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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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SUMMARY

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

Introduction

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

Material and methods

Study design and inclusion criteria

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

Clinical outcome

Failure was defined as: (i) the need for prosthesis removal (one or two-stage exchange, amputation, Girdlestone for hips or arthrodesis for knees), (ii) the need for suppressive antibiotic therapy because of persistent clinical or biochemical signs of infection, (iii) a relapse of infection with the same microorganism during follow-up, (iv) a reinfection with a different microorganism than the initial infection during follow-up, or (v) death due to the infection. PJI related death was defined as death that occurred during (antibiotic) treatment with no other alternative explanation than an uncontrolled infection. The need for a second debridement during antibiotic therapy was not considered as failure. Patients in whom antibiotic suppressive therapy was prescribed for other reasons than persistent signs of infection (e.g. because this was routine practice of the participating hospital and/or because the patient had severe comorbidity and was therefore, not eligible for future surgeries) were excluded. Failure was subsequently categorized into *early failure*: persisting or reappearance of symptoms of infection during antibiotic treatment, and *late failure*: reappearance of symptoms of infection after finishing antibiotic treatment. *Complete remission* was considered in patients with a retained and functional implant after 2 years of follow-up. A functional implant was defined as the ability to walk without pain.

Statistical analysis

A Chi-square test (or a Fisher exact-test when appropriate) was used to analyze the difference between groups for categorical variables, and a student *t*-test (or Mann Witney *U* test when data was not normally distributed) for continuous variables. A Kaplan Meier survival curve with a cox-regression analysis was used to evaluate failure rate in time. Possible risk factors for failure were selected and analyzed using univariate analysis by Pearson's correlation. Variables with a significance level of < 0.2 were analyzed in a binary multivariate logistic regression model. A separate CART (classification and regression tree) analysis was performed to assess which variable was the most potent in predicting treatment outcome. All variables were tested for multicollinearity and additionally analyzed in a cox regression analysis. Preoperative variables with the highest odds ratio (OR) in the multivariate logistic regression model were included in a risk score, in which the beta coefficient of each variable served as an indicator for the height of the score. A subanalysis was performed for early and late failure. In the analysis of early failure, late failures were considered as non-failures and included as such. All analyses were two-tailed and *p*-values < 0.05 were considered as statistically significant. Data were presented as mean ± Standard Deviation (SD) when data was normally distributed or median ± Inter Quartile Range (IQR) when data was not normally distributed. Statistical analysis was performed using SPSS, version 23.0 (SPSS Inc., Chicago, IL).

Results

Characteristics of late acute PJI

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

Failure rate and clinical outcome

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

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

Table 1
Isolated microorganisms.

Isolated microorganism(s)	*n* (%)
Gram positives	**247 (72.7)**
Staphylococcus aureus	113 (33.2)
Methicillin susceptible *S. aureus*	16 (4.7)
Methicillin resistant *S. aureus*	4 (1.2)
Staphyloccocus lugdunensis	20 (5.8)
Other coagulase negative staphylococci	7 (2.1)
Enterococcus species	20 (5.9)
Streptococcus species	15 (4.4)
Streptococcus pyogenes	18 (5.3)
Streptococcus dysgalactiae	5 (1.5)
Streptococcus agalactiae	4 (1.2)
Streptococcus pneumoniae	11 (3.2)
Streptococcus anginosus	7 (2.1)
Group viridans streptococci, not specified	7 (2.1)
Group G streptococci, not specified	
Other *Streptococcus* species	
Gram negatives	**40 (11.8)**
Escherichia coli	14 (4.1)
Klebsiella pneumoniae	5 (1.5)
Enterobacter cloacae	4 (1.2)
Pseudomonas aeruginosa	4 (1.2)
Proteus mirabilis	1 (0.3)
Other[a]	12 (3.5)
Anaerobes	**2 (0.6)**
***Candida* species**	**1 (0.3)**
Polymicrobial	**25 (7.4)**
Including *S. aureus*	10 (2.9)
Including *Enterococcus* species	4 (1.2)
Including *Streptococcus* species	10 (2.9)
Including coagulase negative staphylococci	6 (1.8)
Including Gram negatives	11 (3.2)
Including *Candida* species	3 (0.9)
Culture negative	**25 (7.4)**

[a] Other: *Salmonella* spp (3), *Morganella morganii* (3), *Serratia marcescens* (2), *Acinetobacter baumannii* (1), *H. influenza* (1), *Helicobacter cinaedi* (1), *Campylobacter fetus* (1).

