The impact of surgical strategy and rifampin on treatment outcome in *Cutibacterium* periprosthetic joint infections

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Summary. In this retrospective study, we observed no significant benefit of using rifampin to avoid relapses or new infections but a benefit when the prosthesis was removed or exchanged and an antibiotic treatment was given for at least 6 weeks.

Abstract

Background: *Cutibacterium* species are common pathogens in periprosthetic joint infections (PJI). These infections are often treated with β-lactams or clindamycin as monotherapy, or in combination with rifampin. Clinical evidence supporting the value of adding rifampin for treatment of *Cutibacterium* PJI is lacking.

Materials/methods: In this multicenter retrospective study, we evaluated patients with *Cutibacterium* PJI. The primary endpoint was clinical success, defined by the absence of infection relapse or new infection within a minimal follow-up of 12 months. We used Fisher's exact tests and Cox proportional hazards models to analyze the effect of rifampin and other factors on clinical success after PJI.

Results: We included 187 patients (72.2% male, median age 67 years) with a median follow-up of 36 months. The surgical intervention was two-stage exchange in 95 (50.8%), one-stage exchange in 51 (27.3%), debridement and implant retention (DAIR) in 34 (18.2%), and explantation without reimplantation in 7 (3.7%). Rifampin was included in the antibiotic regimen in 81 (43.3%) cases. Infection relapse occurred in 28 (15.0%), and new infection in 13 (7.0%) cases. In the time-to-event analysis, DAIR (adjusted HR=2.15, p=0.03) and antibiotic treatment over 6 weeks (adjusted HR=0.29, p=0.0002) significantly influenced treatment failure. We observed a tentative evidence for a beneficial effect of adding rifampin to the antibiotic treatment – though not statistically significant for treatment failure (adjusted HR=0.5, p=0.07) and not for relapses (adjusted HR=0.5, p=0.10).

Conclusions: We conclude that a rifampin combination is not markedly superior in *Cutibacterium* PJI but a dedicated prospective multicenter study is needed.

Keywords. *Cutibacterium* species, *Propionibacterium* species, Periprosthetic joint infections, rifampin, antibiotic treatment

Introduction

Cutibacterium species (mainly *Cutibacterium acnes* and *Cutibacterium avidum*), are, after staphylococci and streptococci, amongst the most frequently isolated pathogens causing periprosthetic joint infections (PJIs) (1). *C. acnes* predominantly infects shoulder and hip implants (2), whereas *C. avidum* is associated with hip arthroplasty infection (3–6). In general, PJIs are difficult to cure since bacteria grow as biofilms on implants. In biofilms, the sessile bacteria are embedded in a matrix of extracellular polymeric substances, which are at least partially produced by the bacteria themselves; bacteria in biofilms are protected against the immune system (7,8). Sessile bacteria have a low metabolism and consequently replicate at a slow rate (7).

Rifampin has a low minimal bactericidal concentration (MIC) against sessile *Staphylococcus aureus* and coagulase-negative staphylococci (9). Accordingly, rifampin has been shown to cure experimental implant-associated staphylococcal infections in animal models and combination with rifampin has been found to be more efficacious than standard therapy in observational studies as well as in a controlled trial of patients with orthopedic device-associated infection managed with debridement and retention of prosthesis (DAIR) (10–14). In analogy to treatment concepts for staphylococcal infections, antibiotic regimens including rifampin are used to treat *Cutibacterium* PJIs in some orthopedic centers due to low MIC. In small case series, rifampin was combined with clindamycin (15,16) or amoxicillin (17). There are, however, some suggestions that support adding rifampin in the treatment of *Cutibacterium* infections. Furustrand et al. showed in a guinea pig model that antibiotic regimens containing rifampin in *Cutibacterium* infections yielded favorable results when an implant is present (18). Rifampin cured 63% of the infected cages in combination with daptomycin, 46% with vancomycin, and 25% with levofloxacin whereas monotherapy with daptomycin, vancomycin, or levofloxacin cured only 4%, 17%, and 0% of infections, respectively. Thus, combinations with rifampin were superior to single regimens without rifampin in this study, though beta-lactams were not administered to animals. However, no

large study evaluating rifampin in humans is available. Due to the lack of large clinical studies, it is unclear if addition of rifampin is indeed necessary for cure of *Cutibacterium* PJI.

In a large cohort of patients with *Cutibacterium* PJI, we tested the hypothesis that adding rifampin to an antibiotic regimen for cure of infection is not superior to antibiotic regimen without rifampin. Moreover, we hypothesized that the choice of surgical treatment concept is a major element determining successful outcome of these infections.

Methods

Study setting and population

This is a multicenter retrospective study including patients from 9 countries (18 centers) with a PJI diagnosis between 2005 and 2018. We evaluated patients with *Cutibacterium* PJI, defined by growth of *Cutibacterium acnes, Cutibacterium avidum*, or *Cutibacterium granulosum* from at least two different diagnostic samples including tissue biopsies, sonication fluid, or synovial fluid. Samples for microbiology were cultivated for 14 days in 13/18 (72.2%) and 6-10 days in 5/18 (27.8%) of the study centers. We recorded information about clinical presentation, antibiotic and surgical treatment, and infection outcome. The case report form (CRF) relies on the PJI database app developed by the study group ESGIAI supported by ESCHMID (https://apps.apple.com/us/app/pji-database/id1331588615). We only included patients who underwent surgery for curative management of *Cutibacterium* PJI, i.e., one-stage or two-stage exchange of the prosthesis (with or without spacer implantation), DAIR, or explantation without new prosthesis. Patients were followed until infection relapse, new infection or death with a minimum follow-up of 12 months after the surgical intervention for *Cutibacterium* PJI. We did not include cases with only one positive *Cutibacterium* sample but treated as infection, polymicrobial infection, an antibiotic treatment longer than 6 months or labelled as lifelong suppressive treatment, no surgical treatment at all, insufficient or a short follow-up of less than 1 year.

