

Debridement, antibiotics, irrigation and retention in prosthetic joint infection : predictive tools of failure

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Debridement, antibiotic, irrigation and retention of the implant (DAIR) is an attractive treatment for periprosthetic joint infection (PJI). The purpose of this study is to determine predictive factors of failure. We reviewed all DAIR procedures for hip PJI performed between 2002-2017 (n=69). Data recorded included all factors correlated with treatment failure. KLIC score, McPherson adapted score were analyzed. Infection eradication for early PJI (< 4 weeks) was achieved in 68% of patients and was correlated with treatment success (p=0.01). KLIC score (p=0.036), McPherson adapted score (p=0.01), CRP (p=0.025) and late PJI (p=0.031) were significantly predictive of failure treatment. We have established an equation in order to predict failure treatment that has to be validated.

DAIR is an effective treatment for early PJI. KLIC score and McPherson adapted score are two ways to predict outcome of a DAIR procedure and should help making the decision in PJI treatment.

Keywords : Hip arthroplasty ; periprosthetic joint infection ; debridement and irrigation ; failure.

INTRODUCTION

Total hip arthroplasty (THA) gives excellent results for the patients and the amount of procedures increases years after years due to the ageing of the population. Fortunately, the complication rate is low but among the various complications related to this intervention, the prosthetic joint infection (PJI) is one of the most dreaded. It involves many difficulties.

for its diagnosis which can often be complex as well as the medical and surgical treatment. The failure can even lead to a hip resection reducing the quality of life (1).

Debridement, antibiotic, irrigation and retention of the implant (DAIR) is a small procedure, not very invasive for the patient and not particularly expensive compared to a revision, especially if a two-stage revision is performed. DAIR procedure is validated for the treatment of early and hematogenous PJI. However, PJI early stage period is not clearly defined. From an institution to another, it can

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differ from 4 weeks (2-5), 6 weeks (6,7) to 3 months (8-11).

The host is an important factor that influences the outcome and the classification of McPherson (12) makes it possible to evaluate in a more objective way the profile of the patient by integrating the type of infection, the systemic profile and its local aspect.

Recently, Tornero et al. (8) established a score in order to predict failure rate after DAIR procedure for early PJI occurring within 90 days after THA. The KLIC score (Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value) was highly predictive of early failure after DAIR and an external validation of the KLIC score has been published (11).

We retrospectively reviewed the circumstances when DAIR procedures have been performed and aimed to determine predictive factors of failure. We planned also to establish the maximal period which can be validated for a DAIR procedure.

MATERIALS AND METHODS

We retrospectively analyzed 69 patients treated by DAIR procedure for PJI in hip arthroplasty in our institution between 2002 and 2017. All patients were divided into three groups according to their type of infection. The early postoperative infections were defined as any infections occurring in the four weeks following surgery without suspicious signs of an hematogenous infection. DAIR procedures were also applied to hematogenous infections. Hematogenous infection was defined as any infection of a primary or aseptic revision hip arthroplasty with a demonstrated hematogenous spread. Finally, DAIR was extended to some late or chronic infections (failure of prior septic revision) for patients not being able to support an invasive surgical treatment with one- or two-stage revision.

Musculoskeletal Infection Society (MSIS) criterias (13) were used to define the diagnosis of PJI and patients who didn't meet the criterias were excluded. The success of the treatment was defined by the absence of infection (absence of clinical signs of infection, normalization of C-reactive protein and absence of new radiological signs of infection) for at least two years following the procedure and in the

absence of suppressive antibiotic treatment. DAIR procedure was considered as a failure in case of infection recurrence with the same microorganism or when the patient died within 90 days following their surgery.

The retained factors for the study were selected according to the analysis of the literature. The demographic data and the medical histories of the patients were obtained from the medical file (Medical Explorer v3r49b7). The Charlson Comorbidity Index (CCI) (14), The McPherson classification (12) and KLIC score (8) were established for each patient. The classification of McPherson was modified to use one, two or three points per category, and then added together to create a grade that defines the profile of the patient. The best profile is a score of 3/9 and the worst a score of 9/9 (Table I).

