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Trends in the treatment of orthopaedic prosthetic infections

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The most commonly used therapy for prosthetic joint infection is a two-stage prosthetic exchange separated by 6 weeks of intravenous antibiotic therapy. This often results in long periods of hospitalization, morbidity, severe functional impairment and sometimes increased mortality. Therefore novel and challenging therapeutic approaches have been attempted, particularly in hip prosthetic infection. This includes, whenever possible, according to the type of microorganism, antibacterial susceptibility and clinical presentation (including age and comorbidities): (i) less aggressive surgical techniques (debridement and prosthesis retention, or re-implantation with a single-stage exchange arthroplasty); and (ii) antibiotic combinations active against biofilm-associated bacteria, including rifampicin (particularly with quinolones) with excellent bio-availability which allow prolonged and efficient oral therapy.

Keywords: total joint infection, exchange prosthesis, one-stage prosthetic reimplantation, two-stage prosthetic reimplantation

Introduction

Joint replacement surgery, particularly of the hip and knee, has become one of the most frequent prosthetic surgeries over the past decades due to its success in restoring function to disabled arthritic individuals. It is estimated that more than a million joint replacements are performed each year worldwide. However, these operations are not without complications, the most frequent being aseptic loosening. But of greater concern is infection, the second most frequent complication.¹

The treatment of infection following total joint arthroplasty involves surgery and antimicrobial therapy. Surgical alternatives include debridement and prosthesis retention; re-implantation with either a single- or two-stage exchange arthroplasty; arthrodesis (knee); and excision arthroplasty (shoulder, hip). There are no prospective trials comparing different combinations of surgical procedures. Antimicrobial therapy should always be combined with surgery. When used alone, as with chronic suppressive treatment of infection, antimicrobial therapy is rarely successful.

The duration of the infection is an important factor in determining optimal treatment. With an infection of greater than 1 month duration, it has been postulated that biofilm-associated bacterial disease has progressed to such a degree that cure with prosthetic retention is less achievable than with resection.²

As regards surgical procedures, two-stage re-implantation is considered the standard in the treatment of septic prosthetic joints, but is expensive, may result in large skeletal defects, long periods of hospitalization, severe functional impairment and occasionally death.

This has stimulated re-visiting other surgical techniques and new concepts in antimicrobial therapy. The main difficulty in comparing reported studies in the literature is the wide variability concerning a number of specific variables, including: the host immune system;³ the type and route of infection; the surgical procedure; the bacteria cultured; and the antibiotics employed. We will review some of the leading microbiological and clinical studies published in the last decade that have led not only to a better understanding of the disease, but also to novel and more controversial therapeutic approaches.

Surgical therapy: controversy between two-stage and one-stage revision

The two-stage re-implantation technique involves removal of the prosthesis and resection of all infected tissue. The pre-requisites for this method of treatment include adequate bone stock and minimal medical co-morbidities to allow for multiple surgical procedures. However, there are many variables associated with two-stage exchange protocols. These include: use of antibiotic-loaded cement in the form of beads or a temporary spacer between the first and second stage; duration of post-operative antibiotic therapy; timing of re-implantation; use of allograft bone; and selection of a cemented or a cementless implant.⁴ The ideal pause between surgeries is not well established, but frequently results in considerable economic hardship and morbidity. The interval usually accepted is a minimum of 6 weeks, during which antibiotic therapy is prescribed.⁵ Once this antibiotic period is completed, and if the results of diagnostic studies indicate eradication of the infection, a new prosthesis is implanted. The

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decline in the level of C-reactive protein seems to be the best test for monitoring the effectiveness of antibiotic treatment. The value of aspiration and culture of the previously infected joint to detect those patients who remain infected is controversial, but its sensitivity seems high in the detection of infected prostheses.^{6,7} Whereas a two-stage approach provides a high success rate (about 95%) for eradication of the infection, it frequently results in major morbidity due to prolonged immobilization of the patient, who is typically elderly.