Definitions

We distinguished between early acute infections with time to septic surgery less than 4 weeks after last surgery and chronic infections with time to septic surgery longer than 4 weeks. The primary endpoint of our study was treatment failure, defined as either infection relapse, new infection or death due to PJI. Infection relapse was defined as proven, when persisting signs or symptoms of infection (pain, swelling, redness, wound secretion, or elevated serum inflammatory parameters) were present and two new diagnostic samples microbiologically identified the same *Cutibacterium* species. We defined it as possible, when not microbiologically proven but suggested by persisting symptoms or signs of infection. A new infection was defined as a microbiologically proven infection in case of a new pathogen detected in ≥2 diagnostic samples during the follow-up time. The follow-up time started at the date of the initial surgery for *Cutibacterium* PJI, specifically, the date of explantation in case of a two-stage exchange of the prosthesis.

Antibiotic treatment

Patients were grouped into a rifampin-group in case rifampin was used after the surgery for *Cutibacterium* PJI for at least one week, with a sensitivity analysis using the thresholds of at least 4 weeks and at least 6 weeks. Antibiotic treatment duration was calculated as the total duration for all drugs (including rifampin) combined, as well as for intravenous (iv), per oral (po), and rifampin use.

Statistical Analyses

Patient characteristics between the group of patients who received rifampin and those who did not receive rifampin were analyzed using t-tests (continuous variables) and chi-squared tests (categorical variables). The effect of adding rifampin to the antibiotic regimen on clinical success was tested in two ways, cross-sectionally as well as longitudinally (time to treatment failure): First, a cross-sectional analysis (chi-squared test) was used to analyze the effect of rifampin on the outcome (failure, relapse, new infection) stratified by surgical

strategy. Second, the time to treatment failure and time to relapse was assessed using cox proportional hazards models, with explanatory variables including rifampin as well as the most important demographic and clinical parameters. Proportional hazards assumptions were analyzed using Schoenfeld residuals available in the R package survival (19). Models were adjusted for total duration of antibiotic use as well as the surgical strategy, i.e., the two clinically most relevant factors. To assess the effect of the treatment center, we performed a sensitivity analysis using a mixed effect model, where the country was included as a random effect. Statistical analyses were performed using R (version 3.4.4). Moreover, to assess the effect of the most commonly used treatment regimen in literature (clindamycin/rifampin), we performed a sensitivity analysis in which we looked at hazard ratios of other rifampin combinations than clindamycin, clindamycin alone, and other monotreatment.

Results

Study Population

We included 187 patients from 9 countries, the median time of follow-up after infection treatment was 36 months. Most patients were male (72.2%) with a median age of 67 years and a median BMI of 28 kg/m^2 (Table 1). The median time to PJI after the last surgical procedure was 20 months, with a chronic infection (> 1 month) in 177 (94.7%) patients and early postoperative infection (< 1 month) in 10 (5.3%). All but one had a treatment failure in the late postoperative phase. The one patient with an early postoperative treatment failure had a new infection (Supplementary **Table S1**). The most common joint prostheses were hip (51.9%), shoulder (37.3%) and knee (9.1%). In most cases, the isolated pathogen in two or more diagnostic samples was *C. acnes* (84.5%) (Table 1).

Two-stage exchange of the prosthesis was performed in 95 (50.8%), one-stage exchange of the prosthesis in 51 (27.3%) and DAIR in 34 (18.2%) patients (see **Table S1** for the surgical strategy in acute versus chronic cases). The median overall antibiotic duration was 12 weeks; median = 14 days for iv antibiotics and median = 9, weeks for po antibiotic treatment.

Most patients (174, 93.0%) were prescribed iv antibiotics. Rifampin was prescribed in 81 (43.3%) cases, the median duration of rifampin use was 10 weeks (**Table 2 and Figure S1**).

Rifampin

There were no significant differences regarding gender, age, BMI and the involved joint prosthesis between patients who received rifampin and those who did not. There was, however, a difference regarding the surgical strategy: While one-stage exchange of prosthesis was performed in 31/81 (38.3%) and two-stage exchange in 32/81 (39.5%) of patients who received rifampin, this was the case in 20/106 (18.9%) and 63/106 (59.4%) of patients who did not receive rifampin, respectively, (p = 0.037).

We also saw differences in the countries in which the patients were treated, ranging between no patients and more than half patients receiving rifampin (**Table S2**). Moreover, there was no clear time trend in prescribing rifampin during the study time frame (**Figure S2**). Overall, follow-up time and the overall antibiotic duration was longer in patients who received rifampin compared to those who did, for all antibiotics combined or iv or po antibiotics separately (**Table 2**). The combination treatment with rifampin is documented in Supplementary **Table S3**.

Outcome

Overall, treatment failure (relapse and new infection) manifested in 38 (20.3%) cases. Infection relapses occurred in 28 (15.0%) cases (proven relapse: 16, possible relapse: 12), and new infection in 13 (7.0%). During follow-up, 13 (7.0%) patients died, PJI did not result in death (**Table 2**). Among the patients treated with rifampin, treatment failure was observed in 10 (12.3%) cases, as compared to 28 (26.4%) cases among patients not treated with rifampin (p = 0.029). This difference was however not significant for relapse and new infection separately, which was observed in 8 (9.9%) and 2 (2.5%) cases of patients who received rifampin, respectively, compared to 20 (18.9%) and 11 (10.4%) cases in patients who did not receive rifampin (p = 0.13 for relapse and p = 0.069 for new infection). Stratified

by surgical strategy, the frequency of treatment failures was highest in patients for whom DAIR was performed (11/34, 32.4%), as compared to one-stage (6/51, 11.7%) or two-stage exchange (20/95, 21.1%) of prosthesis. In each group (DAIR, one-stage exchange, two-stage exchange), fewer treatment failures in patients who received rifampin were observed. This difference was not significant looking cross-sectionally at overall treatment failures of relapses only (**Figure 1**). In a sensitivity analysis, we restricted to the first 3 years after surgical intervention with no significant difference either (see **Figure S3**).

Dynamic of failure overall and relapse

The median time to treatment failure was 19.3 months (IQR = 7.0 – 58.1) (**Figure 2A**). We observed increased hazards of treatment failure in patients not treated with rifampin as compared to patients treated with rifampin (unadjusted hazard ratio (HR) = 2.50 CI = [1.21, 5.16], p = 0.013, **Figure 2B**) as well as increased hazards of treatment failure in patients who underwent DAIR as compared to one-stage exchange (unadjusted HR = 3.4 [1.26, 9.27], p = 0.016) or two-stage exchange (unadjusted HR = 1.6 [0.78, 3.42], p = 0.19) of prosthesis (**Figure 2C**).