Antibiotic treatment

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

To exclude empirical antibiotic treatment, the type of antibiotic was only analyzed if prescribed for more than five days (Supplementary Table 2). For staphylococcal infections in whom data on the oral regimen was available, the failure rate was 49.3% (66/134) when rifampin was added versus 67.7% (21/31) when rifampin was not added to the antibiotic regimen (*p* 0.06). In addition, failure

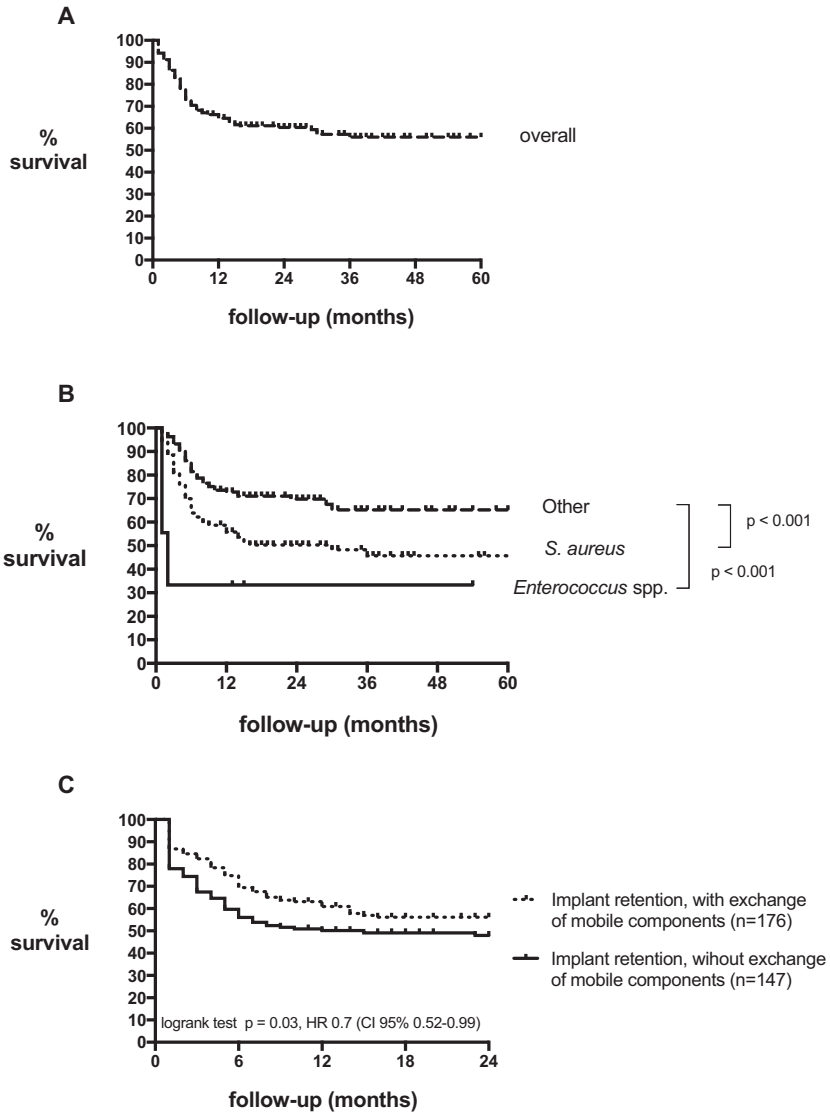

Fig. 1. Kaplan–Meier survival curve late acute PJI treated with DAIR.
Survival is defined as treatment success, as described in the material and method section. *A.* Overall survival ($n = 340$). *B.* Survival categorized in PJI caused by *S. aureus* ($n = 139$, including 10 cases with polymicrobial infection), *Enterococcus* spp ($n = 11$ including 4 cases with polymicrobial infection) and other microorganisms ($n = 190$). *C.* Survival according to the exchange of mobile components during debridement. In the survival group ($n = 187$), 44 cases (23.5%) had a follow-up of less than 12 months.

