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## Clinical outcome and risk factors for failure in late acute prosthetic joint infections treated with debridement and implant retention

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## Highlights

- Late acute prosthetic joint infection (PJI) treated with surgical debridement and implant retention have a high failure rate, especially when caused by *S. aureus*.
- The exchange of mobile components during surgical debridement is the most potent predictor for treatment success.
- Preoperative risk factors for failure are: fracture as indication for the prosthesis, rheumatoid arthritis, an age above 80 years, male gender, chronic obstructive pulmonary disease, and a C-reactive protein >150 mg/L at baseline.
- Treatment strategies for late acute PJIs should be individualized according to the preoperative risk for failing and the microorganism causing the infection.

## ABSTRACT

*Objectives:* Debridement, antibiotics and implant retention (DAIR) is the recommended treatment for all acute prosthetic joint infections (PJI), but its efficacy in patients with late acute (LA) PJI is not well described. *Methods:* Patients diagnosed with LA PJI between 2005 and 2015 were retrospectively evaluated. LA PJI was defined as the development of acute symptoms ( $\leq 3$  weeks) occurring  $\geq 3$  months after arthroplasty. Failure was defined as: i) the need for implant removal, ii) infection related death, iii) the need for suppressive antibiotic therapy and/or iv) relapse or reinfection during follow-up. *Results:* 340 patients from 27 centers were included. The overall failure rate was 45.0% (153/340). Failure was dominated by *Staphylococcus aureus* PJI (54.7%, 76/139). Significant independent preoperative risk factors for failure according to the multivariate analysis were: fracture as indication for the

30 prosthesis (odds ratio (OR) 5.4), rheumatoid arthritis (OR 5.1), age above 80 years (OR 2.6),  
31 male gender (OR 2.0) and C-reactive protein >150 mg/L (OR 2.0). Exchanging the mobile  
32 components during DAIR was the strongest predictor for treatment success (OR 0.35).  
33 *Conclusion:* LA PJIs have a high failure rate. Treatment strategies should be individualized  
34 according to patients' age, comorbidity, clinical presentation and microorganism causing the  
35 infection.

36

37 **Keywords**

38 Prosthetic joint infection; Acute; Hematogenous; Risk factors, failure

ACCEPTED MANUSCRIPT

## 39 INTRODUCTION

40 Prosthetic joint infections (PJI) can be subdivided into early post-surgical, chronic and late  
41 acute infections, the latter being considered to be mostly hematogenous of origin [1]. These  
42 subdivisions have been introduced to identify patients in whom the infected prosthesis can be  
43 debrided and retained (in case of acute infections) and to identify those in whom the infected  
44 prosthesis should be removed (in case of chronic infections). Despite these well-recognized  
45 categories of PJIs in literature, specific data on the clinical outcome of patients with a late  
46 acute infection is scarce. Several studies indicate that late acute PJIs have a higher failure rate  
47 compared to early acute (post-surgical) infections, especially when the infection is caused by  
48 *Staphylococcus aureus* (*S. aureus*) [2-8]. Some studies show higher failure rates in late acute  
49 PJIs caused by other microorganisms than *S. aureus* as well [9-10], but this has been  
50 discarded by others [11-13]. Current guidelines recommend the same surgical (debridement  
51 and implant retention (DAIR)) and antimicrobial strategy for both early and late acute  
52 infections [14], but late acute PJIs may require a different treatment approach. More evidence  
53 on the clinical outcome and identification of risk factors for failure in a larger cohort of  
54 patients is important to optimize treatment for this specific patient group. Therefore, we  
55 performed a large multicentre observational study to describe clinical outcome and risk  
56 factors for failure in late acute PJI treated with DAIR. We hypothesized that late acute PJIs  
57 have a high failure rate, especially when caused by *S. aureus*.

58

59

## 60 MATERIAL AND METHODS

61

62 *Study design and inclusion criteria*

63 We performed an international multicenter retrospective observational study in which data of  
64 all consecutive patients with a late acute PJI between January 2005 and December 2015 were  
65 collected. All patients who underwent surgical debridement according to the surgical records  
66 were retrospectively evaluated. If centers were not able to provide cases during the complete  
67 study period, a minimum of at least 10 consecutive cases was required to participate in the  
68 study. In each center, all DAIR procedures performed within the studied period according to  
69 the surgical records were evaluated, and only cases that met the strict definition of late acute  
70 PJI were included. Late acute PJI was defined as patients, with a prior history of normal  
71 function of the index arthroplasty, who developed a sudden onset of symptoms and signs of a  
72 PJI, such as acute pain and/or swelling of the prosthetic joint, more than 3 months after the  
73 implantation. Patients with a sinus tract and/or symptoms existing for longer than 3 weeks  
74 before surgical debridement were excluded from the analysis. Informed consent was retrieved  
75 when required by the ethics committee of the participating center. A PJI was defined  
76 according to the diagnostic criteria described by the Musculoskeletal Infection Society  
77 (MSIS) [15]. Multiple variables on patient characteristics, clinical presentation, medical  
78 microbiology results, surgical & antibiotic treatment and outcome were collected and  
79 analyzed.

80

### 81 *Clinical outcome*

82 Failure was defined as: i) the need for prosthesis removal due to persistent or recurrent  
83 clinical signs of infection (one or two-stage exchange, amputation, Girdlestone for hips or  
84 arthrodesis for knees) due to persistent clinical signs of infection, ii) the need for suppressive  
85 antibiotic therapy because of persistent clinical or biochemical signs of infection, iii) a relapse  
86 of infection with the same microorganism during follow-up, iv) a reinfection with a different  
87 microorganism than the initial infection during follow-up, or v) death due to the infection.