The median time to infection relapse was 23.3 months (IQR = 8.6 – 60.5) (**Figure 2D**). Again, increased hazards of infection relapse were observed in patients who did not receive rifampin (unadjusted HR = 2.28 [1.00, 5.18], p = 0.05) (**Figure 2E**) and patients who underwent DAIR as compared to one-stage exchange (HR = 3.08 [1.0, 9.52], p = 0.05) or two-stage exchange (HR = 1.76 [0.74, 4.23], p = 0.20) of prosthesis (**Figure 2F**). The median time to new infection was 11.4 months (IQR = 6.8 – 39.1).

Effect of rifampin and other factors

The effect of adding rifampin to the antibiotic combination therapy was not significant after adjusting for surgical strategy and overall duration of antibiotic treatment (adjusted HR: 0.50 [0.23, 1.05], p = 0.07) (**Figure 3A**). However, using DAIR instead of a surgical strategy involving the change of prosthesis was significantly associated with higher hazards of

treatment failure, even after adjusting for antibiotic duration (HR: 2.15 [1.06, 4.37], p = 0.03). Moreover, an overall antibiotic duration of more than 6 weeks was associated with a reduced hazard for treatment failure even after adjusting for surgical strategy (adjusted HR: 0.29 [0.15, 0.56], p = 0.0002). Similar results were obtained for relapse only (**Figure 3B**). In a sensitivity analysis, we only grouped patients into the rifampin stratum in case the intake lasted at least 4 or 6 weeks, respectively, and obtained similar results (**Table S4**). Most patients included in this study came from one country (n = 105) (country 1, Table 1) but the rate of rifampin strongly differed between countries. Therefore, we used a mixed effects model to include the effect of different countries, again leading to similar results (**Figure S4**).

Due to the heterogeneity of our study population with different antibiotic regimens (Table S3), we did not stratify treatment outcome for all different antibiotic regimens. However, in a sensitivity analysis, success rate was highest for the combination with rifampin and clindamycin, although the difference was not statistically significant (Table S3 and Figure S5).

Discussion

In this multicenter study, we included 187 patients with *Cutibacterium* PJI and evaluated the added value of rifampin as part of antibiotic regimens following septic surgery. We observed an overall successful treatment outcome in 79.7% cases, with relapses in 15% and new infection in 7% cases. We observed a tentative evidence for a beneficial effect of adding rifampin to the antibiotic treatment – though not statistically significant, the hazards for developing treatment failure was halved in the group of patients treated with rifampin. A statistically significant effect halving the hazards of developing treatment failure was observed for choosing the exchange of the prosthesis instead of DAIR to successfully treating *Cutibacterium* PJI and an antibiotic treatment of at least 6 weeks.

In this largest case series up to now on *Cutibacterium* PJI, we show that clinical success is mainly dominated by performing a surgical approach with removal or exchange of the prosthesis instead of a DAIR procedure. As described in the treatment concept by

Zimmerli et al. (20) and treatment outcome studies (21–24) is the proper selection of patients for DAIR to achieve high clinical success. Barberan et al. showed in 60 staphylococcal PJI (25) that the treatment success rate with a DAIR regimen decreased from 83.4% when symptoms were less than month to 65.2% when between 2 and 6 months and to 30.8% when more than 6 months of symptoms. We counted a chronic infection in 94.7% with a median time to infection of 11.4 months in which an exchange of the prosthesis should be performed due to mature biofilm. However, a DAIR without removal of the implant approach was chosen in a higher proportion of the patients with 18.2% even though some of these patients had a chronic infection. Looking at patients with an exchange of the prostheses, we observed less treatment failures when performing one-stage exchange as compared to two-stage exchange (**Figure 1**). Despite the reduced risk for the patients by having only one operation instead of two operations, one-stage exchange is so far rarely the concept of choice. However, several studies highlighted the good clinical outcome of one-stage exchange (26–29).

We observed an overall treatment success rate of 80% and 85% when only looking at relapses, which was not significantly different in patients treated with rifampin *versus* those without (89.9% versus 81.5%). This is in line with the study by Jacobs et al. (15) analyzing 60 patients with *Cutibacterium* PJI and observing an overall success rate of 86% after 2 years follow-up and no significant difference between clindamycin/rifampin *versus* clindamycin alone. However, caution is needed when prescribing rifampin in combination antibiotic therapy. Besides several known side effects of rifampin (e.g. nausea, hepatitis) and drug interactions, emergence of resistance to rifampin is a complication when used in staphylococcal infections (30). There are a few reports also describing rifampin resistance in *Cutibacteria* (31–34). Since *Cutibacterium* isolates from relapse cases were not stored as a routine, we could not determine whether emergence of resistance is a relevant problem in our cohort.

Besides the chosen surgical strategy, the length of antibiotic treatment was an important factor for clinical success in our study. We found that antibiotic regimens of more than six weeks were superior to regimens less than six weeks which we interpreted as a need for treating biofilm infections. IDSA guidelines also recommend an antibiotic treatment of at least 6 weeks (35). Compared to the success rate of 86% in the paper of Jacobs et al (15) with 60 *Cutibacterium* PJI, our lower success rate of 79% overall could be due to the treatment of less than 6 weeks in 7.5% (14 out of 187) of the cases. We did not detect any difference between intravenous antibiotic duration of more or less than 14 days. An intravenous treatment of 2-4 weeks to treat PJIs was suggested in the review article by Zimmerli et al. in 2004 (20) with the rationale of a better bone penetration with intravenous antibiotics (36). In line with our results, a benefit of iv treatment longer than 7 days was not shown in the recently published OVIVA trial (37,38).