For these reasons, there is enthusiasm for a one-stage revision. The one-stage re-implantation technique involves the excision of all prosthetic components and infected tissue, and the implantation of new components during the same operation. It is applied mainly for hip prostheses. For other prosthetic joints (knee, shoulder, elbow), a two-stage exchange, with the use of antibiotic-loaded cement, is preferred.

Whereas a one-stage revision procedure appears to be much more attractive because it allows earlier mobility, it exposes the patient to the risk that remaining bacteria will lead to re-infection of the newly implanted prosthesis. This procedure is currently used in many centres—mostly for hip prosthesis—with good results reported in ~80% of patients. The consensus is that a one-stage revision should be used only if the following specific conditions are met: there is no need for a bone graft; no fistula is present; the met is not due to difficult-to-treat bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*; the debridement is extensive, such that an independent surgeon arriving mid-operation should not be able to determine that there was a pre-existing infection; and cement loaded with a targeted antibiotic will always be used. Commercially available cement can be obtained for a few antibiotics, usually aminoglycosides, clindamycin, colistin or erythromycin. Aminoglycosides are not ideal for infection resulting from MRSA, which are often resistant to such therapy.⁸ Many surgeons prepare the cement-antibiotic mixture during surgery, with local recipes that have not undergone strict validation.

The microorganism should be cultivated before surgery by biopsy and/or aspiration cultures so that it may be treated with the appropriate pre-operative or intra-operative antibiotic regimen (which will be expanded upon in the section 'Antimicrobial therapy'). The optimal length of post-operative antibiotic therapy is not known. Controlled studies are mandatory to address the issue of one-stage versus two-stage revision, as well as to define the ideal duration of antibiotic therapy.

Surgical therapy: definitive excision arthroplasty (hip) or arthrodesis (knee)

Such techniques have demonstrated moderate success with respect to pain relief and eradication of infection, but are rarely indicated because of the poor functional outcome. After the resection, the patient receives an antibiotic regimen similar to that used for the re-implantation techniques. The accepted indications for these techniques include: poor quality of bone and soft tissues; highly resistant organisms; patients unsuitable for more demanding reconstructive surgery; and failure of exchange arthroplasty

Is 'conservative' surgical therapy possible?

The technique of debridement and prosthesis retention involves debridement of infected tissue, exchange of the polyethylene insert and large volume (9–12 L) pulsatile irrigation with physiological serum or antiseptic solution. If necessary, debridement may be

repeated. Whereas such an approach can result in low morbidity with a high success rate, it requires further study.^{9–11} The current consensus is that debridement and retention of the prosthesis is a potentially successful treatment for early post-operative infection, or late acute haematogenous staphylococcal or streptococcal infection. However, success is dependent on surgery being performed in the first few days or up to 2 weeks after the onset of symptoms, and that in the later onset cases, the prosthesis had been functioning well.

A recent mathematical model has been performed on the clinical effectiveness of two different management strategies—prosthesis removal versus debridement and prosthesis retention—for the infected, well-fixed, total hip arthroplasty in the elderly.¹² This analysis considered that removal of a stable implant can be a difficult operation in itself, added to which is the subsequent morbidity of immobilization. Initial debridement and retention, on the other hand, may be associated with increased patient survival and have a favourable cost-effectiveness ratio for all patients. Debridement and retention were shown to increase life expectancy by 2.2–2.6 quality adjusted life months, and had a favourable cost-effectiveness ratio.

Other surgical alternatives, such as re-implantation with single-stage exchange, arthrodesis or definitive excision are not evaluated in this mathematical model.

Antimicrobial therapy

Antimicrobial therapy should be always combined with surgery. The main difficulty in analysing the efficacy of antibiotic therapy for treatment of prosthetic joint infections is in knowing exactly what type of surgical procedure was performed. Another factor is the heterogeneous nature and small number of cases of prosthetic joint infection included in antimicrobial therapy studies.

