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Epidemiology and risk factors of *Staphylococcus aureus* CC398 bone and joint infections

Kevin Bouiller^{1*} , Didier Hocquet^{2,3,4}, Marlene Sauguet^{2,3,4}, Xavier Bertrand^{2,3} and Catherine Chirouze^{1,3}

Abstract

Background: A particular ability of the *Staphylococcus aureus* clonal complex 398 (CC398) to cause bone and joint infections (BJI) remains questionable, since some studies have described high prevalence of MSSA CC398 in prosthetic joint infection (PJI) and diabetic foot osteomyelitis (DFO). Here, we described the long-term epidemiology of CC398 among *S. aureus* isolated from BJI and identified risk factors associated with CC398.

Methods: We included all bone and joint samples with *S. aureus*-positive culture in our university hospital between January 2010 and December 2017. Logistic regression was used for univariate and multivariate analysis.

Results: We identified 124 CC398 isolates among the 958 BJI-associated *S. aureus*. The proportion of CC398 among *S. aureus* increased steadily from 4% in 2010 to 26% in 2017. Only 4 isolates of CC398 were resistant to methicillin. The distribution of BJI types due to CC398 and non CC398 isolates was similar. In multivariate analysis, age ($p = 0.034$, OR = 3.9), McCabe score ($p = 0.005$, OR = 5) and inoculation mechanism ($p = 0.020$, OR = 3.7) were associated with PJI-related CC398. The year of infection ($p < 0.001$, OR = 1.6), Charlson's score ($p = 0.001$, OR = 1.5) and grade 4 (severe) of the International Working Group of the Diabetic Foot classification ($p < 0.001$, OR = 8.5) were associated with DFO-related CC398.

Conclusion: We highlighted here the emergence and spread of CC398-MSSA in BJI. Patients with comorbidities are at high risk of CC398 MSSA PJI and DFO. The spread of CC398 in the community and hospital settings remains unclear and further epidemiological studies are needed to identify the determinants of its success.

Keywords: Prosthetic joint infection, Bone joint infection, Diabetic foot infection, Human ST398, Methicillin susceptible *Staphylococcus aureus*, CC398

Background

Bone and joint infections (BJI) are a heterogeneous disease in their pathophysiology, clinical presentation, and management [1] and *Staphylococcus aureus* is the most common pathogen in almost all types of BJIs.

Foot ulcers are common in diabetic patients and bone infection is a major causal factor for lower-limb amputation

[2]. Prosthetic joint infection (PJI) remains a dreaded complication following total joint arthroplasty. PJI is reported in approximately 0.3–1.9% of all total arthroplasties.

In recent years, infections with *S. aureus* clonal complex 398 (CC398) have emerged worldwide. Whereas Methicillin-Resistant *S. aureus* (MRSA) CC398 is associated with livestock and most often responsible of colonization and mild infection in humans and animals [3], Methicillin-Susceptible *S. aureus* (MSSA) CC398 is a frequent source of infections in humans, and was described frequently in severe infections such as bloodstream infections (BSI) [4, 5]. Specifically, the

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incidence of BSIs due to MSSA CC398 has been increasing since 2007 in France [6].

The frequency of CC398 PJI isolates varied from 1.8 to 14% [7, 8] whereas 21.7% of isolates belonged to CC398 in patients with DFO [9]. Since several studies have documented a high prevalence of MSSA CC398 in prosthetic joint infection (PJI) and in diabetic foot osteomyelitis (DFO) [6, 7], a particular ability of this clone to cause BJIs remains questionable. However, risk factors for ST398 BJI remain largely unknown. In the study of Valour et al., no difference was observed between patients with MSSA ST398 and non-ST398 PJI, excepted for outcome with a less treatment failure in patients with MSSA ST398 infection.

In this study, the prevalence of CC398 among BJI-related *S. aureus* was determined and patients with BJI-related *S. aureus* CC398 were compared to patients with BJI-related *S. aureus* non-CC398, in a university hospital over 8 years, to identify risk factors associated to infections with CC398. A focus was made on patients with PJI and DFO.

Methods

Inclusion

All bone and joint bacteriological samples (per-cutaneous joint fluid aspiration, bone or joint surgical sample) with *S. aureus* positive culture between 1st January 2010 and 31 December 2017 in a French university hospital were retrospectively included.

Definitions

BJI diagnosis was based on clinical and biological evidence of infection. We extracted the clinical information from the electronic medical records of the patients.