This study has several strengths and limitations. A strength is that we were able to include a large number of cases from different countries, with in-depth patient and clinical information, with a curative treatment regimen, and a long follow-up time. Gathering data from different centers increases the risk of different ways of data management, hence a center bias in our results cannot be excluded. We included a sensitivity analysis where we performed a mixed effects approach including the center as random effect. Moreover, due to the retrospective nature of this project – as compared to a prospective clinical trial – optimal data quality cannot be guaranteed, included missing information. However, huge efforts were taken to clean the data and retrospectively get information about missing and inconsistent data, leading to good quality in the main outcome variables. One limitation concerns the definition of infection relapse. First, we included not only microbiologically proven relapses but also probable relapses. Second, we included relapses happening more than 2 years after septic surgery. It could be the case that these relapses are actually new infections with another *Cutibacterium* isolate, which is not distinguishable without characterizing the isolates. To overcome this problem, we concentrated on analyzing clinical success, i.e., combining relapses and new infections, and analyzed relapses separately.

We conclude that a rifampin combination is not markedly superior, although considering the mixed data both in the literature and this study's results, it is still inconclusive as to whether rifampin should be recommended. Hence this emphasizes the need for a dedicated prospective multicenter study. However, our study results suggest to insist on changing the prosthesis and treating with antibiotics for at least 6 weeks in *Cutibacterium* PJI.

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Conflicts of interest

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Tables and Figures

Table 1. Baseline characteristics of 187 cases treated for a *Cutibacterium* PJI with (n=81, 43.3%) and without (n=106, 56.7%) a rifampin combination. Body mass index (BMI) was defined as the weight (in kg) divided by the height (in m) squared.

		All patients	With rifampin	Without rifampin	Comparison (p value)
Total		**187**	**81**	**106**	
General patient information					
Follow-up time	months (median, IQR)	36 [23, 60]	43 [25, 70]	33 [21, 47]	0.0344
Sex	male	135/187 (72.2%)	60/81 (74.1%)	75/106 (70.8%)	0.7359
	female	52/187 (27.8%)	21/81 (25.9%)	31/106 (29.2%)	
Age	median, IQR	67 [58, 74]	65 [57, 72]	68 [59, 76]	0.1959
Body mass index	median, IQR	28 [26, 32]	28 [25, 30]	29 [27, 32]	0.2525

		All patients	With rifampin	Without rifampin	Comparison (p value)
Country	Country 1	105/187 (56.1%)	62/81 (76.5%)	43/106 (40.6%)	0.0002
	Country 2	28/187 (15.0%)	10/81 (12.3%)	18/106 (17.0%)	
	Country 3	19/187 (10.2%)	4/81 (4.9%)	15/106 (14.2%)	
	Country 4	13/187 (7.0%)	0/81(0.0%)	13/106 (12.3%)	
	Country 5	7/187 (3.7%)	1/81 (1.2%)	6/106 (5.7%)	
	Country 6	7/187 (3.7%)	2/81 (2.5%)	5/106 (4.7%)	
	Country 7	6/187 (3.2%)	2/81 (2.5%)	4/106 (3.8%)	
	Country 8	1/187 (0.5%)	0/81 (0.0%)	1/106 (0.9%)	
	Country 9	1/187 (0.5%)	0/81 (0.0%)	1/106 (0.9%)	
Prosthesis					

		All patients	With rifampin	Without rifampin	Comparison (p value)
Joint prosthesis	hip	97/187 (51.9%)	40/81 (49.4%)	57/106 (53.8%)	0.3501
	shoulder	70/187 (37.4%)	34/81 (42.0%)	36/106 (34.0%)	
	knee	17/187 (9.1%)	7/81 (8.6%)	10/106 (9.4%)	
	other (foot, elbow)	3/187 (1.6%)	0/81 (0.0%)	3/106 (2.8%)	

Table 2: Infection characteristics of 187 patients with a *Cutibacterium PJI* treated with rifampin** (n = 81) and without (n = 106)

		Total	With rifampin	Without rifampin	Comparison (p value)
Total		**187**	**81**	**106**	
Cutibacterium species	*C. acnes*	158/187 (84.5%)	66/81 (81.5%)	91106 (85.8%)	0.6189
	C. avidum	20/187 (10.7%)	10/81 (12.3%)	10/106 (9.4%)	
	C. granulosum	9/187 (4.8%)	4/81 (4.9%)	5/106 (4.7%)	
Clinical presentation					

		Total	With rifampin	Without rifampin	Comparison (p value)
Total		**187**	**81**	**106**	
Sinus tract	n, %	19/187 (10.2%)	4/81 (4.9%)	15/106 (14.2%)	0.0685
Pain	n, %	164/187 (87.7%)	67/81 (82.7%)	97/106 (91.5%)	0.1119
Pathogenesis outcome					
Time to PJI	months (median, IQR)	20 [6, 41]	20 [4, 42]	18 [8, 39]	0.1304
Acute early (≤ 4 weeks after last surgery)	n, %	10/187 (5.3%)	7/81 (8.6%)	3/106 (2.8%)	
Chronic late (> 4 weeks after last surgery)	n, %	177/187 (94.7%)	74/81 (91.4%)	103/106 (97.2%)	
Antibiotic treatment					
Overall antibiotic treatment	weeks (median, IQR)	12 [7, 13]	12 [11, 14]	9 [6, 12]	0.0013

		Total	With rifampin	Without rifampin	Comparison (p value)
Total		**187**	**81**	**106**	
duration***					
Overall duration > 6 weeks	n, %	141/187 (75.4%)	69/81 (85.2%)	72/1066 (67.9%)	-
IV antibiotics duration	days (median, IQR)	14 [10, 24.5]	14 [9, 18]	16 [10.2, 28]	0.0087
IV antibiotics	n, %	174/187 (93.0%)	73/81 (90.1%)	101/106 (95.3%)	0.2781
IV duration > 14 days	n, %	89/187 (47.6%)	30/81 (37.0%)	59/106 (55.7%)	-
P.O antibiotics duration	weeks (median, IQR)	9 [4, 11]	10 [7, 12]	7 [4, 10]	<0.0001
Rifampin duration	weeks (median, IQR)		10 [6, 12]		-
Rifampin duration > 6 weeks	n, %		58/81 (71.6%)		-
Treatment: Surgical concept	Debridement and retention of prosthesis (DAIR)	34/187 (18.2%)	15/81 (18.5%)	19/106 (17.9%)	0.0368