Nevertheless, the addition of rifampicin to antibiotic regimens for treatment of prosthetic joint infection has been shown to be beneficial, and in addition it is believed that combination therapy is more effective in preventing the failure of treatment secondary to the emergence of resistant organisms. Penicillin-susceptible streptococcal prosthetic joint infection treated with prosthesis retention and intravenous penicillin, or once-daily ceftriaxone followed by oral amoxicillin-rifampicin, appears to be an effective treatment modality.¹¹ The main advantage of the combination of a quinolone plus rifampicin is their excellent bioavailability, allowing oral administration, with serum levels comparable to those obtained during intravenous therapy. In addition, both drugs display high levels of intracellular penetration and activity against intracellular *Staphylococcus* species.

Zimmerli and colleagues¹³ reported a double-blind, randomized, controlled clinical trial assessing the role of rifampicin in 33 patients with staphylococcal infection in a variety of orthopaedic implants, including eight following arthroplasty. All patients underwent surgical debridement and were randomized to long-term ciprofloxacin with or without rifampicin. The combination rifampicin-ciprofloxacin achieved a cure without removal of the implant (relapse after follow-up of 35 months: 0% in the ciprofloxacin-rifampicin group versus 42% in the placebo and ciprofloxacin group). The authors did not explicitly outline the results for the total arthroplasty group. Nevertheless, these results are promising for the treatment of patients who are unable to have extensive surgery.

A different approach has been pursued by others. Drancourt *et al.*¹⁴ reported on a non-randomized trial comparing a combination of ofloxacin or fusidic acid and rifampicin in 46 patients with prosthetic infections caused by staphylococcus. Patients with an infected hip implant were treated for 6 months, with removal of any

unstable prosthesis after 5 months treatment. Those with infected knee prostheses were treated for 9 months, with removal of the knee prosthesis after 6 months of therapy. Treatment was successful for 11 (55%) of 20 patients treated with rifampicin and fusidic acid and for 11 (50%) of the 22 treated with rifampicin and ofloxacin.

Unfortunately, the use of quinolones may be limited in the future as quinolone resistance continues to increase. High doses of oral co-trimoxazole led to a successful outcome in only six of 12 (50%) arthroplasty patients; three of the four failures occurred because of intolerance to the drug.¹⁵

Pseudomonas aeruginosa and MRSA prosthetic and bone infection remain difficult challenges, and two-step exchange revision remains the rule. Brouqui *et al.*¹⁶ utilized a combination of ceftazidime and ciprofloxacin, and achieved a cure in nine of nine patients with *P. aeruginosa*-infected osteosynthetic material, and four of five patients with hip and knee prostheses, without removing the implants. Ariza *et al.*¹⁷ have proposed that most failures in MRSA prosthetic infections are associated with hetero-resistance to vancomycin. For MRSA following surgery, continuous outpatient perfusion of vancomycin with steady-state plasma levels of ~25 mg/L for several months, has been used with success.¹⁸ Teicoplanin administered once daily for very prolonged periods appears also to be efficacious.¹⁹ The duration of antibiotic therapy for the treatment of prosthetic infections is not clearly defined and ranges from 6 weeks to 6 months, with 6 weeks being the most common.

Chronic suppressive therapy

This method of treatment includes long-term antibiotic therapy without any adjunctive surgical intervention. Early experience has led to the universal consensus that antimicrobial therapy alone is frequently unsuccessful and surgery is necessary in the majority of cases. In the literature, only successful results are reported and the number of failures is obviously much higher.

Conclusions and challenges

Success in the treatment of an infected prosthesis demands the best surgical strategy associated with optimal antibiotic therapy, tailored to the individual patient. Over the last decade significant progress has been made in both these areas. More conservative surgical approaches, such as one stage-revision and debridement without prosthesis removal, are more frequently utilized. Improved antimicrobial combinations using optimal pharmacokinetics for prolonged periods have led to higher rates of cure. In spite of this, however, these infections present considerable challenges. Hopefully, more targeted therapeutic options will derive from a better understanding and characterization of the mechanisms of prosthetic joint infection and microbial pathogenicity. In addition, there is a need for large-scale multicentre trials and extensive databases that take into account all the variables involved in such complex infections, and that lend themselves to rigorous statistical analysis.

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