88 PJI related death was defined as death that occurred during (antibiotic) treatment with no  
89 other alternative explanation than an uncontrolled infection. The need for a second  
90 debridement during antibiotic therapy was not considered as failure. Patients in whom  
91 antibiotic suppressive therapy was prescribed for other reasons than persistent signs of  
92 infection (e.g. because this was routine practice of the participating hospital and/or because  
93 the patient had severe comorbidity and was therefore, not eligible for future surgeries) were  
94 excluded. Failure was subsequently categorized into *early failure*: persisting or reappearance  
95 of symptoms of infection during antibiotic treatment, and *late failure*: reappearance of  
96 symptoms of infection after finishing antibiotic treatment. *Complete remission* was  
97 considered in patients with a retained and functional implant after 2 years of follow-up. A  
98 functional implant was defined as the ability to walk without pain.

99

#### 100 *Statistical analysis*

101 A Chi-square test (or a Fisher exact-test when appropriate) was used to analyze the difference  
102 between groups for categorical variables, and a student t-test (or Mann Whitney U test when  
103 data was not normally distributed) for continuous variables. A Kaplan Meier survival curve  
104 with a cox-regression analysis was used to evaluate failure rate in time. Possible risk factors  
105 for failure were selected and analyzed using univariate analysis by Pearson's correlation.  
106 Variables with a significance level of  $< 0.2$  were analyzed in a binary multivariate logistic  
107 regression model. A separate CART (classification and regression tree) analysis was  
108 performed to assess which variable was the most potent in predicting treatment outcome. All  
109 variables were tested for multicollinearity and additionally analyzed in a cox regression  
110 analysis. Preoperative variables with the highest odds ratio (OR) in the multivariate logistic  
111 regression model were included in a risk score, in which the beta coefficient of each variable  
112 served as an indicator for the height of the score. A subanalysis was performed for early and

113 late failure. In the analysis of early failure, late failures were considered as non-failures and  
114 included as such. All analyses were two-tailed and p-values < 0.05 were considered as  
115 statistically significant. Data were presented as mean  $\pm$  Standard Deviation (SD) when data  
116 was normally distributed or median  $\pm$  Inter Quartile Range (IQR) when data was not normally  
117 distributed. Statistical analysis was performed using SPSS, version 23.0 (SPSS Inc., Chicago,  
118 IL).

119

120

## 121 RESULTS

122

### 123 *Characteristics of late acute PJI*

124 A total of 340 cases were included in the analysis. From the total cohort, 247 out of 340 cases  
125 (72.6%) had a PJI of the knee. Isolated microorganism(s) on patient level are shown in Table  
126 1. Surprisingly, coagulase negative staphylococci (CoNS) were isolated in 30 cases (8.8%),  
127 including 24 monomicrobial infections. After exclusion of *S. lugdunensis* (n=4), a pathogen  
128 with a higher virulence compared to other CoNS, 1 out of 20 CoNS PJIs had bacteremia  
129 (bloodcultures taken in 10 out of 20 cases), and none of them was diagnosed with  
130 endocarditis. In 170 out of 340 cases (50%) a source of the PJI was identified: i) skin  
131 infection (n=62, 36.5%), ii) dental procedure (n=18, 10.6%), iii) recent surgery (n=24,  
132 14.1%), or iv) other (n=66, 38.8%). A preceding skin infection was described in 35/139  
133 (25.2%) of *S. aureus* and in 22/97 (22.7%) of streptococcal infections. In gram-negative PJIs,  
134 recent surgery or another source than skin infection, was marked in 21 out of 50 cases (42%).

135

### 136 *Failure rate and clinical outcome*



137 The overall failure rate of late acute PJI was 45.0% (153/340). With a limited number of  
138 cases, failure rate was highest in PJI caused by *Enterococcus* species (72.7%, 8/11). There  
139 was no major difference in failure rate between *Enterococcus* species: treatment failed in 4  
140 out of 5 cases (80%) with *E. faecium* and in 4 out of 6 cases (67%) with *E. faecalis*. The  
141 overall treatment failure was dominated by *S. aureus*, with a failure rate of 54.7% (76/139).  
142 The average failure with other microorganisms was around 40% (CoNS 40.0% (12/30),  
143 *Streptococcus* species 37.1% (36/97), gram-negatives 36.0% (18/50)). Patients with an  
144 unidentified source of infection showed a trend towards a higher failure rate (58.8%, 90/184)  
145 compared to those with an identified source of infection (41.2%, 63/156) (p 0.12). The  
146 percentage of failure in time according to the Kaplan-Meier survival curve is depicted in  
147 Figure 1.

148 *Early* failure occurred in 53.5% of failed cases (82/153), which mostly resulted in the need for  
149 implant removal (73.0%, 60/82) and in death due to the infection (13.4%, 11/82). The median  
150 time to failure during antibiotic therapy was 26 days (IQR 12 – 89). *Late* failure occurred in  
151 46.5% of cases (71/153) and was mostly due to a relapse of infection with the same  
152 microorganism during follow-up (63.3%, 45/71), followed by reinfection with another  
153 microorganism (11.2%, 8/71). The remaining patients were put on suppressive antibiotic  
154 therapy because of persistent signs of inflammation and/or had a relapse of infection without  
155 an identified microorganism. The median time to failure after finishing antibiotic therapy was  
156 6 months (IQR 4 – 11), in which 81.1% of patients failed within the first year after DAIR.  
157 The median follow-up of non-failures was 25.0 months (IQR 11 – 31). Seventy-two of the  
158 non-failures had a follow-up of 2 years, in whom complete remission was achieved in 75%  
159 (54/72).

160

161 *Antibiotic treatment*

162 The median days of intravenous (IV) antibiotic treatment was higher in failures compared to  
163 non-failures (22 days (IQR 12 – 42) versus 19 days (IQR 10 – 34) respectively, p 0.007). To  
164 analyze the effect of the total duration of IV and oral antibiotic treatment, *early* failures were  
165 excluded from the analysis. The rate of *late* failure was the same for those treated for less than  
166 60 days (28.5%, 51/179) compared to those treated for more than 60 days (25.3%, 20/79) (p  
167 0.56).