rate was significantly lower when rifampin was combined with a fluoroquinolone compared to other regimens (failure rate 45.5% (46/101) versus 64.1% (41/64), respectively, p 0.02). In the rifampin treated cases, there was no significant difference in failure rate in fluoroquinolone-based regimens compared to other antibiotics (46.0% (46/100) vs 58.8% (20/34), respectively, p 0.20). For streptococci, failure rate was 22.7% (5/22) when rifampin was added versus 42.5% (31/73) when rifampin was not added to the antibiotic regimen (p 0.13). With a limited number of gram-negative PJIs analyzed, the use of fluoroquinolones was not associated with treatment success in our analysis (failure rate of 34.3% (12/35) when using a fluoroquinolone versus 38.5 % (5/13) when using another antibiotic regimen, p 0.79).

Risk factors for failure

Table 2 shows the results of the univariate and multivariate binary logistic regression analysis in identifying risk factors for failure. From the total of 340 cases, all variables were complete without missing data in 232 cases and were included in the final model. Patients in whom no blood cultures were obtained were considered as blood culture negative. The results of the multivariate analysis for other variables did not change when the blood culture variable was omitted from the analysis. The Hosmer and Lemeshow test had a p-value of 0.89, indicating that the model was adequate, with a predicting capacity of 71.1% according to the classification table.

Male gender, age above 80 years, rheumatoid arthritis (RA), fracture as indication for the prosthesis, C-reactive protein (CRP) above 150 mg/L, infection caused by *S. aureus* and the use of local antibiotics were all significant independent variables for failure in the multivariate analysis. Local antibiotic therapy mainly consisted of gentamicin beads or gentamicin sponges. There were no significant clinical differences between patients who were treated with local antibiotics compared to patients in whom it was withheld (data not shown), with the exception of the American Society of Anesthesiologist (ASA) classification score, which was higher in the local antibiotic group (ASA score ≥ 3 in 66.7% (20/30) versus 44.3% (102/230) respectively, p 0.02). With an OR of 2.9, COPD was also associated with a higher failure rate, although it did not

Table 2
Risk factors for failure.

