



## Outcome Predictors in Prosthetic Joint Infections – Validation of a risk stratification score for Prosthetic Joint Infections in 120 cases

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Prosthetic joint infections are a major challenge in total joint arthroplasty, especially in times of accumulating drug resistancies. Even though predictive risk classifications are a widely accepted tool to define a suitable treatment protocol a classification is still missing considering the difficulty in treating the causative pathogen antibioticly. In this study, we present and evaluate a new predictive risk stratification for prosthetic joint infections in 120 cases, treated with a two-stage exchange.

Treatment outcomes in 120 patients with proven prosthetic joint infections in hip and knee prostheses were regressed on time of infection, systemic risk factors, local risk factors and the difficulty in treating the causing pathogen. The main outcome variable was “definitely free of infection” after two years as published. Age, gender, and BMI were included as co-variables and analyzed in a logistic regression model. 66 male and 54 female patients, with a mean age at surgery of  $68.3 \text{ years} \pm 12.0$  and a mean BMI of  $26.05 \pm 6.21$  were included in our survey and followed for  $29.0 \pm 11.3$  months. We found a significant association ( $p < 0.001$ ) between our score and the outcome parameters evaluated. Age, gender and BMI did not show a significant association with the outcome.

These results show that our score is an independent and reliable predictor for the cure rate in prosthetic joint infections in hip and knee prostheses treated within a two-stage exchange protocol. Our score illustrates, that there is a statistically significant, sizable decrease in cure rate with an increase in score. In patients with prosthetic joint infections the valida-

tion of a risk score may help to identify patients with local and systemic risk factors or with infectious organisms identified as “difficult to treat” prior to the treatment or the decision about the treatment concept. Thus, appropriate extra care should be considered and provided.

**Keywords :** infection ; revision ; resistance ; score ; risk factors.

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## INTRODUCTION

Prosthetic joint infections (PJI) represent one of the most severe complications after total joint arthroplasty (TJA) (1,2,3). An adequate treatment protocol is essential to achieve optimized results. Patient specific risk factors, the infecting organism and potential resistances against antibiotics have to be considered when deciding upon the treatment strategy. A risk factor classification may help to find and establish an individualized protocol. In a study of 50 patients with PJI after total hip arthroplasty, McPherson *et al* showed that the rate of re-infection of PJI in hips is significantly associated with the type of infection as well as systemic and local risk factors (4). This is consistent with other studies in hip and knee PJI (5-8). However a possible limitation of their approach was that no classification of infectious organisms was included in their protocol. This factor is important because infectious organisms “difficult to treat” represent an exceptional subgroup in the treatment of PJI and are extraordinary challenging to treat (9-14). Additionally no standardized treatment protocol exists based on established risk classifications involving resistant bacteria (15,6-8).

In this study we present a new risk factor stratification when treating PJIs. We wanted to validate the predictive potential of our score to anticipate the outcome of PJIs. This was performed in a survey in 120 patients with proven PJIs in hip and knee prostheses treated with a two-stage exchange. In our protocol we included 1) type of infection, 2) local and 3) systemic risk factors and 4) the grade of difficulty in treating the causative pathogen by antibiotic therapy in a single classification. Potential confounding factors considered were age, gender, and body mass index (BMI). Our hypothesis was that age, gender and BMI are not associated with re-infection outcome but that our risk factor stratification would predict successful clearance of infection.

## METHODS

From November 2006 until November 2009, 120 consecutive patients with confirmed PJI of total hip arthro-

plasties (THA) or total knee arthroplasties (TKA) were included and treated with a two-stage exchange according to a slightly modified treatment algorithm as described by Zimmerli *et al* (16-18). Due to the clinical experience in our department we used Vancomycin and Rifampicin as our initially antibiotic therapy. All patients received two stage exchanges. Patients were treated in a single hospital, 4 different surgeons performed the operations. No patients were excluded because of systemic or local risk factors, previous infections, prior operations, unsuccessful treatment attempts in the past or presenting in a septic condition. Routine clinical data were collected and analyzed retrospectively as anonymized aggregate data, thus no consent was obtained according to the appropriate regulations. None of the authors have a competing interest to disclose in relation with this work.