168 To exclude empirical antibiotic treatment, the type of antibiotic was only analyzed if  
169 prescribed for more than five days (Supplementary Table 2). For staphylococcal infections in  
170 whom data on the oral regimen was available, the failure rate was 49.3% (66/134) when  
171 rifampin was added versus 67.7% (21/31) when rifampin was not added to the antibiotic  
172 regimen (p 0.06). In addition, failure rate was significantly lower when rifampin was  
173 combined with a fluoroquinolone compared to other regimens (failure rate 45.5% (46/101)  
174 versus 64.1% (41/64), respectively, p 0.02). In the rifampin treated cases, there was no  
175 significant difference in failure rate in fluoroquinolone-based regimens compared to other  
176 antibiotics (46.0% (46/100) vs 58.8% (20/34), respectively, p 0.20). For streptococci, failure  
177 rate was 22.7% (5/22) when rifampin was added versus 42.5% (31/73) when rifampin was not  
178 added to the antibiotic regimen (p 0.13). With a limited number of gram-negative PJIs  
179 analyzed, the use of fluoroquinolones was not associated with treatment success in our  
180 analysis (failure rate of 34.3% (12/35) when using a fluoroquinolone versus 38.5 % (5/13)  
181 when using another antibiotic regimen, p 0.79).

182

### 183 *Risk factors for failure*

184 Table 2 shows the results of the univariate and multivariate binary logistic regression analysis  
185 in identifying risk factors for failure. From the total of 340 cases, all variables were complete  
186 without missing data in 232 cases and were included in the final model. Patients in whom no

187 blood cultures were obtained were considered as blood culture negative. The results of the  
188 multivariate analysis for other variables did not change when the blood culture variable was  
189 omitted from the analysis. The Hosmer and Lemeshow test had a p-value of 0.89, indicating  
190 that the model was adequate, with a predicting capacity of 71.1% according to the  
191 classification table.

192 Male gender, age above 80 years, rheumatoid arthritis (RA), fracture as indication for the  
193 prosthesis, C-reactive protein (CRP) above 150 mg/L, infection caused by *S. aureus* and the  
194 use of local antibiotics were all significant independent variables for failure in the  
195 multivariate analysis. Local antibiotic therapy mainly consisted of gentamicin beads or  
196 gentamicin sponges. There were no significant clinical differences between patients who were  
197 treated with local antibiotics compared to patients in whom it was withheld (data not shown),  
198 with the exception of the American Society of Anesthesiologist (ASA) classification score,  
199 which was higher in the local antibiotic group (ASA score  $\geq 3$  in 66.7% (20/30) versus 44.3%  
200 (102/230) respectively, p 0.02). With an OR of 2.9, COPD was also associated with a higher  
201 failure rate, although it did not reached statistical significance. Cox regression analysis  
202 showed the same predictors for failure. Analysis on multicollinearity revealed that COPD was  
203 accompanied by a higher prevalence of ischemic heart disease and heart failure. Exchanging  
204 the mobile components during DAIR was the only variable that was independently associated  
205 with treatment success. In addition, according to the CART analysis, exchanging the mobile  
206 components was the most potent variable in predicting treatment outcome.

207 Multivariate analysis showed that COPD, RA, CRP above 150 mg/L and *Enterococcus*  
208 species were significant independent predictors for *early* failure, while *S. aureus* was the only  
209 predictor for *late* failure (Supplementary Table 1).

210 Based on the results of the multivariate binary logistic regression, a risk score was developed,  
211 by using the preoperative variables that were associated with failure. In addition, as the

212 possibility to exchange the mobile components can be known preoperatively as well, the  
213 protective effect of exchanging the mobile components during DAIR was also included  
214 (Figure 2A). Because failure was dominated by *S. aureus*, a separate analysis was performed  
215 for the presence or absence of *S. aureus* (Figure 2B-C). Our results indicate that the  
216 preoperative model has the strongest predictive value for failure in PJIs caused by other  
217 microorganisms than *S. aureus*. In *S. aureus* PJI in whom mobile components were  
218 exchanged during DAIR, the rate of failure decreased from 47.1% to 36.6% when patients  
219 were treated with a fluoroquinolone in combination with rifampin.

220

#### 221 *Blood culture positive versus blood culture negative cases*

222 Since cases with positive blood cultures are considered as the 'classical' late acute /  
223 hematogenous infections, we performed an additional analysis on blood culture positive  
224 versus proven blood culture negative cases. Table 3 shows the clinical differences between  
225 both groups. From the 259 cases in whom blood cultures were obtained, 42% (109/259) were  
226 blood culture positive. The rate of bacteremia was higher in hip PJIs and in implants of more  
227 than 2 years of age, and was more often associated with fever, infections caused by *S. aureus*  
228 and endocarditis. Echocardiography was performed in 72.5% of cases with *S. aureus*  
229 bacteremia (50/69). In the majority, this mainly comprised transthoracic echocardiography  
230 (53.6%). Endocarditis was diagnosed in 10% of cases (7/69). The overall failure rate was 15%  
231 higher in blood culture positive cases and was mostly ascribed to early failure (p 0.01)  
232 (Supplementary Table 1). From the failures in the blood culture positive group, 9 out of 61  
233 cases (14.8%) died because of the infection. All of these 9 cases, with the exception of one,  
234 were diagnosed with endocarditis.

235

236

237 **DISCUSSION**

238 Due to the low incidence of late acute PJIs [16], clinical data and specific treatment  
239 recommendations for this subgroup of patients is limited. By the effort of many centers  
240 involved, we were able to describe the clinical characteristics of late acute PJIs, evaluate its  
241 outcome, and identify risk factors for failure. In a large cohort of 340 late acute PJIs treated  
242 with DAIR, we demonstrated a failure rate of 45%, in which treatment failure was most  
243 prominent when caused by *S. aureus*.

