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Is the prognosis the same for periprosthetic joint infections due to *Staphylococcus aureus* versus coagulase-negative staphylococci? A retrospective study of 101 patients with 2-year minimum follow-up

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Abstract

Background *Staphylococcus aureus* (SA) and Coagulase-negative staphylococci (CoNS) are often responsible for infections of total hip arthroplasty (THA) and total knee arthroplasty (TKA). One of the main differences between these two microorganisms is their virulence, with SA presumed to be more virulent; however, few studies have specifically investigated the impact of this virulence. This inspired us to carry out a retrospective study to evaluate whether the healing rate differed between SA and CoNS infections.

Hypothesis We hypothesised that the healing rate is lower for SA prosthetic joint infections.

Materials and methods This was a retrospective study of 101 consecutive *Staphylococcus* infection cases that occurred between 2007 and 2011. There were 56 men and 45 women with an average age of 69 years (range 23–95). The infection was associated with TKA in 38 cases and THA in 63 cases. Thirty-two percent of patients had one or more comorbidities with infectious potential. In our cohort, there were 32 SA infections (31.7 %) and 69 CoNS infections (68.3 %) with 58 of the infections being methicillin-resistant (15 SA and 43 CoNS); there were 27 polymicrobial infections (26.7 %).

Results With a minimum 24-month follow-up after the end of antibiotic treatment, the healing rate was 70.3 % overall (71 patients). The healing rate was 75 % in the SA group

(24 patients) versus 68.1 % (47 patients) in the CoNS group ($P = 0.42$).

Conclusion Our hypothesis was not confirmed: the healing rate of SA prosthetic joint infections was not lower than that of CoNS infections.

Level of evidence III, retrospective case-control study.

Keywords Periprosthetic joint infection · *Staphylococcus* spp. · Total knee arthroplasty · Total hip arthroplasty

Introduction

The healing rate for periprosthetic joint infections (PJIs) following total hip arthroplasty (THA) and total knee arthroplasty (TKA) ranges from 26 to 100 %, depending on the study and type of treatment [1–9]. *Staphylococcus* is often found in PJIs [10], with *Staphylococcus aureus* (SA) and coagulate-negative Staphylococci (CoNS) each being implicated in about 25 % of infections [11–13].

Staphylococcus aureus has a higher intrinsic virulence than CoNS [14, 15], but no published studies have specifically compared the healing rates after PJI caused by these two microorganisms. Parvizi et al. [1] found no difference between them when the healing rate of methicillin-resistant *Staphylococcus* infections was compared. However, this was a controversial, underpowered study, in which multiple treatment methods (lavage-debridement, prosthesis change, etc.) were used. Published data cannot be used to conclude that a difference exists between the outcome of PJIs caused by SA or CoNS.

This encouraged us to carry out a study to determine whether the healing rate after PJI differed between SA and CoNS infection after a minimum follow-up of 2 years. We

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hypothesised that because SA is more virulent than CoNS, the healing rate of PJIs due to SA would be lower than that of PJIs due to CoNS.

Materials and methods

Patients

This continuous, retrospective study included all the cases of primary THA or TKA septic revision (single- or two-stage revision) due to *Staphylococcus* infection performed between January 2007 and December 2011 at the Reference centre for complex joint infections in the greater south-western area of France (CRIOAC-GSO). Patients who had already undergone a surgical procedure before our treatment (lavage, prosthesis change) and those who were treated conservatively (lavage with synovectomy, suppressive antibiotic therapy) were excluded. If no preoperative microbiology results were available, empirical intravenous dual antibiotic treatment (vancomycin + third-generation cephalosporin) was initiated immediately after the intraoperative samples had been collected. When possible, the treatment was shifted after the first week to oral antibiotics adapted to the microorganism identified and its resistance, for a minimum of 45 days. If preoperative joint aspiration was performed and provided useful information, the antibiotics were adapted to the microorganism identified and its resistance.