Resistance was defined as rifampicin or quinolone resistance according to the antibiograms. The limit for the duration of the symptoms was set at seven days from the onset of symptoms, like Tsang et al. (15) suggest from their meta-analysis.

Surgical treatment consisted in opening the previous/prior incision, doing a large excision of the periprosthetic tissues and in some cases an exchange of the femoral head followed by an irrigation with high pressure. An antimicrobial treatment was administrated for at least 12 weeks. The antibiotic regime included rifampicin in association with quinolones whenever the microorganism antibiotic profile sensitivity did allow it. All cases were discussed and treatment protocols established as part of a multidisciplinary approach with orthopaedic surgeons, infectiologists and microbiologists.

Table I. — McPherson adapted score

Infection Type	Point
Early infection (<4 postoperative weeks)	1
Hematogenous infection	2
Late chronic infection (>4 weeks duration)	3
Systemic Host Grade	
Uncompromised	1
1-2 compromising factors	2
>2 compromising factors	3
Local Extremity Grade	
Uncompromised	1
1-2 compromising factors	2
>2 compromising factors	3

We performed an univariate analysis with all the factors using a Chi-squared test in order to determine which ones directly influence the issue of the DAIR procedure. In addition, a receiver operating characteristic (ROC) curve was used to define the threshold of each significant factors. Finally, a multiple logistic regression was built. Analyses were performed using SigmaPlot version 13. For each variable, the odds ratios and confidence intervals at 95% were calculated. A p value <0.05 was considered as significant.

RESULTS

Throughout the studied period, 69 patients underwent a DAIR procedure for hip PJI. We excluded 3 patients who didn't corresponded to the infection criteria according to MSIS. 11 other patients were excluded from the study because their follow-up period was lower than two years. They were all disease free at the last follow-up. Finally, 7 other patients treated for late or chronic infections required a suppressive antibiotic treatment and were also excluded. In total 48 patients were retained for the statistical analysis.

The average age of cohort was 67.8 years and 25 patients were male (52%). Other patient characteristics are described in Table II. 22 hips

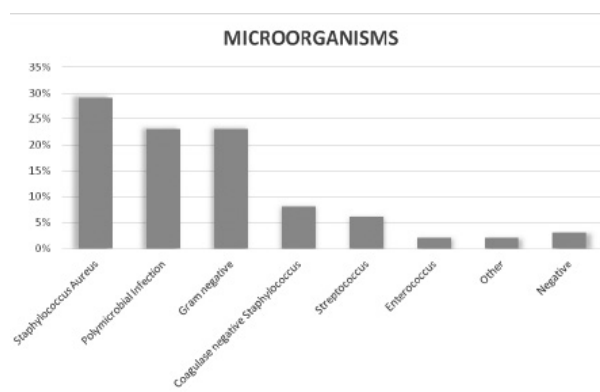


Figure 1. — Microorganisms distribution of all PJI.

(46%) were treated following an early infection, which had occurred in the first month following arthroplasty. 8 patients (17%) were present in the group of the hematogenous infections and finally 18 patients (37%) presented a late infection. For late PJI, the mean days was 164 ; median was 51 days ; minimal was 33 days and maximal was 716 days.

Figure 1 illustrates the distribution of the pathogens responsible for PJI. This is dominated by *staphylococcus aureus*, multi-organism and gram-negative bacteria. We observed 6% of negative cultures, considered infected by the presence of a fistula in contact with the implant, as described by the MSIS criteria.