244 The high failure rate observed in our study may partly be explained by: i) The presence of an  
245 unidentified source of infection in case of bacteremia. Although not statistically significant,  
246 an unidentified source of infection was associated with a higher failure rate in our study.  
247 Endocarditis may have been underdiagnosed in our study, as a transesophageal  
248 echocardiography was not performed in all *S. aureus* bacteremias. Thus, continuous seeding  
249 of bacteria to the prosthetic joint with the development of biofilm may be the cause of failure  
250 in these cases. Indeed, we demonstrated that a relapse of infection during follow-up was  
251 mostly caused by *S. aureus*, which supports this hypothesis. However, it is important to note  
252 that the reported incidence of endocarditis in *S. aureus* bacteremia in literature is comparable  
253 to our study [17], and failure rate was still 40% in blood culture negative cases. ii) A  
254 previously unrecognized chronic PJI. Although we held on to a clear definition of a sudden  
255 onset of symptoms in a priorly asymptomatic joint, we cannot completely rule out that  
256 chronic PJIs that deteriorated acutely also comprised a small part of the cohort. CoNS were  
257 identified in a limited number of patients and these microorganisms are not common  
258 pathogens for causing acute infections. Indeed, most of these cases were blood culture  
259 negative and were not diagnosed with endocarditis, which makes an acute infection in these  
260 cases unlikely. However, the failure rate in CoNS was not higher than in others (40%), and  
261 patients with a proven hematogenous infection had a higher failure rate compared to blood

262 culture negative cases iii) Mobile components were not exchanged in almost half of our  
263 studied cohort. As the CART analysis showed that this is the most potent variable for  
264 predicting failure, treatment success may be substantially higher when mobile exchange was  
265 performed in all cases. The low number of exchange may be due to the fact that the study  
266 extends over ten year time period and only in recent years, the importance of this surgical  
267 technique became clear. In addition, mobile components are not available in acute settings in  
268 some centers. However, even with the exchange of mobile components, overall failure rate  
269 was still 36%, and even higher in case of *S. aureus* infections.

270 At the moment, a DAIR procedure is the recommended surgical approach for all acute PJIs  
271 with stable implants and susceptibility to potent anti-biofilm regimens [14]. Our data suggest  
272 that a DAIR should be reconsidered in late acute PJIs for certain patient categories. As  
273 previously mentioned, especially *S. aureus* PJI has a high risk of failure, especially when  
274 mobile components cannot be exchanged and treatment with a rifampin-based regimen is not  
275 possible. Failure rate was much lower in a study performed by Tande et. al., in which late  
276 acute PJI caused by *S. aureus* was treated with revision surgery or if the DAIR was followed  
277 by chronic suppressive antibiotic therapy [8]. Therefore, identifying the causative  
278 microorganism and its susceptibility pattern preoperatively may be helpful to choose the best  
279 surgical approach in an acute setting. To elaborate, studies have shown that Gram staining of  
280 synovial fluid has a poor sensitivity in diagnosing PJI, but its value is mostly evaluated in  
281 chronic cases, and may be more useful and sensitive in acute infections [18]. Unfortunately,  
282 early molecular detection does not show any benefit so far in acute PJIs, but its diagnostic  
283 accuracy maybe optimized in upcoming years [19]. For late acute PJIs caused by another  
284 microorganism than *S. aureus*, the CRIME80 score could be useful in identifying high-risk  
285 patients. According to our analysis, patients who received a prosthetic implant because of a  
286 fracture and patients with rheumatoid arthritis are at highest risk to fail. Previous studies have

287 shown, that these variables are also strongly correlated with failure in early postsurgical and  
288 chronic PJIs [5, 11, 20]. In addition, our data indicate that patients with male gender, COPD,  
289 a CRP above 150 mg/L at presentation and an age above 80 years are also more prone to fail.  
290 Accordingly, a DAIR procedure is probably not advisable in late acute PJI with a high a priori  
291 chance of failure. In addition, some studies suggest that revision surgery applied as salvage  
292 therapy after DAIR failure is associated with poorer outcome [21-22]. Therefore, our results  
293 suggest the need for revision surgery as a first surgical approach .

294 Non-surgical strategies to increase the chance of treatment success seem limited. In our study,  
295 the addition of rifampin in staphylococcal infections, especially when combined with a  
296 fluoroquinolone, improved treatment outcome, which is in accordance with previous findings.  
297 [2,23]. A longer duration of intravenous antibiotic treatment and/or the use of local antibiotics  
298 was associated with a higher failure rate, but this may be due to selection bias as antibiotic  
299 treatment is most often intensified in more severe infections. Indeed, we found a higher ASA  
300 classification score in patients who received local antibiotics compared to patients in whom  
301 local antibiotics was withheld. Therefore, the exact value of local antibiotics, the type of  
302 antibiotic, the use of chronic suppressive therapy and certain antibiotic combinations should  
303 be addressed in future studies, ideally in a randomized controlled study design. For this  
304 reason, we want to emphasize that our results on the effect of antibiotic treatment on clinical  
305 outcome should be evaluated in light of the aforementioned limitations and interpreted with  
306 caution.

307 In conclusion, late acute PJIs treated with DAIR have a high failure rate, especially when  
308 caused by *S. aureus* and without the exchange of mobile components. Treatment strategies  
309 should be tailored and optimized to improve the outcome. This should be addressed in future  
310 studies.

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314 No funding was obtained for this study.