BJIs were classified as follow: (i) orthopaedic implant (i.e. PJI or peripheral or vertebral osteosynthesis) (ii) DFO (iii) BJI related to decubitus ulcer (iv) BJI related to peripheral vascular disease (v) osteomyelitis and (vi) arthritis.

Acute (≤ 4 weeks) and chronic infections were defined on the basis of the duration of signs of infection at the prosthesis site to diagnosis.

The Charlson's comorbidity index was calculated as previously described [10]. The McCabe score was also used to evaluate underlying illness severity. Patients were classified as rapidly fatal (< 1 year), ultimately fatal (1–4 years) and non-fatal (> 5 years) underlying disease [11].

For DFO, we used the IWGDF/IDSA (International Working Group on the Diabetic Foot/ Infectious Diseases Society of America) classification which defined four grades of severity [12]. Grade 1 and 2 infections were only skin and soft tissue infections (SSTI) and were not included in the current study. Grade 3 defined infections in stable patients with local complication such as joint or bone infection. Grade 4 defined infections in patients with systemic toxicity or metabolic instability.

CC398 *S. aureus* identification

Only the first isolate from each patient was included. *S. aureus* isolates retrieved from bone and joint cultures were stored at the Centre de Ressources Biologiques Filière Microbiologique, Besançon (CRB-FMB, Biobanque BB-0033-00090). MALDI-TOF MS Microflex LT identified all the isolates as *S. aureus* with a log score value ≥ 2 according to the manufacturer's recommendations (Bruker Daltonik GmbH, Bremen, Germany). Cefoxitin susceptibility was determined using the disk diffusion method according to EUCAST recommendations (www.eucast.org). We used a CC398-lineage specific MALDI-TOF MS method to screen all *S. aureus* isolates, as described previously [13, 14] and CC398 status was confirmed by a CC398-lineage specific PCR [15].

Statistical analysis

All variables were examined by univariate analysis using the chi-square or Fisher's exact test, as appropriate. Continuous variables were analyzed by Student's t-test. All statistical tests were two tailed and $p < 0.05$ was considered statistically significant. Multivariate analysis was performed by logistic regression. A backward stepwise selection with an entry and stay level of $p = 0.2$ was used to build the final multivariate logistic regression model. Statistical analyses were computed by SPSS 22.0 (IBM, Armonk, NY, USA).

Results

Over the eight-year survey, 1080 non-duplicate *S. aureus* BJI were isolated from inpatients of our hospital. Among these, 958 (88.7%) were available for further analysis. Within this *S. aureus* BJI collection, 124 (12.9%) isolates belonged to CC398. Only 4 isolates were resistant to methicillin (one isolate in 2013 and 2015, and 2 isolates in 2017). The proportion of CC398 among *S. aureus* isolates increased steadily from 4% in 2010 to 26% in 2017 ($p < 0.001$) (Fig. 1).

Distribution of the 124 BJI-related *S. aureus* CC398 was showed in Table 1. The distribution of the types of BJIs due to isolates of *S. aureus* CC398 and non-CC398 was similar (Table 1).

A total of 144 patients had a *S. aureus* PJI (12.9%), with 23 due to CC398 isolates (Table 2). Patients with *S. aureus* CC398 PJI were younger ($p = 0.041$), had more severe illness (McCabe score) ($p = 0.016$), were more likely to have early PJI (< 3 months after primary arthroplasty) ($p = 0.023$) and had an inoculation mechanism more frequent ($p = 0.032$) than patients with *S. aureus* non-CC398 PJI. In multivariate analysis, age ($p = 0.034$, OR = 3.9 (1.3–12.0)), McCabe score ($p = 0.005$, OR = 5 (1.6–15.3)) and inoculation mechanism ($p = 0.020$, OR = 3.7 (1.2–11.3)) were associated with PJI due to *S. aureus* CC398.

