Treatment of acute periprosthetic infections with prosthesis retention: Review of current concepts

Jesse WP Kuiper, Robin Tjeenk Willink, Dirk Jan F Moojen, Michel PJ van den Bekerom, Sascha Colen

Abstract

Periprosthetic joint infection (PJI) is a devastating complication after total joint arthroplasty, occurring in approximately 1%-2% of all cases. With growing populations and increasing age, PJI will have a growing effect on health care costs. Many risk factors have been identified that increase the risk of developing PJI, including obesity, immune system deficiencies, malignancy, previous surgery of the same joint and longer operating time. Acute PJI occurs either postoperatively (4 wk to 3 mo after initial arthroplasty, depending on the classification system), or via hematogenous spreading after a period in which the prosthesis had functioned properly. Diagnosis and the choice of treatment are the cornerstones to success. Although different definitions for PJI have been used in the past, most are more or less similar and include the presence of a sinus tract, blood infection values, synovial white blood cell count, signs of infection on histopathological analysis and one or more positive culture results. Debridement, antibiotics and implant retention (DAIR) is the primary treatment for acute PJI, and should be performed as soon as possible after the development of symptoms. Success rates differ, but most studies report success rates of around 60%-80%. Whether single or multiple debridement procedures are more successful remains unclear. The use of local antibiotics in addition to the administration of systemic antibiotic agents is also subject to debate, and its pros and cons should be carefully considered. Systemic treatment, based on culture results, is of importance for all PJI treatments. Additionally, rifampin should be given in Staphylococcal PJIs, unless all foreign material is removed. The most important factors contributing to treatment failure are longer duration of symptoms, a longer time after initial arthroplasty, the need for more debridement procedures, the retention of exchangeable components, and PJI caused by Staphylococcus (aureus or coagulase negative). If DAIR treatment is unsuccessful, the following treatment option should be based on the patient health status and his or her expectations. For the best functional outcome, one- or two-stage revision should be performed after DAIR failure. In conclusion, DAIR is the obvious choice for treatment of acute PJI, with good success rates in selected patients.

Key words: Arthroplasty; Prosthesis; Infection; Periprosthetic joint infection; Retention; Debridement antibiotics and implant retention; Debridement; Acute

Core tip: Acute periprosthetic joint infection (PJI) is a major complication after total joint arthroplasty, and occurs either postoperatively or via hematogenous spreading. Debridement, antibiotics and implant retention (DAIR), the primary treatment for acute PJI, should be performed as soon as possible after the development of symptoms, and has success rates around 60%-80%. Whether single or multiple debridement procedures are more successful remains unclear.
With an average infection rate of approximately 1%–2%, periprosthetic joint infection (PJI) is a relatively frequent and devastating complication after performing joint arthroplasty[1–3]. It is especially debilitating for patients, as it requires prolonged hospitalization and often multiple surgical procedures. Besides the clinical impact of PJI, there is a high economic impact with tremendously increased health care costs[3]. With a rising population and overall increasing age, the number of total hip arthroplasties performed is expected to increase significantly thereby having a growing effect on the number of PJIs and, subsequently, on overall health care costs[4].

Most PJIs are caused by intra-operative contamination and cause either early or delayed infection[4]. Hematogenous seeding is less common, and is most often seen years after the initial arthroplasty[2,3]. Although these types of infection have a different pathogenesis, both early postoperative and hematogenous infection usually have an acute onset and, therefore, both attribute to “acute infection”, based on similar symptoms and treatment options[5]. Chronic late infections are usually caused by less virulent microorganisms, and although these are also thought to occur from intraoperative contamination, symptoms develop very slowly. Therefore, patient complaints are often similar to those seen in aseptic arthroplasty loosening[7].

Although recent guidelines published by Osmon et al[3] have provided some directive, classification of acute PJI remains difficult in borderline cases. For early postoperative PJI, the period after initial arthroplasty is reported, in literature, as being between 0-4 wk[3] and 0-3 mo[1]. For acute hematogenous infections, the (vague) definition encompasses acute symptoms in “a previously symptom free period in which the arthroplasty functioned properly. First we will clarify the definition of these infections. Which diagnostic tools can be used? Which risk factors are associated with developing PJI? Which micro-organisms are a predominant cause of acute PJI? What kind of treatment options exist and what is the outcome of each of these treatment options? Finally we will discuss the risk factors associated with failure of these treatments.