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316

317 **CONFLICT OF INTEREST**

318 None of the authors declared any conflict of interest.

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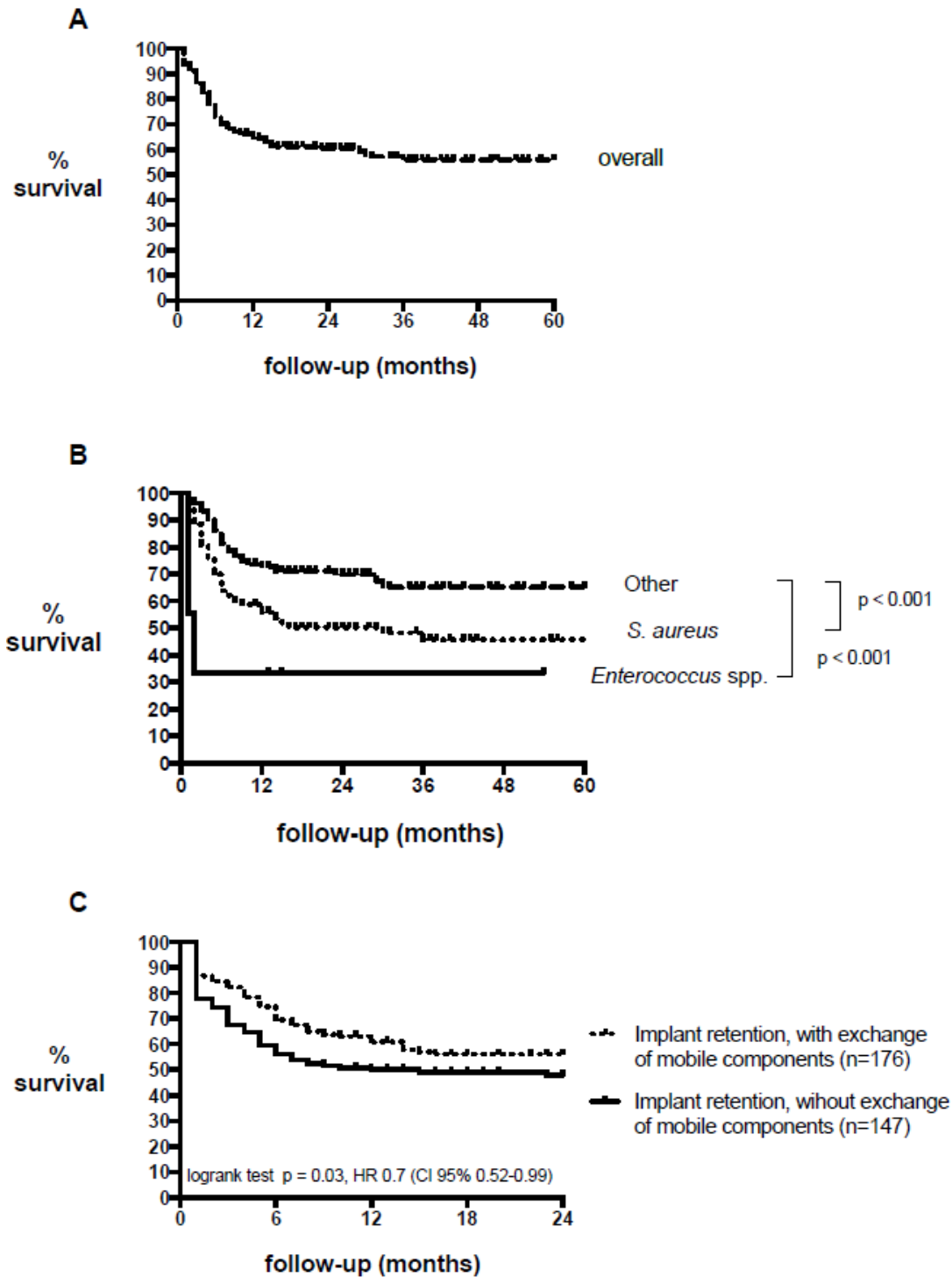
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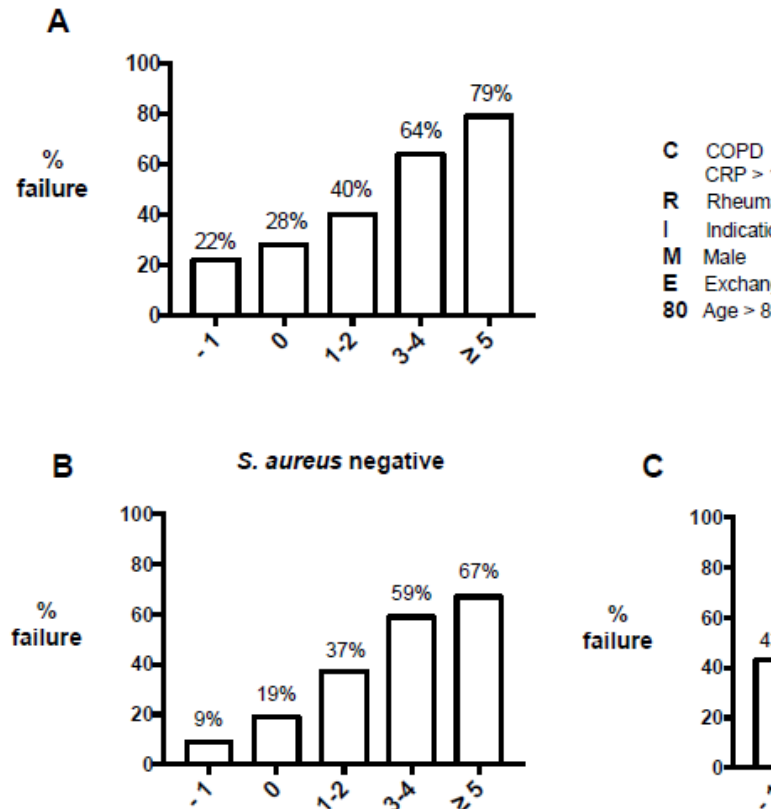
388 **Figure 1.** Kaplan-Meier survival curve late acute PJI treated with DAIR.

389 Survival is defined as treatment success, as described in the material and method section. A. Overall survival  
 390 (n=340). B. Survival categorized in PJI caused by *S. aureus* (n=139, including 10 cases with polymicrobial  
 391 infection), *Enterococcus* spp (n=11 including 4 cases with polymicrobial infection) and other microorganisms  
 392 (n=190). C. Survival according to the exchange of mobile components during debridement. In the survival  
 393 group (n=187), 44 cases (23.5%) had a follow-up of less than 12 months.

