Non-compliance with IDSA guidelines for patients presenting with methicillin-susceptible Staphylococcus aureus prosthetic joint infection is a risk factor for treatment failure

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Abstract
The long-term impact of treatment strategies proposed by the IDSA guidelines for patients presenting with methicillin-susceptible S. aureus (MSSA) prosthetic joint infection (PJI) is not well-known.


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Short communication

Non-compliance with IDSA guidelines for patients presenting with methicillin-susceptible *Staphylococcus aureus* prosthetic joint infection is a risk factor for treatment failure

Le non-respect des recommandations de l’IDSA pour les infections de prothèses à *Staphylococcus aureus* sensible à la méthicilline est un risque d’échec

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Abstract

**Objective.** – The long-term impact of treatment strategies proposed by the IDSA guidelines for patients presenting with methicillin-susceptible *S. aureus* (MSSA) prosthetic joint infection (PJI) is not well-known.

**Patients and methods.** – Retrospective (2000–2010) cohort study including patients presenting with MSSA hip or knee PJI. A univariate Cox analysis was performed to determine if the non-compliance with IDSA surgical guidelines was a risk factor for treatment failure.

**Results.** – Eighty-nine patients with a mean follow-up of 2.8 years were included. Non-compliance with IDSA surgical guidelines was associated with treatment failure (hazard ratio 2.157; 95% CI [1.022–4.71]). The American Society of Anesthesiologists score, inadequate antimicrobial therapy, and a rifampicin-based regimen did not significantly influence patient outcome.

**Conclusion.** – Based on the IDSA guidelines, if a patient presenting with MSSA PJI is not eligible for implant retention, complete implant removal is needed to limit treatment failure.

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**Keywords:** Prosthetic joint infections; MSSA; Guidelines

Résumé

**Objectif.** – L’impact des stratégies proposées par les recommandations de l’IDSA pour les patients présentant une infection de prothèse articulaire (IPA) à *S. aureus* sensible à la méthicilline (MSSA) n’est pas connu.

**Patients et méthodes.** – Étude de cohorte rétrospective (2000–2010) incluant des patients avec une IPA à MSSA. Une analyse univariée de Cox a été utilisée pour déterminer si le non-respect de la stratégie chirurgicale proposée par l’IDSA était associé à un échec.

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1. Introduction

Prosthetic joint infections (PJI) are uncommon, but they represent the most serious complication following arthroplasty. Their management is based on both surgery and long-term antimicrobial therapy. According to treatment algorithms reinforced by Zimmerli et al. in 2004, surgical options described in the IDSA guidelines include debridement and implant retention (DAIR), one- or two-stage exchange, or permanent explantation or arthrodesis, depending on the clinical presentation [1,2]. Based on the Zimmerli algorithm, conservative treatment with implant retention should be reserved for patients with duration of symptoms <3 weeks, a stable implant, and with intact or slightly damaged soft tissue [1]. Two previous retrospective studies including 60–70 patients presenting with PJI due to a wide range of pathogens, reported that the risk of treatment failure was significantly higher for those treated with a surgical strategy other than that recommended by Zimmerli et al. [3,4]. The IDSA guidelines mention a slightly different criterion as conservative treatment with implant retention should be reserved for patients with a duration of symptoms <3 weeks or a joint age <30 days, and a stable implant without sinus tract.

*Staphylococcus aureus* is one of the most frequent microorganisms involved in PJI and is particularly associated with treatment failure, presumably due to biofilm formation, virulence of the pathogen, and the ability to transform into small-colony variants (SCV) [5–7]. Based on animal experiments and in vitro data, rifampicin-based regimens are recommended for *S. aureus* PJI [1,2], but rifampicin could be associated with gastrointestinal disorders, drug-drug interactions, and the dose for patients presenting with PJI is debated (600 mg/d irrespective of the weight in Spain, 600 to 900 mg/d in the IDSA guidelines, 20 mg/kg/d in the French guidelines) [1,2,8,9]. Methicillin-resistant *S. aureus* (MRSA) is considered more difficult to treat as it is usually resistant to many clinically important non-beta-lactam drugs, such as rifampicin and fluoroquinolones. Moreover, several studies demonstrated that implant retention was a risk factor for treatment failure in PJI due to methicillin-resistant staphylococci [10,11]. To date, little data is available on methicillin-susceptible *S. aureus* (MSSA) in terms of impact of medical and surgical strategies on patient outcome.

