■ ASPECTS OF CURRENT MANAGEMENT

The management of peri-prosthetic infection in total joint arthroplasty

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Deep peri-prosthetic infection following total joint arthroplasty is a major complication. Although it only occurs in a small percentage of patients it results in substantial morbidity and a decline in functional outcome. The risk of infection is generally quoted as being 1%. The lowest reported rate, 0.3%, was from the British Medical Research Council¹ but, no subsequent studies have validated this figure. A rate of 2.2% was described in a review of 236 140 American patients who underwent total hip arthroplasty (THA) between 1986 and 1989.² The Scandinavian Arthroplasty registers have demonstrated that between 7% and 16% of THA revisions are carried out for infection.^{3,4}

Infection presents a significant clinical and financial burden in both diagnosis and treatment. However, these are not areas where there is clear unambiguous evidence to guide surgeons. We are currently faced with an increasingly complex case mix, with a higher prevalence of immunocompromised patients, comorbidities and antibiotic-resistant bacteria. The challenge is to maintain the current success rate while achieving advances in accurate diagnosis and the development of more effective and less risky antimicrobial treatment. This article aims to update and summarise the recent refinements in diagnosis and the subsequent results of treatment. Although most of the current literature is focused on peri-prosthetic infection in the hip, much will be applicable to other deep joint infections.

Classification

It is useful to be able to subdivide peri-prosthetic infection into groups, as described by Fitzgerald et al,⁵ because the presentation, differential diagnosis and treatment differ according to the timing of presentation. We favour a slight modification of the original system, such that stage I infections are those that occur acutely within the first six weeks, stage II is a delayed presentation with a chronic indolent infection regardless of when it presents,

and stage III describes those that occur suddenly in an otherwise well-functioning hip replacement, with an acute presentation of infection secondary to haematogenous spread. A fourth type, when a positive culture is found at the time of revision without previous evidence of infection, has been proposed by Tsukayama, Estrada and Gustilo.⁶

Diagnosis

The diagnosis of peri-prosthetic infection requires a high index of clinical suspicion. There is no standard single reliable test, but the diagnosis is based on clinical evaluation, serological investigations, diagnostic imaging and microbiological analysis.

Clinical evaluation. Significant elements include predisposing factors for infection, delayed wound healing, post-operative superficial infection, persisting drainage and/or pain. Physical examination must include assessment of the patients' general medical condition as well as features localised to the affected lower limb and hip. The wound must be thoroughly assessed for signs of infection, inflammation and tenderness. Although fever is commonly associated with infection, the normal post-operative physiological febrile response must be considered. A rise in temperature may occur in the first five days after operation following hip and knee replacement.⁷ Patients in this series were treated with a course of prophylactic antibiotics for 48 hours and 19% were noted to have a temperature of more than 38°C. There were no cases of peri-prosthetic infection over the two-year period of follow-up. Although some infections may be accompanied by fever, pyrexia on its own is not suggestive of infection and cannot be relied upon to denote its presence.

Serological investigations. Assessment of the white blood cell count is of limited benefit as it is frequently normal. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are key indicators in the patient who has no other reasons for their elevation such as rheu-

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matic diseases or other inflammatory conditions. An ESR > 30 mm per hour has been shown to have a sensitivity of 82%, a specificity of 85%, a positive predictive value of 58% and a negative predictive value of 95%.⁸ The CRP is a better indicator of infection as it is more sensitive and returns to normal within the first three weeks after operation, compared to the ESR, which can take up to one year to become normal.⁹ A CRP value > 10 mg/l has been associated with a 96% sensitivity, a 92% specificity, a 74% positive predictive value and a 99% negative predictive value. If both the ESR and CRP are elevated, the probability of infection has been noted to be 83%, and when both are negative infection may be reliably excluded.⁸

Diagnostic imaging. Many methods of imaging have been used in the assessment of peri-prosthetic infection.

Plain radiographs. These are of limited value in acute infection because of the absence of reliable diagnostic features. However, they should be still used in evaluation as a vital step in excluding other diagnoses. Chronic infection can cause radiographic changes, including periostitis, osteopenia, endosteal reaction, and rapid progressive loosening or osteolysis. Osteolysis and loosening may have other causes but the possibility of infection must always be considered when these processes are rapid, particularly when there are no indicators of a mechanical cause.