	Non-failures	Failures	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Baseline characteristics						
Gender, male	47.6% (89/187)	56.2% (86/153)	1.41 (0.92 – 2.17)	0.11[a]	2.02 (1.05 – 3.89)	**0.04**
Age > 80 years	17.6% (33/187)	26.1% (40/153)	1.65 (0.98 – 2.78)	0.06[a]	2.60 (1.15 – 5.91)	**0.02**
BMI > 30	51.2% (66/129)	45.8% (44/96)	0.81 (0.47 – 1.37)	0.43		
ASA classification ≥ III	46.9% (76/162)	50.8% (64/126)	1.12 (0.73 – 1.86)	0.52		
Medical history						
Hypertension	59.7% (111/186)	59.5% (91/153)	0.99 (0.64 – 1.53)	0.97	2.9 (0.99 – 8.68)	**0.05**
Ischemic heart disease	10.2% (19/187)	14.4% (22/153)	1.48 (0.77 – 2.86)	0.24	1.76 (0.59 – 5.35)	0.31
Heart failure	8.6% (16/187)	9.9% (15/152)	1.12 (0.56 – 2.45)	0.68	5.13 (1.08 – 24.34)	**0.04**
Diabetes Mellitus	23.0% (43/187)	27.5% (42/153)	1.19 (0.73 – 1.92)	0.49		
COPD	8.0% (15/187)	12.4% (19/153)	1.63 (0.79 – 3.32)	0.18[a]		
Chronic renal insufficiency	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		
Active malignancy	7.5% (14/187)	9.8% (15/153)	0.65 (0.06 – 7.22)	0.04[a]		
Rheumatoid arthritis	3.7% (7/187)	13.1% (20/153)	3.87 (1.59 – 9.41)	0.001[a]		
Medication						
Oral anticoagulant	16.2% (30/185)	20.5% (31/151)	1.34 (0.77 – 2.33)	0.31	0.53 (0.17 – 1.63)	0.27
Immune-suppressive drugs	8.0% (15/187)	15.7% (24/153)	2.13 (1.07 – 4.23)	0.03[a]		
Characteristics infected implant						
Knee	74.9% (140/187)	69.9% (107/153)	0.78 (0.48 – 1.26)	0.31	5.39 (1.42 – 20.46)	**0.01**
Indication prosthesis: fracture	2.8% (5/177)	8.8% (12/136)	3.32 (1.14 – 9.69)	0.02[a]	1.21 (0.60 – 2.45)	0.60
Revision prosthesis	23.8% (44/185)	34.0% (52/153)	1.65 (1.03 – 2.66)	0.04[a]	0.96 (0.49 – 1.89)	0.90
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[a]		
Clinical presentation						
Duration of symptoms > 10 days	17.1% (32/187)	25.5% (39/153)	1.66 (0.98 – 2.80)	0.06[a]	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[a]	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[a]	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[a]	2.00 (1.04 – 3.86)	**0.04**
Leucocytes > 15 cells/ µL	38.5% (67/174)	46.2% (66/143)	0.93 (0.49 – 1.74)	0.39	0.96 (0.45 – 2.05)	0.91
Bacteremia[b]	25.8% (48/186)	39.9% (61/153)	1.91 (1.20 – 3.02)	0.005[a]		
Endocarditis	2.7% (5/187)	5.2% (8/153)	2.00 (0.64 – 6.27)	0.22		
Causative micro-organism						
Staphylococcus aureus	34.8% (65/187)	49.7% (76/153)	1.85 (1.19 – 2.86)	0.005[a]	3.52 (1.78 – 6.96)	**< 0.001**
Methicillin resistant	4.3% (8/187)	7.2% (11/153)	1.73 (0.68 – 4.42)	0.25	3.71 (0.64 – 21.59)	0.14
Enterococcus species	1.6% (3/187)	5.2% (8/153)	3.38 (0.88 – 12.98)	0.06[a]		
Surgical techniques DAIR						
Exchange of mobile components	61.5% (112/182)	45.5% (64/141)	0.52 (0.33 – 0.81)	0.004[a]	0.35 (0.18 – 0.67)	**0.002**
> 1 DAIR	8.0% (15/187)	14.4% (22/153)	1.93 (0.96 – 3.86)	0.06[a]	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[a]	3.78 (1.39 – 10.22)	**0.009**

[a] Variables included in the multivariate binary logistic regression analysis.
[b] Patients in whom no bloodcultures were obtained were considered as bloodculture negative cases. BMI: Body Mass Index, ASA: American Society of Anesthesiologist, COPD: Chronic Obstructive Pulmonary Disease, CRP: C-Reactive Protein, DAIR: Debridement, Antibiotics and Implant Retention.

reached statistical significance. Cox regression analysis showed the same predictors for failure. Analysis on multicollinearity revealed that COPD was accompanied by a higher prevalence of ischemic heart disease and heart failure. Exchanging the mobile components during DAIR was the only variable that was independently associated with treatment success. In addition, according to the CART analysis, exchanging the mobile components was the most potent variable in predicting treatment outcome.

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

Based on the results of the multivariate binary logistic regression, a risk score was developed, by using the preoperative variables that were associated with failure. In addition, as the possibility to exchange the mobile components can be known preoperatively as well, the protective effect of exchanging the mobile components during DAIR was also included (Fig. 2A). Because failure was dominated by *S. aureus*, a separate analysis was performed for the presence or absence of *S. aureus* (Fig. 2B and C). Our results indicate that the preoperative model has the strongest predictive value for failure in PJIs caused by other microorganisms than *S. aureus*. In *S. aureus* PJI in whom mobile components were exchanged during DAIR, the rate of failure decreased from 47.1% to 36.6% when patients were treated with a fluoroquinolone in combination with rifampin.