Table II. — Patients characteristics

VARIABLE		COHORT
Age (years), Mean (range)		68 (14-90)
Gender, n (%)	Male	25 (52%)
	Female	23 (48%)
BMI (kg/m ²), Mean (range)		26.2 (14.4-45.7)
ASA score, n (%)	I	2 (4.2%)
	II	24 (50%)
	III	20 (41.6%)
	IV	2 (4.2%)
Microorganism	Most frequent	Staphylococcus aureus (29%)
	Seconds most frequent	Polymicrobial (23%) Gram negative (23%)
Resistance		8 (16%)
Fistula		26 (54%)
Exchange of modular component		4 (8.3%)
Symptoms >7 days		9 (18%)
CCI Mean (range)		60.18% (0-98.30%)

The global success rate was 23/48 (48%). 10 patients died including 8 people in the postoperative month and 2 others in the 3 postoperative months. 5 patients required a second DAIR procedure because the wound was not dry after one week postoperative. The second DAIR saved 4/5 patients. 15/22 patients (68%) from the early infections group were considered healed after two years. 3/8 patients from the hematogenous infections (37.5%) and 5/18 patients (28%) from the late infections group were cured. 75% patients from the hematogenous group were treated within 3 weeks from the onset of symptoms and 50% of them were cure. All patients treated after 3 weeks from the symptoms resulted in a failed treatment.

Out of the 90 days postoperative deceased patients, 70% were older than 75 years old and 70% presented a bad profile according to the classification of McPherson with a grade $\geq 6/9$.

The univariate analysis showed some significant results described in Table III. A DAIR procedure performed for a PJI within the first month after arthroplasty, was correlated with a successful treatment ($p = 0.01$ - $\chi^2 = 6.684$). On the other hand, when a DAIR procedure was carried out after this period of time, considered as late infection, there was a significant higher failure rate ($p = 0.031$ - $\chi^2 = 4.680$). A C-reactive Protein (CRP) higher than

Table III. — Univariate analysis (significant factors)

VARIABLE	c ²	ODD RATIO	P-VALUE
Early infection	6.684	4.82	0.01
Late infection	4.680	3.9	0.031
CRP > 73,5mg/L	5.056	5.91	0.025
McPherson ≥ 6	6.7	4.93	0.01
KLIC $\geq 3,5$ (all PJI)	4.410	3.61	0.036
KLIC $\geq 3,5$ (early PJI)	4	4	0.046

73,5mg/L at the admission also showed a significant correlation with failure ($p = 0.025$ - $\chi^2 = 5.056$).

A bad profile according to the classification of McPherson, evaluated with $\geq 6/9$ was correlated with treatment failure ($p = 0.01$ - $c^2 = 6.700$) and those with a KLIC score ≥ 3.5 ($p = 0.036$ - $c^2 = 4.410$). KLIC score $\geq 3,5$ also predicted failure for PJI occurring within the first 3 months ($p = 0.046$ - $c^2 = 4$).

CCI was calculated for all patients in order to predict treatment failure. Indeed, CCI has been developed to predict risk of death from comorbid diseases. There was no significant correlation with death and therefore treatment failure.

In the multiple logistic regression, two factors appeared significant: treatment of an early PJI within 30 days ($p = 0.01$) and preoperative CRP higher than 73.5mg/L ($p = 0.01$). The results of the

Table IV. — Multiple logistic regression

VARIABLE	COEFFICIENT $\pm$ SD	ODD RATIO [CI5-95]	P-VALUE
Gender (Female)	-0.533 $\pm$ 0.97	0.59 [0.0-3.9]	0.58
Age	0.933 $\pm$ 1.01	2.5 [0.3-18.4]	0.35
BMI	0.640 $\pm$ 1.39	1.8 [0.1-29.4]	0.64
Tobacco	1.111 $\pm$ 1.12	3.0 [0.3-27.5]	0.32
Fistula	0.031 $\pm$ 1.09	1.0 [0.1-8.7]	0.97
Deep infection	0.164 $\pm$ 1.11	1.1 [0.1-10.4]	0.88
Revision	-0.366 $\pm$ 0.97	0.6 [0.1-4.6]	0.70
Exchange of modular components	-2.684 $\pm$ 1.79	0.06 [0.0-2.3]	0.13
Early infection	-2.685 $\pm$ 1.14	0.06 [0.0-0.6]	0.01
Hematogenous infection	1.243 $\pm$ 1.45	3.46 [0.1-60.5]	0.39
Polymicrobial infection	0.127 $\pm$ 1.09	1.1 [0.1-9.6]	0.90
<i>Staphylococcus aureus</i>	-0.309 $\pm$ 1.20	0.7 [0.06-7.8]	0.79
MRSA	0.393 $\pm$ 2.26	1.4 [0.0-126.3]	0.86
Resistance	0.907 $\pm$ 1.39	2.4 [0.1-38.2]	0.51
CRP >73,5mg/L	3.789 $\pm$ 1.45	44.1 [2.5-758]	0.01
Symptoms >7 days	-2.578 $\pm$ 1.46	0,07 [0.0-1.3]	0.07