Magnetic resonance imaging. Magnetic resonance imaging (MRI) is not widely used as the prosthesis interferes with the quality of the study.¹⁰ White et al¹⁰ have described technical modifications to the MRI that reduce prosthetic artefact and may lead to an increased use of MRI in the assessment of infection. The place of MRI in evaluating the location and severity of osteolysis has been investigated.¹¹ Although the ability of MRI to detect peri-prosthetic infection was not specifically discussed, the authors stated that their modified technique allowed visualisation of the bone-prosthesis interface and adjacent soft tissues, which may be clinically useful in the future.

Radionuclide bone scan. A technetium-Tc99m (^{99m}Tc) isotope bone scan is often performed in the assessment of a failed THA. Although it has a high sensitivity, the low specificity for infection limits its use.¹² Indium-111-labelled white cell scans have a much higher sensitivity in infection, which has been found to be 77%, with specificity of 86%, a positive predictive value of 54%, and a negative predictive value of 95%.¹³ However, this test is expensive and time consuming. Other isotopes have been investigated but none has demonstrated clinically useful sensitivity or specificity.¹⁴⁻¹⁸ The use of radioactive immunoglobulin G has also been described but has not become common, as its sensitivity and specificity were similar to those of standard laboratory investigations.¹⁹

Positron emission tomography. Positron emission tomography using fluorine-19-fluoro-2-deoxy-D-glucose has been used to detect sites of increased metabolic activity, suggestive of infection. The reported sensitivity of this method was 91.7%, with 96.6% specificity. However, areas that

showed a non-specific increase in uptake were seen up to an average of 71 months after operation, even in uninfected THA.²⁰ The authors concluded that the area of increased uptake may be more important than the intensity.²¹ Although these results are encouraging, further study is required.

Microbiological analysis. The organisms most commonly isolated in infected THA are *Staphylococcus aureus* and *Staphylococcus epidermidis*, followed by Gram-negative bacteria. A recent review of the results of culture noted that coagulase-negative staphylococci were increasing in prevalence and that Gram-negative infections were decreasing.²² The antibiotic sensitivities of infecting organisms have also been shown to vary. The sensitivity of *Staph. aureus* to methicillin and cephalosporins has been reported to range between 53% and 95%,^{23,24} whereas the reported sensitivity of *Staph. epidermidis* to methicillin was 70%.^{23,25} Vancomycin resistance, in particular with enterococci, has been reported in as many as 23% of enterococcal peri-prosthetic infections.²⁴ This emphasises the importance of identifying the pathogen before initiating antibiotic treatment.

Pre-operative aspiration, culture and sensitivity. When there is a high index of suspicion of peri-prosthetic infection, the hip should be aspirated and the culture and sensitivities determined. The patient should not have been treated with antibiotics for a minimum of two weeks prior to aspiration. Such investigations have revealed a sensitivity of between 50% and 92% and a specificity ranging from 88% to 97%.^{8,26,27} This variability has resulted from differences between studies regarding the technique used and the criteria for positive findings. We obtain three samples, including one tissue sample, at the time of aspiration of the hip. A positive test is defined as a growth in two separate specimens. Growth in one specimen is generally not considered a cause for concern unless the clinical and serological features are worrisome, in which case the aspiration is repeated.

Molecular biological investigation. Polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay have both been evaluated in the diagnosis of infected THAs. The PCR is highly sensitive. It is, however, limited by its reliance on a previously created database of DNA sequences, as well as an inability to distinguish between active and eradicated infections.^{28,29} Immunofluorescence microscopy and PCR have isolated colonisation with an organism in between 63% and 73% of extracted prostheses, compared to standard techniques, which detected colonisation in only 4% to 22%.³⁰ The enzyme-linked immunosorbent assay technique has been associated with a 93% sensitivity and a 97% specificity, but its use is limited by the technical requirement to compare individual samples directly with each potential organism.³¹

Intra-operative confirmation

Intra-operative appearance. Without pre-operative confirmation of infection the ability to detect it at operation is unreliable. On the basis of the gross appearance of the hip

at the time of surgery, one study reported a sensitivity of 70% and a specificity of 87%.³²

Intra-operative gram stain. Reports on the intra-operative value of Gram staining have been variable, with sensitivity ranging between 14.7% and 92% and specificity between 98% and 100%.^{8,33-37} In our experience the Gram stain is of little use in the intra-operative diagnosis of infection, particularly in stage II infections, and should not be relied upon. Owing to the wide variation in the reported sensitivity, intra-operative Gram staining should be interpreted with caution.