**DEFINITION OF A PROSTHETIC JOINT INFECTION**

Several definitions of PJI have been used in the past decades. The Workgroup of the Musculoskeletal Infection Society published a well restricted definition[4]. In their definition the diagnosis of PJI can be made if: (1) there is a sinus tract communicating with the prosthesis; or (2) a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthesis.

In patients presenting without such clear indications four of the following six criteria have to be present to prove the presence of PJI: (1) elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration; (2) elevated synovial leukocyte count; (3) elevated synovial polymorphonuclear neutrophil percentage (PMN%); (4) presence of purulence in the affected joint; (5) isolation of a microorganism in one culture of periprosthetic tissue or fluid; and (6) more than five neutrophils per high-power field in five high-power fields observed from histological analysis of periprosthetic tissue at × 400 magnification.

Other authors have described similar definitions, of which some are used more frequently, either directly or slightly adapted[5,10-12]. There are yet other studies which mention the diagnosis (“staged revision for septic loosening”)[13], or mentioning only that the diagnosis was made based on several laboratory values and culture results[17].

**DEFINITION OF ACUTE, LATE CHRONIC AND ACUTE LATE PJI**

Two classification systems are most often used to determine whether or not there is an acute, late chronic or acute late PJI. Tsukayama et al[5] suggested a system which divides the occurrence of infection into four groups: positive intra-operative cultures (at time of implantation of the prosthesis), early postoperative infection (< 4 wk), late chronic (> 4 wk, indolent onset), and acute hematogenous (acute onset). This system was adapted by Toms et al[14] to early postoperative (type 1, acute, < 6 wk), chronic (type...
II, chronic, indolent onset) and acute hematogenous (type III, acute onset in a well-functioning prosthesis, secondary to hematogenous spread). The other commonly used classification, proposed by Zimmerli et al.,[1] defines the PJI as early (occurring within 3 mo postoperatively), delayed (3-24 mo) and late (> 24 mo).

Parvizi et al.[20] also mentioned a period of 3 mo after performing arthroplasty as the cutoff to determine whether the infection can be regarded as being acute or not, however, they referred to an article only including patients undergoing aspiration within 6 wk postoperatively.[20]

**DIAGNOSIS**

Classical cornerstones of PJI diagnosis are, as for any disease, a thorough patient interview and physical examination. This includes evaluation of the patient’s history and comorbidities, medication use, postoperative wound problems and duration of infectious symptoms.

In addition to this, different diagnostics, such as infection parameters in the patient’s blood (ESR and CRP), pre-operative joint aspiration results (cell count, cell differentiation and culture) and intra-operative tissue and fluid culture results are equally important in order to determine the diagnosis of PJI.[2,14]

**Blood analysis**

Blood leukocyte count is unable to differentiate between the absence or presence of PJI.[1] ESR and CRP have a more discriminating ability, and ESR higher than 30 mm/h, and CRP higher than 10 mg/L are suggestive for the presence of PJI.[14] However, shortly after surgery (such as in early infections), these parameters generally remain elevated for a prolonged period (30-60 d).[14] Thus, a single high value is difficult to interpret, and serial measurements are recommended to aid in diagnosing PJI.[1]

Several other serum markers have been studied for this purpose, such as interleukin-6. Studies have shown promising results, with high sensitivity and very high specificity, but it has not yet been included in recently published guidelines.[2,21,22]

**Pre-operative joint aspiration**

When PJI is suspected, preoperative aspiration is recommended in almost all cases, the exceptions being when it will not change further choice of treatment (eg, presence of a sinus tract), and when the diagnosis (including the causative microorganism) has already been established.[10]

The synovial fluid should be sent for culture, cell count and differentiation, for the determination of the percentage polymorphonuclear leukocytes.

Gram staining has a limited role in PJI diagnosis according to most authors.[21-26]. Despite the fact that its specificity and positive predictive value are high, false positive results have also been mentioned. Furthermore, with a sensitivity of 20%, many PIs are missed.[21-26].