## Patients

A total of 120 patients, 66 males and 54 females, were included. 70 (58%) patients received revision of a THA, 50 (42%) of a TKA, The mean age at surgery was  $68.3 \pm 12.0$  years. These patients were followed for  $29.0 \pm 11.3$  (range 1-56) months on average. The mean BMI was  $26.05 \pm 6.21$  (range 15-45).

## PJI-Risk Classification and Scoring-System

The risk stratification system presented includes the following categories : The type of PJI was classified as “I” (“acute” PJI (onset of symptoms  $\leq 3$  weeks after primary operation ; = 1 point in score)) and “II” (late chronic PJI (onset of symptoms  $\geq 3$  weeks, = 2 points in score)). Local risk factors were classified as “0” (no local risk factor, = 0 point in score), “1” (1-2 local risk factors, = 1 points in score) and 2 (> 2 local risk factors or open wounds or fistulae, = 2 points in score) as published. Systemic risk factors were classified as “A” (no systemic risk factors, = 0 point in score), “B” (1-2 systemic risk factors, = 1 points in score) and, “C” (> 2 systemic risk factors, = 2 points in score) as published (4). Systemic risk factors included age  $\geq 80$  y, alcoholism, chronic malnutrition, hepatic or pulmonary insufficiency, immunosuppressive drugs, dialysis and others. Local risk factors included an active infection present longer than 3-4 month, multiple incisions, synovial subcutaneous fistula, prior local irradiation, vascular insufficiency and others (4). According to the causative pathogen all treated PJI were divided in two subgroups, “-” (“not difficult to treat” (= 1 point in score)) versus “+” (“difficult to treat” (= 2 points in score)). Infectious organism graded

Table I. — Demographics

	Mean	SD
Sex [m / f] (n total; % male)	66 / 54 (n = 120; 55)	
Hips [n=] (%)	70 (58.3)	
Knees [n=] (%)	50 (41.6)	
Age [years]	68.3	12.0
Weight [kg]	75.1	15.15
Height [m]	1.68	0.09
BMI [kg / m <sup>2</sup> ]	26.05	6.21
Mean follow – up [months]	29.0	11.3

as “difficult to treat” in our survey include 1) fungi, 2) small colony variants, 3) pseudomonas, especially chinolon-resistant pseudomonas, 4) enterococcus species and antibiotic-resistant subspecies of staphylococci, especially vancomycin-resistant enterococci/staphylococci and chinolon-resistant enterococci/methicillin-resistant staphylococci, 5) Rifampicin-resistant staphylococci, and 6) extended-spectrum beta-lactamases. The infectious organisms classified as “difficult to treat” are summarized in table II (19). In our newly designed score each category was summed up linearly as one step increase in an ordinal scale (range : 2-8).

### Two-stage exchange

The two-stage exchange includes the removal of the infected prosthesis followed by an extensive surgical debridement, an antibiotic-loaded cement-spacer was used if indicated as published (16,20). Antibiotic therapy was

administered for at least 14 days intravenously, followed by an oral therapy for 4 weeks. Then a break of two weeks without antibiotics was taken before aspiration of the joint under sterile conditions for microbiologic examination. In cases of no pathogen detection after long term incubation and non - elevated infection parameters (CRP < 10 mg/dL ; WBC < 10.2 G/l) a new prosthesis was reimplanted. In cases of a pathogen detection one or multiple operative debridements were performed. Antibiotic therapy was chosen according to the causative pathogen detected prior to the operation and administered postoperatively for 6 weeks (14 d intravenous., 4 weeks oral). In cases of pathogen detection from samples acquired during reimplantation, debridement and retention of the prosthesis was performed, followed by a 3-6-months antibiotic therapy according to the susceptibility pattern of both implantation and re-implantation pathogens.

