Journal of Infection ■■ (2018) ■■–■■

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevierhealth.com/journals/jinf

Letter to the Editor

## Outcome of acute staphylococcal prosthetic joint infection treated with debridement, implant retention and antimicrobial treatment with short duration of rifampicin

*Dear Editor,*

Ascione et al. recently reported in this journal a favorable outcome of prosthetic joint infections (PJI) related to adherence to a pre-established diagnostic and treatment protocol.[1] The use of rifampicin was associated with an increased success rate. Current treatment guidelines for acute staphylococcal PJI advocate surgical debridement and at least 12 weeks of combination therapy including rifampicin.[2] The evidence for shorter antimicrobial treatment duration with rifampicin is limited. In many studies and also in the study of Ascione et al. rifampicin is started when antimicrobial susceptibility is known and wounds are dry.[1] However, rifampicin might be most effective during the first days after debridement, the time period in which new biofilm formation on the surface of the implant needs to be prevented. Therefore, over the last 14 years, in our tertiary institution for orthopedic implant surgery, all patients with an acute staphylococcal PJI who underwent a DAIR (Debridement, Antibiotics and Implant Retention) were treated with only five days of rifampicin in combination with at least 6 weeks of betalactam/glycopeptide antibiotics, both started intraoperatively.

In this letter, we report the clinical outcome of these patients and assessed whether intraoperative start of rifampicin induced rifampicin resistance in patients who developed a relapse. Oncology patients with an infected megaprosthesis were also included. Patients were excluded if more than one prosthetic joint was infected. PJI was defined according to the IDSA criteria.[2] The criterion for "acute" infection (three weeks) was extended to two months as DAIR was also performed in patients with longer duration of symptoms. The primary outcome was cure, defined as absence of infection and a stable retained implant for at least six months after stopping antibiotics. Failure was defined as either chronic suppressive antibiotic therapy with implant retention or removal of the implant. Treatment consisted of extensive surgical debridement, rinsing with povidone iodine and pulsed lavage with at least 3 liters of saline. Standard procedure required 3–6 periprosthetic tissue samples to be taken for culture. Empiric antibiotic therapy with a betalactam, an aminoglycoside and rifampicin (600 mg b.d.) was started intraoperatively, after debridement. Rifampicin was stopped after five days. After two weeks, intravenous antibiotics were switched to an oral alternative depending on antimicrobial susceptibility testing, flucloxacillin oral absorption test[3] and the clinical response. Total treatment duration of six to twelve weeks depending on clinical response and inflammatory parameters. Follow-up was at least one year.

Forty-one patients were included; baseline characteristics are shown in Table 1. *Staphylococcus aureus* was involved in 30 cases and coagulase-negative staphylococci (CNS) in 10 cases. One patient had both an *S. aureus* and a CNS. In Table 2 cure rates as categorized by affected joint, type of prosthesis and use of immunosuppression are summarized. Overall cure rate was 63%. Notably, patients without a megaprosthesis with a staphylococcal hip PJI (n = 18) had a cure rate of 83%. Mean antimicrobial treatment duration in cured patients was 9.7 weeks (median 7.1 weeks). Twelve patients were treated for six weeks; their cure rate was 83%. Mean follow up of cured patients was 392 days (range 97–802 days).

Of the 15 failures, five had a functional cure (retention of the prosthesis with chronic suppressive therapy). Eight of those failures were caused by the same type of micro-organism as the primary infection (six *S. aureus*, two CNS). Rifampicin susceptibility in seven of those latter cases had not changed. In the eighth patient one out of five positive cultures with *S. aureus* showed rifampicin resistance.

The high cure rate for staphylococcal hip PJI exceeded those for knee PJI as observed in previous cohort studies.[4,5] Proportion of megaprostheses was higher in knee PJI (53%) compared to hip PJI (18%), which might explain differences in cure rate. The overall cure rate of 63% may be caused by group heterogeneity with respect to underlying disease (i.e. rheumatoid arthritis, bone- and soft-tissue tumors). Also, changing the liner or femoral head was not a routine procedure until three years ago, which might have decreased the likelihood for cure in our patients as well. Antibiotic treatment duration of six weeks was not associated with an increased relapse rate. Allegedly, clinicians are able to select patients who can be treated with a shorter course of antibiotic treatment, based on clinical and laboratory parameters.

The current advocated treatment policy for acute staphylococcal PJI is based on a small randomized trial in which patients were treated with rifampicin combination therapy for at least 12 weeks.[6] Of note, in this underpowered study 50% of the patients had osteosynthesis-associated infection and not a PJI. The drop-out rate due to rifampicin-related adverse events was 33% (6/18). Cure rates with combination therapy were thereafter reported to be 65–90% in observational studies.[1,4–8] No studies have been published in which short treatment duration with rifampicin was investigated. Our data suggest that prolonged treatment with rifampicin might not be needed as its added bactericidal and biofilm-preventing effect has already taken place in the first few postoperative days.[9] Rifampicin monotherapy and high bacterial loads are well known risk factors for evolving resistance. The absence of development of rifampicin resistance might be explained by the short treatment duration with rifampicin. However, resistance usually develops within two to three days of starting rifampicin monotherapy.[10]

