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REVIEW

Infection in total hip replacement: meta-analysis

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Abstract While total hip arthroplasty has progressed to become one of the most successful surgical procedures ever developed, infection remains a serious complication. We have conducted a review of the literature pertaining to management of deep infection in total hip arthroplasty, specifically focusing on clinically relevant articles published in the last five years. A search was conducted using MEDLINE and PubMed, as well as a review of the Cochrane database, using the terms "total hip arthroplasty", "total hip replacement" and "infection". References for all selected articles were cross-checked. While the so-called two-stage revision is generally considered to be the gold standard for management, numerous studies now report outcomes for implant retention and reassessing one-stage revision strategies. There are encouraging reports for complex reconstruction options in patients with associated severe bone stock loss. The duration of antibiotic therapy remains controversial. There is concern about increasing bacterial resistance especially with the widespread use of vancomycin and ertapenem (carbapenem).

Introduction

Infection remains a serious complication of total hip arthroplasty (THA). During the last 30 years, management options have developed to improve clearance of infection while maintaining joint function during treatment and improve outcome at reimplantation. The gold standard in management is generally considered to be implant removal and thorough debridement with antibiotic therapy delivered systemically and locally with impregnated spacers. One of the difficulties in treating infected THA is the heterogeneous nature of the disease. Surgeons and physicians must contend with numerous species of bacteria with variable antibiotic sensitivity. They then need to plan reconstruction in the face of an abnormal bone and soft tissue environment while contending with patient comorbidity. The theoretical gold standard is difficult to apply in all patients, while high-quality literature dealing with alternatives is sparse.

While meta-analysis is a better means of combining studies with related hypotheses, the widely variable nature of research into infected prostheses makes it extremely difficult to construct criteria for assessment. Unfortunately this leaves systematic review of mainly level IV studies as the alternative.

Numerous literature reviews have been conducted and readers' attention is drawn to excellent articles by Fitzgerald, Garvin and Hansen, and Toms et al. [14, 16, 38], which summarise earlier literature. We have systematically reviewed the literature, focusing on articles published from 2005 to the present day regarding advances in the treatment of periprosthetic infection in THA. A search was conducted using MEDLINE and PubMed with a review of the Cochrane database. Search terms were "total hip arthroplasty" or "replacement" or "prosthesis" and "infection". References reported in these articles were then cross-checked.

Classification

Unless otherwise specified, we have used the classification system published by Coventry in 1975 [9] with the

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modification of Tsukayama et al. [40]: stage I infections occurring acutely within six weeks of implantation; stage II infections being delayed chronic presentations; stage III infections occurring in a previously well functioning joint replacement; and stage IV being unexpected positive culture results in what was thought to be an aseptic revision.

Management of infection

Implant retention

Suppressive antibiotics

In general, treatment with suppressive antibiotics is considered in patients who have contraindications to revision surgery. This is usually due to severe or multiple medical comorbidity and those with limited life expectancy. Few recent studies have looked at the use of antibiotic treatment alone. Trebse et al. [39] prospectively followed a group of 24 patients with culture-confirmed infection. Seven of these patients were treated with combination antibiotic therapy alone. While no recurrence occurred during the 3-year follow-up period, this group is too small to draw definitive conclusions.

Debridement and implant retention

Surgical debridement with antibiotic therapy and implant retention may be considered in patients with early type I and type III infections. The reported rate of eradication varies from 26 to 71% [38]. An open approach with thorough debridement, lavage and exchange of modular parts should be considered.

Byren et al. [6] have the largest series of patients managed with debridement, antibiotics and implant retention. They conducted a retrospective review of 112 cases, which included 52 infected THA. Antibiotics were withheld when safe until intraoperative samples had been obtained. Any antibiotic started before presentation was stopped 48 h prior to surgery. Intraoperatively, patients commenced vancomycin and meropenem. These were rationalised when the infecting organism was identified. Meropenem was ceased at 48 h if no aerobic gram-negative organisms were cultured. *Staphylococcus aureus* was the most common organism affecting 42% of cases, with methicillin-resistant *Staphylococcus aureus* (MRSA) accounting for only 8%. A large number of antibiotics were employed with the mean treatment course being 1.5 years. Successful salvage at 1, 2 and three years was 89, 81 and 78%, respectively. Infection with *Staphylococcus aureus* was found to be an independent risk for failure. The authors' analysis suggested an increased rate of failure after ceasing antibiotics. This supports the theory that long-term antibiotics act as suppressive agents in some patients.