		Total	With rifampin	Without rifampin	Comparison (p value)
Total		**187**	**81**	**106**	
	One-stage exchange of prosthesis	51/187 (27.3%)	3181 (38.3%)	20/106 (18.9%)	
	Two-stage exchange of prosthesis with spacer	63/187 (33.7%)	20/81 (24.7%)	43/106 (40.3%)	
	Two-stage exchange of prosthesis without spacer	32/187 (17.1%)	12/81 (14.8%)	20/106 (18.9%)	
	Explantation without new prosthesis	7/187 (3.7%)	3/81 (3.7%)	4/106 (3.8%)	
Outcome					
Overall failure*	(n, %)	38/187 (20.3%)	10/81 (12.3%)	28/106 (26.5%)	0.0288
Relapse	proven and possible (n, %)	28/187 (15.0%)	8/81 (9.9%)	20/106 (18.9%)	0.1334
	proven (n, %)	16/28 (57.1%)	5/8 (62.5%)	11/20 (55.0%)	

		Total	With rifampin	Without rifampin	Comparison (p value)
Total		**187**	**81**	**106**	
	possible (n, %)	12/28 (42.9%)	3/8 (37.5%)	9/20 (45.0%)	
Relapse: Time of occurrence	at implantation (n, %)	11/28 (39.3%)	3/8 (37.5%)	8/20 (40.0%)	
	during AB treatment (n, %)	8/28 (28.6%)	2/8 (25.0%)	6/20 (30.0%)	
	after AB treatment stop (n, %)	9/28 (32.1%)	4/8 (50.0%)	5/20 (25.0%)	
New infection	n, %	13/187 (7.0%)	2/81 (2.5%)	11/106 (10.4%)	0.0692
New infection: Time of occurrence	at implantation (n, %)	2/13 (15.4%)	0/2 (0.0%)	2/11 (18.2%)	
	during AB treatment (n, %)	2/13 (15.4%)	0/2 (0.0%)	2/11 (18.2%)	
	after AB treatment stop (n, %)	9/13 (69.2%)	1/2 (50.0%)	8/11 (72.7%)	
Death	overall (n, %)	13/187 (7.0%)	4/81 (4.9%)	9/106 (8.5%)	0.5116

		Total	With rifampin	Without rifampin	Comparison (p value)
Total		**187**	**81**	**106**	
	due to PJI (n, %)	0/187 (0.0%)	0/81 (0.0%)	0/106 (0.0%)	

* Several patients had an infection relapse as well as a new infection.

** rifampin doses were prescribed as 450mg bid in 44.4%, 600mg mid in 27.8%. In 33.3% doses was not recorded

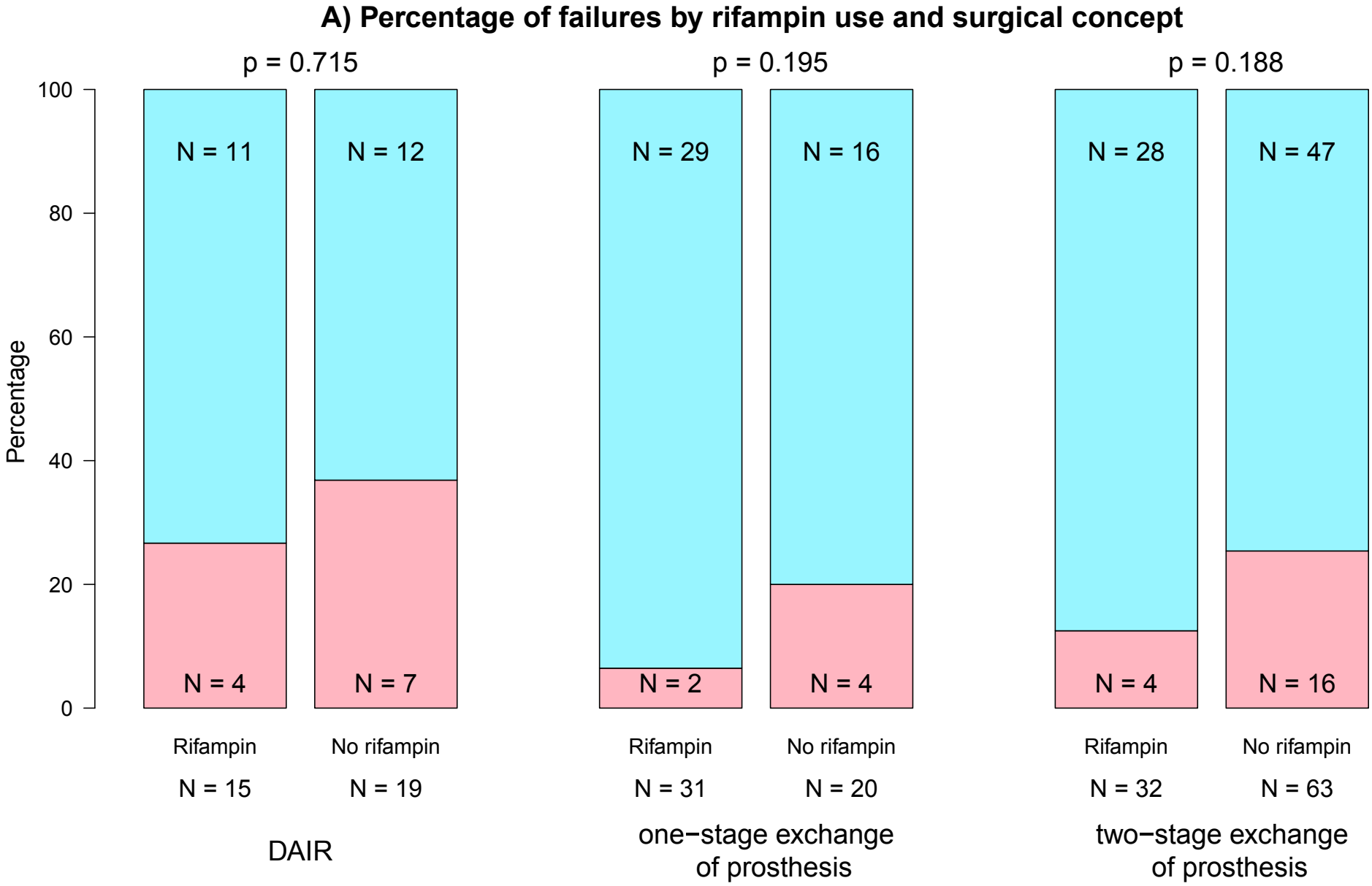
*** In patients treated with a two-stage exchange of prosthesis with a long interval of at least 6 weeks of antibiotic treatment followed by an antibiotic-free window of 2 weeks, antibiotic treatment duration was counted until the start of the antibiotic window. In those patients with a two-stage exchange and a short first interval of antibiotic treatment, iv and po antibiotic treatment duration was combined after the explantation and the implantation date of the prosthesis.