Among the 245 surgical revision procedures for PJI performed during this period, 101 were due to *Staphylococcus* infection. Patients with intraoperative samples positive for both SA and CoNS were excluded. The cohort consisted of 56 men and 45 women with an average age of 69 years (range 23–95). There were 63 THA infections and 38 TKA infections. These were treated by single-stage revision in 40 cases (32 THA and 8 TKA) and two-stage revision in 61 cases (31 THA and 30 TKA). A two-stage procedure was carried out if a resistant bacterium was identified, a polymicrobial infection was present, or a fistula was identified. Using the criteria outlined by Joulie et al. [9], it was determined that 32 % of patients had one or more comorbidities with infectious potential. The 32 SA infections (31.7 %) and 69 CoNS infections (68.3 %) are described in detail in Table 1. The *Staphylococcus* was methicillin-resistant in 58 cases (15 SA, 43 CoNS). Among these infections, 27 were polymicrobial (multiple bacteria species): 12 in the SA group and 15 in the CoNS group. The two groups were comparable in age, sex ratio, mono-microbial nature or polymicrobial nature of the infection, type of procedure (single- or two-stage revision), follow-up, and the presence of comorbidities. Conversely, there were more methicillin-resistant infections in the CoNS group (43 versus 15 cases, $P < 0.05$) (Table 2).

Table 1 Types of microorganisms found in the coagulate-negative Staphylococci group

Coagulase-negative Staphylococci	Number of cases
<i>S. epidermidis</i>	47
<i>S. capitis</i>	9
<i>S. hominis</i>	9
<i>S. lugdunensis</i>	3
<i>S. auricularis</i>	1

The diagnosis of PJI was based on:

1. At least three positive samples (three intraoperative samples or two intraoperative samples + one joint aspiration sample taken a few days before surgery) identifying a bacterium from the skin flora (e.g., CoNS, *Propionibacterium acnes*, *Corynebacterium* spp., etc.) that may have resulted from skin contamination during sample collection.
2. At least one positive sample (one joint aspiration sample or one intraoperative or blood culture sample) identifying a bacterium that is not part of the skin flora and, therefore, cannot be attributed to skin contamination (SA, *Enterobacter* spp., *Pseudomonas aeruginosa*, etc.).
3. The presence of a rare bacterium that cannot be attributed to skin contamination (e.g., *Streptococcus pneumoniae*, *Salmonella*, *Listeria*, *Campylobacter*, *Pasteurella*, etc.).

Sample size calculation

For a 70 % healing rate and detectable difference of 25 % (5 % alpha risk and 80 % beta risk), at least 80 patients were needed in the study.

Assessment method

The only healing criterion used was the lack of surgical revision at the last follow-up. If there was a potential recurrence of the infection, the patient underwent additional testing, such as joint aspiration or surgical biopsy, if needed. Failure was defined as a new surgical procedure being carried out or a pharmaceutical treatment being provided (suppressive antibiotic therapy) during the treatment period. Demographics, comorbidities, surgical parameters, and laboratory test results were also analysed. Patients were reviewed regularly after the end of antibiotics therapy at day 45, day 90, 6 months, 1 year, and then annually for 5 years with laboratory tests (CRP, CBC), clinical examination, and X-rays being performed.

Table 2 Characteristics of the patients in the *Staphylococcus aureus* and coagulase-negative Staphylococci groups

	<i>S. aureus</i> (32 cases)	Coag-neg <i>S.</i> (69 cases)	<i>P</i>
Mean age	63.2 years (78–43)	64.7 years (84–46)	n/s
Gender ratio (M/F)	19 M/13 F (1.46:1)	37 M/32 F (1.16:1)	n/s
THA/TKA distribution	23/32 (70 %)	48/69 (71 %)	n/s
Average follow-up	2.9 years (2–5)	2.6 years (2–5)	n/s
Two-stage procedure	22 cases (68 %)	43 cases (62.3 %)	n/s
Methicillin resistance	15/32 (46.8 %)	43/69 (62.3 %)	<0.05
Healing rate	24 cases (75 %)	47 cases (68.1 %)	n/s
Frequency of comorbidities	10/32 (31 %)	22/54 (41 %)	n/s
Rate of polymicrobial infections	12/32 (37.5 %)	15/54 (28 %)	n/s

Statistical methods

Statistical tests were carried out with the StatView software (SAS Institute Inc, Cary, NC, USA). Nominal variables were reported using the number of patients and percentages. Continuous variables were described using the mean, standard deviation, and maximum and minimum values. The normal distribution of the variables was verified with the Shapiro–Wilk test. The two groups were compared using the parametric test (Student’s independent *t* test) if the data were normally distributed and a non-parametric test (Mann–Whitney) if they were not. Significance threshold was set at $P < 0.05$.

