Prosthetic joint infections: new diagnostic and therapeutic strategies

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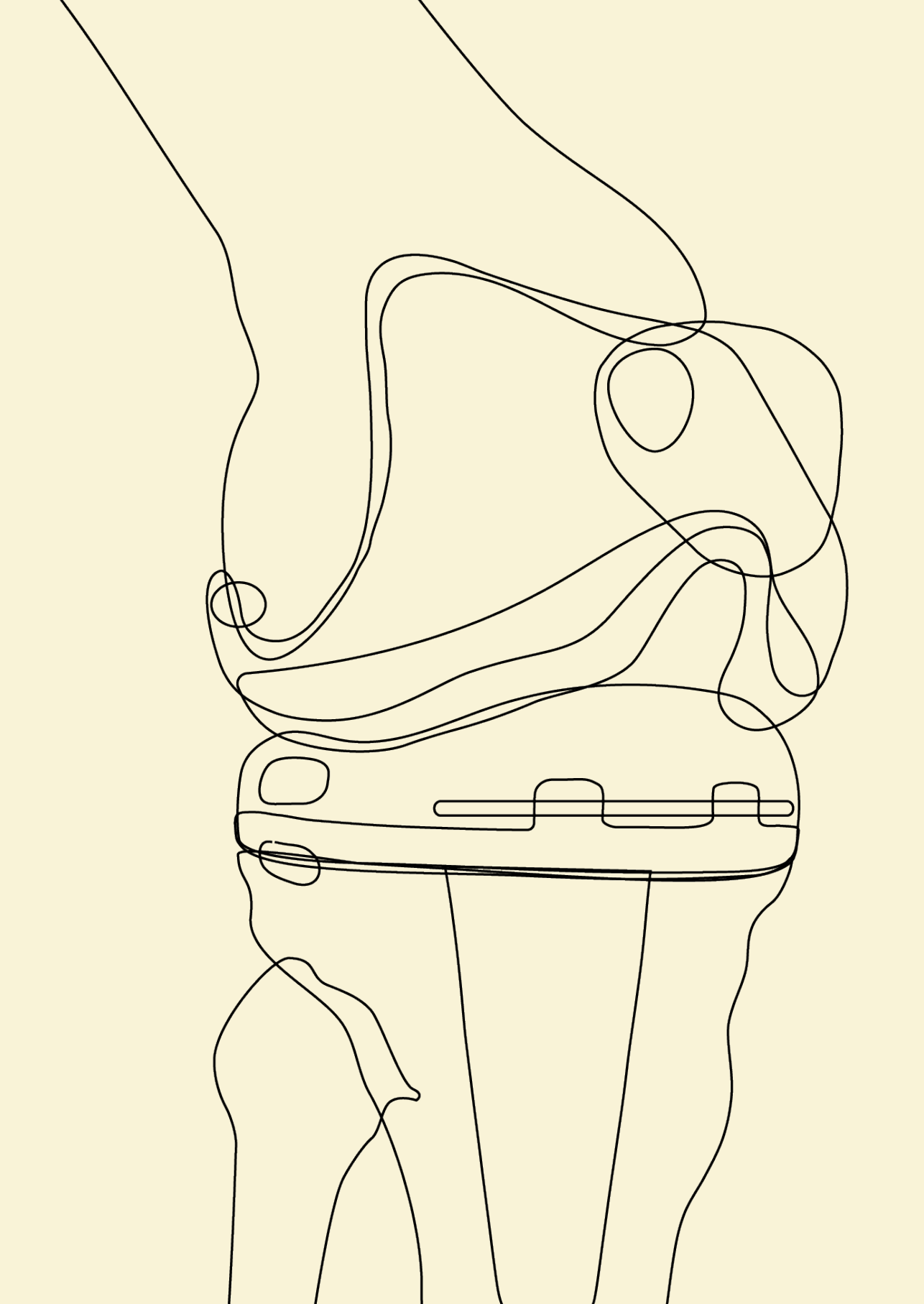

Part III. New antimicrobial strategies for PJI

CHAPTER 6

Effectiveness of different antimicrobial strategies for staphylococcal prosthetic joint infection: results from a large prospective registry-based cohort study

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Abstract

Background

Treatment of staphylococcal prosthetic joint infection (PJI) usually consists of surgical debridement and prolonged rifampicin combination therapy. Tailored antimicrobial treatment alternatives are needed due to frequent side effects and drug-drug interactions with rifampicin combination therapy. We aimed to assess the effectiveness of several alternative antibiotic strategies in patients with staphylococcal PJI.

Methods

In this prospective, multicenter registry-based study, all consecutive patients with a staphylococcal PJI , treated with DAIR or one-stage revision surgery between January 1st, 2015 and November 3rd, 2020, were included. Patients were treated with a long-term rifampicin combination strategy (in two centers) or a short-term rifampicin combination strategy (in three centers). Antimicrobial treatment strategies in these centers were defined before the start of the registry.. Patients were stratified in different groups, depending on the used antimicrobial strategy. Cox proportional hazards models were used to compare outcome between the groups.

Results

Two hundred patients were included and, based on the antimicrobial treatment, stratified in one long-term rifampicin group (traditional rifampicin combination therapy) or one of the three short-term rifampicin groups (clindamycin or flucloxacillin or vancomycin monotherapy, including rifampicin for only five postoperative days). Adjusted hazard ratios for failure for patients treated with either flucloxacillin or clindamycin were almost equal to patients treated with long-term rifampicin combination therapy (aHR 1.21, 95%CI 0.34-4.40).

Conclusions

A short-term rifampicin strategy with either clindamycin or flucloxacillin and only five days of rifampicin was found to be as effective as traditional long-term rifampicin combination therapy. A randomized controlled trial is needed to further address efficacy and safety of alternative treatment strategies for staphylococcal PJI.

