MAJOR ARTICLE

A Large Multicenter Study of Methicillin–Susceptible and Methicillin–Resistant *Staphylococcus aureus* Prosthetic Joint Infections Managed With Implant Retention

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Background. Several series predicting the prognosis of staphylococcal prosthetic joint infection (PJI) managed with debridement, antibiotics, and implant retention (DAIR) have been published, but some of their conclusions are controversial. At present, little is known regarding the efficacy of the different antibiotics that are used or their ability to eliminate methicillin-resistant *S. aureus* (MRSA) infection.

Methods. This was a retrospective, multicenter, observational study of cases of PJI by *S. aureus* that were managed with DAIR (2003–2010). Cases were classified as failures when infection persistence/relapse, death, need for salvage therapy, or prosthesis removal occurred. The parameters that predicted failure were analyzed with logistic and Cox regression.

Results. Out of 345 episodes (41% men, 73 years), 81 episodes were caused by MRSA. Fifty-two were hematogenous, with poorer prognoses, and 88% were caused by methicillin-susceptible *S. aureus* (MSSA). Antibiotics were used for a median of 93 days, with similar use of rifampin-based combinations in MSSA- and MRSA-PJI. Failure occurred in 45% of episodes, often early after debridement. The median survival time was 1257 days. There were no overall prognostic differences between MSSA- and MRSA-PJI, but there was a higher incidence of MRSA-PJI treatment failure during the period of treatment (HR 2.34), while there was a higher incidence of MSSA-PJI treatment failure after therapy. Rifampin-based combinations exhibited an independent protective effect. Other independent predictors of outcome were polymicrobial, inflammatory, and bacteremic infections requiring more than 1 debridement, immunosuppressive therapy, and the exchange of removable components of the prosthesis.

Conclusions. This is the largest series of PJI by *S. aureus* managed with DAIR reported to date. The success rate was 55%. The use of rifampin may have contributed to homogenizing MSSA and MRSA prognoses, although the specific rifampin combinations may have had different efficacies.

Keywords. prosthetic joint infection; *Staphylococcus aureus*; MRSA; rifampin; antibiotics and implant retention (DAIR).

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Staphylococcus aureus is the microorganism most frequently responsible for prosthetic joint infection (PJI), especially in acute cases where debridement, antibiotics, and implant retention (DAIR) may be attempted [1–3]. This approach may cure the patient, reduce costs, and prevent the loss of bone stock and the need for additional operations [3–6].

An increased risk of joint failure has been associated with *S. aureus* infection [3, 7, 8], as well as with delay in administration of debridement, older age of the implant, prosthesis loosening, or the presence of a sinus tract [1, 2, 9, 10]. However, clinical series of PJI by *S. aureus* addressing the efficacy of DAIR usually include small samples, frequently in combination with coagulase-negative *Staphylococci* (CNS) [4, 11]. Moreover, the efficacy of DAIR may have improved with the introduction of rifampin during the last decade [12].

Infection by methicillin-resistant *S. aureus* (MRSA) could worsen the prognosis [13–18], due to the more limited range of antibiotics available [19]. However, this poorer prognosis of MRSA-PJI is controversial because case series include small numbers of MRSA infections, and the outcome of some of these patients was improved when treated with rifampin [8, 9, 20].

We present a large, multicenter series of cases of PJI by *S. aureus* treated with DAIR. The aim of this study was to assess the efficacy of DAIR, to identify factors predicting failure, and to establish the impact of MRSA and the use of rifampin combinations on prognosis.

METHODS

Setting and Patients

A retrospective, observational study was carried out in 17 hospitals in Spain, in the framework of the Spanish Network for Research in Infectious Diseases between 2003–2010. All cases of PJI originally caused by *S. aureus* and managed with DAIR were included, regardless of the age of the implant at the time of symptom onset. Patients with an unstable prosthesis or with surrounding soft tissues badly damaged did not undergo DAIR. Polymicrobial infections were also included. Cases where *S. aureus* did not cause the original PJI but participated later as a superinfecting microorganism were excluded. The identification of cases with *S. aureus* PJI was made from previously registered databases of PJI or from the general archives in each hospital. The decision to undergo DAIR and antimicrobial therapy was made by the attending medical team, based upon current recommendations [2, 5].

PJI by *S. aureus* was defined by ≥2 surgical, joint-aspirated or blood cultures yielding *S. aureus*, or by 1 such positive culture plus the presence of typical clinical symptoms and signs, such as joint pain, erythema and other inflammatory signs, or the presence of a sinus tract or purulence around the prosthesis during surgery [9]. Microorganisms were identified according to standard criteria [21] after samples had been seeded in liquid (thioglycolate) and solid media (5% sheep blood, chocolate, and MacConkey agar) and incubated for at least 7 days. PJI was subsequently classified as post-surgical or hematogenous, being the latter characterized by an acute clinical presentation associated with documented or suspected bloodstream infection [1, 2].

Data on clinical presentation, risk factors for PJI, and baseline characteristics were recorded. Rheumatoid arthritis was defined by diagnostic criteria [22]. Chronic renal impairment was defined as a level of creatinine>150 μmol/L. Diagnostic prosthesis radiography was considered to be abnormal if there were signs of loosening or infection. Information regarding surgical treatment, exchange of removable pieces of the prosthesis (in at least 1 debridement), and type and duration of antimicrobials were also recorded. A composite variable based upon Zimmerli's algorithm [2] was considered if the patient was submitted to debridement within the first 21 days after symptom onset, plus if the prosthesis radiography was normal, plus if the prosthesis had been placed less than 3 months after the beginning of symptoms (for post-surgical cases).

All information was introduced in a specifically designed Microsoft Access database. All cases were critically reviewed by 2 authors (J.L-T. & J.A.). Any controversy or contradiction found was double-checked by the investigator at each hospital.

Clinical and Surgical Management

DAIR management has been described elsewhere [8]. Standard procedure consists of checking the solid fixation of the prosthesis, and when possible, the prosthetic exchangeable components are removed. After debridement, intravenous antibiotics of wide antimicrobial-spectrum are administered. Once the antimicrobial susceptibility was available, antibiotics were adjusted according to current guidelines. The intravenous route was maintained for a variable period depending on each hospital protocol, usually followed by oral antibiotics also for a variable time.

DAIR was considered to initiate with the first debridement procedure. Cases initially treated with antibiotics for >7 days without evident signs of infection during debridement, and if samples taken yielded no microorganisms, were not included in this analysis.

Outcome and Follow-Up

Failure was defined as: a) death related to the infection; b) prosthesis removal within 2 years of the beginning of treatment, for any cause, or after 2 years due to persistence/relapse of the staphylococcal infection and/or caused by other superinfecting microorganisms; c) the need for extra debridements

30 days after the first; or d) the need for extra courses of antibiotic after the initial scheduled treatment, including long-term antibiotic suppressive therapy (AST). Although these last 2 criteria (extra debridements and AST in patients with a foreseeable bad outcome) are not well established reasons for failure, they were assumed as a consensus among the investigators.