This study adds new insights to the concept of antimicrobial treatment for patients with a staphylococcal PJI. Short-term postoperative treatment with rifampicin resulted in high cure rates in patients with staphylococcal hip PJI. Immediate intraoperative start of combination therapy did not result in rifampicin resistance. Additional prospective studies are warranted to elucidate the optimal

https://doi.org/10.1016/j.jinf.2018.01.009

**Table 1**
Baseline characteristics of 41 patients with acute staphylococcal PJI.

| | All (n = 41) |
|---|---|
| **Demographics** | |
| Age at diagnosis (mean, range) | 58 (15–92) |
| Sex (male, %) | 24 (59%) |
| Implant site (n, %) | |
| Hip | 22 (54%) |
| Knee | 19 (46%) |
| Revision[a] (n, %) | 14 (34%) |
| **Comorbidities** (n, %) | |
| Diabetes mellitus | 4 (10%) |
| Rheumatoid arthritis | 9 (22%) |
| Orthopaedic oncology[c] | 14 (34%) |
| Use of immunosuppressants[d] | 11 (27%) |
| **Clinical characteristics** (n, %) | |
| Bacteraemia | 9 (22%) |
| Duration of symptoms | |
| 1–7 days | 30 |
| 8–14 days | 6 |
| 15–21 days | 1 |
| 22–29 days | 2 |
| 29–60 days | 2 |
| **Microbiology** | |
| Number of cultures taken (median, range) | 5 (2–9) |
| Number of positive cultures per patient[d] (median, range) | 4 (0–8) |
| Micro-organisms | |
| *Staphylococcus aureus* | 31 (76%) |
| *CNS* | 10 (24%) |

[a] Patients with revision preceding PJI.
[b] Use of any of MTX/TNFa-inhibitors/steroids in the months preceding PJI.
[c] Patients with a tumour prosthesis in situ.
[d] Two patients with evident pus but cultures remaining negative.

duration of rifampicin as part of the antimicrobial therapy in patients with a staphylococcal PJI.

## Conflicts of interest

None.

**Table 2**
Subgroup analyses of outcome of DAIR and 5 days of rifampicin for acute staphylococcal PJI.[a]

| | n | Complete cure[b] | Functional cure[c] |
|---|---|---|---|
| All patients | 41 | 63% | 76% |
| Patients without megaprosthesis | 27 | 70% | 78% |
| Hip PJI | 18 | 83% | 89% |
| Knee PJI | 9 | 44% | 56% |
| Patients with a megaprosthesis[d] | 14 | 50% | 71% |
| All patients with steroids/anti-TNF/MTX | 11 | 46% | 55% |

[a] Acute: symptoms or last operation/revision < 8 weeks.
[b] Complete cure: absence of infection and a stable retained implant for at least six months after stopping antibiotic therapy.
[c] Functional cure: stable prosthesis in situ but with chronic suppressive antimicrobial therapy.
[d] Mega prosthesis: patients with bone- or soft-tissue tumors.
Anti-TNF: tumor necrosis factor inhibitors, MTX: methotrexate.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References

1. Ascione T, Pagliano P, Mariconda M, Rotondo R, Balato G, Toro A, et al. Factors related to outcome of early and delayed prosthetic joint infections. J Infect 2015; 70(1):30–6.
2. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2013;56(1): e1–25.
3. Dijkmans AC, Hartigh J, van Dissel JT, Burggraaf J. A simplified oral flucloxacillin absorption test for patients requiring long-term treatment. Ther Drug Monit 2012; 34(3):356–8.
4. Soriano A, Garcia S, Bori G, Almela M, Gallart X, Macule F, et al. Treatment of acute post-surgical infection of joint arthroplasty. Clin Microbiol Infect 2006; 12(9):930–3.
5. Barberan J, Aguilar L, Carroquino G, Gimenez MJ, Sanchez B, Martinez D, et al. Conservative treatment of staphylococcal prosthetic joint infections in elderly patients. Am J Med 2006;119(11):993, e7–10.
6. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. JAMA 1998;279(19): 1537–41.
7. Lora-Tamayo J, Murillo O, Iribarren JA, Soriano A, Sanchez-Somolinos M, Baraia-Etxaburu JM, et al. A large multicenter study of methicillin-susceptible and methicillin-resistant Staphylococcus aureus prosthetic joint infections managed with implant retention. Clin Infect Dis 2013;56(2):182–94.
8. Vilchez F, Martinez-Pastor JC, Garcia-Ramiro S, Bori G, Macule F, Sierra J, et al. Outcome and predictors of treatment failure in early post-surgical prosthetic joint infections due to Staphylococcus aureus treated with debridement. Clin Microbiol Infect 2011;17(3):439–44.
9. Zimmerli W, Frei R, Widmer AF, Rajacic Z. Microbiological tests to predict treatment outcome in experimental device-related infections due to Staphylococcus aureus. J Antimicrob Chemother 1994;33(5):959–67.
10. Kadurugamuwa JL, Sin LV, Yu J, Francis KP, Purchio TF, Contag PR. Noninvasive optical imaging method to evaluate postantibiotic effects on biofilm infection in vivo. Antimicrob Agents Chemother 2004;48(6):2283–7.

Henk Scheper*, Daphne van Hooven, Leo Visser, Mark de Boer
*Department of Infectious Diseases, Leiden University Medical Centre, Albinusdreef 2, 2333ZA, The Netherlands*
* Corresponding author. Department of Infectious Diseases, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands.*E-mail address:* h.scheper@lumc.nl (H. Scheper).

Michiel van de Sande, Robert van der Wal, Rob Nelissen
*Department of Orthopaedics, Leiden University Medical Centre, Albinusdreef 2, 2333ZA, The Netherlands*

Martha van der Beek
*Department of Medical Microbiology, Leiden University Medical Centre, Albinusdreef 2, 2333ZA, The Netherlands*

Accepted 27 January 2018

https://doi.org/10.1016/j.jinf.2018.01.009