Introduction

A prosthetic joint infection (PJI) is a serious complication occurring in 1-2% of patients with a joint arthroplasty resulting in prolonged hospitalization, impaired mobility and long-term antibiotic treatment[1,2]. Most PJIs are caused by staphylococci most of which most are highly susceptible for rifampicin, clindamycin and flucloxacillin in The Netherlands (MRSA is virtually absent in our region)[3]. Treatment of acute PJI consists of thorough surgical debridement combined with antimicrobial therapy. Adequate debridement is of utmost importance as the biofilm that has been formed on the surface of the implant needs to be removed as much as possible to enable cure. Antimicrobial therapy consists of intravenous antibiotics for up to two weeks followed by targeted oral antimicrobial therapy[4].. For staphylococcal PJI, rifampicin and fluoroquinolone combination therapy is advocated by most national guidelines. However, its use is hampered in practice by drug-drug interactions and significant side effects underscoring the need for safe and effective alternative antimicrobial regimens for PJI[5,6]. Further, the evidence for this antibiotic strategy in clinical studies for staphylococcal PJI is lacking[7,8]. Also, studies investigating tailored alternative strategies for rifampicin combination treatment are scarce[9,10]. In 2015, a regional group of specialized centers for PJI decided to intensify collaboration and harmonized their local protocols for antimicrobial and surgical treatment. In those centers, several different antibiotic strategies, which were consistent within a center, were accepted as routine care to treat staphylococcal PJI after DAIR (Debridement, Antibiotics and Implant Retention) or 1-stage exchange: a long-term rifampicin strategy (consisting of 12 weeks rifampicin combination therapy) and several short-term rifampicin strategies, consisting of only five days of rifampicin combination treatment, started immediately postoperative, followed by clindamycin, flucloxacillin or vancomycin monotherapy. The collaborating centers initiated a web-based quality registry to evaluate the outcome of PJI after implementation of this protocol. The main objective of this prospective study is to compare the effectiveness of long-term rifampicin combination treatment with several short-term rifampicin antimicrobial strategies for the treatment of staphylococcal PJI.

Methods

Study Design

This multicenter, prospective registry-based cohort study was conducted as part of the Prosthesis Protect Project (PPP). This prospective quality registry comprised five regional hospitals in the south-western area in the Netherlands that coordinated treatment for patients with PJI. A treatment protocol for PJI was written by all collaborators prior to data collection in the database. As for registration of data, all treatment decisions and deviations from the protocol were discussed during weekly multidisciplinary meetings (MDT) with orthopedic surgeons, infectious diseases physicians and/or clinical microbiologists. Data were collected in a secured online database and double-checked by the coordinating investigator; discrepancies were resolved by consensus. The study was approved by the institutional review board and conducted according to Dutch law and regulations regarding medical research. All patients with PJI were informed by their treating physician about the quality registry and were included in the database unless they opted out.

Patient Consent Statement

The study was approved by the institutional review board of Leiden University Medical Center with a waiver of written informed consent and conducted according to Dutch law and regulations regarding medical research. All patients with PJI were informed by their treating physician about the quality registry and were included in the database unless they opted out.

Data collection and treatment protocol

For the current study, all patients aged 18 years or older with staphylococcal PJI treated with DAIR or one-stage exchange between January 1st, 2015 and November 3rd, 2020 were eligible for inclusion. Only these surgical strategies were included because the focus of this study is on the role of antimicrobial therapy in the context of retained or newly inserted implants in an infected area. Patients with polymicrobial PJI including staphylococci were also included. Patients with infected megaprostheses (e.g., after tumor resections) were excluded. PJI was defined in compliance with the Infectious Diseases Society of America (IDSA) guideline on PJI[4]. The diagnostic and debridement procedure was completely standardized between the centers (see Supplemental Table 1). Patients with acute PJI were treated with DAIR. One-stage exchange was performed in patients with chronic PJI. Empiric antimicrobial therapy for PJI was started after intraoperative cultures were taken.

Definitions

PJI was defined as acute PJI when diagnosed within 3 weeks after onset of clinical symptoms or within 3 weeks after implantation or last revision of the implant. All other PJIs were defined as chronic PJI. For the current study, patients were also stratified in early acute PJI

(within three weeks after arthroplasty or revision), early chronic PJI (between three weeks and three months after arthroplasty or revision), late chronic PJI (more than three months after arthroplasty or revision, caused by low-virulent micro-organisms) and late acute PJI (more than three months after arthroplasty or revision, caused by virulent micro-organisms (e.g., *S. aureus*). Cure was defined as absence of clinical symptoms of infection and a retained implant during at least 12 months follow-up after antibiotic therapy was terminated AND if failure criteria were not met. Failure was defined as either (i) chronic suppressive antibiotic therapy with implant retention, (ii) a second debridement after finishing antibiotic therapy, (iii) the need for more than two debridements, (iv) removal of the implant or (v) PJI-related death. Secondary failures with other micro-organisms were also counted as failure.

Table 1. Overview of treatment schedules in the protocol for both the long-term and the short-term rifampicin strategies.

Protocol strategies	Long-term rifampicin strategy	Short-term rifampicin strategy
Antibiotic groups	rifampicin-based*	flucloxacillin-based$ clindamycin-based& vancomycin-based@
1st phase: intravenous antibiotics	flucloxacillin or vancomycin^	flucloxacillin or vancomycin^
2nd phase: targeted antibiotics	rifampicin + levofloxacin (or other antibiotics#)	flucloxacillin or clindamycin or vancomycin (or other antibiotics#)
Timing of start rifampicin	when wound is dry and antibiotic sensitivity is known	immediately postoperative after DAIR
Dose of rifampicin	300mg twice daily	600mg twice daily
Treatment duration with rifampicin	12 weeks	5 days
Total antibiotic treatment duration	12 weeks	6-12 weeks**

*Rifampicin-based: survival after DAIR >2weeks and rifampicin use for >14 days and rifampicin use for >50% of time.

$Flucloxacillin-based: survival after DAIR >2weeks and rifampicin use ≤14 days and (flucloxacillin for >50% of time or intravenous flucloxacillin for >4 weeks of time) and flucloxacillin use longer than vancomycin use (if both were used)

&Clindamycin-based: survival after DAIR >2weeks and rifampicin use ≤14 days and clindamycin use >50% of time and intravenous flucloxacillin/vancomycin < 4 weeks of time

@Vancomycin-based: survival after DAIR >2weeks and rifampicin use ≤14 days and vancomycin for >50% van time or intravenous vancomycin for >4 weeks of time and rifampicin use ≤14days and vancomycin used longer than flucloxacillin (if both were used)

#Other antibiotics: all treatment schedules that did not fit in strategies that were defined above. For long-term rifampicin combination therapy, other strategies ware accepted as long as rifampicin was combined with a second antibiotic.

^Vancomycin was given for flucloxacillin-resistant Coagulase-negative staphylococci and certain polymicrobial co-infections (e.g., corynebacteriae, enterococci). MRSA is very rare in the Netherlands (there are no patients with MRSA PJI in this cohort).

** For short-term rifampicin strategies, exact duration of antibiotics was decided in multidisciplinary team meeting. Total duration of antibiotic treatment was calculated until end of treatment or until the day of failure.