We performed an *Overall Failure* analysis. In order to evaluate the impact of antimicrobial therapy, we took into account failure dynamics and also performed a separate analysis of parameters predicting failure depending on the moment when it occurred:

- *Early Failure*: failure within 30 days of debridement surgery.
- *Late Failure*: failure while the patient was still under antimicrobial therapy, but occurring after the first 30 days after debridement.
- *Failure After Therapy*: failure after the end of antimicrobial therapy.

Statistical Analysis

Comparative analyses were performed with X^2 or Fisher's test for categorical variables, and the Mann-Whitney *U*-test for continuous variables. Multivariate analysis of parameters predicting *Early Failure* was made by logistic regression. Univariate and multivariate analyses of parameters predicting *Overall Failure*, *Late Failure*, and *Failure After Therapy* were made with Cox-regression, considering failures as main events, while loss of follow-up, death unrelated to infection, a new episode of PJI, or prosthesis removal any time 2 years after the beginning of treatment for orthopedic reasons were considered censored cases.

The length of antibiotic therapy could be shortened in cases failing prematurely and would not actually be the cause of failure but its consequence, and therefore, the antimicrobial therapy parameters were only analyzed when the comparison groups had had the same possibilities of receiving antibiotics. For this reason, this influence was not analyzed in *Overall* and *Early Failures*. The influence of antibiotics administered during the first 30 days was analyzed for *Late Failure* and *Failure After Therapy*, and the influence of the whole length of treatment was analyzed for *Failure After Therapy*.

Data were analyzed using SPSS (Statistical Package for the Social Sciences) software (version 15.0). All analyses were 2-tailed, and a P value $< .05$ was considered statistically significant.

RESULTS

Description of the Series

A total of 561 cases of PJI by *S. aureus* were diagnosed. Among them, 349 (62%) were managed with DAIR. Four (1%) patients were removed from this set due to a significant lack of data. Therefore, our analysis was carried out with 345 episodes occurring in 342 patients, of whom 140 (41%) were men, with a median age of 73 years (range 27–95). MRSA caused 81 (23%) episodes.

Infection was polymicrobial in 64 cases (19%). The most frequent microorganisms accompanying *S. aureus* were *Enterobacteriaceae* (of 33 cases, 11 were *Proteus* spp and 9 were *E. coli*), followed by CNS (10 isolates), *Pseudomonas* spp (8 isolates), *Enterococci* (7 isolates) and *Streptococci* (6 isolates).

There were 78 (23%) post-surgical cases with symptoms that began more than 30 days after the placement of the prosthesis (median of 64 days, interquartile range [IQR]: 35–184). In 50 (64%) cases, symptoms began within the initial 90 days.

All patients received appropriate initial empirical antibiotic therapy, and further specific antibiotic regimens were double-checked with microbiological susceptibility tests.

Hematogenous Versus Post-Surgical PJI

Table 1 shows a comparative analysis between post-surgical and hematogenous infections. The latter occurred more frequently among immunosuppressed patients, was often located in knee prostheses, and was monomicrobial, being caused by methicillin-susceptible *S. aureus* (MSSA) in 88% of cases. Hematogenous infections presented a more inflammatory clinical picture and a poorer prognosis, in spite of undergoing earlier debridement.

MRSA- Versus MSSA-PJI

Table 1 also presents a comparative analysis of MRSA and MSSA cases. MRSA-PJIs were most often suppurative and post-surgical hip-PJIs, occurring in older patients with more frequent comorbidity, especially chronic renal impairment. However, when hematogenous infections were excluded, no significant differences in the clinical presentation were observed (data not shown).

The surgical approach was alike in the MRSA and MSSA groups. Also, the length of antimicrobial therapy was similar in patients who completed the scheduled treatment without failing (94 days [IQR 61–162] vs 91 days [IQR 74–120]; $P = .922$). As expected, there were major differences between MRSA and MSSA cases regarding the specific antibiotics administered (Table 2). However, in both scenarios, rifampin was extensively used and to a similar extent: 303 (88%) patients were treated at some point with rifampin. Among patients not presenting *Early Failure,* 222 (76%) had been treated for ≥2 weeks during the first month after debridement, and among the patients who did not fail during the scheduled treatment, 189 (80%) had received rifampin for ≥4 weeks. In addition, rifampin treatment was initiated very early [delay of 0 days after debridement (IQR: 0–5)]. In the case of MSSA

Table 1. Case Series Description and Comparative Analysis of Methicillin-Susceptible *Staphylococcus aureus* and Methicillin-Resistant *S. aureus* Cases, and Hematogenous and Post-Surgical Infections

		All Cases (n = 345)	MSSA (n = 264)	MRSA (n = 81)	*P*	Post-Surgical (n = 293)	Hematogenous (n = 52)	*P*
Baseline features	Sex (men)	140 (41%)	112 (42%)	28 (35%)	.208	119 (41%)	21 (40%)	.975
	Age (years)	73 (64–79)	71 (63–77)	78 (71–82)	<.001	72 (64–78)	74 (65–79)	.337
	Diabetes mellitus	68 (19%)	47 (18%)	21 (26%)	.097	60 (20%)	8 (15%)	.389
	Chronic renal impairment	19 (6%)	7 (3%)	12 (15%)	<.001	16 (5%)	3 (7%)	1.000
	Rheumatoid arthritis	30 (9%)	26 (10%)	4 (5%)	.187	23 (8%)	7 (13%)	.188
	Immunosuppressive therapy	22 (6%)	18 (7%)	4 (5%)	.576	14 (5%)	8 (15%)	.010
	Revision prosthesis	67 (19%)	46 (17%)	21 (26%)	.091	58 (20%)	9 (17%)	.676
	Prosthesis location							
	Knee	195 (57%)	166 (63%)	29 (36%)	<.001	157 (54%)	38 (73%)	.022
	Hip	146 (42%)	97 (37%)	49 (60%)		133 (45%)	13 (25%)	
	Other	4 (1.2%)	1 (0.4%)	3 (3.7%)		3 (1%)	1 (2%)	
Clinical presentation	Type of infection							
	Hematogenous	52 (15%)	46 (17%)	6 (7%)	.057	–	–	–
	Post-surgical[a] <30 days	215 (62%)	157 (59%)	58 (72%)		–	–	
	Post-surgical[a] >30 days	78 (23%)	61 (23%)	17 (21%)		–	–	
	Time to infection (days)[a]	19 (11–31)	19 (11–31)	18 (10–29)	.237	–	–	–
	Polymicrobial infection	64 (19%)	49 (19%)	15 (19%)	.992	63 (22%)	1 (2%)	.001
	MRSA infection	81 (23%)	–	–	–	75 (26%)	6 (12%)	.028
	Bacteremia	54 (16%)	44 (17%)	10 (12%)	.349	25 (9%)	29 (56%)	<.001
	Temperature >37°C	154 (45%)	127 (48%)	27 (33%)	.029	113 (39%)	41 (79%)	<.001
	Joint pain	272 (79%)	214 (81%)	58 (72%)	.064	221 (75%)	51 (98%)	<.001
	Sinus tract	50 (14%)	38 (14%)	12 (15%)	.942	48 (16%)	2 (4%)	.016
	Suppuration	189 (56%)	132 (50%)	57 (70%)	.001	187 (64%)	2 (4%)	<.001
	Leukocytes (10^9/L)	9.4 (6.6–13.4)	9.7 (6.9–13.8)	7.9 (5.1–11.2)	.014	9.0 (6.3–12.6)	11.9 (8.5–16.0)	<.001
	C-reactive protein (mg/L)	63 (20–172)	55 (20–177)	82 (21–167)	.355	53 (12–132)	225 (48–353)	<.001
Treatment and outcome	Debridement delay (days)[b]	7 (4–14)	7 (4–14)	9 (4–16)	.107	8 (4–16)	6 (3–11)	.031
	≥2 debridements	30 (9%)	22 (8%)	8 (10%)	.666	24 (8%)	6 (12%)	.425
	Polyethylene exchange[c]	221 (73%)	171 (75%)	50 (68%)	.249	194 (75%)	27 (63%)	.080