Blood culture positive versus blood culture negative cases

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

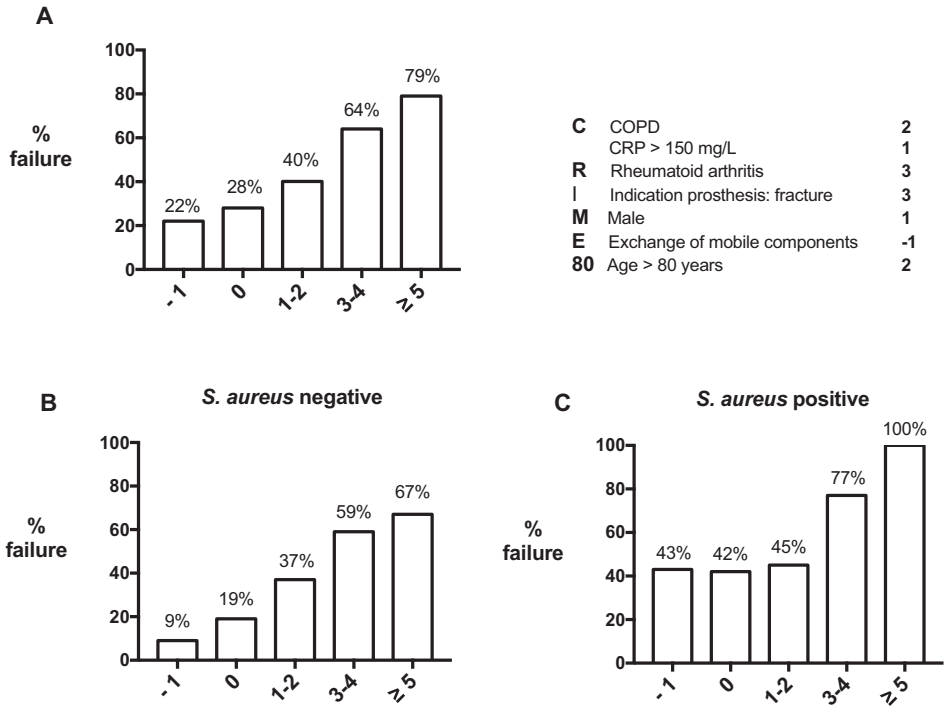

Fig. 2. Failure rate according to CRIME80 risk score.
The risk score was developed according to the results of the multivariate bivariate regression analysis, including preoperative variables that were independently associated with failure, and exchange of mobile components as a predictor for treatment 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.

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

	Blood culture positive ($n = 109$)	Blood culture negative ($n = 150$)	*p*-value
Characteristics infected implant			
Knee	58.7% (64/109)	78.0% (117/150)	**0.001**
Revision prosthesis	24.1% (26/108)	30.7% (46/150)	0.25
Cemented stem	73.2% (52/71)	82.7% (81/98)	0.14
Age of the implant > 2 years	78.0% (85/109)	60.7% (91/150)	**0.003**
Clinical presentation			
Duration of symptoms > 10 days	22.9% (25/109)	20.7% (31/150)	0.66
Temperature > 38.5 °C	33.9% (37/109)	19.2% (28/146)	**0.007**
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)	0.30
Endocarditis	10.1% (11/109)	1.3% (2/150)	**0.001**
Causative micro-organism			
Staphylococcus aureus	63.3% (69/109)	30.0% (45/150)	**<0.001**
Streptococcus species	24.3% (25/103)	33.3% (50/150)	0.14
Outcome			
Overall failure	56.0% (61/109)	41.3% (62/150)	**0.02**
Early failure	34.9% (38/109)	20.7% (31/150)	**0.01**
Late failure	21.1% (23/109)	20.7% (31/150)	0.85

of these 9 cases, with the exception of one, were diagnosed with endocarditis.