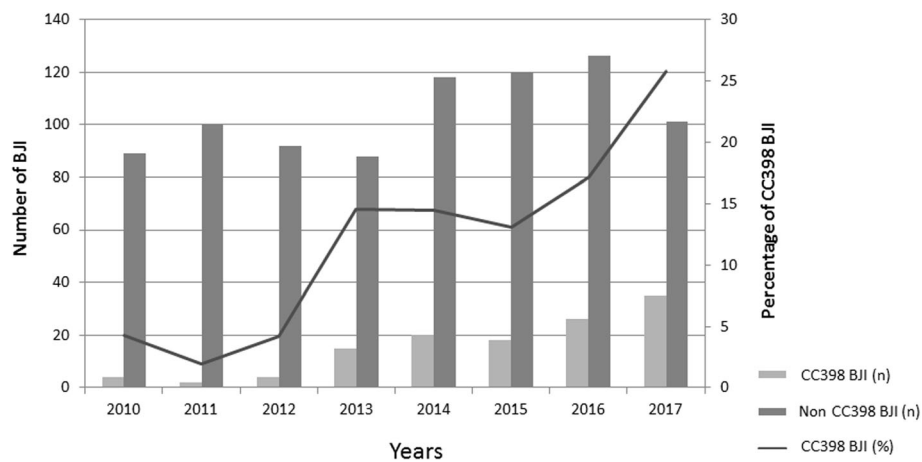


Fig. 1 Proportion of *Staphylococcus aureus* (SA) belonging to the complex clonal 398 ($n = 124$) among the SA retrieved in Bone joint and infection ($n = 958$) between 2010 and 2017 in the University Hospital of Besancon, France

Of the 244 patients with DFO (25.5%), 37 were infected with CC398 isolates (Table 3). A higher Charlson's comorbidity score ($p < 0.001$), and grade 4 of the IWGDF/IDSA classification were more frequent in patients with DFO due to *S. aureus* CC398 than in patients with non-CC398 isolates ($p < 0.001$). Multivariate analysis associated the year of infection ($p < 0.001$, OR = 1.6 (1.3–2)), the Charlson's score ($p = 0.001$, OR = 1.5 (1.2–2)) and grade 4 of the IWGDF/IDSA classification ($p < 0.001$, OR = 8.5 (3.5–20.7)) with DFO due to *S. aureus* CC398.

Discussion

In our hospital, the number of BJIs due to *S. aureus* was stable between 2010 and 2013 and then increased in 2014 to stabilize until 2017. However, the prevalence of CC398 among *S. aureus* responsible for BJIs increased steadily from 4% in 2010 to 26% in 2017. Our results describe the increasing trend of MSSA CC398 in BJIs over a 8-year period, echoing what we observed in blood-stream infections in our hospital [4].

The spread of this clone has also been reported in BJIs in other French hospitals with a prevalence varying from 1.8 to 21.7% [7–9, 16, 17]. These differences were explained by different study periods and characteristics of some types of BJI. Indeed, the frequency of CC398 PJI isolates varied from 1.8% from 14% [7, 8], whereas 21.7% of isolates belonged to CC398 in patients with DFO [9]. Interestingly, Senneville et al. showed that *S. aureus* CC398 isolates were significantly more frequent in osteomyelitis than in SSTI for patients with diabetic foot infection and suggested the possible tropism for bone of this clone [9].

This clonal group has been also described in BJIs elsewhere over the world. Uhlemann et al. identified 3 out of 64 (4.7%) CC398 positive samples with osteomyelitis in the United States [18].

Recently, ST398 was found to be the most prevalent clone in BSI-related MSSA in China (14.1%, 32/227), and the prevalence of MSSA ST398 increased from 2013 to 2019 (5.5–18.4%). However, characteristics of BSI including the presence of BJI were not described [5].

Although this clone spread globally, BJI infections with MSSA CC398 had specially been reported in France. It can be explained by the limited surveillance of MSSA in other countries and because most previous international staphylococcal clonal distribution studies have mainly focused on MRSA.

As expected, only 4 isolates were resistant to methicillin. It has been shown that MRSA ST398 and MSSA ST398 belonged to distinct lineages [19]. MRSA ST398 lineage was mainly associated with livestock. It has become a worldwide threat within the past decade and was most often responsible for mild infections, such as SSTI. Few studies had described MRSA CC398 in BJI [20–22]. In contrast, MSSA CC398 was a frequent source of *S. aureus* human infections, and was described frequently in severe infections such as BSI [5, 6, 18, 23]. No contact with livestock was found for the 4 patients with MRSA CC398 isolates. We assume that these 4 isolates were MSSA CC398 from human origin that acquired *mecA* resistance gene but further studies are needed to clarify this point.

The low resistance profile of this clone was confirmed from different studies, who found no particular resistance gene (except for an isolated resistance to macrolides related to the *ermT* gene). Regarding the virulence profile, none of the major, most well-known staphylococcal virulence genes were described in CC398 isolates, except in China, where PVL toxin was found in 80% of CC398 MSSA [5]. However, almost all isolates harboured mobile genetic element belonging to the immune evasion cluster (*chp* and *scn* genes) and the $\phi 3$ -prophage specific from human lineage and lost in the animal-adapted MRSA CC398 [8, 24, 25].