Table 1 continued.

	All Cases (n = 345)	MSSA (n = 264)	MRSA (n = 81)	*P*	Post-Surgical (n = 293)	Hematogenous (n = 52)	*P*
Global failure[d]	146 (45%)	112 (44%)	34 (46%)	.778	114 (41%)	32 (65%)	.001
Early Failure during therapy[e]	42 (12%)	31 (12%)	11 (14%)	.573	33 (11%)	9 (18%)	.220
Late Failure during therapy[d]	47 (14%)	28 (11%)	19 (26%)	.001	40 (14%)	7 (14%)	.861
Failure After Therapy[d]	57 (17%)	53 (21%)	4 (5%)	.012	41 (15%)	16 (33%)	<.001

Categorical variables expressed in absolute number and (percentage); continuous variables expressed in median and (interquartile range).
Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.
[a] Time to infection: time from prosthesis placement to onset of symptoms (excluding hematogenous infections).
[b] Debridement delay: time from onset of symptoms to debridement surgery.
Analysis excludes the following:
[c] 44 patients (36 MSSA–prosthetic joint infection [PJI] + 8 MRSA-PJI; 35 post-surgical cases + 9 hematogenous-PJI) with no information regarding polyethylene exchange.
[d] 17 patients with unknown outcome (10 MSSA-PJI + 7 MRSA-PJI; 14 post-surgical cases + 3 hematogenous-PJI).
[e] 7 patients with unknown outcome at this point (3 MSSA-PJI + 4 MRSA-PJI; 6 post-surgical cases and 1 hematogenous-PJI).

infections, combinations of rifampin were mostly made with beta-lactams (13%) or quinolones (75%, mainly levofloxacin), while MRSA cases were treated with combinations of rifampin and glycopeptides (18%, namely vancomycin), cotrimoxazole (46%), linezolid (24%), or clindamycin (10%).

Outcome

Seventeen patients (5%) were lost to follow-up and/or had an unknown outcome. Among the 328 remaining patients, failure was documented in 146 (45%): there were 10 (7%) related deaths; 114 (78%) patients required the removal of the prosthesis to control the infection (in 81% due to staphylococcal persistence or relapse); 14 (10%) patients needed further courses of antibiotics and/or debridements more than 30 days after the initial one; and 8 (5%) patients needed long-term AST.

Among 60 cases treated with rifampin and finally presenting staphylococcal persistence or relapse, development of resistance to this antibiotic was observed in 6 (10%). Three were MRSA-PJIs: 2 received vancomycin and 1 cotrimoxazole; and 3 were MSSA-PJI: 1 was treated with cotrimoxazole and 2 with fluoroquinolones (1 also developed resistance to levofloxacin). Among polymicrobial infections, no patient failed exclusively due to persistence or relapse of the initially accompanying microorganisms other than *S. aureus*. The median survival time without failure was 1257 days (95% confidence interval: 361–2153). The rate of failure was not related with any particular period of the study.

Dynamics of Failure

Figure 1*A* illustrates that the likelihood of failure was much higher during the first few weeks after debridement. Among all failures, 42 (29%) occurred within the first 30 days of surgery. Table 3 shows the parameters associated with *Early Failure*: patients with inflammatory, polymicrobial, and bloodstream infections, rheumatoid arthritis, or male sex were more likely to fail.

After the initial 30 days, 47 (32%) patients failed while still on therapy (*Late Failure*). Older immunosuppressed patients with the presence of a sinus tract and MRSA-PJIs were more likely to fail, as well as patients needing ≥2 debridements.

There were 57 (39%) *Failures After Therapy*. Independent predictors were hematogenous infection, PJI by MSSA, delayed debridement, and the need for ≥2 debridements to control the infection.

Table 4 summarizes the parameters related with *Overall Failure*. Immunosuppression and the degree of complexity of the infection (polymicrobial, bacteremic, or presenting with high CRP levels) were independent predictors of failure. The need for ≥2 debridements also increased the likelihood of

Table 2. Antimicrobial Treatment in Methicillin-Susceptible *Staphylococcus aureus* and Methicillin-Resistant *S. aureus* Prosthetic Joint Infection

	Whole Treatment (n = 235)[a]					Treatment During the First 30 Days After Debridement (n = 296)[b]				
	MSSA		MRSA			MSSA		MRSA		
	Days[c]	>28 Days (%)	Days[c]	>28 Days (%)	*P*[d]	Days[c]	>14 Days (%)	Days[c]	>14 Days (%)	*P*[d]
Any antibiotic	117 ± 90	–	105 ± 58	–	.922	–	–	–	–	–
Rifampin	90 ± 90	78	93 ± 63	93	.263	21 ± 11	75	23 ± 11	77	.193
Quinolones	82 ± 84	76	9 ± 43	5	<.001	13 ± 10	50	0.6 ± 2.6	2	<.001
plus Rifampin	67 ± 85	64	9 ± 43	5	<.001	11 ± 10	42	0.4 ± 2.3	2	<.001
Beta-Lactams	16 ± 22	17	4 ± 14	2	<.001	13 ± 10	39	3 ± 7	8	<.001
plus Rifampin	10 ± 16	9	3 ± 14	2	<.001	8 ± 10	25	0.9 ± 4.1	3	<.001
Glycopeptides	2 ± 7	1	18 ± 17	12	<.001	2 ± 5	4	14 ± 11	49	<.001
plus Rifampin	1 ± 6	1	14 ± 16	10	<.001	1 ± 4	3	10 ± 11	36	<.001
Cotrimoxazole	15 ± 53	11	52 ± 54	60	<.001	1 ± 5	4	6 ± 10	17	<.001
plus Rifampin	8 ± 34	6	48 ± 53	57	<.001	1 ± 4	3	5 ± 9	15	<.001
Clindamycin	6 ± 25	6	11 ± 34	14	.081	0.5 ± 3.1	2	2 ± 6	8	.033
plus Rifampin	3 ± 20	3	9 ± 31	12	.029	0.2 ± 1.6	1	2 ± 6	8	.001
Linezolid	1 ± 8	2	15 ± 25	21	<.001	0.5 ± 3.2	2	4 ± 7	14	<.001
plus Rifampin	0.3 ± 3.5	0.5	12 ± 24	17	<.001	0.2 ± 2.1	0.4	4 ± 7	11	<.001