Estes et al. [11] retrospectively reviewed 20 patients treated with a two-stage retention debridement protocol. Only four had infected THA. Patients were only included if they had diagnosed infection, had surgery within 28 days of diagnosis and had stable implants at surgery. Two patients with type I infection and 18 with type III infection were treated with debridement and placement of antibiotic cement beads containing gentamicin or tobramycin with vancomycin and cefazolin. A second debridement was conducted at day seven with removal of the beads and exchange of modular components. Intravenous antibiotics were continued for six weeks with variable courses of oral antibiotics ranging from six weeks to lifelong. Patients were followed to minimum 1 year post cessation of antibiotics or minimum one year post debridement in the case of suppressive therapy. Eighteen patients did not show ongoing evidence of infection at one year; however, eight were treated with ongoing antibiotic therapy due to poor host immunity. No patient in the THA group had failed.

Soriano et al. [36] attempted to rationalise antibiotics with retained implants. They reported on 47 patients followed prospectively for two years. This included 11 THA and 21 hip hemiarthroplasty. Eight patients died during treatment. Thirty patients were treated with oral antibiotics and nine with intravenous. Average treatment duration was 2.7 months. The most common regimen included levofloxacin and rifampicin. The infection-free rate in surviving patients was 76.9%. MRSA and *Enterococcus* spp. were associated with a higher rate of treatment failure.

The lack of level I or level II evidence makes definitive conclusion regarding retention difficult. A higher success rate with implant retention may be expected in patients with type I or III infections and those with a short duration of symptoms (less than 1 month). Combination therapy has demonstrated encouraging results, although studies report very variable antibiotic use. Very long courses of oral antibiotics are not clearly beneficial but may benefit frail patients in aiding suppression.

One-stage revision

One-stage revision or direct exchange arthroplasty has obvious advantages in the management of infected THA. With one major procedure, the patient is exposed to lower, cumulative perioperative risk. A functional revision is completed without exposure to the complications associated with spacers (see below). There are also benefits both financially and in terms of resource allocation. This approach is often overlooked because of fears of recurrent

infection without the use of local antibiotics delivered by spacers.

In an older publication, Jackson and Schmalzried [21] conducted a literature review to determine which factors were associated with a successful outcome. Twelve studies, including a total of 1,299 infected THA, were assessed. While antibiotic-impregnated cement was used in 99% of cases, there were wide variations in antibiotic choice, administration and duration. The average time of follow-up was 4.8 years (0.1–17.1 years). Overall infection-free rate was 83% at final follow-up. Factors associated with success were (1) absence of wound complications after the initial THA, (2) good general health, (3) sensitive *Staphylococcus* or *Streptococcus* spp. and (4) organism sensitive to the antibiotic in the cement. Factors associated with poor outcome were (1) polymicrobial infection, (2) gram-negative organisms, especially pseudomonas, and (3) MRSA and group D *Streptococcus*. The authors suggested that using cementless implants or bone graft may be a contraindication to the technique.

One-stage revision with cementless implants has been reported. Yoo et al. [44] published a retrospective review of 12 patients treated with a variety of cementless implants. Eleven had type II infections. Patients were only selected for the procedure if they met the criteria for success outlined above; 83.3% implant survival was reported at a mean follow-up of 3.6 years. There was one recurrence of infection and one aseptic loosening. Eight patients had bone graft, both bulk and particulate, which did not contain antibiotic.

Winkler et al. [42] published outcomes for 37 patients, treated with one-stage, uncemented reimplantation. Of the patients, 12 had a type I infection, nine type II and 16 type III. Cancellous particulate graft was employed, mixed with vancomycin with or without tobramycin. An infection-free rate of 92% was reported with an average follow-up of 4.4 years. Five cases of MRSA were successfully treated.

Rudelli et al. [32] published outcomes for 32 patients treated with one-stage revision and particulate graft. Of the patients, 12 had a type I infection, 17 type II and 3 type III. A combination of cemented, cementless and hybrid fixation was used. In 15 patients, reconstruction mesh was used to support grafts. No antibiotics were added to bone grafts; however, antibiotic-loaded cement was used with cemented prostheses. They reported an infection-free rate of 93.7% at a mean follow-up of 103 months.

Success has been reported with a variety of techniques and in patients with chronic infection. Surgeon training and experience should play a role in choosing the reconstruction option. Meticulous surgical debridement, to clear dead space and residual bacterial colonisation, is emphasised by all authors. Culture-specific antibiotics can be impregnated successfully into bone grafts. The antibiotic levels in cement are limited as high levels can reduce mechanical integrity. The benefits of one-stage revision make ongoing research worthwhile.

Two-stage revision

Two-stage revision is generally regarded as the gold standard for the treatment of infected THA. Eradication rates over 90% have consistently been reported [16]. The principles of two-stage revision are the removal of all components including cement with radical debridement of all possible infected tissue and bone. Local antibiotics are then administered with the use of an antibiotic-loaded cement spacer. Systemic antibiotics are used in conjunction. Infection is deemed to be eradicated with resolution of clinical signs and symptoms and with negative repeat aspiration and normalisation of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) blood markers. The second stage is then undertaken with repeat frozen sections conducted at the time prior to reimplantation. Presence of ongoing infection requires repeat use of a spacer with ongoing antibiotics or consideration of excision arthroplasty. Most centres prescribe a period of six weeks intravenous antibiotics therapy with a further period of oral antibiotics. Reimplantation is conducted at six to 12 weeks and may be altered depending on multiple factors. Several questions remain, particularly around the timing of antibiotic administration, the appropriate use of articulating spacers and timing to reimplantation.