Empiric and targeted antimicrobial strategy

In all centers, empiric antibiotic therapy after surgery consisted of flucloxacillin (6gram i.v./24hrs) plus an aminoglycoside until targeted therapy could be started, based on cultures and antibiotic sensitivity. The timing of the iv-to-oral switch was after one to two weeks. In three centers, rifampicin (600mg twice daily) was added to empiric treatment for only five postoperative days, starting immediately postoperative[11]. For the purpose of this study, this was defined as a 'short-term rifampicin' strategy. In this strategy, oral targeted therapy consisted of clindamycin (600mg three times daily) or flucloxacillin (1000mg 4 or 5 times a day), dependent on susceptibility, documented allergy or intolerance. For flucloxacillin, an adequate absorption test was required, defined as a serum flucloxacillin concentration that increased at least 10mg/L after an oral loading dose of 1000mg[12]. If preferred treatment options were not available, alternative antibiotics were chosen, depending on the antibiogram. Total treatment duration was between six and twelve weeks, based on the clinical and biochemical response, such as to be decided by the MDT.

In two other centers patients with staphylococcal PJI were treated with long-term rifampicin combination therapy, the accepted standard-of-care treatment for staphylococcal PJI after DAIR[4]. Oral rifampicin (300mg twice daily) was first added to intravenous treatment once antibiotic susceptibility for rifampicin was confirmed and the postoperative wound was dry. After two weeks, it was combined with levofloxacin for a fixed treatment duration of 12 weeks. The differences in timing and duration of rifampicin between the two clusters were defined in advance in the protocol, using hospital as an instrumental variable with patients being assigned to either a long-term or one of the short-term rifampicin strategies. For the purpose of this study, patients were classified in five groups: a rifampicin-based group, a flucloxacillin-based group, a clindamycin-based group, a vancomycin-based group and a non-defined 'other antibiotics' group consisting of patients who did not meet the criteria for the first four groups (Table 1).

Statistical analysis

Clinical characteristics at baseline were summarized using descriptive statistics, stratified by antibiotic strategies. Differences between antibiotic groups were compared with Chi-square testing for categorical variables, one-way ANOVA for continuous variables and Mann-Whitney U tests for non-normally distributed continuous variables. Kaplan-Meier curves were constructed to report outcome by the different antibiotic groups. Patients were counted as failure if PJI was the direct cause of death. Patients were censored at the time of death if they died during follow up due to an event not related to PJI. A Cox proportional hazards regression model was used to investigate whether differences in outcome were associated with baseline differences between groups. Variables in the multivariate model were selected based on the univariate regression analysis. Results

are reported as hazard ratios (HR) with 95% confidence intervals (95%CIs). To prevent immortal time bias in the five antibiotic groups and to focus on the targeted treatment phase for PJI, the minimal survival time required for inclusion in the survival analysis was defined as at least 15 days after debridement. SPSS Statistics for Windows was used (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY)

Results

Of 493 patients currently registered in the database, 200 patients were included (Figure 1). Baseline clinical characteristics of the five antimicrobial strategy groups are summarized in Table 2. The proportion of *S. aureus* PJI, and bacteremia and were higher in the flucloxacillin-based group compared to the other groups ($p<0.05$). Patients in the vancomycin-based and other antibiotics group had more polymicrobial PJI, including enterococci and corynebacteriae. Follow up data are summarized in Table 3. According to the protocol, treatment duration with rifampicin was only five days in the short-term rifampicin groups. Total antimicrobial treatment duration was longer in the long-term rifampicin group (12 weeks) compared to the short-term rifampicin groups (8 weeks) (p 0.006). Four patients in the rifampicin-based group received rifampicin for only 3-6 weeks. In the flucloxacillin group, cure rate was 88% (14/16) in patients who continued with oral flucloxacillin after two weeks intravenous flucloxacillin and 74% (23/31) in patients with prolonged intravenous flucloxacillin (Table 3). In only 32% of failures, the same causative staphylococci could be cultured again.

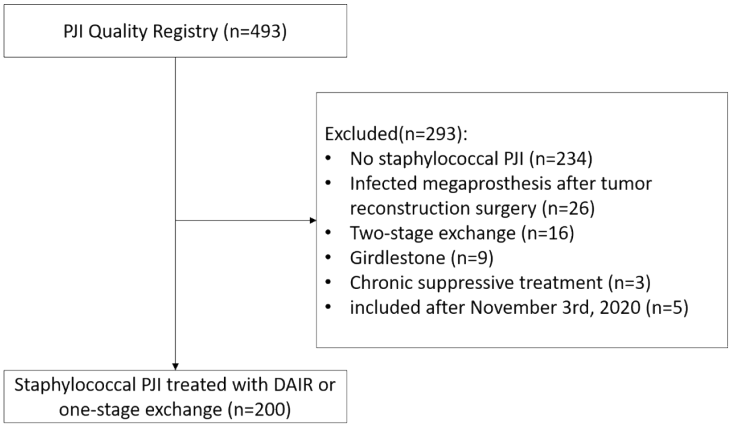

Figure 1. Flowchart of inclusion for current study.

Table 2. Baseline characteristics of all patients and after stratification for antibiotic treatment strategy.