Common doses administered of these antibiotics were as follows: Rifampin 600 mg/d *per os* (oral administration; po) or intravenous (iv); Levofloxacin 750 mg/d po/iv; Ciprofloxacin 750–1000 mg/12 hours po or 200–400 mg/12 hours iv; Moxifloxacin 400 mg po; Cloxacillin 2 g/4 hours iv; Amoxicillin-clavulanate 1 g/8 hours iv; Cefepime 2 g/8–12 hours iv; Vancomycin 1 g/12 hours (and adjustment of doses depending on serum levels); Teicoplanin 400 mg/24 hours iv; Cotrimoxazole 800/160 mg /12 hours po/iv; Clindamycin 600 mg/6–8 hours po/iv; Linezolid 600 mg /12 hours iv/po.

Abbreviations: MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a] Analysis made in patients who completed the scheduled treatment without failure.

[b] Analysis made in patients who did not fail during the first 30 days of treatment.

[c] Duration of antibiotic treatment expressed in mean of days ± standard deviation.

[d] Compared with the Mann-Whitney *U*-test.

failure, and the exchange of the polyethylene component was an independent predictor of success.

Overall, there were 82 patients (25%) who were managed with DAIR even though they did not accomplish Zimmerli's algorithm [2]. Failure was slightly higher among these patients (52% vs 42%; $P = .095$) and it presented earlier (920 ± 113 vs 1440 ± 94 days; $P = .065$).

MRSA Versus MSSA Outcome – Influence of Antimicrobial Therapy

Overall, there were similar failure rates for MRSA- and MSSA-PJI (46 vs 44%; $P = .778$), but with different dynamics (Figure 1*B*). During the antimicrobial treatment and after the first 30 days, MRSA cases were more than twice as likely to fail as MSSA-PJIs. In contrast, after treatment, MSSA cases failed more than MRSA-PJIs (Figure 2). This was still observed after excluding hematogenous cases (data not shown).

Patients treated with rifampin during the first 30 days of treatment showed a lower likelihood of *Late Failure* (Table 3). An analysis of post-surgical PJIs, without the influence of hematogenous cases, is presented in Table 5, which shows that rifampin-based combinations exerted an independent favorable influence.

We were not able to demonstrate the influence of antibiotics administered after the first 30 days. Figure 3 also illustrates that longer treatments were not associated with better outcomes. Finally, post-surgical cases with onset of symptoms more than 90 days after the placement of the prosthesis had a tendency towards a worse outcome (Figure 4).

DISCUSSION

In this series of PJI by *S. aureus*, DAIR was able to save 55% of implants in the long-term. While this percentage is in the middle range of staphylococcal-PJI series managed with DAIR (13–75%) [7–11, 16, 18, 23], it was low when compared with other recent cohorts using rifampin-based regimens [10, 20, 23]. Our rate of success may have been lowered by a longer delay in the administration of debridement and the inclusion of hematogenous cases and prosthesis placed >90 days before the beginning of symptoms, as well as the criteria we used,