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Isolated microorganism(s)	n (%)
<b>Gram positives</b>	<b>247 (72.7)</b>
<i>Staphylococcus aureus</i>	
Methicillin susceptible <i>S. aureus</i>	113 (33.2)
Methicillin resistant <i>S. aureus</i>	16 (4.7)
<i>Staphylococcus lugdunensis</i>	4 (1.2)
Other coagulase negative staphylococci	20 (5.8)
<i>Enterococcus</i> species	7 (2.1)
<i>Streptococcus</i> species	
<i>Streptococcus pyogenes</i>	20 (5.9)
<i>Streptococcus dysgalactiae</i>	15 (4.4)
<i>Streptococcus agalactiae</i>	18 (5.3)
<i>Streptococcus pneumoniae</i>	5 (1.5)



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**Figure 2.** Failure rate according to CRIME80 risk score.

The risk score was developed according to the results of the multivariate bivariate regression analysis, including

preoperative variables that were independently associated with failure, and exchange of mobile components as a

predictor for treatment success as depicted in Table 1. A. Overall failure (n=340). B. Failure rate in *S. aureus*

negatives cases (n=201). C. Failure rate in *S. aureus* positive cases (n=139). COPD: Chronic Obstructive

Pulmonary Disease, CRP: C-Reactive Protein.

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**Table 1.** Isolated microorganisms.

\*Other: *Salmonella* spp (3), *Morganella morganii* (3), *Serratia marcescens* (2), *Acinetobacter baumannii* (1),

*H. influenza* (1), *Helicobacter cinaedi* (1), *Campylobacter fetus* (1).

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	Non-failures	Failures	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<i>Streptococcus anginosus</i>	4 (1.2)	4 (1.2)				
Group viridans streptococci, not specified	11 (3.2)	11 (3.2)				
Group G streptococci, not specified	7 (2.1)	7 (2.1)				
Other <i>Streptococcus</i> species	7 (2.1)	7 (2.1)				
<b>Gram negatives</b>	<b>40 (11.8)</b>	<b>40 (11.8)</b>				
<i>Escherichia coli</i>	14 (4.1)	14 (4.1)				
<i>Klebsiella pneumoniae</i>	5 (1.5)	5 (1.5)				
<i>Enterobacter cloacae</i>	4 (1.2)	4 (1.2)				
<i>Pseudomonas aeruginosa</i>	4 (1.2)	4 (1.2)				
<b>Baseline characteristics</b>	<b>1 (0.3)</b>	<b>1 (0.3)</b>				
Gender, male	47.6% (89/187)	56.2% (86/153)	1.41 (0.92 – 2.17)	0.11*	2.02 (1.05 – 3.89)	<b>0.04</b>
Age > 80 years	17.6% (33/187)	26.1% (40/153)	1.65 (0.98 – 2.78)	0.06*		
<b>Anaerobes</b>	<b>2 (0.6)</b>	<b>2 (0.6)</b>				
BMI > 30	51.2% (66/129)	45.8% (44/96)	0.81 (0.47 – 1.37)	0.43	2.60 (1.15 – 5.91)	<b>0.02</b>
<b>Candida species</b>	<b>1 (0.3)</b>	<b>1 (0.3)</b>				
ASA classification ≥ III	46.9% (76/162)	50.8% (64/126)	1.12 (0.73 – 1.86)	0.52		
<b>Morbidity</b>	<b>25 (7.4)</b>	<b>25 (7.4)</b>				
Hypertension	59.7% (111/186)	59.5% (91/153)	0.99 (0.64 – 1.53)	0.97		
Ischemic heart disease	10.2% (19/187)	14.4% (22/153)	1.48 (0.77 – 2.86)	0.24		
Including <i>Enterococcus</i> species	8.6% (16/187)	9.9% (15/152)	1.12 (0.56 – 2.45)	0.68		
Heart failure	23.0% (43/187)	27.5% (42/153)	1.19 (0.73 – 1.92)	0.49		