SD= standard deviation- CI= confidence interval.

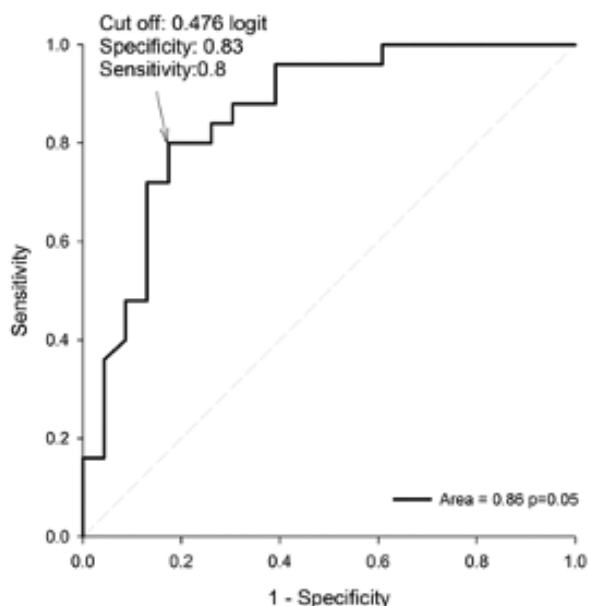


Figure 2. — ROC curve of equation 1.

analysis with their p -value and risks relative (odd ratio) are shown in Table IV. The other variables didn't appear significant.

ROC curve of the McPherson classification has a threshold at 5.5/9 and an area under the curve of 0.69 ($p = 0.02$).

A first ROC curve of the KLIC score (Figure 3) was carried out on the whole range of patients with a threshold at 3.25 with an area under the curve of 0.72 ($p = 0.01$). In term of comparison with the initial study, the patients with a score of ≤ 2 , $>2-3.5$, $4-5$, $>5-6.5$, ≥ 7 , respectively obtained a failure rate of 33.3%, 55.5%, 100%, 75% and 100%.

To be more coherent with the development of the KLIC score, a second ROC curve was carried out with early PJI within the first 3 months. It follows the same shape, with a similar area under the curve (0.72) and a $p = 0.024$. The threshold is 3.5. Patients with a score of ≤ 2 , $>2-3.5$, $>4-6.5$, ≥ 7 , respectively obtained a rate of failure of 33.3%, 60%, 71% and 100%.

ROC curve of the time period since arthroplasty and treatment failure show a threshold at 44.5 days, with an area under the curve of 0.60 but a non-significant p value ($p = 0.21$).