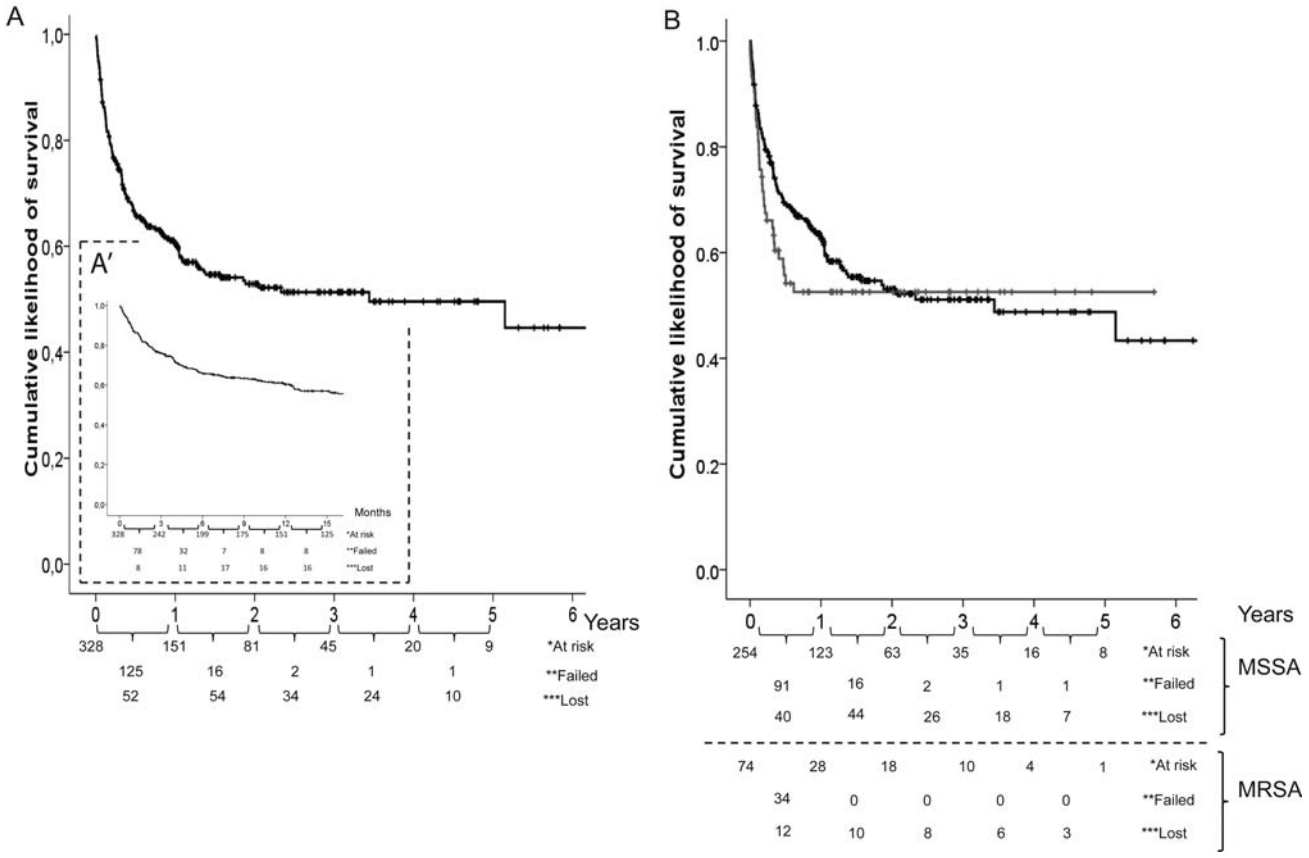

Figure 1. Kaplan-Meier survival diagram of patients with prosthetic joint infection by *Staphylococcus aureus*. *A*, Overall survival curve. *A′*, Survival curve during the first 15 months of follow-up. *B*, Survival curve for methicillin-susceptible *S. aureus* (black curve) and methicillin-resistant *S. aureus* (grey curve); log-rank test: $P = .374$; *Number of patients at risk for failure at the beginning of the period. **Patients failing during the period. ***Number of patients lost to follow-up during the period.

such as considering the patients as failures if they underwent long-term AST. However, because this is a multicenter study with a larger sample than previous analyses ($n = 21$–53), our data may be closest to the real likelihood of healing and retaining a joint prosthesis after staphylococcal PJI [7–11, 16].

Overall, the treatment of MRSA infections was not less successful than MSSA-PJI. This contrasts with previous reports of MRSA-PJI, which suggested poorer rates of success (16–35%) [11, 13, 16, 17]. Interestingly, most of our MRSA infections were early and extensively treated with rifampin. This antibiotic has been shown to maintain strong antimicrobial activity against clinical and experimental staphylococcal foreign body infections [12, 19, 24–26]. Indeed, modern series of PJI using rifampin for MRSA infections have shown better results than earlier ones, with success rates of 67%–100% [8, 10, 20].

Nevertheless, the behavior of MRSA- and MSSA-PJI was not the same: 88% of MRSA failures occurred during the first weeks after debridement while patients were still on therapy; in contrast, half of MSSA failures occurred once the antibiotic was withdrawn. When we excluded hematogenous patients, we again observed these different dynamics in failure, as well as a similar clinical presentation of MRSA- and MSSA-PJI. The surgical approach in the 2 groups was very similar, and so the main difference in treatment between MRSA and MSSA cases was the specific rifampin-based combination used in each group. Although a direct comparison between the specific combinations was not possible, this may suggest that not all treatments with rifampin are the same. The specific combination of quinolones plus rifampin has been considered the treatment of choice of MSSA-PJI [2, 23]. Thus, rifampin combinations for MRSA-PJI did not avoid failure as much as rifampin-fluoroquinolone combinations did among MSSA-cases, not failing until the withdrawal of the antibiotics. In addition, the development of resistance to rifampin among failures was less frequent when rifampin was combined with quinolones rather than other antimicrobials.

In our series, the type of antibiotic therapy administered during the first 30 days after debridement had an influence on

Table 3. Univariate and Multivariate Analysis of Parameters Predicting *Early Failure, Late Failure* and *Failure After Therapy*

	Early Failure (n = 338; failure = 42)				Late Failure (n = 284; failure = 47)				Failure After Therapy (n = 231; failure = 57)			
	Unadjusted OR (95%CI)	*P*	Adjusted OR (95%CI)	*P*	Unadjusted HR (95%CI)	*P*	Adjusted HR (95%CI)	*P*	Unadjusted HR (95%CI)	*P*	Adjusted HR (95%CI)	*P*
Sex (male)	1.78 (.93–3.41)	.081	2.48 (1.19–5.19)	.016	.70 (.37–1.31)	NS	–	–	.68 (.39–1.19)	NS	–	–
Age (years)	1.02 (.99–1.06)	NS	–	–	1.03 (1.00–1.06)	.032	1.03 (1.00–1.07)	.052	.98 (.96–1.00)	NS	–	–
Diabetes mellitus	.67 (.27–1.66)	NS	–	–	1.46 (.74–2.88)	NS	–	–	1.29 (.68–2.45)	NS	–	–
Chronic renal impairment	1.44 (.40–5.19)	NS	–	–	2.54 (1.00–6.45)	.081	–	–	1.69 (.41–6.95)	NS	–	–
Rheumatoid arthritis	2.91 (1.20–7.04)	.018	3.88 (1.44–10.4)	.007	1.49 (.63–3.52)	NS	–	–	1.39 (.55–3.48)	NS	–	–
Immunosuppressive therapy	2.20 (.77–6.32)	NS	–	–	2.41 (1.07–5.42)	.054	3.05 (1.30–7.14)	.010	1.86 (.58–5.98)	NS	–	–
Revision prosthesis	1.56 (.74–3.28)	NS	–	–	2.00 (1.08–3.70)	.036	–	–	.89 (.42–1.88)	NS	–	–
Hip prosthesis	1.06 (.55–2.03)	NS	–	–	1.72 (.95–3.13)	.080	–	–	.81 (.46–1.40)	NS	–	–
Hematogenous infection	1.65 (.74–3.69)	NS	–	–	.85 (.38–1.91)	NS	–	–	2.93 (1.64–5.25)	.001	2.46 (1.35–4.48)	.003
Infection by MRSA	1.24 (.59–2.59)	NS	–	–	2.75 (1.53–4.94)	.001	2.33 (1.25–4.33)	.008	.33 (.12–.91)	.012	.33 (.12–.92)	–
Bacteremia	4.18 (2.06–8.50)	<.001	5.03 (2.11–12.0)	<.001	1.26 (.57–2.76)	NS	–	–	1.97 (.97–4.01)	.078	–	–
Polymicrobial infection	3.65 (1.83–7.29)	<.001	7.50 (3.23–17.4)	<.001	2.56 (1.31–5.01)	.011	–	–	.75 (.34–1.67)	NS	–	–
CRP at diagnosis (per 100 mg/L)	1.45 (1.11–1.89)	.007	1.52 (1.11–2.09)	.010	1.08 (.84–1.40)	NS	–	–	–	–	–	–
Temperature >37°C	1.71 (.89–3.29)	NS	–	–	.98 (.55–1.74)	NS	–	–	–	–	–	–
Sinus tract	1.05 (.42–2.66)	NS	–	–	2.18 (1.13–4.21)	.029	1.88 (0.94–3.77)	.076	.69 (.25–1.92)	NS	–	–
Abnormal radiography	.98 (.36–2.64)	NS	–	–	2.58 (1.34–4.99)	.010	2.28 (1.14–4.54)	.019	1.49 (.67–3.29)	NS	–	–
Debridement delay[a,b]	.97 (.78–1.21)[a]	NS	–	–	2.00 (1.13–3.54)[a]	.019	–	–	1.002 (1.001–1.004)[b]	.062	1.004 (1.001–1.006)[b]	.028
Polyethylene exchange[c]	.59 (.29–1.20)	NS	–	–	.40 (.21–.77)	.008	–	–	.63 (.33–1.20)	NS	–	–
Need for ≥ 2 debridements	1.04 (.38–2.83)	NS	–	–	2.13 (1.08–4.18)	.042	2.25 (1.11–4.56)	.025	2.58 (1.33–4.99)	.011	2.51 (1.27–4.98)	.008
Rifampin[d]	–	–	–	–	.56 (.31–1.01)	.062	0.49 (0.26–0.91)	.024	.60 (.34–1.07)	.095	–	–
Levofloxacin + Rifampin[d]	–	–	–	–	.33 (.12–0.92)	.014	–	–	1.00 (.56–1.77)	NS	–	–
Vancomycin + Rifampin[d]	–	–	–	–	.82 (.25–2.66)	NS	–	–	.36 (.09–1.46)	NS	–	–