We performed a retrospective cohort study to determine if the non-compliance with IDSA surgical guidelines in patients presenting with MSSA prosthetic joint infection had a long-term impact on outcome.

2. Methods

We performed a retrospective cohort study of all patients admitted between January 1, 2000 and December 31, 2010 to the Geneva University Hospitals, Geneva, Switzerland, and the Hospices Civils de Lyon, Lyon, France, with a diagnosis of hip or knee PJI due to MSSA. The databases of the hospitals’ administrative coding systems, bacteriology laboratories, and the orthopedic and infectious diseases units were used for patient selection. The study was performed according to local ethics committee guidelines at both institutions. Data was collected from medical reports using a standardized data collection tool. To limit missing outcome data, patients, their family, or their healthcare providers were contacted by telephone and asked about the infection outcome. The burden of the patient’s comorbidity was assessed using the American Society of Anesthesiologists (ASA) score. PJIs were categorized into early (<3 months after implantation), delayed (>3 to <12 months after implantation), or late (>12 months after implantation) infection. Based on the IDSA guidelines, the surgical treatment was considered inadequate if patients did not qualify for implant retention and if a complete implant removal was not performed (i.e., if implant retention, total or partial one-stage exchange, or incomplete implant or cement removal was performed instead of a complete implant removal). Medical treatment was considered inadequate if patients did not receive intravenous therapy with antistaphylococcal activity during the first 15 days of therapy (fluclaxacinil, oxacillin, cloxacillin, or vancomycin) followed by a combination of antimicrobials based on rifampicin-fluoroquinolone combination for a duration of at least three months. As the French guidelines suggest 15 days of intravenous therapy followed by a combination of antistaphylococcal oral drugs that cannot contain rifampicin (e.g., fluoroquinolone-clindamycin, fluoroquinolone-fusidic acid, clindamycin-fusidic acid), we did not consider that this medical strategy was inadequate [8]. Treatment failure was defined by the need for subsequent surgery to control the infection (or to treat superinfection) or amputation or death attributed to the PJI. Univariate Cox analysis was used to assess interactions between treatment strategies and the study center. Univariate Cox analysis and
Kaplan Meier curves were performed to determine risk factors for treatment failure. Statistical analyses were performed using SPSS Statistics Base 17.0 (Softonic International, San Francisco, CA, USA).

3. Results

Eighty-nine patients (mean age: 66 ± 15 years; 55 males) were included (54 hip infections). Infection was early, delayed, or late in 33 (37%), 11 (12%), and 45 (51%) patients, respectively (Table 1). Most patients presenting with early PJI had a duration of clinical signs of infection before the surgery < 30 days. Median ASA score was 3 (IQR: 2–4). Duration of clinical symptoms was > 3 weeks in 25 patients (28%). The soft tissue was considered significantly damaged (mainly large abscesses) in 25 patients (28%) and the implant was unstable for the surgeon in 15 patients (17%). The implant was retained in 62 patients (70%), whereas two-stage exchange would have been better for 35 patients according to the IDSA guidelines. Among the 33 patients presenting with acute PJI, retention of the implant was considered inadequate for 16 of them (49%) as the surgery was performed > 30 days after prosthesis implantation or > 3 weeks after the first clinical symptom (13 patients), and/or as poor local conditions were observed (10 patients), and/or as the implant was unstable (10 patients), and/or as a fistula was observed (5 patients). For 16 patients presenting with late chronic infections, surgery with implant retention was considered inadequate in seven of them. Antimicrobial therapy was considered inadequate in 25 patients (28%), including five who did not receive suppressive antimicrobial therapy. During a long-term follow-up of 2.8 ± 2.2 years, treatment failure occurred in 37 patients (42%), including 27 (30%) with a recurrence of MSSA persistence. Of note, 38 of the 56 delayed or late PJs were not considered chronic postoperative infections, but of hematogenous origin as patients developed acute clinical symptoms. In this subpopulation of patients, the rate of relapse was high as 14 patients (37%) experienced a relapse with *S. aureus* still in culture.