Intra-operative tissue culture. The highest standard in the diagnosis of an infected THA has always been intra-operative tissue culture. Using a minimum of two positive samples, the sensitivity is 94%, with 97% specificity, a 77% positive predictive value and a 99% negative predictive value.⁸

However, intra-operative tissue culture is not always positive, even in patients who are positive by all the other criteria mentioned and who symptomatically improve with management of their presumed infection. Most of the diagnostic tests have been cross-referenced and validated against each other, and in the absence of a single reliable test this is probably the best we can do.

Isolation of organisms from the removed components can be enhanced through ultrasonification of the prosthesis. This process disrupts the glycocalyx, allowing better isolation of bacteria. One study demonstrated that 22% of prostheses which were not thought to be infected were colonised by *Propionibacterium acnes* in 12 and staphylococcal species in ten of a total of 26.³⁸ Another study found that the occurrence of occult organisms was less frequent using this method, occurring in only two of 21 cases.³⁹ The true significance of these results is yet to be elucidated, as has the need to treat on the basis of a positive result with ultrasonification.

Intra-operative frozen section. Various definitions of a positive frozen section have been investigated in the literature. Studies that considered five polymorphonuclear leucocytes per high-power field to be indicative of infection have demonstrated a sensitivity between 43% and 100%, with a specificity ranging from 94% to 100%.^{8,32,39-41} Lonner et al⁴¹ used a threshold of both five and ten white blood cells per high power field and found that the sensitivity and negative predictive value did not change between the two criteria, although the specificity increased from 96% to 99% and the positive predictive value from 70% to 89% with the more stringent criteria. A frozen section can also be used to assess eradication of infection during re-implantation in a two-stage revision. Using a definition of eradication of fewer than ten white blood cells per high-power field, the sensitivity was 25%, the specificity 98%, the positive predictive value 50% and the negative predictive value 95%.⁴²

Treatment

Unexpected positive intra-operative cultures. There have been a few studies describing the management of unexpected

positive intra-operative cultures when pre-operative assessment has failed to show infection. One series of 31 patients were treated with a six-week course of parenteral antibiotics, with three persistent and two recurrent infections at a follow-up of two years.⁶ Another study of 15 patients who were not given antibiotics reported six recurrent infections.⁴³ Based on these two studies, it seems prudent to treat patients with unexpected positive intra-operative cultures with six weeks of intravenous antibiotics.

Antibiotic suppression. Suppression of infection with antibiotics is indicated in patients who are unable to undergo revision arthroplasty, usually because of medical comorbidities, although extreme bone loss, especially on the pelvic side, is another relative contraindication. There have been several studies investigating the rate of recurrence of infection with antibiotic suppression therapy, but the patient populations, the staging of the infection and methods of treatment have varied, making comparison of results difficult. One study of 33 infections around implants due to staphylococci, treated with surgical debridement and subsequent randomisation to antibiotic therapy with ciprofloxacin or ciprofloxacin and rifampicin, found eradication in 58% with the single agent and 100% with the combination.⁴⁴ The addition of rifampicin was thought to interfere with the glycocalyx, thereby potentiating the action of the antibiotic. Infection with methicillin-resistant *Staph. aureus* (MRSA) requires treatment with linezolid, which has resulted in eradication in two reported cases with a follow-up of nine and eight months, respectively.⁴⁵ Rao et al⁴⁶ investigated the rates of eradication of antibiotic-resistant organisms with suppression therapy and noted eradication in 86% at a mean follow-up of five years, with five recurrent infections all within the first three years. Three recurrences resulted from antibiotic-sensitive and two from resistant organisms. This treatment should be reserved for those in whom revision surgery is contraindicated.

Operative debridement. Operative debridement and retention of the infected prosthesis should be reserved for acute infections (stage I and III). The reported rate for eradication has been between 26% and 71% following open debridement.^{6,47} Arthroscopic irrigation and debridement within 48 hours of the onset of symptoms has been described in eight hips that were infected with streptococci, with no recurrence of infection at a mean follow-up of 70 months.⁴⁸ These results should not be extrapolated to infections with other organisms. The duration of symptoms prior to debridement has been shown to affect outcome. Brandt et al⁴⁹ found a cure rate of 56% following debridement within two days of the onset of symptoms, compared with 13% when carried out after two days. Similarly, another study did not encounter a single instance of eradication among 42 cases after two weeks of symptoms.⁴⁷ Statistical analysis of the indications for operative debridement⁵⁰ showed improved quality adjusted life expectancy and cost-effectiveness when revision arthroplasty was performed in young, healthy patients, whereas debridement was more beneficial

in patients with reduced life expectancy. This statistical model has not been confirmed clinically.

