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BRIEF REPORT

Staphylococcus aureus Bloodstream Infection in Patients With Prosthetic Joints in the Prospective VIRSTA Cohort Study: Frequency and Time of Occurrence of Periprosthetic Joint Infection

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Among 143 patients of the VIRSTA cohort study with *Staphylococcus aureus* bacteremia and an arthroplasty implanted for more than a year, *S. aureus* periprosthetic joint infection was observed in 19%. Signs of infection (pain and swelling) were always present, in median 1 day (range, 0–21 days) after onset of bacteremia.

Staphylococcus aureus has both a high potential for metastatic infection and a high affinity for foreign material. Possible prosthesis infection is of clinical concern in all patients with preexisting prosthetic materials experiencing *S. aureus* bloodstream infection (SAB). Prosthetic joints are especially prone to infection during the course of bacteremia, with a risk of infection much higher with *S. aureus* than with other microorganisms, 20% vs 7%, in a recent prospective study [1]. As early intervention with debridement in prosthetic joint infection (PJI) is paramount to retain the implant and to prevent infection relapse; eliminating PJI after SAB is important. However, additional data are needed to better describe the clinical characteristics of PJI after SAB in particular time lapses and whether systematic imaging of the prosthesis could be necessary after SAB. We described the frequency and clinical presentation of PJIs observed among patients with prosthetic joints implanted for >1 year before bacteremia and enrolled in the VIRSTA study, a multicenter prospective cohort study of patients with SAB.

Keywords. bloodstream infection; prosthetic joint infection; *Staphylococcus aureus*.

METHODS

The VIRSTA cohort study prospectively enrolled 2091 consecutive patients with SAB in 2009–2011 in 8 university hospitals in France [2]. In this ancillary study, we selected patients with at least 1 prosthetic joint in the 6 participating centers in which investigators agreed to further analyze medical charts of patients with prosthetic joints. In particular, investigators obtained (i) information on the history of the arthroplasty before the occurrence of SAB and (ii) longer follow-up of subjects with prosthetic joints than the 12 weeks after onset of SAB initially scheduled in the cohort. PJI was defined as isolation of *S. aureus* in the joint fluid or periprosthetic tissues or presence of purulent PJI without any other explanation [3]. Patients with PJI occurring <1 year after implantation or revision were considered to have possible primary PJI due to surgery and were excluded. Because PJI may not have sufficient time to develop or may not be diagnosed in the most severe cases, we also excluded patients who died during the first 7 days after onset of SAB.

Factors associated with the presence of a PJI were studied using nonparametric tests for univariable analyses and logistic regression for multivariable analysis. Statistical analyses were performed using R software, version 3.5.1. The VIRSTA cohort study was approved by the Comité de Protection des Personnes Sud-Méditerranée IV.

RESULTS

Among the patients with SAB enrolled in the participating centers, 195 had at least 1 prosthetic joint; 25 patients were excluded because at least 1 prosthesis had been implanted or revised <1 year before SAB, and 27 were excluded because they died within 7 days of SAB onset. A total of 143 patients with SAB harboring 223 joint prostheses implanted for a median of 7 years were analyzed. Among them, 27 (19%) had at least 1 PJI, and a total of 28 prostheses (13%) were infected. Culture of joint aspirate was positive for *S. aureus* in 19/28 PJIs (68%), whereas in the other PJIs, fluid was purulent but sterile. All patients had pain or swelling affecting the infected joints during their first hospital stay for SAB. The median time between onset of SAB and the first symptoms of PJI was 1 day (range, 0–21 days). No additional PJI occurred after a median follow-up (interquartile range [IQR]) of 261 (58–1174) days overall and of 478 (124–1971) days in survivors. Diagnosis of PJI was confirmed by joint examination during the hospitalization for SAB in all patients

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but 1. The only exception was a case in whom first yielding of *S. aureus* in a prosthetic hip was made 8 months after onset of SAB. Initially, this man had an endocarditis with multiple foci of infection. Clinical symptoms affecting the prosthetic hip were present during the first days of SAB, but a computed tomography scan of the joint was unremarkable. He then received 4 months of antibiotic therapy, but his hip pain recurred 4 months after stopping antibiotics.