Recent studies have focused on two new synovial fluid diagnostics including synovial CRP levels and the use of leukocyte esterase strips (also used to diagnose urinary tract infections). These diagnostics appear to be promising in the diagnosis of PJI, but are not yet widespread.

**Intra-operative samples**

For the definitive diagnosis of PJI, multiple intra-operative samples should be obtained. It is recommended that between 4 to 6 samples should be sent for bacterial culturing[2]. The incubation period should be at least 7 d, but preferably 14 d.[10]. The samples should be tissue samples or samples obtained from dislodging the bacterial biofilm from the prosthetic parts.[2]. For dislodging, sonication is the preferred method.[10]. Scraping the biofilm from the foreign material has a lower yield of micro-organisms.[13].

A relatively new but promising method is the use of dithiothreitol (DTT), an agent that has the ability to dislodge bacteria while also keeping them alive.[14]. In addition to the culture samples, it is recommended that at least one sample is sent for histopathological determination of acute inflammation[2]. For a positive result, the average presence of 1 or more neutrophil polymorphs per high power field in at least 10 high power fields is required.[14].

**RISK FACTORS FOR (ACUTE) PJI**

Considering the substantial incidence of PJI it is important to recognize certain risk factors associated with the development of such an infection (risk factors associated with debridement, antibiotics and implant retention (DAIR) treatment failure will be discussed further on in this review).

Chen et al.[20] performed a meta-analysis regarding risk factors for total knee arthroplasties. Patient related factors that increase PJI risk include high body mass index (> 30), diabetes mellitus, hypertension, steroid use and rheumatoid arthritis. Everhart et al.[20] support these risk factors and found that revision surgery, tobacco abuse, MRSA colonization and infection and (a history of) bone cancer also play an essential role in PJI development. They claim, however, that super obesity (i.e., A BMI > 50) is a critical risk factor. Choong et al.[13] found that there is a direct correlation between a BMI ≥ 30 and an increased risk of infection. This correlation also exists if there are more than 2 co-morbidities present.

According to Liabaud et al.[27] there is a significant, linear correlation between BMI and operating time which is in line with Willis-Owen’s results claiming that prolonged operating time and male gender are associated with an increased incidence of infection.[30]. Luessenhop et al.[30] also found that a patient diagnosed with rheumatoid arthritis (and subsequent use of steroids) has a greater risk for developing PJI.

Berbari et al.[30] showed that a patient with a system surgical patient risk index score of 1 or 2, the presence of a malignancy, and a history of joint arthroplasty are
TREATMENT

For acute infections with a stable implant and adequate soft tissue mass, the latest guidelines recommend implant retention treatment (also referred to as DAIR: debridement, antibiotics and implant retention) for PJI occurring within 30 d after arthroplasty, or with less than 3 wk of symptoms. Osmon et al. noticed that DAIR may be used in patients who do not meet these criteria, but state that worse results can then be expected.

When patients do not meet the criteria to undergo DAIR treatment, revision surgery is the preferred treatment, either in one stage (when tissue quality and microorganism susceptibility allow for direct exchange) or in multiple stages. Mere medical treatment should be reserved for patients in whom surgery is not the most preferred option or when it is medically irresponsible. Resection arthroplasty (without reimplantation), arthrodesis and amputation are options for difficult to treat and chronic PJI, and these treatment options only very rarely have a role in acute PJI cases.

DAIR

DAIR treatment is probably the most widely performed initial treatment option for acute PJI, although the exact data on the number of such procedures performed is yet unknown. When acute PJI is suspected (or confirmed by the previously mentioned criteria) a debridement procedure should be performed as soon as possible, meanwhile keeping in mind that patient health optimization should also be maintained. For example, it has been seen that factors such as hypoglycemia and malnutrition adversely affect outcome after total joint surgery.

The procedure includes acquiring multiple tissue samples, excessive debridement and removal of all infected (and necrotic) tissue, exchange of modular components and extensive irrigation. Compared to arthroscopic washout, DAIR is associated with higher success rates: Byren et al. reported a success rate of 47% for arthroscopic washout, vs 88% for open washout, with a hazard ratio of 5.4. Retention of modular components is also associated with a higher failure risk. A recent study including hip and knee arthroplasties showed higher success rates for exchange of modular components: 59% for exchange vs 44% for retention (HR = 1.54). Another study showed 53% success for exchange vs 0% success for retention of modular parts for infected knee arthroplasties.