Discussion

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

The high failure rate observed in our study may partly be explained by: (i) The presence of an unidentified source of infection in case of bacteremia. Although not statistically significant, an unidentified source of infection was associated with a higher failure rate in our study. Endocarditis may have been underdiagnosed in our study, as a transesophageal echocardiography was not performed in all *S. aureus* bacteremias. Thus, continuous seeding of bacteria to the prosthetic joint with the development of biofilm may be the cause of failure in these cases. Indeed, we demonstrated that a relapse of infection during follow-up was mostly caused by *S. aureus*, which supports this hypothesis. However, it is important to note that the reported incidence of endocarditis in *S. aureus* bacteremia in literature is comparable to our study,[17] and failure rate was still 40% in blood culture negative cases. (ii)

A previously unrecognized chronic PJI. Although we held on to a clear definition of a sudden onset of symptoms in a priorly asymptomatic joint, we cannot completely rule out that chronic PJIs that deteriorated acutely also comprised a small part of the cohort. CoNS were identified in a limited number of patients and these microorganisms are not common pathogens for causing acute infections. Indeed, most of these cases were blood culture negative and were not diagnosed with endocarditis, which makes an acute infection in these cases unlikely. However, the failure rate in CoNS was not higher than in others (40%), and patients with a proven hematogenous infection had a higher failure rate compared to blood culture negative cases (iii) Mobile components were not exchanged in almost half of our studied cohort. As the CART analysis showed that this is the most potent variable for predicting failure, treatment success may be substantially higher when mobile exchange was performed in all cases. The low number of exchange may be due to the fact that the study extends over ten year time period and only in recent years, the importance of this surgical technique became clear. In addition, mobile components are not available in acute settings in some centers. However, even with the exchange of mobile components, overall failure rate was still 36%, and even higher in case of *S. aureus* infections.

At the moment, a DAIR procedure is the recommended surgical approach for all acute PJIs with stable implants and susceptibility to potent anti-biofilm regimens.[14] Our data suggest that a DAIR should be reconsidered in late acute PJIs for certain patient categories. As previously mentioned, especially *S. aureus* PJI has a high risk of failure, especially when mobile components cannot be exchanged and treatment with a rifampin-based regimen is not possible. Failure rate was much lower in a study performed by Tande et al., in which late acute PJI caused by *S. aureus* was treated with revision surgery or if the DAIR was followed by chronic suppressive antibiotic therapy.[8] Therefore, identifying the causative microorganism and its susceptibility pattern preoperatively may be helpful to choose the best surgical approach in an acute setting. To elaborate, studies have shown that Gram staining of synovial fluid has a poor sensitivity in diagnosing PJI, but its value is mostly evaluated in chronic cases, and may be more useful and sensitive in acute infections.[18] Unfortunately, early molecular detection does not show any benefit so far in acute PJIs, but its diagnostic accuracy maybe optimized in upcoming years.[19] For late acute PJIs caused by another microorganism than *S. aureus*, the CRIME80 score could be useful in identifying high-risk patients. According to our analysis, patients who received a prosthetic implant because of a fracture and patients with rheumatoid arthritis are at highest risk to fail. Previous studies have shown that these variables are also strongly correlated with failure in early postsurgical and chronic PJIs.[5,11,20] In addition, our data indicate that patients with male gender, COPD, a CRP above 150 mg/L at presentation and an age above 80 years are also more prone to fail. Accordingly, a DAIR procedure is probably not advisable in late acute PJI with a high a priori chance of failure. In addition, some studies suggest that revision surgery applied as salvage therapy after DAIR failure is associated with poorer outcome.[21–22] Therefore, our results suggest the need for revision surgery as a first surgical approach.

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

In conclusion, late acute PJIs treated with DAIR have a high failure rate in patients with a high CRIME80 score, especially if the infection is caused by *S. aureus* and a rifampin-based regimen cannot be administered. Treatment strategies should be tailored and optimized to improve the outcome. This should be addressed in future studies.

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Conflict of interest

None of the authors declared any conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.07.014.

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