Diabetes Mellitus	23.0% (43/187)	27.5% (42/153)	1.19 (0.73 – 1.92)	0.49		
Including coagulase negative staphylococci	8.6% (16/187)	12.4% (19/153)	1.63 (0.79 – 3.32)	0.18*	2.9 (0.99 – 8.68)	<b>0.05</b>
Chronic obstructive pulmonary disease	8.6% (16/187)	6.5% (10/153)	0.75 (0.33 – 1.69)	0.49		
Liver cirrhosis	2.7% (5/187)	3.9% (6/153)	1.49 (0.44 – 4.97)	0.52		
Including <i>Candida</i> species	7.5% (14/187)	9.8% (15/153)	0.65 (0.06 – 7.22)	0.04*	1.76 (0.59 – 5.35)	0.31
Active malignancy	7.5% (14/187)	9.8% (15/153)	0.65 (0.06 – 7.22)	0.04*	1.76 (0.59 – 5.35)	0.31
<b>Culture negative</b>	<b>25 (7.4)</b>	<b>25 (7.4)</b>				
Rheumatoid arthritis	3.7% (7/187)	13.1% (20/153)	3.87 (1.59 – 9.41)	0.001*	5.13 (1.08 – 24.34)	<b>0.04</b>
<b>Medication</b>						
Oral anticoagulant	16.2% (30/185)	20.5% (31/151)	1.34 (0.77 – 2.33)	0.31		
Immune-suppressive drugs	8.0% (15/187)	15.7% (24/153)	2.13 (1.07 – 4.23)	0.03*	0.53 (0.17 – 1.63)	0.27
<b>Characteristics infected implant</b>						
Knee	74.9% (140/187)	69.9% (107/153)	0.78 (0.48 – 1.26)	0.31		
Indication prosthesis: fracture	2.8% (5/177)	8.8% (12/136)	3.32 (1.14 – 9.69)	0.02*	5.39 (1.42 – 20.46)	<b>0.01</b>
Revision prosthesis	23.8% (44/185)	34.0% (52/153)	1.65 (1.03 – 2.66)	0.04*	1.21 (0.60 – 2.45)	0.60
Tumor prosthesis	4.4% (8/181)	4.1% (6/145)	0.93 (0.32 – 2.75)	0.90		
Cemented stem	75.9% (107/141)	74.5% (79/106)	0.93 (0.52 – 1.67)	0.81		
Age of the implant > 2 years	59.4% (111/187)	68.6% (105/153)	1.49 (0.96 – 2.35)	0.08*	0.96 (0.49 – 1.89)	0.90
<b>Clinical presentation</b>						
Duration of symptoms > 10 days	17.1% (32/187)	25.5% (39/153)	1.66 (0.98 – 2.80)	0.06*	1.21 (0.54 – 2.74)	0.64
Temperature > 38.5°C	18.0% (32/178)	25.2% (38/151)	1.53 (0.90 – 2.61)	0.11*	1.84 (0.84 – 4.03)	0.13
Physical signs of inflammation	84.2% (149/177)	78.2% (115/147)	0.68 (0.38 – 1.19)	0.17*	1.81 (0.74 – 4.45)	0.20
CRP > 150 mg/L	57.7% (101/175)	63.7% (93/146)	1.29 (0.82 – 2.02)	0.06*	2.00 (1.04 – 3.86)	<b>0.04</b>
Leucocytes > 15 cells/ μL	38.5% (67/174)	46.2% (66/143)	0.93 (0.49 – 1.74)	0.39		
Bacteremia <sup>1</sup>	25.8% (48/186)	39.9% (61/153)	1.91 (1.20 – 3.02)	0.005*	0.96 (0.45 – 2.05)	0.91
Endocarditis	2.7% (5/187)	5.2% (8/153)	2.00 (0.64 – 6.27)	0.22		
<b>Causative micro-organism</b>						
<i>Staphylococcus aureus</i>	34.8% (65/187)	49.7% (76/153)	1.85 (1.19 – 2.86)	0.005*	3.52 (1.78 – 6.96)	<b>&lt; 0.001</b>
Methicillin resistant	4.3% (8/187)	7.2% (11/153)	1.73 (0.68 – 4.42)	0.25		
<i>Enterococcus</i> species	1.6% (3/187)	5.2% (8/153)	3.38 (0.88 – 12.98)	0.06*	3.71 (0.64 – 21.59)	0.14
<b>Surgical techniques DAIR</b>						
Exchange of mobile components	61.5% (112/182)	45.5% (64/141)	0.52 (0.33 – 0.81)	0.004*	0.35 (0.18 – 0.67)	<b>0.002</b>
> 1 DAIR	8.0% (15/187)	14.4% (22/153)	1.93 (0.96 – 3.86)	0.06*	2.30 (0.88 – 6.02)	0.09
Use of local antibiotics	7.8% (13/167)	12.6% (18/143)	1.71 (0.81 – 3.62)	0.16*	3.78 (1.39 – 10.22)	<b>0.009</b>