Resection arthroplasty. Resection arthroplasty should be reserved for patients whose medical condition makes a more extensive procedure unsafe. A series of 33 cases of resection arthroplasty noted eradication of infection in 32, although there was a deterioration in functional outcome to an unsatisfactory level in each.⁵¹ Another study of 78 patients with a mean follow-up of five years demonstrated cure in 86% and good pain relief in 83%.⁵² Overall, the poor functional results compared to revision THA make resection only a salvage procedure for the patient unable to tolerate a full revision.

Single-stage exchange revision. Single-stage exchange revision using antibiotic-loaded cement was first popularised in Europe. This technique has been recommended in immunocompetent patients with an acute infection, sensitive to first-line antibiotics.⁵³⁻⁵⁸ The rate of recurrence with this treatment at a minimum follow-up of ten years was 8.3% in 24 patients.⁵⁹ For this technique to be successful, thorough debridement must be carried out and a course of parenteral antibiotics administered post-operatively for a minimum of six weeks.⁵⁹ A larger series of 162 cases with a mean follow-up of 12.3 years showed eradication of infection in 85.2%, with 12.3% requiring further revision for recurrent infection.⁶⁰

A number of studies comparing single-stage *versus* two-stage exchange all favoured the two-stage procedure. Elson⁶¹ had a 12.4% rate of failure with the single-stage method, compared to 3.5% with the two-stage procedure. Very similar results were reported by Garvin et al⁶² in a large study, with a recurrence rate of 10.1% and 5.6% of cases, respectively.

Two-stage exchange revision. This has become the standard procedure throughout North America. Following removal of the infected components, a minimum course of six weeks of parenteral antibiotics is given and resolution of the infection confirmed through the ESR, CRP, and repeated aspiration of the hip. In most instances a temporary spacer of antibiotic-loaded cement is inserted at the first stage and removed at the second operation. A further aspiration of the hip prior to the second stage has been recommended in one study, in which there was a recurrence rate of 3% among those who underwent aspiration compared with 14% in those who did not.⁶³ High doses of antibiotic in the cement have been shown not to cause systemic toxicity. Springer et al⁶⁴ used a mean of 3.4 packages of cement combined with a mean of 10.5 g of vancomycin and 12.5 g of gentamicin in 36 infected total knee arthroplasties. There was only one transient rise in the serum creatinine, which lasted one day, and no instances of renal failure or other systemic toxicity.

Despite its widespread acceptance, two-stage revision has several controversial aspects, including the timing of the procedure, the use of antibiotic-loaded cement at the second stage, the role of allograft bone grafting and the use

of uncemented components. The ideal duration of antibiotic therapy between stages has not been established, but a minimum of six weeks is the standard. As regards the timing of the second stage, recent studies have advocated revision between six weeks and three months after the first stage. Lieberman et al⁶⁵ reported a rate of recurrence of 9% with revision at six weeks. Others have compared the rate of recurrence between revisions performed within six weeks and those with a delayed procedure. In one series the rate of re-infection was 22% among those revised after 22 weeks, compared to 14% in those operated on within six weeks.⁶⁶ Other studies have produced similar results.^{6,62}

The use of antibiotic-loaded cement at revision has been shown to reduce the rates of re-infection. Gentamicin-loaded cement was associated with eradication in 95% of patients at five years in one study.⁶⁷ Hanssen and Rand⁶⁸ had a cure rate of 82% without antibiotic cement at the second stage, compared with 90% when an antibiotic was used.