Success rates of DAIR treatment in general also show a great variety. Most small studies report success in approximately 60%-80% of the cases, but these are selected groups. When looking at cohorts with more than 100 patients (including both hip and knee PJI), success rates lie between 31% and 78% (Table 1). A recent meta-analysis showed a combined success rate of 46% for DAIR with one debridement procedure (n = 710), and 52% for multiple procedures (n = 175).

Single vs multiple debridement procedures

Different strategies regarding debridement surgery can be divided into either performing only one debridement, single debridement with repeat surgery on indication, or standard repeated debridement procedures. Traditionally, when only local antibiotic cement beads were used, especially popular in Europe, the strategy of multiple debridements was necessary, because these beads always had to be removed again after initial insertion. However, when using resorbable local antibiotic carriers or no local antibiotics, a single debridement might be a sufficient alternative. Although the authors do not specifically mention it in their publication, in the Zimmerli algorithm a single open debridement seems to be favored as well.

Two studies on combined groups of total hip and knee patients suggest that a repeat debridement on indication increases the infection eradication rate compared to a single debridement. There are also two studies that show good results using the strategy of routine multiple debridements. Unfortunately, to date, no comparative studies between different strategies are available and therefore no hard recommendations regarding which one to use can be made. For every strategy different studies are published with results ranging from poor to excellent (21% to 90% success rate). All of them are retrospective case-series, which are often quite heterogeneous regarding inclusion, exact treatment and outcomes.

Local antibiotic treatment

Carriers for local antibiotic release include antibiotic loaded bone cement (polymethylmethacrylate, PMMA), beads and dissolvable sponges. The rationale for using local antibiotic treatment is to achieve a high local concentration of antibiotic agents, thereby killing the causative microorganism, without the side-effects of high systemic concentrations.

Beads are usually loaded with gentamicin, but vancomycin and tobramycin are also used. The beads are most often fabricated in chains of 30 beads. Locally, concentrations of around 300 µg/mL are achieved, far above minimum inhibitory concentration (MIC) values for most micro-organisms. A disadvantage of antibiotic beads is the additional removal surgery that is necessary, and their capability of forming a foreign body on which a biofilm can develop, after the antibiotic release. Their use in DAIR treatment has been reported in a few studies, with relatively high success rates. Tsukayama et al. (n = 20, success 75%), Tintel et al. (n = 9, 100% success), Estes et al. (n = 20, 90% success), and Geurts et al. (n = 89, 83% success). Kuiper et al. also mentioned a subgroup treated with beads, albeit with lower success rates (n = 12, 33% success).

Gentamicin loaded collagen sponges, which are dissolvable, do not need removal surgery. Due to the quick expansion of the collagen, when water is added, the release of gentamicin is fast, resulting in a very high local antibiotic concentration in the first hours, up to 3800 µg/mL. The addition of hydrophobic gentamicin salt (gentamicin crobafat) has shown a longer release pattern,
resulting in high concentrations (approximately 1000 µg/mL) for the first 40 h. Up to 3-5 sponges can be used in patients, without reaching toxic serum concentrations\(^\text{[61]}\). A disadvantage of gentamicin sponges might be prolonged and increased wound secretion\(^\text{[61]}\). The clinical success rate of antibiotic loaded sponges in DAIR treatment for hip PJI has only been reported in one retrospective study, with a success rate of 70%\(^\text{[62]}\).

Local continuous irrigation with an antibiotic pump or catheter is another option for local delivery. Its main advantage is that the agent can be changed, as well as the fact that it drains the intra-articular fluid. However, the burden for the patient is very high\(^\text{[63]}\). Reported success rates vary from 18%-85%\(^\text{[63-66]}\).