For the multivariate analysis, variables with a *P* value < .10 in the univariate analysis were included in a stepwise backward selection process (*P*-in<.05 and *P*-out<.10 were used in each step).

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; NS, non-significant (*P* > .10); OR, odds ratio.

Debridement delay, time from onset of symptoms to debridement ([a]more than10 days; [b]days to debridement).

[c] Multivariate analyses do not include polyethylene exchange due to a significant lack of data.

[d] Data regarding antibiotics refer to antimicrobials administered for more than 14 days during the first 30 days after therapy.

Table 4. Univariate and Multivariate Analysis of Parameters Predicting Overall Failure

				Unadjusted Analysis		Adjusted Analysis	
	Categories (n)	Days Without Failure[a]	Percentage of Failure (%)	HR (95%CI)	*P*	HR (95%CI)	*P*
Sex (male)	Male (131)	1502 ± 117	42	.90 (.64–1.26)	NS	–	–
	Female (197)	1085 ± 80	46				
Age (years)	–	–	–	1.01 (.99–1.02)	NS	–	–
Diabetes mellitus	Yes (62)	1102 ± 140	47	1.10 (.73–1.66)	NS	–	–
	No (266)	1372 ± 93	44				
Chronic renal impairment	Yes (15)	553 ± 192	67	2.03 (1.07–3.87)	.051	–	–
	No (313)	1390 ± 84	44				
Rheumatoid arthritis	Yes (29)	732 ± 163	66	1.84 (1.14–2.99)	.021	–	–
	No (297)	1409 ± 88	42				
Immunosuppressive therapy	Yes (21)	278 ± 67	71	2.31 (1.35–3.94)	.006	2.23 (1.18–4.20)	.013
	No (307)	1416 ± 85	43				
Revision prosthesis	Yes (64)	968 ± 126	53	1.41 (.96–2.07)	.092	–	–
	No (264)	1412 ± 92	42				
Prosthesis location (hip)	Hip (137)	1375 ± 132	42	.98 (.70–1.37)	NS	–	–
	Other (191)	1147 ± 77	46				
Hematogenous infection	Yes (49)	689 ± 136	65	1.83 (1.24–2.72)	.004	–	–
	No (279)	1473 ± 89	41				
Infection by MRSA	Yes (74)	1126 ± 120	46	1.19 (.81–1.75)	NS	–	–
	No (254)	1364 ± 93	44				
Bacteremia	Yes (52)	650 ± 136	65	2.29 (1.54–3.42)	<.001	1.81 (1.12–2.92)	.015
	No (276)	1481 ± 89	41				
Polymicrobial infection	Yes (61)	1013 ± 173	59	1.76 (1.21–2.57)	.005	1.77 (1.17–2.70)	.007
	No (267)	1445 ± 86	41				
CRP at diagnosis (per 100 mg/L)	–	–	–	1.29 (1.13–1.48)	<.001	1.22 (1.03–1.43)	.021
Temperature >37°C	Yes (148)	982 ± 92	51	1.54 (1.10–2.14)	.011	–	–
	No (180)	1530 ± 112	39				
Sinus tract	Yes (47)	845 ± 122	47	1.27 (.81–2.01)	NS	–	–
	No (281)	1409 ± 88	44				
Abnormal radiography	Yes (40)	611 ± 118	60	1.66 (1.07–2.57)	.033	–	–
	No (288)	1430 ± 87	42				
Debridement							
delay >10 days[b]	Yes (117)	1475 ± 101	50	1.39 (1.00–1.94)	.050	–	–
	No (211)	1165 ± 149	42				
Polyethylene exchange	Yes (212)	1484 ± 98	41	.56 (.39–.82)	.004	0.65 (0.44–0.95)	.026
	No (75)	701 ± 99	56				
Need for ≥2 debridements	Yes (38)	649 ± 142	71	1.98 (1.30–3.01)	.003	1.63 (1.03–2.59)	.039
	No (290)	1452 ± 89	41				

For the multivariate analysis, variables with a *P* value < .10 in the univariate analysis were included in a stepwise backward selection process (*P*-in<.05 and *P*-out<.10 were used in each step).

According to this model, in a non-immunosuppressed patient with a monomicrobial prosthetic joint infection and no bacteremia, CRP less than 100 mg/L and the need for only 1 debridement with exchange of removable pieces, the likelihood of success at 6 months would be 77%, while for a patient with the opposite situation, it would be less than 1%.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; NS, non-significant (*P* > .10).

[a] Days without failure expressed in mean ± standard deviation.

[b] Debridement delay: time from onset of symptoms to debridement.

the outcome, indicating the importance of the initial antibiotics given just after surgery, when all efforts to remove the inoculum and the biofilm have been made.