		5 antibiotic treatment strategy groups (n= 200)[$]					
	All	**Rifampicin-based**	**Clindamycin-based**	**Flucloxacillin-based**	**Vancomycin-based**	**All other strategies***	**P value**
N patients	**200**	**23**	**56**	**47**	**26**	**48**	**-**
General characteristics							
Male sex (%)	95 (48)	11 (48)	29(52)	23 (49)	10 (39)	22 (46)	0.86
Age in years (SE mean)	70.3 (0.9)	68.8 (2.9)	67.2 (1.7)	70.1 (2.1)	72.3 (2.1)	73.6 (1.7)	0.12
Joint							
Hip	131 (66)	14 (61)	37 (66)	30 (64)	20 (77)	30 (63)	0.75
Total hip arthroplasty	109 (85)	12 (86)	32 (87)	28 (93)	15 (75)	22 (73)	0.70
Hemiarthroplasty	20 (16)	2 (14)	5 (13)	2 (7)	5 (25)	8 (27)	-
Total knee arthroplasty	63 (32)	7 (30)	17 (32)	16 (34)	6 (23)	16 (33)	0.90
Shoulder	5 (2.5)	2 (9)	1 (2)	1 (2)	0	1 (2)	-
Elbow	1 (0.5)	0	0	0	0	1 (2)	-
Previous revision	52 (26.0)	8 (35)	11 (20)	9 (19)	5 (22)	19 (40)	0.08
Previous PJI of same implant	10 (5.0)	0	1 (2)	4 (9)	0	5 (10)	0.09
Comorbidities							
Diabetes n (%)	48 (24.0)	5 (22)	12 (21)	10 (21)	9 (35)	12 (25)	0.73
Chronic kidney disease (eGFR <60ml/min)	21 (10.6)	3 (13)	4 (7)	4 (9)	4 (15)	6 (13)	0.73
Rheumatoid arthritis	13 (6.5)	3 (13)	2 (4)	3 (6)	1 (4)	4 (8)	0.57
Immunosuppressants	15 (7.5)	2 (9)	3 (5)	6 (13)	0	4 (8)	0.35
Malignancy	14 (7.0)	0	6 (11)	3 (6)	1 (4)	4 (8)	0.49
Reported smoking (n=160)	26 (13.0)	9 (39)	6 (11)	2 (4)	3 (12)	6 (13)	-
Body Mass Index (mean, SE)	30 (0.42)	28 (1.3)	30 (0.8)	29 (1.0)	30 (1.0)	30 (0.8)	0.57
Clinical Presentation							
Bacteraemia	25 (12.5)	4 (17)	4 (7)	11 (23)	0	6 (13)	0.02
Antibiotic pretreatment	31 (15.5)	3 (13)	10 (18)	7 (15)	2 (8)	9 (19)	-
Reported symptoms:							
Fever >38.3°C	40 (20.0)	5 (22)	10 (18)	16 (34)	1 (4)	8 (17)	-
Pain	107 (53.5)	11 (48)	32 (57)	31 (66)	8 (31)	24 (50)	-
Redness	94 (47.0)	5 (22)	31 (55)	21 (45)	11 (42)	26 (54)	-
Wound leakage	120 (60.0)	16 (70)	31 (55)	22 (47)	23 (89)	28 (58)	-
Fistula	4 (2.0)	0	0	3 (6)	1 (4)	1 (2)	-
Suppuration	25 (12.5)	4 (17)	5 (9)	7 (15)	3 (12)	6 (13)	-
Laboratory values							
CRP (median, range)	81 (1-585)	85 (2-313))	74 (3-443)	157 (1-585)	69 (10-342)	100 (1-491)	0.04
ESR (median, range)	49 (2-140)	53 (8-130)	41 (7-120)	53 (2-120)	46 (4-140)	58 (5-133)	-
Leukocytes (mean, SE)	11.2 (0.3)	11.1 (1.1)	11.2 (0.5)	11.9 (0.7)	10.1 (1.2)	11.1 (0.7)	0.64

Table 2. Continued

	All	5 antibiotic treatment strategy groups (n= 200)[$]					
		Rifampicin-based	Clindamycin-based	Flucloxacillin-based	Vancomycin-based	All other strategies*	P value
Causative microorganisms (n,%)							
S. aureus	120 (60)	13 (57)	35 (63)	39 (83)	8 (31)	25 (52)	0.00
Coagulase-negative staphylococci	89 (45)	11 (48)	22 (39)	9 (19)	20 (77)	27 (56)	0.00
S. epidermidis	64 (32)	5 (22)	12 (21)	7 (15)	19 (73)	21 (44)	-
S. lugdunensis	13 (7)	4 (17)	3 (5)	2 (4)	0	4 (8)	-
S. capitis	8 (4)	2 (9)	6 (11)	0	0	0	-
other CNS	8 (4)	1 (4)	4 (7)	0	1 (4)	2 (4)	-
Polymicrobial PJI	70 (36)	11 (48)	11 (20)	10 (21)	15 (58)	23 (48)	0.00
Staphylococci + streptococci	15 (8)	2 (9)	0	2 (4)	3 (12)	8 (15.1)	-
Staphylococci + Gram negatives	20 (10)	4 (17)	3 (5)	3 (6)	2 (8)	8 (17)	-
Staphylococci + *C. acnes*	5 (3)	0	2 (4)	0	1 (4)	2 (4)	-
Staphylococci + corynebacteriae	16 (8)	1 (4)	1 (2)	4 (9)	6 (23)	4 (8)	-
Staphylococci + enterococci	23 (12)	3 (13)	1 (2)	2 (4)	6 (23)	11 (23)	-
Staphylococci + anaerobic bact.	7 (4)	0	1 (2)	1 (2)	3 (12)	2 (4)	-
Classification PJI – 4 groups[#] (n,%)							
Early postoperative PJI(<3w)	94 (47)	13 (57)	22 (39)	20 (43)	19 (73)	20 (42)	0.13
Early chronic PJI(3w-3m)	53 (27)	6 (26)	19 (34)	11 (23)	5 (19)	12 (25)	0.13
Late chronic PJI(>3m)	18 (9)	1 (4)	8 (14)	2 (4)	1 (4)	6 (13)	0.06
Hematogenous PJI	35 (17)	3 (13)	7 (13)	14 (30)	1 (4)	10 (21)	0.03

[$] Exact inclusion criteria for each antibiotic subgroup are defined in Table 1. All patients in the flucloxacillin, clindamycin, vancomycin or 'other' group were also treated with five days of rifampicin starting immediately postoperative after DAIR.

 # Early postoperative PJI = PJI within 3weken of implantation or last revision. *Early chronic PJI* = PJI after 3 weeks but within 3 months after implantation or last revision. *Late chronic PJI* = PJI > 3months after implantations or last revision AND low-virulent micro-organisms. *Hematogenous PJI* = PJI >3months after last revision or implantation AND highly virulent micro-organisms (*S. aureus*, *E. Coli*, *Pseudomonas aeruginosa*, Enterococci, Streptococci, *Proteus spp*, *Klebsiella spp*, *Enterobacter*, other non-fermenters

* Amoxicillin (n=9), Amoxicillin-clavulanic acid (n=3), Levofloxacin (n=4), Linezolid (n=8), Cefuroxim (n=3), Doxycycline (n=3), Cotrimoxazole (n=10), Ciprofloxacin (n=4)

Table 3. Follow up and treatment outcome characteristics of all patients and after stratification for antibiotic treatment strategy.