**Systemic antibiotic treatment**

In general, to eradicate PJI, both surgical and medical treatments are necessary\(^\text{[1,2]}\). Antibiotic treatment is recommended in all cases, and involves systemic administration of one or more antibiotic agents, based on the microorganism causing the PJI, for a period of at least three months\(^\text{[67]}\). Usually, in the first two to six weeks of treatment, antibiotics are administered intravenously, to achieve a better penetration of periprosthetic tissues, and thus a higher local concentration. Depending on the culture results, the intravenous administration might be switched to oral administration. This is a possibility if the microorganism is susceptible to an agent which reaches high tissue concentrations upon oral intake\(^\text{[2]}\).

Culture results are the leading factor when choosing the appropriate antibiotic agent. Zimmermili et al\(^\text{[1]}\) already described a medical treatment protocol in 2004, pointing out the best (combination of) antibiotic agents per causative organism. This algorithm was adapted by recent guidelines, with the addition of several newer antibiotics, such as daptomycin for Staphylococcal or Enterococcal PJI\(^\text{[53]}\). None of the two studies make a distinction between joints involved\(^\text{[1,53]}\).

All recommendations are based on the knowledge of the causative microorganism. What to do when PJI is suspected, but culture results are not yet known, is not mentioned in the guidelines. Only one study provides a treatment algorithm for empirical antibiotic therapy\(^\text{[67]}\).

They advise the use of vancomycin for acute PJI caused by an unknown microorganism, and to switch to carbapenem if gram-negative bacteria are found\(^\text{[67]}\). Another study, on culture negative PJI, mentioned the parenteral use of cefazolin in 69\%, and vancomycin in 13\% of culture negative cases, but this is a selected group, with many patients that were already treated with antibiotics prior to surgical treatment\(^\text{[60]}\).

In almost all cases of DAIR, the addition of rifampin is useful. Rifampin is thought to penetrate the biofilm, and is recommended in all cases of Staphylococcal PJI treated with DAIR\(^\text{[1,2]}\). Several studies describe the success rates of a regimen including rifampin\(^\text{[15,68-71]}\), but only one prospective clinical study has been performed, which also observed higher success rates when rifampin was added to the antibiotic regimen\(^\text{[72]}\). Another, more recent study, compared a prospective rifampin group with a retrospective rifampin and a retrospective non-rifampin group\(^\text{[73]}\). They found higher success rates with the use of rifampin, but the groups were small, and included more knee rather than hip PJI. Despite the limited evidence, the use of additional rifampin is recommended in the most recent guidelines\(^\text{[5]}\).

**RISK FACTORS FOR DAIR TREATMENT FAILURE**

Several studies mention risk factors associated with a higher chance of treatment failure. PJI caused by a *Staphylococcus* infection is the most well documented and influential risk factor. Azzam et al\(^\text{[4]}\) state that any *Staphylococcus* infection, high American Society of Anesthesiologists score and intra-articular purulence, contribute to a substantial increase in failed treatments. They state that when “none or only one of these risk factors was present, a success rate of at least 67\% was attainable”. Vilechez, Choi and Deiermengian all specifically mention *S. aureus* as being much more virulent than other microorganisms (possibly due to their biofilm production) and having a significant, negative influence on treatment outcome\(^\text{[6,74-76]}\). Peel et al\(^\text{[76]}\) specifically state MRSA infections as leading to a significant decrease in treatment success whereas Kuiper et al\(^\text{[73]}\) report that coagulase negative *Staphylococcus*...
PJI has a higher risk of failure. Martínez-Pastor et al\textsuperscript{[7]} claim that a fluoroquinolone susceptible micro-organism leads to a better chance of treatment success. This is in line with Jáén et al\textsuperscript{[9]} who claim fluoroquinolone resistant bacteria to being risk factors for failure.

Another important risk factor appears to be the number of debridement procedures necessary, although the exact cut-off number varies. Vilechez et al\textsuperscript{[44]} and Lora-Tamayo et al\textsuperscript{[46]} state that the need for $\geq 2$ debridements leads to an increased likelihood of failure, whereas Peel et al\textsuperscript{[77]} set this number at $> 4$. Specifically in knee PJI, lack of component exchange together with a $3. aureus$ infection leads to much lower infection control rates, according to Choi et al\textsuperscript{[73]}. Lora-Tamayo confirm the importance of component exchange, stating that this “is an independent predictor of (treatment) success”\textsuperscript{[46]}. The duration of the presenting symptoms and the time after initial surgery are also important contributors to treatment success, or failure. Some studies state that treatment outcomes decline when the patients undergo a debridement a mere $> 2$ d after onset of symptoms\textsuperscript{[9]}, whereas other studies claim the cutoff is at $7 \text{d}\textsuperscript{[9]}, 21 \text{d}\textsuperscript{[77]}$ or even $28 \text{d}\textsuperscript{[83]}. The time after index surgery showed an even greater scope, ranging from $15 \text{d}\textsuperscript{[81]}$ to two years\textsuperscript{[82]}.