Then, a ROC curve of preoperative value CRP with a threshold at 73.5mg/L was elaborated with

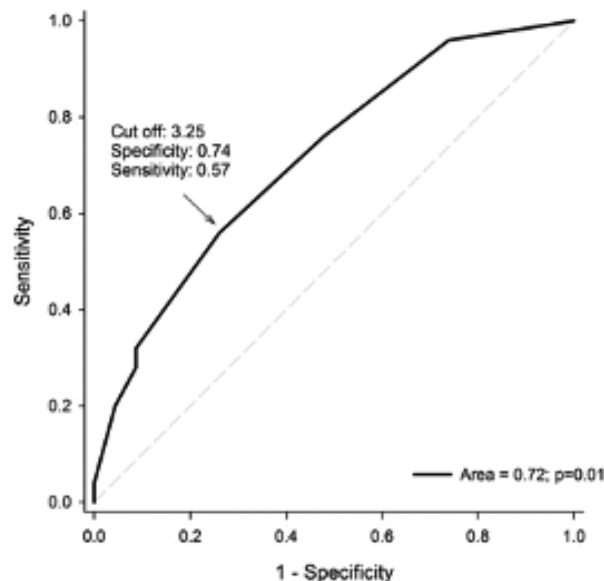


Figure 3. — ROC curve of KLIC score (all PJI).

an area under the curve at 0.61 and a non-significant p value ($p = 0.17$).

Finally, an equation (Equation 1) was established with all factors from the multiple logistic regression :

Logit P = $0.376 - (0.533 * \text{Female}) + (0.933 * \text{Age}) + (0.640 * \text{BMI}) + (1.111 * \text{Tobacco}) + (0.031 * \text{Fistula}) + (0.164 * \text{Deep infection}) - (0.366 * \text{Revision}) - (2.684 * \text{Exchange of the modular component}) - (2.685 * \text{Early PJI}) + (1.243 * \text{Hematogenous PJI}) + (0.127 * \text{Polymicrobial PJI}) - (0.309 * \text{Staphylococcus aureus}) + (0.393 * \text{MRSA}) + (0.907 * \text{Resistance}) + (3.789 * \text{CRP} > 73,5\text{mg/L}) - (2.578 * \text{Onset of symptoms} > 7\text{j})$

This tool predicts treatment failure when Logit P (equation result) is >0.476 with a sensitivity of 80% and a specificity of 83% ($p = 0.05$). The factor influencing the most negatively is CRP and those with the best benefit effects are early PJI DAIR and exchange of the modular components. ROC curve is represented in Figure 2.

DISCUSSION

DAIR is a good option for PJI to heal patient with good profile and to save patients with bad profile when associated with suppressive treatment. We are able to predict treatment failure with KLIC score, McPherson adapted score and our equation.

As the reader could expect it, the early PJI within the 30 days has a higher success rate and has to be realized within 7 days from the onset of symptoms (10). Our results are found in the literature, confirming this factor like key of success for DAIR treatment for early PJI.

Time period from the onset of symptoms seems to be a factor influencing in a very significant way the outcome of the DAIR. For this reason, the algorithm of Zimmerli (16) with a threshold at 3 weeks seems too important when regarding to the literature. We can read that some studies used a threshold of 2 days (17), 5 days (18) and some others 7 days (7,19) and even. Tsang et al, demonstrates with their meta-analysis that there is a significant threshold if DAIR is performed <7 days, value that we used (15). A late PJI, occurring > 30 days from surgery is a predictive variable of a treatment failure with an increase of failure risk of 3.9. These results are confirmed by the scientific data publication.

The importance of a prompt treatment from the onset of symptoms is related to biofilm maturation and the difficulty of biofilm eradicating. According to Stewart (20), who made an in vitro study, biofilm eradication will depend on the biofilm age. If biofilm reached complete maturation, bacteria would become resistant to the antibiotic treatment.

39 patients (81.25%) were operated <7 days from the onset of symptoms in our study but the analysis wasn't significant. It seems that a DAIR procedure done promptly is not the only condition required for success and some others factors influence the outcome of treatment.

Our results on the hematogenous infections confirm what the literature suggests, with a threshold from the onset of symptoms being less than 3 weeks. All hematogenous PJI operated for more than 3 weeks from the onset of symptoms have not been cured. However, our results were non-significant due to the limited number of cases. In the literature, hematogenous PJI have a better success rate if the patient is in good health with a not very virulent pathogen and with one short duration of symptoms (21). The implant has to be well stabilized with good local soft tissues. A study showed less satisfying performances compared with the early infections (22). Symptoms appear sometimes later than the

contamination does, particularly in elderly patients whose inflammatory and immunizing response is less strong.