	All (n= 200)	5 antibiotic treatment strategy groups[#] (n= 200)					
		Rifampicin-based*	Clindamycin-based	Flucloxacillin-based	Vancomycin-based	All other strategies	P value
N patients	**200**	**23**	**56**	**47**	**26**	**48**	**-**
Antibiotic strategy (median days, IQR)							
Duration antimicrobial treatment	57 (6-765)	94 (85-103)	56 (40-62)	41 (33-50)	55 (15-131)	53 (33-73)	0.001
Flucloxacillin i.v.	11 (0-385)	12 (2-22)	13 (8-18)	31 (18-44)	3 (0-5)	3 (0-6)	-
Flucloxacillin p.o.		-	-	33 (24-42)	-	-	-
Duration rifampicin treatment	5 (0-373)	86 (78-94)[&]	5 (5-5)	5 (4-6)	5 (4.5-5.5)	5 (4-6)	0.000
Time to start rifampicin	0 (0-11)	4 (2-6)	0 (0)	0 (0)	0 (0)	0 (0)	0.000
Surgical treatment strategy (n, %)							
DAIR	189 (94)	22 (96)	51 (91)	45 (96)	25 (96)	46 (96)	0.78
Reported head exchange hip	20/122 (16)	2/12 (17)	1/33 (3)	7/27 (26)	4/19 (21)	6/29 (21)	-
Reported liner exchange knee	37/61 (61)	5/7 (71)	13/17 (76)	7/16 (44)	3/6 (50)	9/15 (60)	-
One-stage revision procedure	11 (6)	1 (4)	5 (9)	2 (4)	1 (4)	2 (4)	-
Surgical interventions during treatment							
Re-DAIR needed	86 (43)	9 (39)	13 (23)	23 (49)	16 (62)	25 (52)	0.005
Time to re-DAIR (median days, range)	16 (3-407)	9 (3-14)	18 (3-336)	16 (5-152)	23 (10-407)	15 (5-358)	-
1 Re-DAIR in cured patients	36	6	5	12	7	6	-
2 Re-DAIRs in cured patients	6	0	3	2	1	0	-
Failure							
Failure or death due to PJI	53 (27)	3 (13)	5 (9)	10 (21)	8 (31)	27 (56)[@]	
Time to failure (days, range)	84 (6-410)	191 (103-274)	154 (85-399)	47 (20-397)	33 (21-410)	68 (6-381)	
Confirmed relapse with same staphylococci	17 (32)	1/3 (33)	3/5 (60)	3/10(30)	1/8 (13)	9 (33)	

i.v. intravenously; p.o. per os; DAIR: Debridement, Antibiotics and Implant Retention.

[#] Definitions of inclusion criteria per antibiotic subgroup are defined in Table 1

[&]All patients received at least 3 weeks of rifampicin. 4 patients received rifampicin for only 3-6 weeks

*Used antibiotics in addition to rifampicin: levofloxacin (500mg twice daily n=12), ciprofloxacin (n=2), flucloxacillin (n=3), amoxicillin (n=1), amoxicillin-clavulanic acid (n=1), cefalexin (n=1), clindamycin (n=2), vancomycin (n=1), cotrimoxazole (n=1)

[@]As defined in Table 1, this group contains all failures within 2 weeks (n=9)

The survival curves for the different antibiotic strategies are shown in Figure 2. Cure rates in the clindamycin group (91%) and the flucloxacillin group (79%) did not differ significantly from the rifampicin group (87%, p 0.20). Patients treated with vancomycin or not treated according to a predefined regimen had a worse outcome. Within the vancomycin-based group, success rates were lower for polymicrobial PJI with enterococci (p=0.02). Diabetes mellitus and duration of symptoms more than three weeks were significantly associated with failure in the univariate Cox regression model (Table 4). Late acute PJI, enterococcal PJI and bacteremia were associated with a worse outcome, although not statistically significant (Table 4 and Supplemental Figure 1). The adjusted hazard ratios for failure in the clindamycin group (HR 0.84, 95% CI 0.20-3.55), the flucloxacillin group (HR 2.21, 95% CI 0.60-8.17) or the combined clindamycin and flucloxacillin group (HR1.21, 95% CI 0.34-4.40) remained equal to the rifampicin-based group.

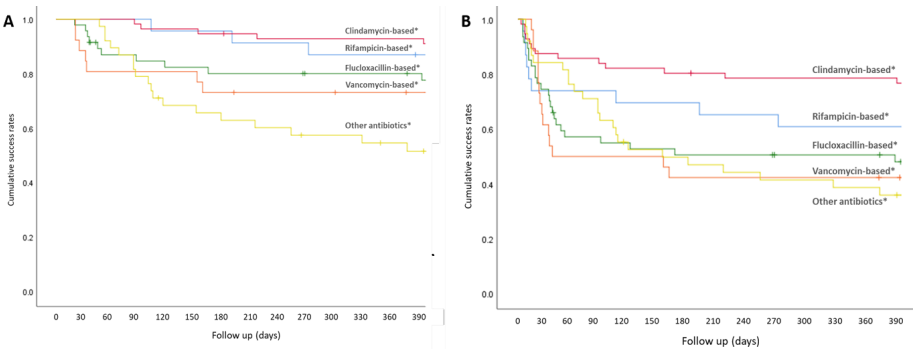

Figure 2. Survival analysis for staphylococcal PJI related to antimicrobial treatment strategy.

Figure 2A: Success rates over time for the different antibiotic groups as defined in Table 1. Figure 2B: success rates over time for the same antibiotic groups but using a narrower definition of failure in which all patient who needed a second surgery were counted as failure.

Table 4. Univariate and Multivariate Cox proportional Hazards model of clinical characteristics associated with failure.

Covariate	Univariate		Multivariate#	
	HR	95% CI	HR	95%CI
Male sex	1.35	0.74-2.46		
Revision before PJI	1.48	0.78-2.79*	1.55	0.79-3.03
Knee PJI	0.99	0.53-1.87		
Corticosteroid use	1.09	0.34-3.53		
DM	2.15	1.16-3.98*	2.12	1.14-3.42
RA	1.20	0.37-3.89		
S. aureus PJI	0.89	0.49-1.61		
Bacteraemia	1.75	0.78-3.93*	2.66	1.09-6.48
Duration of symptoms < 3weeks	0.46	0.23-0.94*	0.37	0.18-0.77
Polymicrobial PJI	0.98	0.53-1.81		
Enterococci as copathogen	1.91	0.89-4.12*	1.48	0.64-3.42
Classification PJI:				
Early postoperative	Ref.	-		
Early chronic	0.94	0.44-2.01		
Late chronic	1.05	0.36-3.08		
Late acute (hematogenous)	1.80	0.84-3.85		
Long-term rifampicin strategy center^	1.26	0.53-2.98		
Treatment strategy:				
Rifampicin-based	Ref.	-	Ref.	-
Either clindamycin- or flucloxacillin-based	1.20	0.35-4.15	1.21	0.34-4.40
Clindamycin-based	0.69	0.16-2.87	0.84	0.20-3.55
Flucloxacillin-based	1.98	0.54-7.19	2.21	0.60-8.17
Vancomycin-based	2.93	0.78-11.06	3.68	0.95-14.24
Other strategy	4.69	1.38-15.96	4.86	1.41-16.78
Exchange of liner	1.27	0.65-2.50		

#Included variables (*) in multivariate model were based on (trend to) significance in univariate model: revision before PJI, bacteremia at diagnosis, diabetes mellitus, duration of symptoms, enterococci, antimicrobial treatment strategy

^long-term rifampicin center: center where default antimicrobial strategy consisted of 12 weeks rifampicin combination therapy (see Table 1)

Discussion

There is an urgent need for alternative antimicrobial strategies for staphylococcal PJI as the current strategy with long-term rifampicin-based combination therapy is associated with significant side effects and interactions[5 6 13]. In the current study, outcome of PJI after DAIR or one-stage exchange was not statistically different between patients treated with long-term rifampicin combination therapy and patients treated with clindamycin or flucloxacillin monotherapy including only five days of rifampicin combination therapy. Moreover, treatment duration was four weeks shorter in the clindamycin-based and flucloxacillin-based groups. After correction for confounding covariates that were not evenly distributed across the groups at baseline, the outcomes in a multivariate Cox proportional hazards model did not change. Diabetes mellitus, bacteremia and a longer duration of symptoms (more than three weeks) were independent risk factors for failure.