**Table 2.** Risk factors for failure.

\*Variables included in the multivariate binary logistic regression analysis. <sup>1</sup>Patients in whom no bloodcultures were obtained were considered as bloodculture negative

414 cases. BMI: Body Mass Index, ASA: American Society of Anesthesiologist, COPD: Chronic Obstructive  
 415 Pulmonary Disease, CRP: C-Reactive Protein, DAIR: Debridement, Antibiotics and Implant Retention.

416 **Table 3.** Characteristics blood culture positive and bloodculture negative cases (n=259). Cases in whom  
 417 bloodcultures were not obtained were excluded from the analysis (n=81).  
 418

	Blood culture positive (n=109)	Blood culture negative (n=150)	p-value				
<b>Characteristics infected implant</b>							
Knee	58.7% (64/109)	78.0% (117/150)	0.001				
Revision prosthesis	24.1% (26/108)	30.7% (46/150)	0.20				
Cemented stem	73.2% (52/71)	82.7% (81/98)	0.24				
Age of the implant > 2 years	78.0% (85/109)	60.7% (91/150)	0.003				
<b>Clinical presentation</b>							
Duration of symptoms > 10 days	22.9% (25/109)	20.7% (31/150)	0.23				
Temperature > 38.5°C	33.9% (37/109)	19.2% (28/146)	0.001				
Physical signs of inflammation	67.0% (71/106)	87.5% (126/144)	<0.001				
CRP > 150 mg/L	67.3% (68/101)	60.8% (87/143)	0.25				
Endocarditis	10.1% (11/109)	1.3% (2/150)	0.01				
<b>Causative micro-organism</b>							
<i>Staphylococcus aureus</i>	63.3% (69/109)	30.0% (45/150)	<0.001				
<i>Streptococcus</i> species	24.3% (25/103)	33.3% (50/150)	0.14				
<b>Outcome</b>	<b>Non-failures</b>	<b>Early Failures</b>	<b>p-value</b>	<b>Adjusted OR (95% CI)</b>	<b>p-value</b>	<b>Non-failures</b>	<b>Late F</b>
Overall failure	56.0% (61/109)	41.3% (62/150)	0.02	0.85			
<b>Baseline characteristics</b>							
Gender, male	42.8% (47/109)	56.8% (85/150)	0.27			47.6% (89/187)	55.6%
Age > 80 years	20.8% (54/259)	23.5% (19/81)	0.62			17.6% (33/187)	29.2%
BMI > 30	50.9% (86/169)	42.9% (24/56)	0.30			51.2% (66/129)	50.0%
ASA classification ≥ III	44.5% (97/218)	61.4% (43/70)	0.01*	1.74 (0.84 – 3.60)	0.14	46.9% (76/162)	37.5%
<b>Medical history</b>							
Hypertension	58.5% (151/258)	63.0% (51/81)	0.48			59.7% (111/186)	55.6%
Ischemic heart disease	12.4% (32/259)	11.1% (9/81)	0.76			10.2% (19/187)	18.1%
Heart failure	8.1% (21/259)	12.5% (10/80)	0.23			8.6% (16/187)	6.9%
Diabetes Mellitus	24.3% (63/259)	27.2% (22/81)	0.76			23.0% (43/187)	27.8%
COPD	8.5% (22/259)	14.8% (12/81)	0.10*	4.26 (1.62 – 11.17)	0.003	8.0% (15/187)	9.7%
Chronic renal insufficiency	6.6% (17/259)	11.1% (9/81)	0.18*	1.14 (0.35 – 3.76)	0.83	8.6% (16/187)	1.4%
Liver cirrhosis	2.3% (6/259)	6.2% (5/81)	0.09*	0.98 (0.11 – 8.64)	0.98	2.7% (5/187)	1.4%
Active malignancy	7.3% (19/259)	12.3% (10/81)	0.16*	2.58 (0.79 – 8.37)	0.12	7.5% (14/187)	6.9%
Rheumatoid arthritis	5.0% (13/259)	17.3% (14/81)	<0.001*	4.20 (1.11 – 15.85)	0.03	3.7% (7/187)	8.3%
<b>Medication</b>							
Oral anticoagulant	16.8% (43/256)	22.5% (18/80)	0.25			16.2% (30/185)	18.3%
Immune-suppressive drugs	9.3% (24/259)	18.5% (15/81)	0.02*	0.60 (0.16 – 2.19)	0.44	8.0% (15/187)	12.5%
<b>Characteristics infected implant</b>							
Knee	74.5% (193/259)	66.7% (54/81)	0.17			74.9% (140/187)	73.6%
Indication prosthesis: fracture	3.8% (9/239)	10.8% (8/74)	0.02*	0.86 (0.38 – 1.95)	0.72	2.8% (5/177)	6.5%
Revision prosthesis	27.2% (70/257)	32.1% (26/81)	0.40			23.8% (44/185)	36.1%
Tumor prosthesis	4.4% (11/249)	3.9% (3/77)	0.84			4.4% (8/181)	4.4%
Cemented stem	76.5% (143/187)	71.7% (43/60)	0.45			75.9% (107/141)	78.3%
Age of the implant > 2 years	62.2% (161/259)	67.9% (55/81)	0.35			59.4% (111/187)	69.4%
<b>Clinical presentation</b>							
Duration of symptoms > 10 days	20.8% (54/259)	21.0% (17/81)	0.98			17.1% (32/187)	30.6%
Temperature > 38.5°C	20.2% (50/248)	24.7% (20/81)	0.39			18.0% (32/178)	25.7%
Physical signs of inflammation	82.9% (204/246)	76.9% (60/78)	0.24			84.2% (149/177)	79.7%
CRP > 150 mg/L	58.2% (142/244)	67.5% (52/77)	0.14*	2.14 (1.01 – 4.54)	0.05	57.7% (101/175)	59.4%
Leucocytes > 15 cells/ μL	13.3% (32/241)	18.4% (14/76)	0.27			14.9% (26/174)	9.0%
Bacteremia <sup>1</sup>	27.9% (72/258)	45.7% (37/81)	0.003*	1.11 (0.54 – 2.31)	0.77	25.8% (48/186)	33.3%
Endocarditis	3.1% (8/259)	6.2% (5/81)	0.21			2.7% (5/187)	4.2%
<b>Causative microorganism</b>							
<i>Staphylococcus aureus</i>	40.2% (104/259)	45.7% (37/81)	0.38			34.8% (65/187)	54.2%
Methicillin resistant	5.4% (14/259)	6.2% (5/81)	0.79			4.3% (8/187)	8.3%
<i>Enterococcus</i> species	1.5% (4/259)	8.6% (7/81)	0.002*	16.0 (3.48 – 73.76)	<0.001	1.6% (3/187)	1.4%
<b>Surgical techniques DAIR</b>							
Exchange of mobile components	58.7% (145/247)	40.8% (31/76)	0.006*	0.43 (0.21 – 0.88)	0.02	61.5% (112/182)	50.8%
> 1 DAIR	9.7% (25/259)	14.8% (12/81)	0.19*	1.65 (0.59 – 4.58)	0.34	8.0% (15/187)	13.9%
Use of local antibiotics	9.0% (21/234)	13.2% (10/76)	0.29			7.8% (13/167)	11.9%

**Supplementary Table 1.**  
Risk factors for early and late failure.

Results of multivariate binary logistic regression analysis for early failure (n=81) and late failure (n=72) in a total of 340

428 cases. \*p-values <0.2 were included in the multivariate regression analysis.

429

430 **Supplementary Table 2.** Oral antibiotic regimen.

	n (%)
<b><i>S. aureus</i> (n=136)</b>	
Rifampin-based regimen	113 (83.1%)
- fluoroquinolone	88 (64.7%)
- cotrimoxazole	9 (6.6%)
- clindamycin	6 (4.4%)
- linezolid	9 (6.6%)
No rifampin-based regimen	23 (16.9%)
- fluoroquinolone	6 (4.4%)
- cotrimoxazole	2 (1.5%)
- clindamycin	5 (3.7%)
- linezolid	1 (0.8%)
<b>Gram negatives (n=48)</b>	
Fluoroquinolone	35 (72.9%)
Cotrimoxazole	2 (4.2%)
Amoxicillin/clavulanate	2 (4.2%)
<b><i>Streptococcus</i> species (n=95)</b>	
Amoxicillin	55 (57.9%)
Clindamycin	12 (12.6%)
Linezolid	4 (4.2%)
Rifampin-based regimen	22 (23.1%)

ACCEPTED MANUSCRIPT