The characteristics of patients and joint prostheses in patients with and without PJI are described in Table 1. Briefly, PJI was significantly more frequent in younger patients and in community-acquired SAB (38%) compared with health care–related SAB (11%). Neither comorbidities nor immunodepression were associated with PJI. PJI was not more frequent in cases of infective endocarditis. Patients with PJI had a lower McCabe score [4] at onset of SAB (data not shown) and died less frequently during follow-up. Knee prostheses were more frequently infected (21%) than hip prostheses (10%). A history of arthroplasty revision of the infected joint was more frequent in patients with PJI (36%, vs 8% in patients with uninfected arthroplasties). All characteristics of SAB associated with PJI with a *P* value <.20 (Table 1) were studied in multivariable analysis. After adjustment, C-reactive protein >220 mg/L (adjusted odds ratio [aOR], 5.0; 95% confidence interval [CI], 1.8–16.6) and community-acquired SAB (aOR, 3.5; 95% CI, 1.3–9.5) were significantly associated with PJI, whereas diabetes was not. Characteristics of prostheses associated with PJI were not studied in multivariable analysis due to the high number of patients with missing data for history of revision.

DISCUSSION

In this prospective multicenter study, we confirmed that patients with prosthetic joints are prone to hematogenous

Table 1. Characteristics of Infection and Joint Prostheses in 143 Patients With a Prosthetic Joint for >1 Year and *Staphylococcus aureus* Bloodstream Infection; VIRSTA Cohort Study 2009–2011

Variables	Absence of PJI	Presence of PJI	Total	*P* Value for Association With PJI
Characteristics of SAB	n = 116 patients	n = 27 patients	n = 143 patients	
Age, y	78 (69–84)	73 (63–80)	77 (66–83)	.03
Female gender	54 (47)	10 (37)	64 (45)	.37
Diabetes mellitus	29 (25)	7 (26)	36 (25)	.92
Arteritis	22 (19)	2 (7)	24 (17)	.25
Immunodepression	37 (32)	8 (30)	45 (32)	.82
Methicillin resistance	19 (16)	2 (7)	21 (15)	.37
CRP at onset of SAB, mg/L	200 (123–291)	340 (247–425)	219 (138–318)	<.001
Prolonged bacteremia[a]	39 (34)	12 (44)	51 (36)	.49
Infective endocarditis[b]	14 (12)	3 (11)	17 (12)	.95
Severe sepsis or septic shock	39 (34)	7 (26)	46 (32)	.20
Setting of acquisition of SAB				.002
Community-acquired	36 (31)	17 (63)	53 (37)	
Non-nosocomial health care–related	23 (20)	2 (7)	25 (17)	
Nosocomial	57 (49)	8 (30)	65 (46)	
Duration of antibiotic therapy, d				
Intravenous	15 (6–24)	21 (10–30)	15 (7–24)	.29
Total	25 (14–42)	59 (22–100)	26 (15–49)	.01
Duration of hospital stay, d	26 (16–46)	33 (27–44)	28 (17–45)	.35
Death during follow-up	58 (50)	6 (22)	64 (45)	<.001
Characteristics of prosthesis	n = 195 prostheses	n = 28 prostheses	n = 223 prostheses	
Location of prosthesis				.03
Hip	133 (68)	14 (50)	147 (66)	
Knee	52 (27)	14 (50)	66 (30)	
Other	10 (5)	0 (0)	10 (4)	
Time since implantation of prosthesis, y	6.7 (2.7–12.1)	9.0 (5.4–14.4)	7.1 (3.1–13.4)	.10
History of prosthesis revision				<.001
Yes	16 (8)	10 (36)	26 (12)	
No	126 (65)	13 (46)	139 (63)	
Unknown	53 (27)	5 (18)	58 (26)	
Time since last revision, y	2.8 (1.8–5.3)	3.2 (1.8–5.8)	2.8 (1.8–5.8)	.78

Continuous variables are expressed as median (IQR), categorical variables as number (%).

Abbreviations: CRP, C-reactive protein; PJI, prosthetic joint infection; SAB, *Staphylococcus aureus* bloodstream infection.

[a]Blood cultures still positive at 48 hours after onset of SAB.

[b]Definite according to modified Duke classification.

infection during SAB and showed that prosthetic infection is revealed during or very early after SAB.

Patients were enrolled in the VIRSTA study between 2009 and 2011. Our findings may thus not be generalizable to patients presenting with SAB now. However, management of SAB and of PJI has not changed substantially since 2009.

The frequency of hematogenous PJI in patients with a prosthetic joint in place at the time of SAB has been diversely evaluated in the literature. In the 5 previous studies performed before our study, PJI during SAB varied from 25% to 41% [5–9], which is higher than the 19% of infected patients and 13% of infected prostheses we observed in our cohort. Our study is larger than these previous studies. The enrollment of a majority of health care–related infections, which are associated with a lower frequency of metastatic seeding, may explain this lower prevalence. Also, high mortality may have led to lack of detection of PJI. We tried to minimize this bias by excluding patients who died within the first week of SAB. In a large recent study following all patients after implantation of a prosthetic joint and looking for occurrence of bacteremia and concomitant PJI, the rate of infection in SAB was 21%, very similar to our findings [1].