Clindamycin monotherapy for staphylococcal PJI

Clindamycin is known to have an excellent bioavailability and penetrates well into synovial fluid and bone[14]. Reasonable outcome with clindamycin therapy for staphylococcal PJI has been incidentally published before, but this is the first study reporting the systematic use of clindamycin monotherapy[15 16]. Physicians in the short-term rifampicin strategy centers had no specific preference for either clindamycin or flucloxacillin, except that clindamycin was easier to use due to a lower pill burden. The choice for either clindamycin or flucloxacillin was completely unbiased in patients with clindamycin-resistant staphylococci or an inadequate flucloxacillin absorption test, but this was the case in only a minority of patients[12]. How should we interpret the finding that eight weeks of clindamycin-based treatment, including five initial days of rifampicin, was equivalent to twelve weeks rifampicin combination therapy and superior to flucloxacillin? Confounding by indication is the most likely explanation because in patients who needed a second debridement or who had persisting high inflammatory parameters, the iv-oral switch from flucloxacillin to clindamycin was postponed on purpose (as illustrated in Table 3 with longer i.v. treatment duration and more second DAIRs in the flucloxacillin-group). Consequently, more patients with a worse course met the criteria for the flucloxacillin-based group, leading to selection bias in favor of the clindamycin-based group. Correction for this confounding was performed by combining both groups, resulting in a cure of 85% in the combined group, which was equivalent to the rifampicin group (87%, p=0.77, Figure 3).

Flucloxacillin monotherapy for staphylococcal PJI

Clinical data regarding the use of flucloxacillin for bone and joint infections are scarce[17]. This study shows 78% success rates for staphylococcal PJI in the flucloxacillin-based group. The high success rate of 88% in the subgroup of patients treated with oral flucloxacillin

monotherapy suggests that oral flucloxacillin may be an adequate treatment strategy for staphylococcal PJI. The results in this study are congruent with an earlier small cohort study by the same authors describing reasonable outcome for staphylococcal PJI with oral flucloxacillin and short-term addition of rifampicin[11]. However, the efficacy of oral flucloxacillin for targeted treatment of staphylococcal PJI should be further assessed in a large trial. Also, a flucloxacillin absorption test is needed to identify patients with adequate oral absorption of flucloxacillin[12].

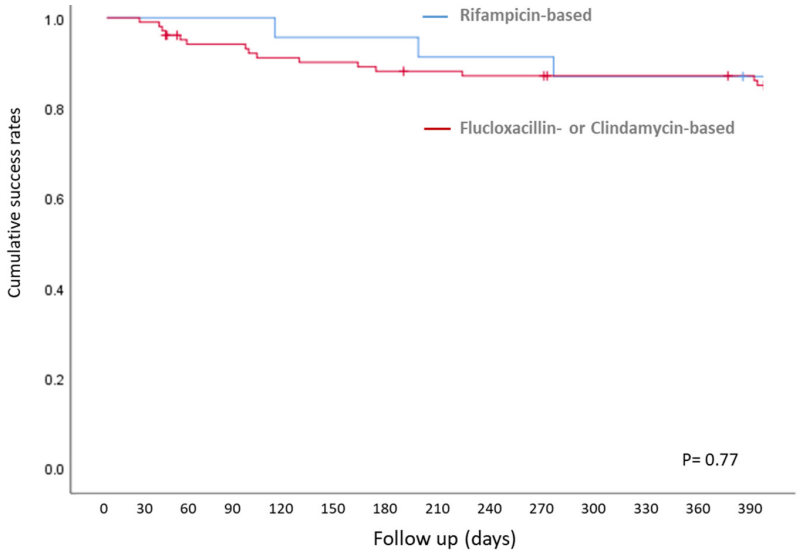

Figure 3. Survival curve after DAIR for staphylococcal PJI comparing a rifampicin-based strategy with a strategy of either flucloxacillin- or clindamycin-based treatment.

Rifampicin combination therapy for staphylococcal PJI

The effectivity of long-term rifampicin combination therapy in this study is in line with other studies reporting good outcome with this strategy[8,18]. The strength of the current study is that two different and predefined strategies between centers could be directly compared, which minimized confounding by indication between the long-term and the short-term rifampicin-based groups. However, treatment may have varied in other ways not captured by the protocol as the treatment teams between the participating centers were different. The outcome of staphylococcal PJI over time did not differ between centers with either a standard short-term or long-term rifampicin treatment strategy (Figure 4). Most surgeons in participating hospitals were educated and trained in the same program. Due to later connection of long-term rifampicin treatment centers to the registry, less patients on long-term rifampicin could be included. However, given the high cure rate in the rifampicin-based group, this would likely lead to an overestimation rather than an underestimation of success rates in the rifampicin group. The results of this study are in line with two

recent systematic reviews in which rifampicin-based strategies were not superior to non-rifampicin strategies[7,8]. The rationale behind the immediate start of the 5-day rifampicin treatment in our region is that the need for a highly bactericidal drug is expected to be most crucial in the early postoperative period after debridement. Rifampicin kills bacteria, including intracellular staphylococci, at a fast rate[19]. Experimental animal models showed that four days of rifampicin combination therapy quickly eradicated implant-associated infections[20]. The RCT in which treatment duration with rifampicin was 3-6 months was regarded as too heavily underpowered to implement long-term rifampicin treatment in our region. Therefore, a five day treatment schedule with rifampicin was chosen to quickly reduce the bacterial load around the implant in the early postoperative period. This should prevent new staphylococcal biofilm formation on the implant and so reduce the odds for a relapse. An important question that arises from our results is whether the first five days of rifampicin contributed at all to the high cure rates in the short-term rifampicin groups. This study cannot answer this question as patients were not treated *without* these five days of rifampicin. The attributive role of long-term rifampicin will be investigated in a large nationwide randomized controlled trial in The Netherlands.