A patient’s BMI and the presence of co-morbidities was only statistically significant in one study; Choong states that a BMI $> 30$ and having $> 2$ co-morbidities are substantial risk factors\textsuperscript{[15]}. Buller et al\textsuperscript{[47]} and Byren et al\textsuperscript{[43]} both claim having a history of infection of the same joint as being associated with treatment failure. Byren et al\textsuperscript{[43]} also state arthroscopic washout as a risk factor. A higher ESR is a potential risk factor\textsuperscript{[7]}, whereas a lower preoperative CRP, of $\leq 15 \text{mg/dL}$, leads to a better outcome\textsuperscript{[7]}. Lora-Tamayo et al\textsuperscript{[46]} confirm this, stating that the degree of complexity of the infection (polymicrobial, bacte- mic, or presenting with high CRP levels) and immunosuppression were independent predictors of failure. Kuiper et al\textsuperscript{[53]} also state rheumatoid arthritis as a significant risk factor.

**DISCUSSION**

This review is intended to provide a concise summary of all the currently available literature regarding acute periprosthetic joint infections. The various classifications, definitions and diagnostic tools used to make the diagnosis of PJI, as well as the use of DAIR were collected and analysed in order to provide a series of solid treatment recommendations.

The initial difficulty researchers and clinicians face is how to properly make the correct diagnosis. Patient interview and physical examination, together with a blood analysis, pre-operative joint aspiration and intra-operative samples are of equal importance and must all be employed. Despite the fact that different authors use different criteria, in general all of these criteria and definitions are useful. The exact definition and cut-off of an acute infection remains unclear, however, due to the fact that some authors claim this be less than 4 wk whereas other implement less than 6 wk or even less than 3 mo. Literature remains unclear whether a period of 3 mo has worse outcome than 4 wk.

Most of the risk factors for developing PJI are the same as the risk factors associated with DAIR treatment failure. A BMI of more than $30 \text{kg/m}^2$, MRSA and the...
presence of multiple co-morbidities put all patients at an extra risk, for both infection development and subsequent treatment failure. However, there are some specific risk factors for failure of DAIR, like the number of debridements and the time between presenting symptoms and initial surgery. The sooner the DAIR is carried out, the better.

DAIR (with modular component exchange) remains the preferred initial treatment choice, one- and two-stage revisions, mostly due to its less invasive character. Unfortunately DAIR has a lower success rate than one- and two-stage revision, respectively 70% vs higher than 90%\(^\text{1}\). There is no consensus regarding the optimal number of debridements necessary.

The use of local treatments such as beads, cement and sponges loaded with antibiotics appear to be promising, though only a handful of studies have been published, all of which analysed a relatively small patient population.

Systemic antibiotic treatment is complementary to surgical treatment. The antibiotic used for PJI is based on the acquired culture results, potentially combined with rifampin in the case of a Staphylococcal infection. However, too few studies have been published regarding the choice of antibiotics when the cultures are not yet known. Vancomycin appears to be a possible antibiotic option though a definite recommendation cannot be made. The duration of antibiotic administration is currently reported to be three months\(^2\).\(^{1,3}\). If the PJI cannot be eradicated using minimally invasive approaches, one- and two stage revisions are eventually the preferred treatment.

Despite many studies providing information about PJI, much evidence is missing. In order to provide stronger scientific evidence additional multicenter prospective randomized trials must be carried out, using a single, uniformly agreed upon definition of APJI based upon equal criteria and diagnostic tools.

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Reprints: J. Van der Linden, M.D., Ph.D., Department of Orthopaedic Surgery, University Medical Center Utrecht, Utrecht, Netherlands (e-mail: j.vanderr@uu.nl)
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