Results

With a minimum follow-up of 24 months and an average follow-up of 32 ± 8 months, the healing rate of the overall cohort was 70.3 % (71 of 101 cases). The SA group had a 75 % healing rate (24 of 32 cases) and the CoNS had a 68.1 % healing rate (47 of 69 cases) ($P = 0.42$). After excluding patients with polymicrobial infections, these rates were still similar: 80 % for the SA group (16 of 20 cases) versus 72 % for the CoNS group (39 of 54 cases) ($P = 0.17$).

In the patients with SA infection, the healing rate was 76.5 % (13 of 17 cases) in the methicillin-susceptible group versus 73.3 % (11 of 15 cases) in the methicillin-resistant group ($P = 0.2$). In the patients with CoNS infection, the healing rate was 73 % (19 of 26 cases) in the methicillin-susceptible group versus 65.1 % (28 of 43 cases) in the methicillin-resistant group ($P = 0.14$).

Discussion

Our initial hypothesis was not confirmed: the healing rate of *Staphylococcus aureus* PJIs was not lower than that of coagulate-negative Staphylococci infections. The polymicrobial

nature of the infection or methicillin resistance did not impact these findings.

This study has several limitations. Other than its retrospective nature, our decision to use a healing endpoint based on the absence of surgical revision at the last follow-up visit can be criticised. All the same, failure of surgical treatment for PJI leading to repeated surgical or pharmaceutical treatment corresponds to our failure criteria. Moreover, the term ‘healing rate’ for PJIs must be used carefully; the term ‘remission’ used in cancer studies would likely be more appropriate. This study’s statistical power was low, thus there is 20 % possibility that we concluded incorrectly that there was no difference. A minimum 24-month follow-up is typically used in published studies evaluating PJI treatment outcomes [16–19]. The inclusion of polymicrobial infections, which made up of one-third of cases, is consistent with published studies [20, 21], but may be a confounding factor for the analysis. This constitutes a risk factor for treatment failure [22], but in our study, the proportion of polymicrobial infections was comparable in the two groups; removing these infections from the study cohort did not alter the results. Finally, inclusion of both THA and TKA infections is a confounding factor, although the proportion of each was comparable in the two groups.

This is the first published study to compare the result of revisions for PJI due to different *Staphylococcus* species. Various studies have analysed the healing rate based on the type of procedure (single- or two-phase revision), antibiotic therapy, type of surgical procedure (conservative or revision), and resistant or susceptible nature of the microorganism [1, 9, 18, 23–31]. Vielpeau et al. [32] reviewed 535 cases of revision for THA infection, but found no evidence that the healing rate varied as a function of *Staphylococcus* species. They found 121 cases of SA infection with an 82 % healing rate and 136 cases of CoNS infection with an 84 % healing rate ($P > 0.05$). Similarly, Parvizi et al. [1] did a study of 127 THA and TKA revisions for infection, but found no evidence of differences in the healing rate for SA infections (37 cases, 67 % healing rate) or CoNS

infections (35 cases, 68 % infection rate). Tornero et al. [33] also evaluated the healing rate after conservative surgical treatment (lavage, debridement) of THA and TKA infections; they found no differences between the two microorganisms.

Other studies focused on the healing rate by the type of microorganism. Joulie et al. [9] analysed the healing rate of SA infections in a cohort of 95 THA and TKA cases with a minimum 12-month follow-up. The healing rate was 81 % overall, with the resistant or susceptible nature of the microorganisms having no impact, as we found in our study. This finding is not universal; however, Salgado et al. [31] showed that the presence of methicillin-resistant SA was a risk factor for failure.

Conclusion

The healing rate of PJI due to SA is not lower than that of PJI due to CoNS. This suggests that CoNS must be treated with the same degree of rigour, especially because the emergence of strains with reduced glycopeptide sensitivity mainly pertains to CoNS [34, 35].

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose relative to this study.

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