Table 1 Characteristics of patients with CC398 Bone and joint infections

| | CC 398 (n = 124) | Non CC 398 (n = 834) | Univariate P value |
|---|--------------------|----------------------|--------------------|
| Age (years), mean \pm SD | 62.2 (\pm 18.6) | 64.3 (\pm 18.7) | 0.24 |
| Male sex, n (%) | 91 (73) | 573 (69) | 0.34 |
| McCabe Score | | | |
| Non fatal, n (%) | 110 (88.7) | 761 (91.2) | 0.19 |
| Ultimately fatal, n (%) | 13 (10.5) | 63 (7.6) | |
| Rapidly fatal, n (%) | 1 (0.8) | 10 (1.2) | |
| MSSA, n (%) | 120 (97) | 701 (84) | < 0.001 |
| Charlson's comorbidity score, mean \pm SD | 2.46 (\pm 2.22) | 2.08 (\pm 1.94) | 0.073 |
| Year of infection | | | |
| 2010 | 4 (3.2) | 89 (11) | < 0.001 |
| 2011 | 2 (1.6) | 100 (12) | |
| 2012 | 4 (3.2) | 92 (11) | |
| 2013 | 15 (12) | 88 (11) | |
| 2014 | 20 (16) | 118 (14) | |
| 2015 | 18 (15) | 120 (14) | |
| 2016 | 26 (21) | 126 (15) | |
| 2017 | 35 (28) | 101 (12) | |
| Recent hospitalisation (< 1 yr), n (%) | 62 (50) | 474 (57) | 0.18 |
| Surgery (< 1 yr), n (%) | 68 (55) | 428 (51) | 0.53 |
| BJI Type | | | |
| Arthritis, n (%) | 8 (6.5) | 47 (5.6) | 0.87 |
| Osteomyelitis, n (%) | 15 (12.1) | 119 (14.3) | 0.52 |
| Vertebral osteomyelitis, n (%) | 0 | 6 (0.7) | 1 |
| Diabetic foot osteomyelitis, n (%) | 37 (29.8) | 207 (24.8) | 0.28 |
| BJI related to decubitus ulcer, n (%) | 4 (3.2) | 40 (4.8) | 0.58 |
| BJI related to peripheral vascular disease | 7 (5.7) | 101 (12.1) | 0.05 |
| Orthopaedic device infection, n (%) | 53 (42.7) | 314 (37.7) | 0.31 |
| including PJI, n (%) | 23 (18.6) | 121 (14.5) | 0.3 |
| including osteosynthesis infection, n (%) | 29 (23.4) | 184 (22.1) | 0.83 |
| including vertebral ODI, n (%) | 1 (0.8) | 9 (1.1) | 1 |
| BJI characteristics | | | |
| Evolution delay (months) | 28 (\pm 62.9) | 37.6 (\pm 101.7) | 0.32 |
| Chronic BJI (i.e. evolution delay > 4 weeks), n (%) | 49 (75) | 270 (68) | 0.29 |
| Bacteremiae, n (%) | 20 (16) | 87 (10) | 0.084 |
| BJI mechanisms | | | |
| Haematogenous, n (%) | 4 (3.2) | 49 (5.9) | 0.32 |
| Inoculation, n (%) | 62 (50) | 369 (44) | 0.27 |
| Contiguity, n (%) | 58 (47) | 416 (50) | 0.58 |

MSSA CC398 isolates could be more virulent than non-CC398, as suggested by the association of grade 4 of the IWGDF/IDSA classification in patients with *S. aureus* CC398 DFO. However, this may also reflect underlying host comorbidities and immunosuppression. This hypothesis was confirmed in our study with a high

Charlson's score index in patients with SA CC398 DFO, and a high McCabe score in patients with SA CC398 PJI. Similarly, we reported in another study that the 30-day all-cause mortality and McCabe score were higher for patients with MSSA CC398 BSI than those with non-CC398 BSI [23]. Moreover, in a study comparing eight