Part of them was probably postoperative and not hematogenous PJs. No interaction between the two centers was detected. No difference was observed between the two centers or between patients with and without treatment failure regarding patient characteristics, type of infection, and medical treatment modalities. Kaplan Meier curves and Cox analysis revealed that an inadequate surgical strategy (i.e., performing implant retention or incomplete implant removal, whereas two-stage exchange was recommended) was the only risk factor for treatment failure (Fig. 1; hazard ratio (HR) 2.157; 95% CI [1.022–4.659]; \(P=0.050\)). Non-compliance with the IDSA surgical guidelines was associated with a cumulative probability of treatment failure of 80% during long-term follow-up. The ASA score (HR, 0.520; 95% CI [0.243–1.110]; \(P=0.091\)), inadequate antimicrobial

Table 1

<table>
<thead>
<tr>
<th>n</th>
<th>Relapse (n [%])</th>
<th>Implant retention (n [%])</th>
<th>Inadequate surgical therapy (n [%])</th>
<th>Rifampicin-based regimen (n [%])</th>
<th>Inadequate antimicrobial therapy (n [%])</th>
</tr>
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<tbody>
<tr>
<td>Acute</td>
<td>33</td>
<td>10 (30)</td>
<td>27 (81)</td>
<td>16 (49)</td>
<td>20 (62)</td>
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<tr>
<td>Delayed</td>
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<td>4 (36)</td>
<td>0 (0)</td>
<td>5 (46)</td>
<td>7 (63)</td>
</tr>
<tr>
<td>Late</td>
<td>45</td>
<td>23 (51)</td>
<td>30 (67)</td>
<td>17 (38)</td>
<td>26 (58)</td>
</tr>
<tr>
<td>Hip</td>
<td>54</td>
<td>20 (37)</td>
<td>20 (37)</td>
<td>27 (50)</td>
<td>32 (59)</td>
</tr>
<tr>
<td>Acute</td>
<td>24</td>
<td>6 (25)</td>
<td>21 (86)</td>
<td>13 (54)</td>
<td>15 (63)</td>
</tr>
<tr>
<td>Delayed</td>
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<td>2 (40)</td>
<td>3 (60)</td>
<td>3 (60)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Late</td>
<td>13</td>
<td>12 (48)</td>
<td>14 (56)</td>
<td>13 (52)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Knee</td>
<td>35</td>
<td>17 (49)</td>
<td>24 (69)</td>
<td>8 (23)</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Acute</td>
<td>9</td>
<td>4 (44)</td>
<td>6 (67)</td>
<td>5 (56)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Delayed</td>
<td>6</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Late</td>
<td>20</td>
<td>11 (55)</td>
<td>16 (80)</td>
<td>4 (20)</td>
<td>1 (65)</td>
</tr>
</tbody>
</table>

* In these patients, implant retention was considered inadequate in 16 of them (49%) as the surgery was performed > 30 days after the prosthesis implantation or > 3 weeks after the first clinical symptom (13 patients) and/or as poor local conditions were observed (10 patients) and/or as the implant was unstable.

* Late infections included infections of suspected hematogenous origins and late chronic infections. In the 16 patients presenting with late chronic PJI, surgery with implant retention was considered inadequate in 7 of them.

therapy (HR, 1.016; 95% CI [0.441–2.336]; P = 0.971), and a rifampicin-based regimen (HR, 0.899; 95% CI [0.791–0.899]; P = 0.791) were not found to significantly influence patient outcome.

