices. The treatment success rate for fracture-fixation device infection caused by *S. lugdunensis* was the same overall whatever the type of surgery. In general, osteosynthesis device removal should be practiced in the cases of delayed or late fracture-fixation device infection caused by *S. lugdunensis* with unstable fracture, in relapsed cases previously treated with surgical lavage and debridement or patients suffering from sepsis.

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Authors' contributions Piseth Seng: 1st author, he was involved clinical data collection, conception, design and drafting the manuscript.

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Compliance with ethical standards

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