Table 2 Characteristics of patients with CC398 PJI

| | CC 398 PJI (n = 23) | Non CC 398 PJI (n = 121) | Univariate P value | Multivariate | |
|--|------------------------|--------------------------------|-----------------------|--------------|-----------------------|
| | | | | P value | OR (IC 95%) |
| Age (years), mean ± SD | 67.7 (±12.3) | 73.6 (±12.3) | 0.041 | 0.034 | 0.9 (0.9–0.99) |
| Male sex, n (%) | 11 (48) | 65 (54) | 0.77 | | |
| Mc Cabe Score | | | | | |
| Non fatal, n (%) | 18 (78) | 114 (94.2) | 0.016 | 0.005 | 5.1 (1.6–15.3) |
| Ultimately fatal, n (%) | 5 (22) | 6 (5) | | | |
| Rapidly fatal, n (%) | 0 (0) | 1 (0.8) | | | |
| MSSA, n (%) | 23 (100) | 108 (89) | 0.13 | | |
| Charlson's comorbidity score, mean ± SD | 2.04 (±1.89) | 1.56 (±1.61) | 0.27 | | |
| Year of infection | | | | | |
| 2010 | 2 (8.7) | 14 (11) | 0.1 | NT | |
| 2011 | 2 (8.7) | 9 (7.3) | | | |
| 2012 | 2 (8.7) | 18 (15) | | | |
| 2013 | 4 (17) | 13 (11) | | | |
| 2014 | 1 (4.3) | 17 (14) | | | |
| 2015 | 2 (8.7) | 16 (13) | | | |
| 2016 | 2 (8.7) | 24 (20) | | | |
| 2017 | 8 (35) | 12 (9.8) | | | |
| Recent hospitalisation (< 1 yr), n (%) | 13 (57) | 74 (60) | 0.92 | | |
| BJI Type | | | | | |
| Shoulder, n (%) | 1 (4.3) | 5 (4.1) | 1 | | |
| Hip, n (%) | 16 (70) | 75 (62) | 0.65 | | |
| Knee, n (%) | 6 (26) | 40 (33) | 0.68 | | |
| Ankle, n (%) | 0 | 1 (0.8) | 1 | | |
| Chronic BJI (i.e. evolution delay > 4 weeks) | 5 (28) | 51 (42) | 0.37 | | |
| Occurrence of infection after primary arthroplasty | | | | | |
| Delay (months) | 23 (±49.3) | 44.4 (±59.2) | 0.023 | NT | |
| < 3 months, n (%) | 14 (61) | 44 (36) | 0.049 | NT | |
| 3–12 months, n (%) | 3 (13) | 17 (14) | 1 | | |
| 12 months, n (%) | 7 (30) | 60 (50) | 0.14 | | |
| Bacteremia, n (%) | 8 (35) | 32 (26) | 0.57 | | |
| BJI mechanisms | | | | | |
| haematogenous, n (%) | 3 (13) | 37 (31) | 0.14 | | |
| inoculation, n (%) | 20 (87) | 74 (61) | 0.032 | 0.020 | 3.7 (1.2–11.3) |
| Contiguity, n (%) | 0 | 10 (8.3) | 0.36 | | |
| Clinical features | | | | | |
| Fever, n (%) | 10 (43) | 48 (40) | 0.66 | | |
| Sinus tract, n (%) | 7 (30) | 48 (40) | 1 | | |
| Abscess, n (%) | 3 (13) | 12 (9.9) | 0.4 | | |
| Biological features | | | | | |
| Maximum CRP value (mg/L) | 163 (±69.1) | 171 (±120) | 0.9 | | |

MSSA Methicillin susceptible *Staphylococcus aureus*, BJI Bone and joint infection, NT Not included in the final model