Although our analysis was unable to show the influence of the therapy after the first few weeks, this does not mean that the antimicrobial therapy administered after this point was

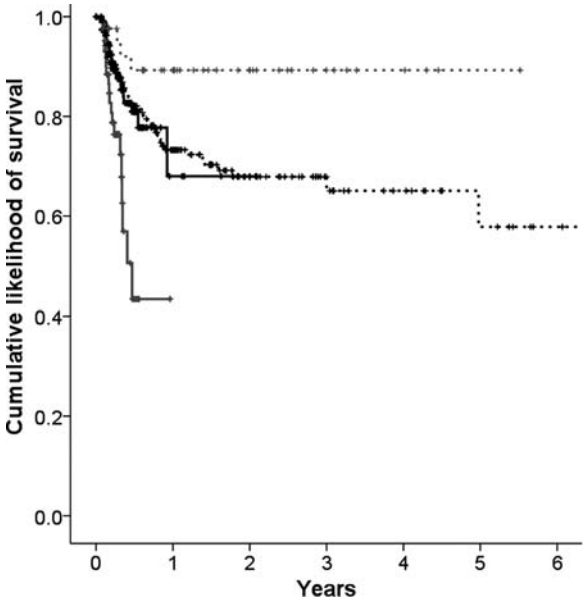

Figure 2. Comparative survival curves for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) prosthetic joint infection (PJI), during and after treatment. Patients with *Early Failure* are excluded. Black lines: MSSA PJI while on therapy (continuous line) and after therapy (discontinuous line); Log-rank test: $P = .996$. Grey lines: MRSA PJI while on therapy (continuous line) and after therapy (discontinuous line); Log-rank test: $P < .001$. Similar results were found when considering only post-surgical cases.

not important. In this regard, our results should be interpreted cautiously: most of our patients were treated for at least 60 days, meaning that a long course of antibiotics was needed; also, the retrospective nature of our work makes it difficult to compare different schedules. Furthermore, the length of treatment was the physician's choice, and so it is likely that longer therapies were applied in more severe cases, in a similar way as seen in Byren's work, which showed that prolonging therapy could delay relapse but not avoid it [8].

The literature mentions many other factors influencing the outcome of PJI that possess varying degrees of importance depending on the series. As noted by other authors [10], we found that the complexity and degree of inflammation of the infection were associated with the prognosis. Patients needing more than 1 debridement were also more likely to fail, probably because they had a more complex and highly inflammatory infection [10]. This inflammatory pattern was more frequent among hematogenous cases, carrying a worse prognosis [27–29].

Patients' baseline features and comorbidity also had an impact, especially in subjects under immunosuppressive therapy. Some studies report that revision prostheses have worse outcome than primary implants [8], but this issue is controversial [9], and we did not find statistical significance in our analysis.

In addition, because of the multicenter nature of our study, there may have been considerable surgical variability that likely influenced the outcome. We found that exchanging the polyethylene component of the prosthesis reduced the risk of failure by 33%, in spite of incomplete retrospective data.

In Brandt's study [9], patients delaying their debridement for >2 days had a poorer prognosis. This cutoff has not been confirmed by more recent studies [7, 8, 10], perhaps due to differences in patient selection or antibiotic management (ie, the addition of rifampin). Also, debridements may be performed earlier in more severe cases (ie, hematogenous infections), which would thus balance the real impact of an early debridement. In our study, we found that the time to debridement from the onset of symptoms was independently associated with prognosis when analyzing patients failing after treatment and also among post-surgical cases.

Recommendations pertaining to the age of the prosthesis at the time of attempting DAIR vary significantly between authors, ranging from less than 4 weeks [1, 3] to less than 90 days [2]. In our analysis, a similar prognosis was observed among these 2 groups of patients.

In summary, we present the largest series of staphylococcal PJIs managed with DAIR and assess the influence of different prognostic factors. A substantial number of patients fail early despite DAIR. Overall, the use of rifampin may contribute to homogenizing the prognosis for MRSA- and MSSA-PJI, although the differences we observed in their outcome may suggest a variable efficacy of the specific rifampin combination used. Further progress in the knowledge of these infections should come from prospective studies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Table 5. Parameters Influencing Failure in Post-Surgical Infections After the First 30 Days of Therapy

	All Post-Surgical Episodes (n = 244; Failures = 81)				MSSA Post-Surgical Episodes (n = 185; Failures = 60)				MRSA Post-Surgical Episodes (n = 59; Failures = 21)			
	Unadjusted HR (95%CI)	*P*	Adjusted HR (95%CI)	*P*	Unadjusted HR (95%CI)	*P*	Adjusted HR (95%CI)	*P*	Unadjusted HR (95%CI)	*P*	Adjusted[a] HR (95%CI)	*P*
Sex (male)	.73 (.46–1.17)	NS	–	–	.75 (.43–1.28)	NS	–	–	.72 (.28–1.87)	NS	–	–
Age (years)	1.00 (.98–1.02)	NS	–	–	.99 (.97–1.02)	NS	–	–	1.00 (.96–1.04)	NS	–	–
Diabetes mellitus	1.35 (.80–2.26)	NS	–	–	1.24 (.66–2.34)	NS	–	–	1.51 (.61–3.75)	NS	–	–
Chronic renal impairment	2.87 (1.24–6.63)	.032	–	–	3.24 (.78–13.5)	NS	–	–	2.08 (.70–6.18)	NS	–	–
Rheumatoid arthritis	1.60 (.80–3.19)	NS	–	–	1.70 (.81–3.59)	NS	–	–	1.70 (.23–12.8)	NS	–	–
Immunosuppressive therapy	2.46 (1.13–5.36)	.045	–	–	3.30 (1.41–7.74)	.018	3.40 (1.39–8.37)	.008	1.05 (.14–7.83)	NS	–	–
Revision prosthesis	1.66 (1.01–2.74)	.056	–	–	1.97 (1.08–3.61)	.038	–	–	1.09 (.44–2.69)	NS	–	–
Hip prosthesis	1.08 (.69–1.68)	NS	–	–	.93 (.55–1.59)	NS	–	–	1.26 (.51–3.12)	NS	–	–
Time to infection >90 days[b]	2.19 (1.18–4.05)	.013	–	–	1.84 (.98–3.45)	.089	2.18 (1.04–4.56)	.039	7.48 (2.01–27.8)	.013	–	–
Infection by MRSA	1.32 (.80–2.18)	NS	–	–	–	–	–	–	–	–	–	–
Bacteremia	1.70 (.77–3.73)	NS	–	–	2.21 (.99–4.95)	.078	2.35 (1.04–5.36)	.040	–	–	–	–
Polymicrobial infection	1.47 (.88–2.47)	NS	–	–	1.19 (.64–2.21)	NS	–	–	2.81 (1.07–7.39)	.052	–	–
CRP diagnosis (100 mg/L)	1.28 (1.02–1.60)	.047	1.32 (1.05–1.66)	.018	1.22 (.94–1.59)	NS	–	–	1.95 (1.02–3.75)	.052	–	–
Temperature >37°C	1.30 (.83–2.04)	NS	–	–	1.23 (.73–2.08)	NS	–	–	1.89 (.75–4.75)	NS	–	–
Sinus tract	1.62 (.93–2.82)	.086	–	–	1.49 (.77–2.89)	NS	–	–	2.15 (.78–5.92)	NS	–	–
Abnormal radiography	2.24 (1.31–3.85)	.007	2.22 (1.30–3.81)	.004	1.77 (.92–3.42)	NS	–	–	3.60 (1.37–9.45)	.019	4.49 (1.68–12.0)	.003
Debridement delay >10 days[c]	1.57 (1.01–2.45)	.049	1.68 (1.07–2.64)	.024	1.85 (.91–3.77)	.089	–	–	1.50 (.63–3.58)	NS	–	–
Polyethylene exchange[d]	.57 (.34–.97)	.045	–	–	.70 (.36–1.37)	NS	–	–	.46 (.19–1.13)	.096	–	–
Need ≥2 debridements	3.15 (1.88–5.28)	<.001	3.82 (2.24–6.51)	<.001	4.34 (2.39–7.89)	<.001	5.36 (2.88–9.98)	<.001	1.62 (.54–4.81)	NS	–	–
Rifampin[e]	.55 (.34–0.87)	.011	.52 (.32–.83)	.006	.67 (.39–1.17)	NS	–	–	.27 (.11–.65)	.007	–	–
Levofloxacin + Rifampin[e]	.48 (.27–.88)	.010	–	–	.50 (.27–.92)	.019	.42 (.22–.80)	.008	–	NS	–	–
Vancomycin + Rifampin[e]	.45 (.17–1.24)	.081	–	–	–	–	–	–	.34 (.11–1.01)	.032	.29 (.10–.87)	.027