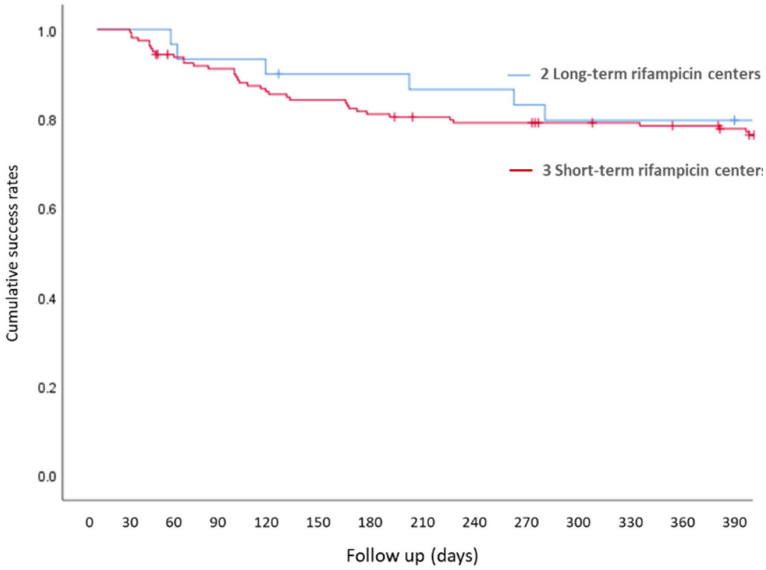

Figure 4. Comparison of success rates for all staphylococcal PJI stratified for centers with a long-term or a short-term rifampicin strategy*.

* Success rates were compared in 31 patients treated in a long-term rifampicin treatment center (in which protocol advised 12 weeks rifampicin combination therapy) and 169 patients treated in a short-term rifampicin center (in which protocol advised targeted monotherapy including only 5 days rifampicin combination therapy (with total treatment duration between six and twelve weeks).

Duration of antimicrobial therapy

Median duration of antibiotic therapy was four weeks shorter in the flucloxacillin- and clindamycin-based groups compared to the rifampicin-based group but with equal cure rates. Success rates were similar after splitting the flucloxacillin- and clindamycin-based groups in two groups based on treatment duration. Success rate was 82.6% if treated for 6 weeks (median treatment duration 40 days) and 86.3% if treated for >6 weeks (median treatment duration 63 days, p = 0.75). These results contradict the results of the recently published DATIPO trial in which twelve weeks of antimicrobial therapy was clearly superior to six weeks[21]. In the DATIPO trial, patients were randomized at the start of the study. In our cohort, the decision to quit antibiotics in the short-term group was made in the sixth week of treatment which has the advantage that the clinical course of the first six weeks could be considered (Table 1). Therefore, our data suggest, in line with other studies, that the decision to stop antimicrobial therapy after six weeks, based on a quickly improved clinical course, a normalized CRP and after MDT discussion, may still be regarded as a safe strategy[21-24].

Strengths and limitations

A major strength of this study is that several well-defined strategies were compared. Comparing one well-defined strategy (e.g., rifampicin, or clindamycin) with all other nón-defined strategies (e.g., non-rifampicin, or non-clindamycin) will usually lead to bias in favor of the well-defined strategy and may lead to unjustified rejection of equally good alternatives within that non-defined group (example of this is shown in Supplemental Figure 2). One possibility to solve this is to define several well-defined groups as was done in this study. However, confounding by indication can still be present in the well-defined groups as discussed for the clindamycin and flucloxacillin groups. Of note, this study also contains a fifth 'non-defined' group of patients, evenly present in all participating centers, with a worse outcome. Different treatment strategies within this group were very heterogeneous (Table 2).

To further strengthen the methodological quality of the study, patients with failure within two weeks after surgery (n=10, evenly distributed among the centers) were excluded from survival analysis. This is because these patients were still on intravenous antibiotics and had not yet started one of the preferred treatment options. Patients with megaprostheses (used in malignancies) were also excluded to reduce bias. Further, a second DAIR during treatment was not automatically considered a failure and resulted in cure in many patients (Table 3). If we would have defined all subsequent surgeries as failure, the overall cure rate would drop from 77% to 55% (Figure 2B). However, this drop in cure rate would evenly affect cure rates among all five antibiotic groups. These differences in cure show the importance of a uniform and clear-cut definition when comparing outcome between PJI studies. We suggest defining subsequent surgery only as a failure if a third debridement was needed or if surgery is needed after finishing antimicrobial therapy.

A limitation of the current study is the heterogeneity by including also patients with chronic PJI and patients with on-stage revision surgery. We thought it was justified to do so because a DAIR can still be a good treatment option in patients with longer duration of symptoms, as reported recently[25]. Although patients with one stage revision surgery were treated with the same short-term or long-term rifampicin strategy in the different centers, the surgical strategy differs from that of a DAIR. Therefore, we repeated the survival analysis, leaving out patients after one-stage exchange. This did not affect outcome (Supplemental Figure 3).

To exclude that the results of this study may be explained by other antibiotics that were used for pathogens in the patients with polymicrobial PJI, we performed an extra survival analysis including only the 130 patients with monobacterial staphylococcal PJI. This resulted in a limited increase in success rate in the vancomycin group (69% to 72%) and no change of success rates in the rifampicin-, flucloxacillin- and clindamycin-based groups, indicating that the activity against staphylococci was probably not caused by other antibiotics.

Summary and future perspectives

This study suggests that clindamycin or flucloxacillin monotherapy with only short-term induction therapy with rifampicin for five days might be considered as a reliable alternative to long-term rifampicin combination therapy. Although adjustment for confounding variables reduced bias as much as possible, the number of patients in the subgroups was still quite low. Future studies should assess whether adjunctive short-term induction therapy with rifampicin in patients treated with clindamycin or flucloxacillin has a significant impact on outcome. A large randomised controlled trial is warranted to definitively confirm the safety and effectivity of clindamycin and/or flucloxacillin monotherapy as appropriate alternatives for rifampicin combination therapy for staphylococcal PJI.

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Conflicts of interests

The authors declare that they have no conflicts of interests.