Management of the deficiency in bone stock at the time of revision is a problem. Although allograft has been recommended for an aseptic revision, there is a theoretical concern that its use following infection may increase the rate of recurrence. Use of allograft in primary THA has been associated with an increased rate of infection, 6.8% compared to 0.2% with no allograft. However, several confounding factors, including the complexity of the procedure, may have influenced the results.⁶⁹ More recent studies of the use of allograft at revision for infection have reported rates of recurrence of up to 7.5%.^{70,71}

As the incidence of antibiotic-resistant organisms has increased, there have been studies investigating their effect on the rates of re-infection. One series of 26 resistant infections was compared with 20 with susceptible pathogens and found an increase in the rate of re-infection from 4.8% to 8% among those with an antibiotic-resistant strain.⁷² Although this difference was not statistically significant, there was a trend toward poorer results in the presence of a resistant infection. Another study of 19 sensitive infections and 16 with resistant organisms had success in 81% with sensitive organisms but only 48% with resistant pathogens.⁷³ This result may be limited by the unusually low rate of eradication, even among those with susceptible organisms. A recent report of 37 methicillin-sensitive infections was compared with nine MRSA infections, with failure due to infection following two-stage revision in 5.4% of those with sensitive organisms compared with 11.1% in those with a resistant infection.⁷⁴ Again, the addition of rifampicin has been reported to increase the rate of eradication, regardless of the antibiotic sensitivities. Among ten patients treated with rifampicin in addition to standard antibiotic cover there were no cases of recurrence at a mean of 23.4 months.⁷⁵

The use of an uncemented prosthesis at the second stage has been questioned, with early studies reporting rates of re-infection as high as 18% and additional cases of loosen-

ing.⁷⁶ Other studies found similar rates of re-infection of between 12.5% and 18%.⁷⁶⁻⁷⁹ However, first-generation cementless implants were used in these series, and subsequent technological advances have improved the results in primary as well as revision THA. More recent investigations have reported rates of re-infection between 8% and 11%.⁸⁰⁻⁸² These more promising results demonstrate that modern cementless components can be used at the time of the second-stage revision, with the potential advantage of enhanced survival of the implant.

Antibiotic-loaded spacers. The articulated spacer provides proper soft-tissue and limb length between stages. This has several advantages, including improved function, preservation of bone stock, prevention of soft-tissue contracture and as a source of local delivery of antibiotics. A review of 81 patients using the original PROSTALAC spacer demonstrated eradication of infection in 95% at two years, with a mean increase in the Harris hip score from 33.5 points pre-operatively to 55.2 between stages and 75.1 at the final follow-up.⁸³ These results have been confirmed by a number of other studies, including one recent review of 23 cases in which the spacer was composed entirely of antibiotic cement, achieving eradication of infection in 95.7%.⁸⁴ The comparison of beads *versus* spacer was made by a retrospective review looking at 70 patients managed with cement beads between stages and 58 who were treated with a custom cement prosthesis.⁸⁵ The rate of eradication of infection was similar between the groups, with an overall rate of 95.3%. However, the custom prosthesis was noted to provide higher hip scores, a reduced hospital stay and enhanced function between stages. At revision there was a reduced surgical time, reduced blood loss and transfusion requirements and a lower rate of post-operative dislocation.

Management of re-infection. The results following infection after a failed two-stage revision have been poor. A review of 34 such patients was associated with a 38% rate of recurrent infection following a variety of operative interventions.⁸⁶ There was a poor functional outcome in the majority of patients. The authors concluded that single-stage revision should not be performed in this situation, and that a two-stage exchange should only be recommended if the infection was due to the initial organism. As there are few studies of the management of this difficult problem the ideal method of treatment is unknown.

Summary

Infection of a total joint arthroplasty is a major complication that requires careful investigation and pre-operative planning before further surgery. A prompt diagnosis permits early treatment, which is important, particularly in stages I and III infections. In the absence of a perfect test, a combined approach using the quadruple assessment of clinical evaluation, serological investigations, diagnostic imaging and microbiological analysis should enable the diagnosis of infection to be made with a high degree of con-

fidence. Following a thorough history and physical examination, with an emphasis on risk factors, symptoms, and signs of infection, the ESR and CRP should be determined. Radiographs should be obtained and compared with previous studies to exclude other diagnoses, with further investigations and treatment being initiated on the basis of these results. Although there are many new methods of imaging none has yet reached a level where it can be relied upon solely in the diagnosis of peri-prosthetic infection. Pre-operative aspiration should be performed and repeated if negative in the face of a high index of suspicion. Every effort should be made to achieve a definitive microbiological diagnosis. There is clearly a role for surgical intervention, but the precise indications for one-stage and two-stage revisions have not been completely delineated. We currently advocate the use of two-stage revision, using an articulated spacer between stages, and have demonstrated a high rate of eradication of infection using this technique.

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