### Antibiotic therapy

Decision on a suitable antibiotic therapy was made in an interdisciplinary discussion at the beginning of the therapy according to both, the detected pathogen and its susceptibility pattern as well as according to published guidelines (16). Weekly interdisciplinary case discussions and rounds (orthopaedic surgeon and clinical microbiologist) guaranteed optimized treatment (empirical and specific) for our patients. Surveillance of kidney and liver function as well as drug monitoring (i.e. vancomycin or gentamicin levels) were standardized parts of the protocol. Effectiveness of antibiotic therapy was monitored constantly by clinical and laboratory parameters (CRP, WBC).

Table II. — Definition of infectious organisms classified as “difficult to treat” (10)

pathogen	
Fungi	Extensive biofilm formation, no therapy against adhering fungi available
SCV	Small colony variants, phenotypic resistancies against multiple antibiotics may occur
Pseudomonas	Fast development of resistancies if treated with a monotherapy, if chinolon-resistant, no oral antibiotics available, extensive biofilm formation
Enterococcus spp.	Extensive biofilm formation
MRS	Methicillin-resistant Staphylococci
VRE/VRS	Vancomycin-resistant Enterococci / Staphylococci
CRE	Chinolon-resistant Enterococci
CRP	Chinolon-resistant Pseudomonas
RRS	Rifampicin-resistant Staphylococci
ESBL	Extended-Spectrum Beta-Lactamase

Table III. — Results

	Patients n [%]		Laboratory infect resolution n [% of knees/hips]		Clinical infect resolution n [% knees/hips]		Definitely free of infection (min. follow up 24 mo) n [% knees/hips]	
	Knees	Hips	Knees	Hips	Knees	Hips	Knees	Hips
Score 2	4 [50]	4 [50]	4 [100]	3 [75]	4 [100]	3 [75]	4 [100]	3 [75]
Score 3	8 [34.8]	15 [65.2]	8 [100]	14 [93.3]	8 [100]	14 [93.3]	8 [100]	13 [93.3]
Score 4	8 [42.1]	11 [57.9]	8 [100]	10 [90.9]	8 [100]	9 [81.8]	7 [87.5]	9 [81.8]
Score 5	8 [53.3]	7 [46.7]	5 [62.5]	7 [100]	6 [75]	5 [71.4]	3 [37.5]	5 [71.4]
Score 6	10 [62.5]	6 [37.5]	9 [90]	6 [100]	9 [90]	6 [100]	7 [70]	5 [83.3]
Score 7	8 [50]	8 [50]	7 [87.5]	6 [95]	5 [62.5]	5 [62.5]	4 [50]	4 [50]
Score 8	5 [21.7]	18 [78.3]	3 [60]	9 [50]	3 [60]	8 [44.4]	2 [40]	7 [38.8]

### Outcome Evaluation

The success rate of our treatment was classified as „definitely free of infection“ with a minimum follow up of two years as published by the criteria by Laffer *et al* (21) (no signs of clinical infection and CRP < 10 mg/dl). Secondary and third endpoints studied were “clinical infect resolution“ (no signs of clinical infection) and “laboratory infect resolution“ (CRP < 10 mg/dl) only.

### Statistical Modeling

The main independent variable was our new designed risk scoring system (range 2-8). As potential confounders we include age, gender and BMI as covariates. All data were double-checked for errors. All variables were tested for normal distribution using P-P normal probability plots and the Shapiro-Wilk test and transformed as needed. All results are presented on the original scale.

To test the predictive power of our PJI score, multivariate generalized logistic regression models are used to calculate the odds ratio of “definitely free of infection”, “clinical infect resolution” and “laboratory infect resolution”. All odds ratios are given with 95% confidence intervals (95% CI). Age, gender and BMI were included as variables in a backward stepwise model, i.e. a full model including all variables was set up and the variable with the lowest strength of association is removed. Subsequently, the model is run again, and again the variable with the lowest strength of association is removed. This process is reiterated until only variables with significant associations with the main endpoints remain. An alpha of 5% was considered significant. All calculations were

done using Stata 10 (StataCorp LP, College Station, Tx, USA).