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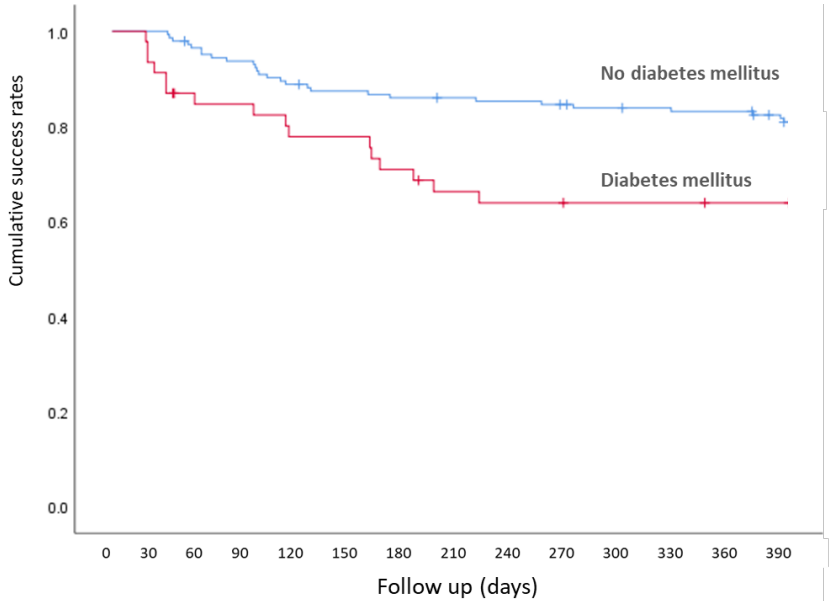
Supplemental files

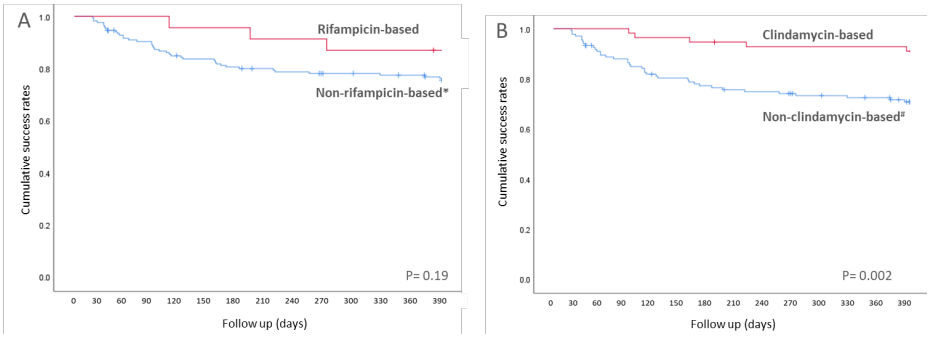
Supplemental table 1. Description of standardized protocol for Debridement procedure

Debridement of an acute prosthetic joint infection (PJI) should preferably start within 24 hours of (suspected) diagnosis. The operation proceeds according to the following step-by-step plan:

1. Preparation and protocol in theatre as for implantation of prosthetic joint
2. Antibiotic prophylaxis against postoperative wound infections is postponed until intraoperative cultures are taken.
3. Always perform an open arthrotomy. An arthroscopy in case of acute PJI is contraindicated.
4. Before starting debridement and antibiotics, 5-6 deep cultures are taken at the site of infection (fluid, tissue, capsule, synovia and bone, especially at the interphase). Culturing subcutaneous tissue cultures or wound smears are not indicated. Cultures are incubated for 14 days.
5. Cultures that are taken are placed directly into a sterile jar. Punctate fluids are directly inserted into a blood culture bottle. Change instrumentarium after each culture that is taken.
6. Cultures should be at the clinical microbiology laboratory as soon as possible.
7. After cultures are taken, extensive debridement takes place with excision of all "suspicious" or necrotic tissue and, if possible, a broad synovectomy. Exchangeable components of the prosthetic joint are removed, to allow for proper debridement of the joint, and replaced with new components.
    a. During exchange of mobile parts, the wound is first completely debrided and rinsed. Then, change gloves, disinfect skin with chlorhexidine, cover with clean covering material and clean instruments for insertion of prosthetic components, and close wound.
8. Next, rinse the prosthesis in situ with at least 6 L of Sodiumchloride 0.9% and use pulsavac. Use a wet gauze to "polish" the prosthetic parts in order to remove the formed glycocalyx macroscopically as much as possible. After 3-4 litres rinse with pulsavac and povidone iodine, then rinse the last litres with NaCl pulsavac.
9. Do not use gentamicin beads or gentamicin mats.
10. The wound is closed and no drains are left behind.



Supplemental Figure 1. Commparison of success rates for staphylococcal PJI between patients with and without diabetes mellitus.

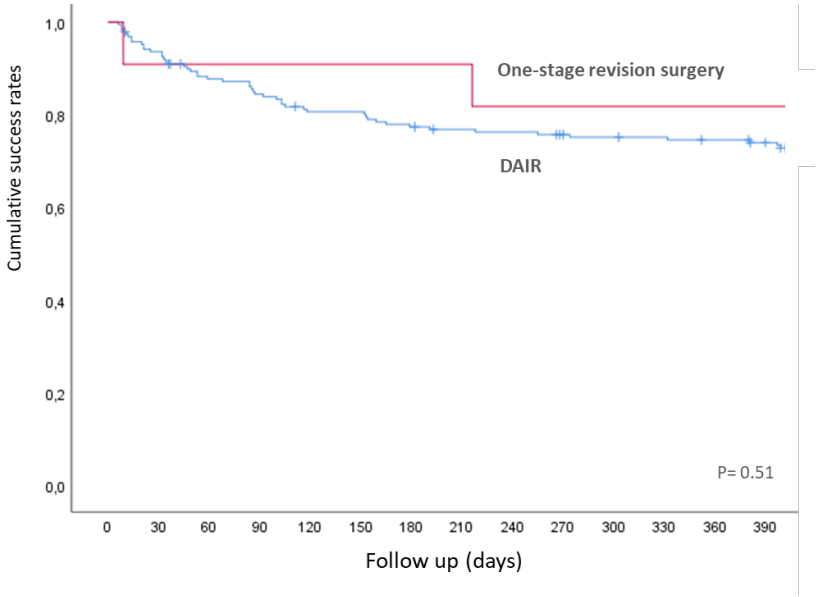


Supplemental Figure 2. Differences in success rates for staphylococcal PJI between well-defined and non-defined antibiotic groups.

This example shows how misinterpretation may occur if well-defined antimicrobial strategy is compared with a non-defined strategy. All failures within two weeks were excluded from this analysis. In graph A, the effectivity of rifampicin compared to non-rifampicin treatment is shown. However, the non-rifampicin group contains all patients treated with clindamycin-based strategy, but clindamycin is shown to be superior to non-clindamycin treatment in graph B. Stratification of the non-defined group may demonstrate potentially effective alternative treatment options.

*Non-rifampicin: all patients who were not treated in the rifampicin-based group.

Non-clindamycin: all patients who were not treated in the clindamycin-based group.



Supplemental Figure 3. Differences in success rates for patients treated with One-stage revision surgery (n=11) or DAIR (n=189) for staphylococcal PJI.