A CRP higher than 73.5 mg/L before DAIR procedure is associated with a treatment failure. According to the Philadelphia consensus in 2013, the threshold differs depending on the type of infection ; > 100 mg/L for an early PJI and > 10 mg/L for a late PJI. Tornero et al. use for their KLIC score, the value of 110mg/L as threshold. These values higher than we determined, could be re-evaluated in order to decrease treatments failure.

Our results on KLIC score were relevant and interesting. Analysis for early (< 3 months) and all PJI, were both significant with a value ≥ 3.5 which predicted treatment failure. We obtained a good area under the curve which is 0.72 in both curves, slightly less than the initial study and better than the external validation. The rate of treatment failure increases proportionally with the KLIC score. We confirm the performance of this score, which is easily applicable.

The score we established with the McPherson classification also revealed significant treatment failure with a grade $\geq 6/9$. Such a score increases the failure rate with a factor of 4.93. The type of infection influences the score with a threshold at 30 days for early PJI. We obtained a better sensitivity for the McPherson score (76%) but a better specificity for KLIC score (73.9%) and the objective is to be able to determine the patients for whom DAIR procedure will not be effective. So KLIC score is more interesting from this point of view and furthermore, is easier to determine because it requires less criterias.

Presence of methicilline-resistant *Staphylococcus aureus* (MRSA) wasn't correlated with treatment failure when compared to other studies (18,23). Probably because of rifampicine which contributes to homogenize the outcomes between a methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA. It already has been shown in a multicentric study carried out on 345 patients (3).

Exchange of modular components wasn't a significant factor but according to the literature, it should be exchanged in order to improve chances of eradication of infection (24).

We had 9 deaths after DAIR procedure and 7 in the first month. 77.7% presented a bad profile with an adapted score to the McPherson classification $>6/9$. Many other patients with important comorbidities survive with a DAIR procedure. So, an alternative treatment would be to propose a DAIR procedure followed by a suppressive treatment for late PJI on old patients presenting many comorbidities (high KLIC or McPherson score) and a well fixed implant. One condition should be that the patient implants remain well fixed.

The equation carried out following the multivariate study (*equation 1*) is a good track. According to our analyzes, a result of the equation $>0,476$ logit gives us the prediction of treatment failure. Ideally, an external validation should be realized, probably on retrospective cases in order to adapt it. Then, a validation using prospective cases should be done before using the equation in practice. It shouldn't include microorganism information to avoid delay in treatment unless we find a way to identify the microorganism faster.

We are conscious that we did a retrospective study which has some limitation, but all risk factors quoted in the literature were identified and analyzed. The other difficulty we met is the number of patients included in the study. Indeed, PJI are fortunately a rare complication and despite having studied a cohort over one long period, we had 48 patients included, as many other studies. It should be noted that we used the MSIS criterias of infection which could exclude some potential infections described by Zimmerli (25).

In order to overcome these difficulties, Tsang and al. propose a creation of a collective database with pertinent criterias (host, type of implant, surgery information, microorganism, antibiotic therapy and outcome). It will help to improve prediction scores and to confirm which factors influence significantly the outcome.

Conclusion. There is still a place for DAIR procedure in critically ill patients with long term antibiotic suppressive therapy. DAIR procedure should be carried out for early PJI occurring in the 30 postoperative days with maximum 7 days from the onset of symptoms. We obtained a relatively high rate of good results with around 70% of success

in our study. Hematogenous PJI treated after than 3 weeks from the onset of symptoms leads to failure treatment. KLIC score and McPherson adapted score are two ways to predict relatively well the outcome of a DAIR procedure in the preoperative period. It will help making the decision for all PJI treatment collecting only few information. Finally, our equation gives us a good perspective and will need an external validation.

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