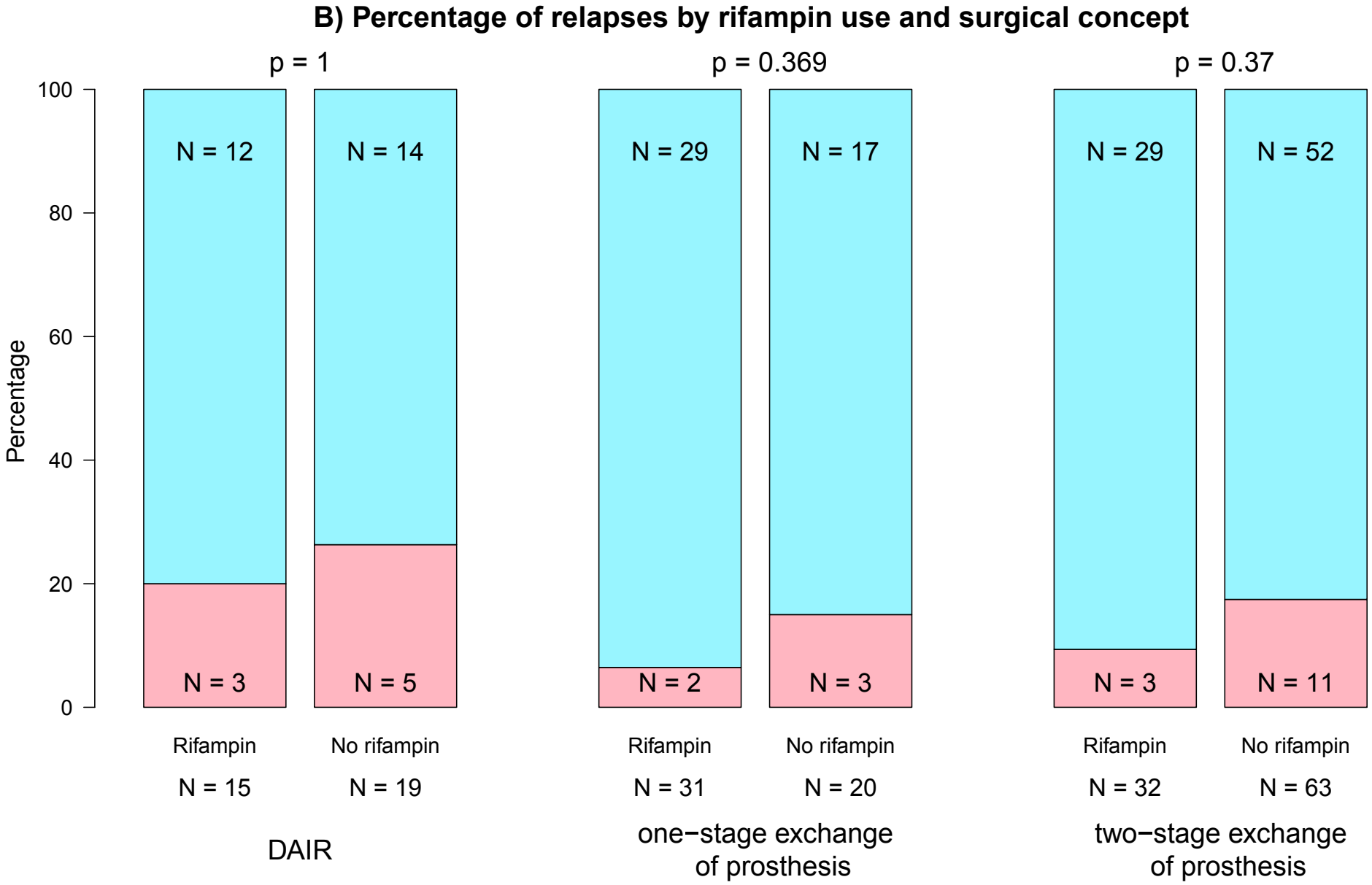
Figure legends

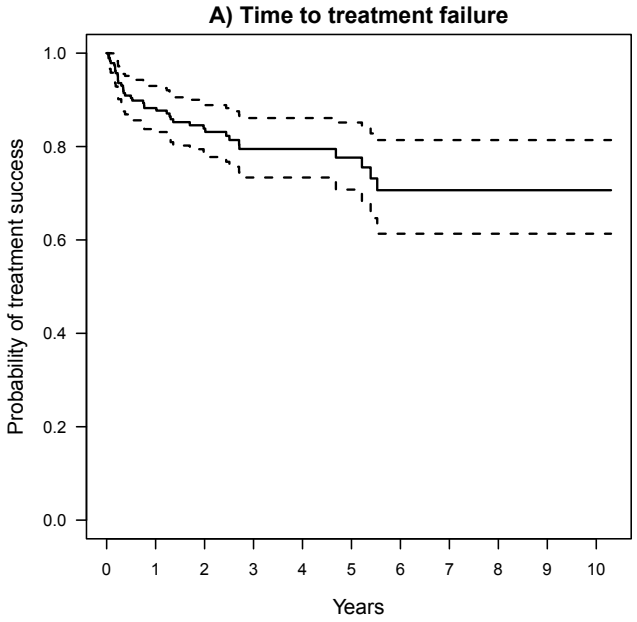
Figure 1. Outcome of *Cutibacterium* PJIs stratified by surgical strategy (DAIR, one-stage exchange, two-stage exchange), either looking at failures in general (panel A), or at relapses only (panel B).