Patients with *Early Failure* were excluded from this analysis. For the multivariate analysis, variables with a *P* value < .10 in the univariate analysis were included in a stepwise backward selection process (*P*-in < .05 and *P*-out < .10 were used in each step, except [a], where *P*-out was <.05).

Abbreviations: CRP, C-reactive protein; HR (95%CI), hazard ratio (95% confidence interval); MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; NS, non-significant (*P* > .10).

[b] Time to infection: time from prosthesis placement to the onset of symptoms.

[c] Debridement delay: time from onset of symptoms to debridement.

[d] Polyethylene exchange not included in multivariate analysis due to a significant lack of data.

[e] All antimicrobial data refer to antibiotics received during more than 14 days within the first 30 days after debridement.

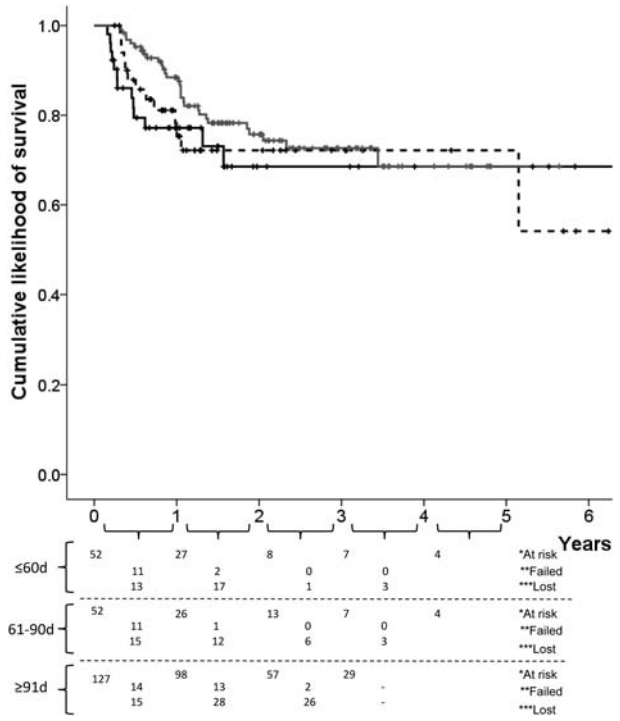

Figure 3. Comparative survival curves of different lengths for treatment among patients who finished the scheduled antimicrobial therapy without failing. Continuous black line: patients treated with antimicrobial therapy for 60 days or less (n = 52); discontinuous black line: patients treated for 61 to 90 days (n = 52); grey line: patients treated for more than 90 days (n = 127); log-rank-test: $P = .434$. *Number of patients at risk for failure at the beginning of the period. **Patients failing during the period. ***Number of patients lost to follow-up during the period.

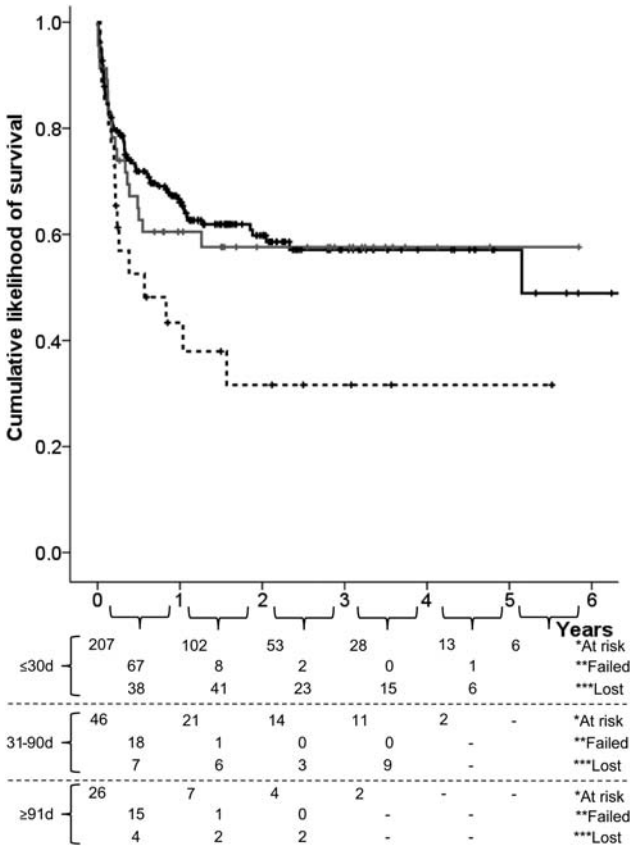

Figure 4. Influence of the time from prosthesis placement to the beginning of symptoms among post-surgical cases. Black continuous line: symptoms beginning less than 31 days after the placement of the prosthesis (n = 207; 38% failures). Grey continuous line: symptoms beginning 31 to 90 days after the placement of the prosthesis (n = 46; 41% failures). Black discontinuous line: symptoms beginning more than 90 days after the placement of the prosthesis (n = 26; 62% failures). Log-rank test: $P = .052$. *Number of patients at risk for failure at the beginning of the period. **Patients failing during the period. ***Number of patients lost to follow-up during the period. Six patients with unknown outcome were excluded from this analysis.

Potential conflicts of interest. All authors declare not to have any conflict of interest concerning this article. Regarding other activities outside this paper, A. S. declares having received honoraria from Pfizer and Novartis as payment for lectures; J. P. H. declares having received honoraria from Novartis, Pfizer, Astellas, MSD and Astra-Zeneca as payment for lectures; N. B. declares having received honoraria from Pfizer for consultancy tasks and development of educational presentations, and from MSD for consultancy tasks and also for the payment of travel/accommodation for scientific purposes; A. B. declares having received honoraria from Abbot, GlaxoSmithKline, Gilead, Novartis and Jansen for consultancy tasks, and also from Astra for lectures. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Appendix

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