Table 3 Characteristics of patients with CC398 diabetic foot infection

| | CC 398 DFI (n = 37) | Non CC 398 DFI (n = 207) | Univariate P value | Multivariate | |
|---|------------------------|--------------------------------|-----------------------|-------------------|-----------------------|
| | | | | P value | OR (IC 95%) |
| Age (years), mean ± SD | 69.3 (±12.5) | 70.3 (±11.3) | 0.65 | | |
| Male sex, n (%) | 28 (76) | 166 (80) | 0.68 | | |
| Mc Cabe Score | | | | | |
| Non fatal, n (%) | 34 (91.9) | 192 (92.8) | 0.81 | | |
| Ultimately fatal, n (%) | 3 (8.1) | 14 (6.7) | | | |
| Rapidly fatal, n (%) | 0 (0) | 1 (0.5) | | | |
| MSSA, n (%) | 36 (97.3) | 171 (83) | 0.013 | NT | |
| Charlson's comorbidity score, mean ± SD | 4.51 (±1.71) | 3.48 (±1.48) | < 0.001 | 0.001 | 1.5 (1.2–2) |
| Year of infection | | | < 0.001 | < 0.001 | 1.6 (1.3–2) |
| 2010 | 0 (0) | 29 (14) | | | |
| 2011 | 0 (0) | 38 (18) | | | |
| 2012 | 2 (5.4) | 23 (11) | | | |
| 2013 | 4 (11) | 25 (12) | | | |
| 2014 | 6 (16) | 24 (12) | | | |
| 2015 | 4 (11) | 24 (12) | | | |
| 2016 | 10 (27) | 22 (11) | | | |
| 2017 | 11 (30) | 22 (11) | | | |
| Recent hospitalisation (< 1 yr), n (%) | 21 (57) | 102 (49) | 0.51 | | |
| Bacteremia, n (%) | 3 (8.1) | 12 (5.8) | 0.71 | | |
| IWGDF-IDSA grade | | | | | |
| 3 (moderate), n (%) | 14 (38) | 174 (84) | < 0.001 | < 0.001 | 8.5 (3.5–20.7) |
| 4 (severe), n (%) | 23 (62) | 33 (16) | | | |

MSSA Methicillin susceptible *Staphylococcus aureus*, IDSA Infectious Diseases Society of America, IWGDF International Working Group of the Diabetic Foot, NT Not included in the final model

PJIs with MSSA CC398 to 67 PJIs with other clones of MSSA, no demographic and clinical differences were observed between these 2 groups. Conversely, MSSA CC398 BJIs were significantly associated with a lower biological inflammatory syndrome and lower treatment failure rates (0% vs. 37.3%). However a very small number of patients were included and a large number of statistical tests have been performed, which make these results difficult to interpret [8].

The mechanism of acquisition of this clone may be discussed. CC398 MSSA PJI was associated with inoculation mechanisms (mostly post-surgical). Moreover, in our study, more than 90% of patients with DFO were hospitalized in the same medical unit (endocrinology ward) and similarly, patients with PJI or device-associated infection were hospitalized in the same surgical ward. However, other patients ($n = 40/124$) were hospitalized in various wards of our hospital (medical wards $n = 10$, other surgical wards $n = 25$, intensive care units $n = 5$), with no overlapping hospital stays and were taken care by different surgeons in different surgical rooms. Because of the many cases in the same ward and the association with inoculation mechanism after surgery, we cannot rule out hospital cross-transmission. However,

the diffusion of this clone in different hospitals in France and in other countries may suggest that this clone spread in both the community and hospital settings. Interestingly, heterogeneity in geographical distribution was observed in France with a prevalence of 3.1 to 23.5% according to the hospital [8]. This heterogeneity could be explained by a greater endemic diffusion in some areas, possibly related to specific routes of transmission.

Our study has some limitations. Firstly, the retrospective collection of data may have introduced information bias. Secondly, we did not determine the population structure of non-CC398, and the control group very probably consisted of genetically diverse *S. aureus*.

Conclusion

Our local data confirm the emergence and the dissemination of MSSA CC398 in BJI, suggesting a well-adapted fitness of this clone to humans and bone.

Patients with comorbidities are at high risk of MSSA CC398 PJIs and DFOs. The mode of diffusion of this clone in community and hospital remain unclear and further epidemiological studies, based on genome exploration, are needed.

Abbreviations

BJI: Bone and joint infection; BSI: Bloodstream infection; CC398: Clonal complex 398; DFO: Diabetic foot osteomyelitis; MRSA: Methicillin-Resistant *S. aureus*; MSSA: Methicillin-Susceptible *S. aureus*; PJI: Prosthetic joint infection; SSTI: Skin and soft tissue infections

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None.

Authors' contributions

X.B., K. B., D. H and C. C conceived the study. K.B. collected and analyzed the data. K.B. wrote the manuscript with support from D.H., X. B and C.C. M.S. performed bacteriological analysis. All authors provided critical feedback and helped shape the research, analysis and manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

According to French legislation in this period, and because no intervention was performed on patients, no written informed consent was given by the patients (Law No. 2012–300 of 5 March 2012: <http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000025441587&categorieLien=id>). Our study protocol followed the ethical guidelines of the declaration of Helsinki and was approved by our institutional review board (Comité de Protection des Personnes – Est (GIRCI Grand Est) N° 2020-A02771–54).

Consent for publication

Not applicable.

Competing interests

None.

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