As systematic exploration of prosthetic joints was not performed in patients with SAB, we cannot exclude that asymptomatic PJIs were missed. However, absence of late infections in asymptomatic patients after >1 year of follow-up in survivors argues against this bias.

Indeed, in our series, frank clinical symptoms of PJI were present during the first days of management of SAB in all patients. Other studies with a shorter follow-up observed similar results.

Most factors we found to be associated with PJI in patients with SAB have been previously described. An association between community acquisition and presence of PJI in SAB was described in the 2 studies in which this specific factor was explored [7, 8]. This association has also been observed in most other deep foci of infection, such as infective endocarditis, and is thought to be related to the shorter duration of infection before introduction of antibiotic therapy in health care–related infections [2, 7]. A higher risk of infection for knee prostheses, which may be related to the more complex mechanics of the knee joint compared with the hip, has also been observed in 2 other series [5, 8]. History of arthroplasty revision was also a risk factor for PJI after SAB in the study by Tande et al. [8]. This may be due to the use of more complex prostheses after revision.

We cannot exclude that PJIs in some of our patients were secondary to implantation and were the source rather than the consequence of SAB. We chose to include only patients with late PJI, defined by occurrence of infection >1 year after implantation, and the very long time elapsed between implantation and PJI was not in favor of this bias. Moreover, *S. aureus* is a virulent pathogen that is responsible for acute postoperative infections that usually become symptomatic a few weeks after implantation. However, due to our inclusion criteria, our findings only apply to prostheses implanted for more than a year.

PJI is thus present in at least 1 in 5 patients with a prosthetic joint at the time of SAB. A high level of suspicion of PJI must thus be raised in cases of SAB in subjects with prosthetic joints, especially if the SAB is community-acquired, C-reactive protein is very high, the patient has a knee prosthesis, or if arthroplasty has been previously revised. Arthroplasty, close clinical follow-up, and early analysis of joint aspirate in case of symptoms are thus necessary. As infection is nearly always clinically obvious during the first days of management of SAB, specific investigations like imaging studies, systematic joint aspirate in asymptomatic patients, extension of their follow-up, or longer antibiotic therapy duration seem not justified [10].

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. Honkanen M, Jamsen E, Karpellin M, et al. Periprostheric joint infections as a consequence of bacteremia. Open Forum Infect Dis **2019**; 6(X):XXX–XX.
2. Le Moing V, Alla F, Doco-Lecompte T, et al; VIRSTA Study Group. *Staphylococcus aureus* bloodstream infection and endocarditis—a prospective cohort study. PLoS One **2015**; 10:e0127385.

3. Parvizi J, Zmistowski B, Berbari EF, et al. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. Clin Orthop Relat Res **2011**; 469:2992–4.
4. McCabe WR, Jackson GG. Gram negative bacteremia. I. Etiology and ecology. Arch Intern Med **1962**; 110;847–53.
5. Murdoch DR, Roberts SA, Fowler VG Jr, et al. Infection of orthopedic prostheses after *Staphylococcus aureus* bacteremia. Clin Infect Dis **2001**; 32:647–9.
6. Lalani T, Chu VH, Grussemeyer CA, et al. Clinical outcomes and costs among patients with *Staphylococcus aureus* bacteremia and orthopedic device infections. Scand J Infect Dis **2008**; 40:973–7.
7. Sendi P, Banderet F, Graber P, Zimmerli W. Periprosthetic joint infection following *Staphylococcus aureus* bacteremia. J Infect **2011**; 63:17–22.
8. Tande AJ, Palraj BR, Osmon DR, et al. Clinical presentation, risk factors, and outcomes of hematogenous prosthetic joint infection in patients with *Staphylococcus aureus* bacteremia. Am J Med **2016**; 129:221.e11–20.
9. Makki D, Elgamal T, Evans P, et al. The orthopaedic manifestation and outcomes of methicillin-sensitive *Staphylococcus aureus* septicaemia. Bone Joint J **2017**; 99-B:1545–51.
10. Kaasch AJ, Kern WV, Joost I, et al. Effect of clinically uninfected orthopedic implants and pacemakers/AICDs in low-risk *Staphylococcus* aureus bloodstream infection on crude mortality rate: a post hoc analysis of a large cohort study. Open Forum Infect Dis **2019**; 6(X):XXX–XX.