4. Discussion

Our results highlight the importance of surgical treatment in the management of PJI due to MSSA. We observed that non-compliance with the IDSA surgical guidelines in patients presenting with MSSA PJI was strongly associated with treatment failure during long-term follow-up.

In 2004, Zimmerli et al. published recommendations for the surgical and antimicrobial treatment of PJI [1]. These guidelines have not yet been prospectively validated and were based on only one randomized study, various cohort studies, expert opinion, and animal experiments [1]. However, Betsch et al. and Giulieri et al. demonstrated the value of current recommendations in cohort studies including patients infected with a broad range of pathogens [3,4]. An inappropriate choice of conservative surgical strategies and inadequate antibiotic treatments were both associated with failure during follow-up. DAIR is recommended in patients presenting with acute postoperative and hematogenous PJI. The suspicion of a hematogenous origin is usually mainly based on acute clinical signs of septic arthritis with fever, but it is sometimes difficult to formally exclude a chronic infection, even if there is no prosthesis loosening, and especially if the patient had negative blood cultures. Marker of PJI chronicity such as delta-toxin detection using MALDI-TOF spectrum analysis may help distinguish acute from chronic PJI, and as a consequence may help the decision to adopt a conservative or a non-conservative strategy [12].

Staphylococci (S. aureus and coagulase-negative staphylococci) are the most frequent causes of implant-associated infections [1–5]. These bacteria have the ability to modify their phenotype in order to persist in vivo. S. aureus, largely associated with relapse and recurrence in patients presenting with PJI, is known to (i) form biofilm on the implant surface, thus leading to an embedded, slow-growing, multi-layered community of bacteria and (ii) persist intracellularly in osteoblast and fibroblast by producing SCVs [6,13]. Rifampicin has demonstrated in vitro bactericidal activity against surface-adhering, slow-growing, biofilm-producing S. aureus strains. For this reason, it is considered the drug of choice for the treatment of S. aureus PJI in combination with an appropriate anti-staphylococcal agent to prevent acquisition of resistance [1,2]. However, little data has clearly demonstrated the superiority of rifampicin-based regimens in comparison with other combinations in patients presenting with S. aureus PJI, and there is a debate on the adequate dose for patients presenting with PJI [9,14–17].

We observed that neither inadequate antimicrobial therapy nor the use of a rifampicin-based regimen influenced patient outcome. This may be due to the low sample size, but also to the strong association between surgical therapy and outcome. Indeed, the non-compliance with IDSA surgical guidelines (i.e., requirement to perform complete implant removal if the patient does not qualify for implant retention) led to a very high cumulative probability of treatment failure in our study (80%), thus highlighting the crucial importance of surgery to eradicate S. aureus-associated biofilm and infected host cells with S. aureus SCVs. Finally, most patients experienced treatment failure in the year following the initial episode of PJI. Thanks to an extended follow-up, we were able to show that some patients experienced treatment failure up to four years after the initial PJI episode.

Our study has limitations. First, the study was performed in two different centers in France and Switzerland. Even if no interaction between treatment strategies and the two centers was detected, we could not absolutely exclude bias due to a treatment difference between the centers. Despite the retrospective study design, we were able to track the long-term follow-up of most patients and collected a large amount of data with very few lost to follow-up.

5. Conclusion

The study findings demonstrate that non-compliance with the IDSA surgical guidelines in patients presenting with MSSA PJI was strongly associated with treatment failure during long-term follow-up. To limit the occurrence of treatment failure, it is crucial to perform complete implant removal if the patient does not qualify for implant retention.

Contribution of authors

TF coordinated the study. AB wrote the first version of the article. All authors contributed to patient care, and improved the article.

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Disclosure of interest

The authors declare that they have no competing interest.

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