

## First report of the predominance of clonal complex 398 *Staphylococcus aureus* strains in osteomyelitis complicating diabetic foot ulcers: a national French study

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### Abstract

*Staphylococcus aureus* is the most common pathogen cultured from diabetic foot infection including diabetic foot osteomyelitis. This French multicentre study determined the genetic content of *S. aureus* isolated from 157 consecutive cases admitted to 12 diabetic foot centres between 2008 and 2011. We describe for the first time the emergence of the CC398 methicillin-susceptible *S. aureus* clone, the main clone in diabetic foot osteomyelitis, and its tropism for bone. This clone spreads to humans from an animal source through its intrinsic virulence. This adaptation of *S. aureus* isolates looks to be a worrisome problem and should be carefully monitored.

**Keywords:** Clonal complex 398, diabetic foot, methicillin-susceptible *Staphylococcus aureus*, osteomyelitis

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Foot ulcers are common in diabetic patients, with a prevalence as high as 25% [1]. These ulcers frequently become infected, and spread of infection to soft tissue and bony structures is a major causal factor for lower-limb amputation [2], making early diagnosis and adequate treatment essential. Depending on the setting and severity of infection, prevalence of bone involvement widely ranges from 10 to 60% [3]. Chronic ulcers of the foot are at high risk for infection and secondary spread to underlying bone structures [4]. Consequently, all factors that contribute to delayed wound healing may increase the risk for developing diabetic foot osteomyelitis (DFOM). Although *Staphylococcus aureus* is the most common pathogen cultured from bone in DFOM in western countries [5,6], there is currently no report on the clones of this microorganism in this condition. *Staphylococcus aureus* clonal complex (CC) 398, which is commonly found as a colonizing strain in pig farming, is emerging as a cause of human infections. In recent years, increasing numbers of studies throughout the world have identified CC398 strain as a livestock colonizing strain, but continuously increasing and alarming cases of human infections have been reported [7]. The present study reports for the first time the emergence of CC398 strains in a French cohort of patients with diabetic foot infections (DFI) and its tropism for bone.

Between 1 January 2008 and 31 December 2010, we prospectively and consecutively screened outpatients attending one of the 12 participating French foot clinics for DFI. The local ethics committee (South Mediterranean III) approved this study. After informed consent was obtained, only patients with a documented DFI were included if they had not received any antibiotic agents in the previous month. Patients were suspected of having osteomyelitis of the foot if they had at least two of the following clinical criteria: (1) a wound with duration  $\geq 2$  weeks, located over an underlying bony prominence, with an area  $> 2$  cm<sup>2</sup> or a depth  $> 3$  mm; (2) a positive probe-to-bone test; and (3) abnormalities consistent with the diagnosis of osteomyelitis either on plain X-rays, radionuclide procedures (three-phase bone scan and/or labelled leucocyte imaging) or magnetic resonance imaging. After wound debridement, samples for bacterial culture were obtained by swabbing the wound base, needle aspiration or tissue biopsy for skin and soft tissue infection (SSTI) and by transcutaneous bone biopsy using a previously described procedure [5]. Only patients with monomicrobial culture for *S. aureus* were included. Genus, species and antibiotic susceptibilities were determined using the Vitek 2 card (BioMérieux, Marcy-l'Etoile, France) and interpreted according to the recommendations of the French Society for Microbiology (<http://www.sfm-microbiologie.org>). The Alere StaphyType DNA microarray was used according to protocols that have been previously detailed [8]. This technology allowed the identification of the clonal complex

(CC) of strains. The affiliation of isolates was assessed by an automated comparison of hybridization profiles to a collection of previously characterized reference strains [8]. Screening for the presence of prophage  $\phi$ Sa3 (*scn*, *chp*, *pvl*, *tetM*) in CC398 was obtained by DNA array [9,10]. The presence of each clonal complex in *S. aureus* strains was compared according to the clinical condition (DFOM or SSTI) using Fisher's exact test. Statistical analysis was performed using the S-PLUS 2000 software package (Insightful Corporation, Seattle, WA, USA) and results were considered significant for  $p < 0.05$ .

During the study period, 157 patients (Table 1) were recruited, in whom *S. aureus* was the sole organism isolated from the bacterial culture of their DFI. Seventy-seven wounds (49%) were associated with osteomyelitis and 80 with SSTI without involving the bone. Among the 77 patients, 81 *S. aureus* isolates were detected; two different *S. aureus* strains ( $\alpha$ -haemolytic and  $\beta$ -haemolytic colonies) were isolated from four patients. Prevalence of methicillin-resistant *S. aureus* (MRSA) was identical in cultures from DFOM ( $n = 13$ , 16%) and from SSTI ( $n = 8$ , 10%). As shown in Table 2, the *S. aureus* isolates displayed a high clonal diversity. A total of 18 known CCs and 11 singletons were identified. CC398 methicillin-sensitive *S. aureus* (MSSA;  $n = 31$ ) was the most frequently found CC in DFOM with a prevalence of 38.3% and was