## RESULTS

120 (66 male (55%), 54 female (45%)) patients were included in our survey (Table I). The average value reached in our score was 5.23. “Definitely free of infection” was the first endpoint studied. A univariate regression model including this endpoint and our score showed a significant association ( $p < 0.001$ ) with an odds ratio of 0.50 (95%CI 0.37 to 0.67). In the full model, there were no significant associations with age ( $p = 0.751$ ), gender ( $p = 0.133$ ) or BMI ( $p = 0.948$ ). The only significant association was between BMI and score ( $p = 0.010$ ). “Laboratory infect resolution” was the second endpoint studied. The univariate regression model including this endpoint and score only showed a significant association ( $p < 0.001$ ) with an odds ratio of 0.58 (95%CI 0.44 to 0.78). In the full model, there were no significant associations with age ( $p = 0.803$ ), gender ( $p = 0.836$ ) or BMI ( $p = 0.469$ ). “Clinical infect resolution” was the third endpoint studied. The univariate regression model including this endpoint and score only showed a significant association ( $p < 0.001$ ) with an odds ratio of 0.53 (95%CI 0.40 to 0.70). In the full model, there were no significant associations with age ( $p = 0.771$ ), gender ( $p = 0.918$ ) or BMI ( $p = 0.781$ ) (Table III).

## DISCUSSION

Prosthetic joint infection remains a key challenge after total joint replacement. However, the optimum method of treatment remains controversial (20,22,23). We modified an established score and designed a new risk classification for an outcome prediction in PJI. In our study we were able to show that our score is a significant predictor of clearance of infection in patients with hip and knee PJI treated with a two-stage exchange. The potential value of risk classification systems in guiding treatment of PJI is recognised (4) but inclusion of infecting organism and resistancies may improve prediction. McPherson *et al* stratified infections into early postoperative and late chronic PJI as well as acute hematogenous infections (4). They noted significantly more complications ( $p = 0.0096$ ) in late chronic PJI (McPherson grade III) compared with early postoperative (McPherson grade I) and acute hematogenous PJI (McPherson grade II). However Tsukayama *et al* observed no significant differences in proportions of patients graded as “definitely free of infection” between early postoperative and acute haematogenous PJI (24). We classified PJI as “acute” (early postoperative and acute haematogenous) and “chronic“. Additionally we choose a shorter time period of symptoms (3 weeks) as described by Zimmerli *et al* to distinguish between acute and chronic PJI (16) compared with the 4 weeks of McPherson *et al*. It is widely accepted that systemic risk factors suppress the physiological ability of the immune-system to eradicate all bacterial load in PJI. Also poor wound conditions, for example in combination with malperfusion in patients with diabetes or peripheral artery disease, reduce the success rates of PJI treatment and prolong the healing process. Consequently it is reasonable to include these categories in a risk scoring system. McPherson *et al* showed a significant correlation between the success rate and the number of local and systemic risk factors (4). Our data support these results. Infectious organisms classified as “difficult to treat” are a significant prognostic outcome parameter in treating PJI by a two-stage procedure (7,11,25). Because of this, and due to increasing resistancies against antibiotics, we included the category «difficult to treat» in eradica-

tion of the causative pathogen by antibiotic therapy in our risk score. Patients with infectious organisms considered «difficult to treat» were significantly less likely to be graded as “definitely free of infection” at follow up. For each patient with an infected prosthesis and an identified infectious organism classified as “difficult to treat” the odds for cure after two years were decreased by about 28.2 %. This is supported by the literature. Hanson and Osmon (6) reported a failure rate of 22% for infectious organisms considered «difficult to treat” in THA. Similarly, Mittal *et al* (7) reported a failure rate of 24% in TKA. We acknowledge that our study has limitations. The sample size is small for development of a risk stratification system but large for a study of treatment of PJI. We assumed that the score would show a linear association with the outcomes but recognise that in a larger sample size the issue of linearity might be explored further. However we did observe a statistically significant and sizable decrease in cure rate with an increase in score. In patients with PJI, a validated risk score may help to identify patients with local and systemic risk factors or with infectious organisms identified as “difficult to treat” and guide subsequent treatment (26). In conclusion we were able to show that the risk-score presented is an independent and reliable predictor for the outcome in treatment of PJI. Further investigations should evaluate the value of the score in guiding treatment modalities and explore possible refinements to the weighting of individual factors.

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