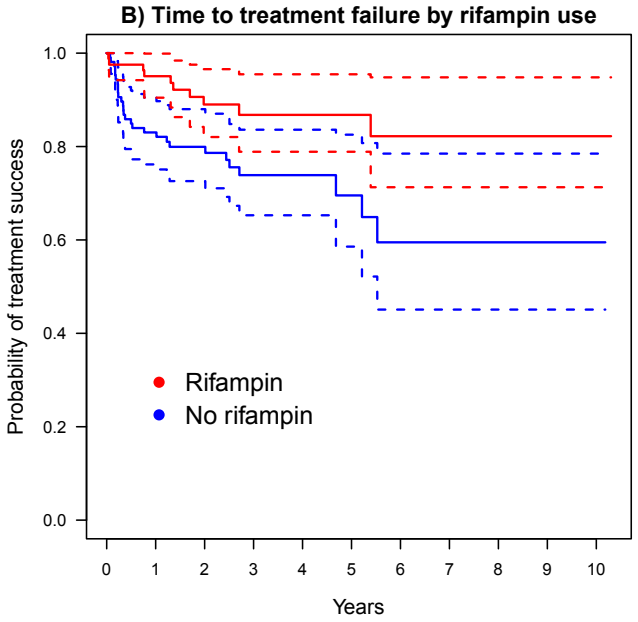
Figure 2: A) Kaplan-Meier curve of all patients (n = 187), with 38 having treatment failure, i.e., infection relapse or new infection; B) Kaplan-Meier curve of patients using rifampin (n = 81, 10 failures) and not using rifampin (n = 106, 28 failures); C) Kaplan-Meier curve of patients stratified by surgical strategy: one-stage exchange (n = 51, 6 failures), two-stage exchange (n = 95, 20 failures), DAIR (n = 34, 11 failures); D) Kaplan-Meier curve of all patients (n = 187), with 28 having an infection relapse; E) Kaplan-Meier curve of patients prescribed rifampin (n = 81, 8 relapses) or not (n = 106, 20 relapses); F) Kaplan-Meier curve of patients stratified by surgical strategy: one-stage exchange (n = 51, 5 relapses), two-stage exchange (n = 95, 14 relapses), DAIR (n = 34, 8 relapses).

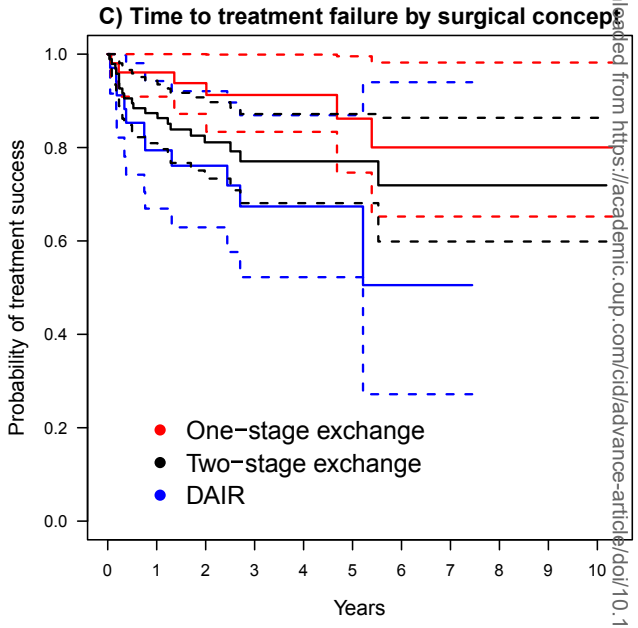
Figure 3: Factors influencing failure overall (panel A) and relapse (panel B). PJI: periprosthetic joint infections, UV: univariable, HR: hazards ratio, MV: multivariable, BMI: body mass index, overweight: BMI >25, obese: BMI >30, iv: intravenous, DAIR = debridement and implant retention.