significantly associated with this condition ( $p < 0.001$ ). Of the MSSA strains, 45.6% belonged to the CC398 clone. On the other hand, CC45 MSSA ( $n = 13$ , 16.3%) was significantly associated with SSTI ( $p 0.05$ ). The antibiotic susceptibilities showed that the CC398 strains were susceptible to all tested antibiotics except penicillin G. The strains were isolated in 10 of the 12 foot clinics. No link could be found between each patient harbouring this clone, suggesting a national propagation of this strain in DFOM. No relation with animal farming density or seasonal effect was noted; the clone was distributed throughout the study period. Interestingly strains with different appearances on blood agar media had the same gene content. Regarding the MRSA strains isolated from DFOM, they mainly belonged to three CCs: CC8 MRSA (Lyon Clone,  $n = 9$ ), the main clone present in French hospitals, CC5 MRSA (New Paediatric,  $n = 2$ ) and ST22 MRSA (Barnim Epidemic Strain, UK-EMRSA-15,  $n = 1$ ). CC398 strains were characterized by some distinctive features regarding the distribution of virulence factors: absence of enterotoxins, presence of haemolysins, and genes encoding intracellular adhesion proteins, *cap5*, together with three genes encoding MSCRAMM (*bbp*, *clfA*, *clfB*). All the isolates were found in *agr* group I. Moreover, the CC398 strains belonged to human MSSA clades carrying the prophage  $\phi$ Sa3 due to the presence of genes encoding human-specific immune evasion cluster (*chp*,  $n = 29$ )

**TABLE 1. Demographic and clinical characteristics of study patients**

Characteristics	Patients with CC398 strains $n = 31$	DFOM $n = 77$	SSTI $n = 80$	Total $n = 157$
Age (range), years	66 (38–91)	66 (38–85)	66.5 (33–101)	66.5 (33–101)
Male/female, $n$ (%)	22 (71)/9 (29)	58 (75.3)/19 (24.7)	58 (72.5)/22 (27.5)	116 (73.9)/32 (26.1)
Type 1/type 2 diabetes mellitus	4 (12.9)/27 (87.1)	7 (9.1)/70 (90.9)	14 (17.5)/66 (82.5)	21 (13.4)/136 (86.6)
HbA1c (%)	8.5	8.4	8.4	8.4
Cardiovascular disease				
Absence	9 (29.0)	23 (29.9)	16 (20)	39 (24.8)
Coronary heart disease	9 (29.0)	23 (29.9)	31 (38.8)	54 (34.4)
Peripheral arterial disease	18 (58.1)	45 (58.4)	57 (71.3)	102 (65.0)
Arterial hypotension	25 (80.6)	60 (77.9)	65 (81.3)	125 (79.6)
Stroke	1 (3.2)	5 (6.5)	5 (6.3)	10 (6.4)
Nephropathy				
Absence	6 (19.4)	15 (19.5)	29 (36.3)	44 (28.0)
Microalbuminuria	6 (19.4)	11 (14.3)	26 (32.5)	37 (23.6)
Proteinuria	10 (32.3)	28 (36.4)	20 (25)	48 (30.6)
Renal failure	9 (29.0)	23 (29.9)	28 (35)	51 (32.5)
Neuropathy				
Peripheral	31 (100)	77 (100)	75 (93.8)	152 (96.8)
Autonomic	7 (22.6)	12 (15.6)	20 (25)	32 (20.4)
Diabetic retinopathy				
Absence	12 (38.7)	32 (41.6)	31 (38.8)	63 (40.1)
Non-proliferative diabetic retinopathy	13 (41.9)	33 (41.6)	40 (50)	73 (46.5)
Proliferative diabetic retinopathy	6 (19.4)	12 (15.6)	10 (12.5)	22 (14.0)
Lifestyle factors				
Obesity	12 (38.7)	31 (40.3)	32 (40)	63 (40.1)
Smoking	8 (25.8)	19 (24.7)	22 (27.5)	41 (26.1)
Alcoholism	5 (16.1)	12 (15.6)	14 (17.5)	26 (16.5)
Sedentary	25 (80.6)	60 (77.9)	62 (77.5)	122 (77.7)
First wound/Recurrence	8 (25.8)/23 (74.2)	17 (22.1)/60 (77.9)	19 (23.8)/61 (76.2)	36 (22.9)/121 (77.0)
IWGDf-IDSA grade				
2 (Mild)	0 (0)	0 (0)	38 (47.5)	38 (24.2)
3 (Moderate)	24 (77.4)	54 (70.1)	42 (52.5)	96 (61.1)
4 (Severe)	7 (22.6)	23 (29.9)	0 (0)	23 (14.7)

DFOM, diabetic foot osteomyelitis; HbA1c, glycated haemoglobin; IDSA, Infectious Diseases Society of America; IWGDf, International Working Group of the Diabetic Foot; SSTI, skin and soft tissue infection.

Values are median and interquartile ranges (25th–75th percentile) or numbers and percentages.

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