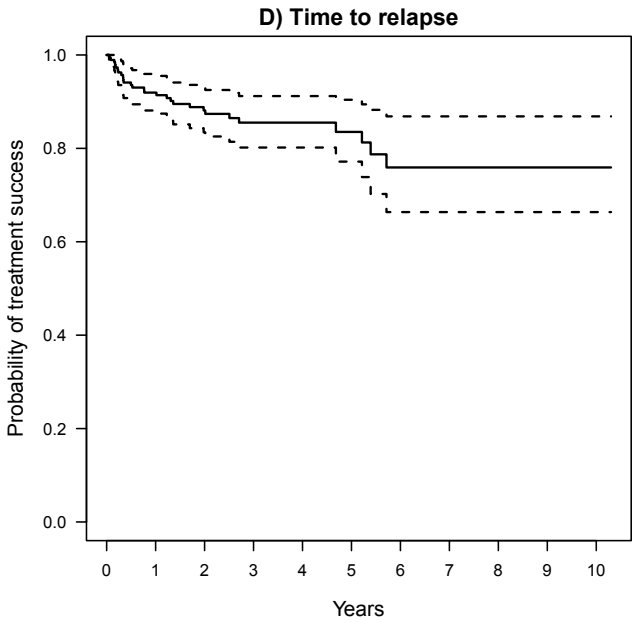


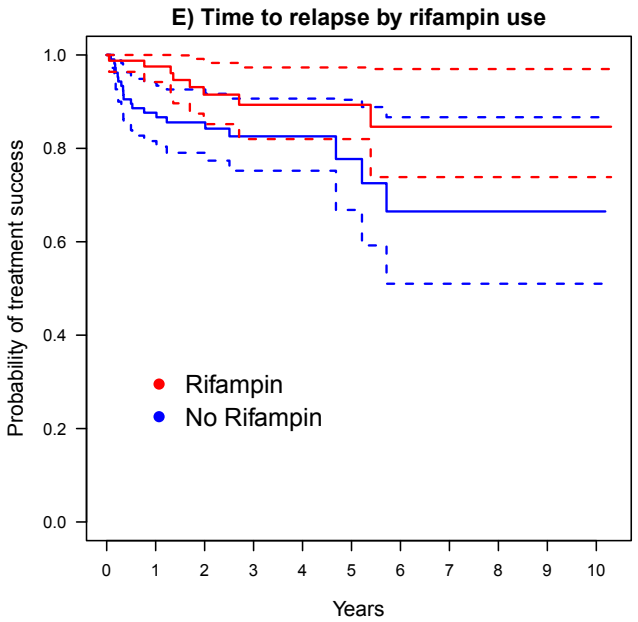


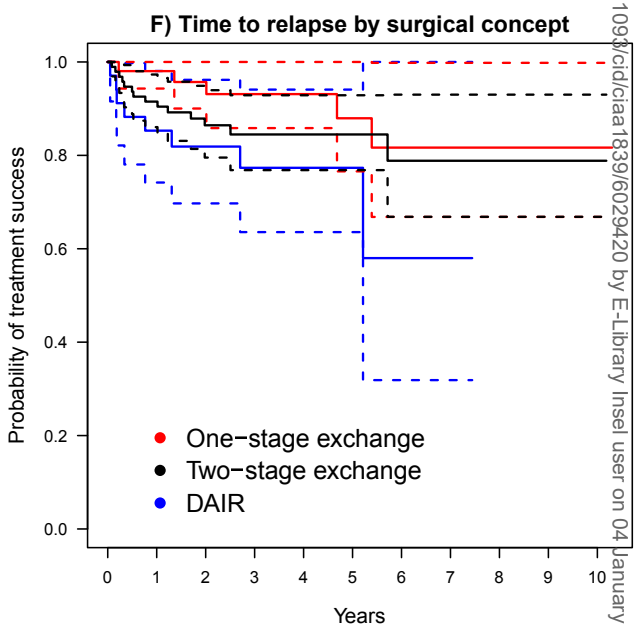








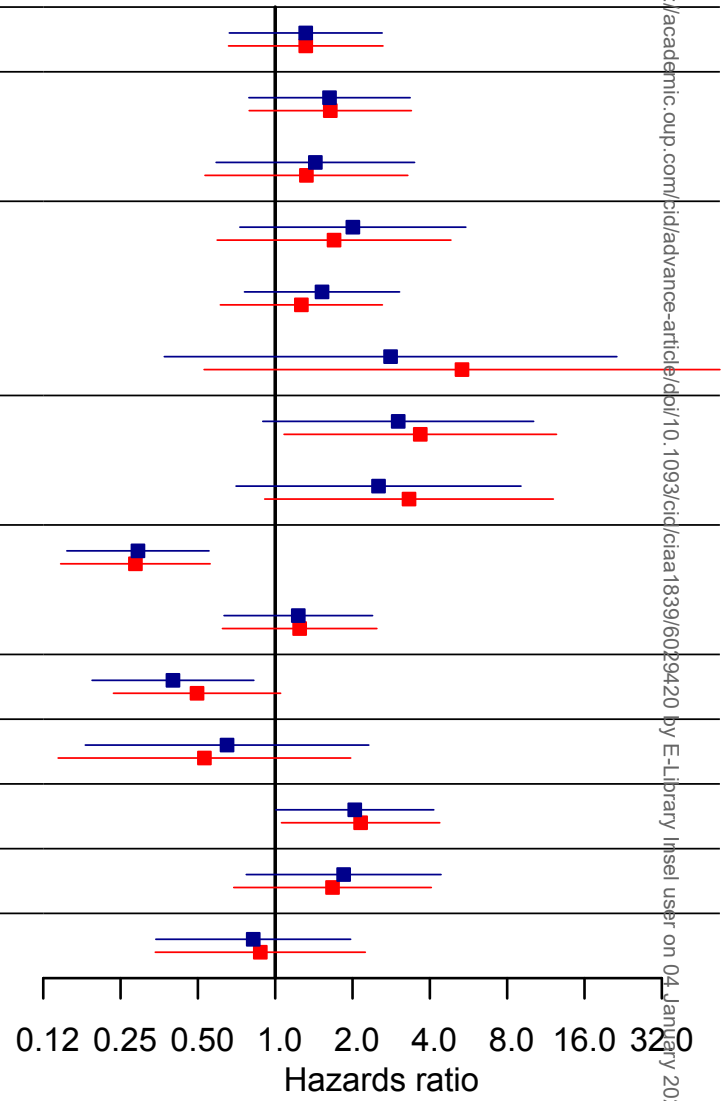




A) Factors influencing treatment failure (relapse or new infection) in patients with PJI

unadjusted adjusted: surgical strategy, total antibiotic duration

		p UV	HR UV	p MV	HR MV
Female gender		0.4336	1.31	0.4380	1.31
Age (ref = < 65)	65−75	0.1866	1.63	0.1831	1.64
	>75	0.4278	1.43	0.5465	1.32
Joint (ref = hip)	knee	0.1778	2.01	0.3238	1.69
	shoulder	0.2367	1.52	0.5267	1.26
	other	0.3176	2.81	0.1557	5.34
BMI (ref = normal)	overweight	0.0750	3.01	0.0369	3.67
	obese	0.1552	2.52	0.0691	3.32
Overall antibiotic duration	> 6 weeks	0.0002	0.29	0.0002	0.29
Antibiotic iv duration	>14 days	0.5421	1.23	0.5347	1.24
Rifampin		0.0132	0.4	0.0667	0.5
Rifampin duration	> 6 weeks	0.5053	0.65	0.3427	0.53
DAIR		0.0484	2.04	0.0343	2.15
SinusTract		0.1683	1.85	0.2553	1.67
Pain		0.6581	0.82	0.7808	0.87



B) Factors influencing infection relapse in patients with PJI

unadjusted adjusted: surgical strategy, total antibiotic duration

		p UV	HR UV	p MV	HR MV
Female gender		0.5763	0.77	0.5559	0.76
Age (ref = < 65)	65−75	0.3638	1.48	0.3837	1.46
	>75	0.4335	1.51	0.4348	1.51
Joint (ref = hip)	knee	0.3147	1.96	0.4965	1.59
	shoulder	0.0536	2.26	0.1633	1.84
	other	0.1371	4.82	0.0533	12.13
BMI (ref = normal)	overweight	0.0602	4.06	0.0294	5.11
	obese	0.3832	2.04	0.2200	2.74
Overall antibiotic duration	> 6 weeks	0.0014	0.3	0.0028	0.31
Antibiotic iv duration	>14 days	0.4836	1.33	0.3875	1.43
Rifampin		0.0504	0.44	0.1038	0.5
Rifampin duration	> 6 weeks	0.7047	0.76	0.5952	0.67
DAIR		0.0800	2.1	0.0663	2.19
SinusTract		0.8415	1.13	0.9883	1.01
Pain		0.4386	0.68	0.5633	0.73