Use of spacers

Antibiotic-loaded cement spacers can be broadly classified as static or articulating spacers. Static spacers consist of a block or beads of antibiotic-impregnated cement, left within the dead space after implant removal. Articulating spacers can also be divided into groups. Monoblock spacers use an antibiotic cement prosthesis supported by a metal endoskeleton. These are available as off-the-shelf implants, for example the Spacer-G (TECRES S.p.A, Verona, Italy) (Fig. 1), but can also be manufactured by the surgeon using moulds with a suitable metal rod for reinforcement [23]. More recently, systems have been developed which use small conventional implants with a metal-on-polyethylene bearing. The prosthesis with antibiotic-loaded cement or PROSTALAC (DePuy, Warsaw, IN, USA) is one such device. Both components are loosely cemented with high concentration, antibiotic-impregnated cement. However, any conventional components designed for cemented fixation are suitable for this purpose (Fig. 2).

The use of spacers has several advantages. They allow the local delivery of antibiotics in high concentration.

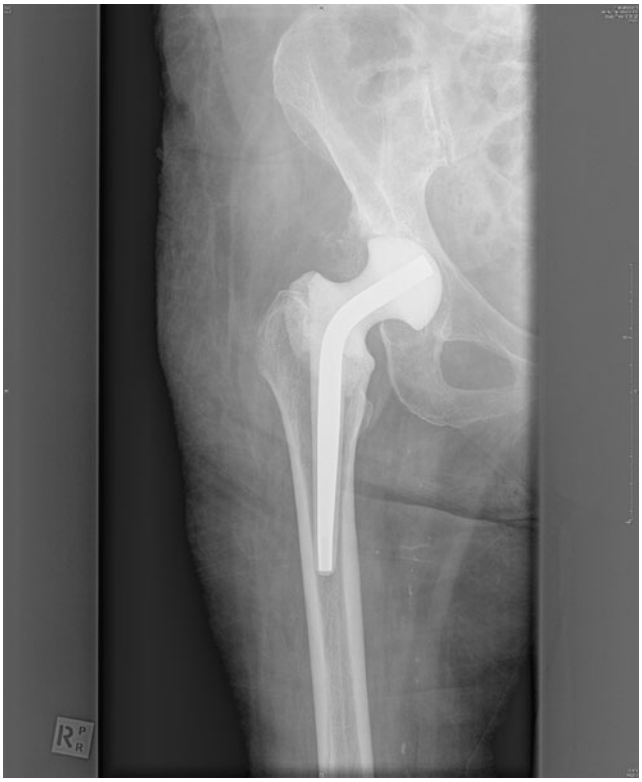

Fig. 1 A preformed gentamicin-loaded articulated femoral spacer

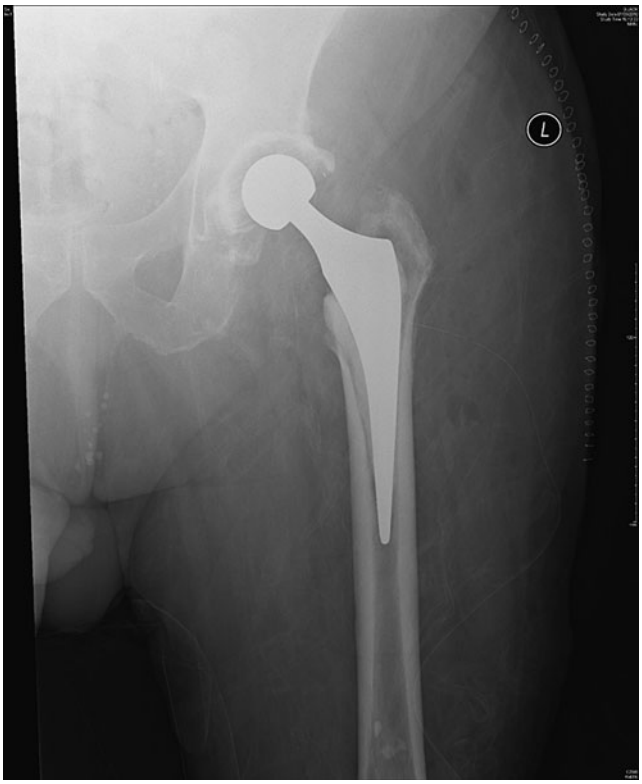

Fig. 2 Inter-stage spacer made of conventional cup and stem components fixed with high-dose antibiotic-loaded polymethyl methacrylate

Articulating spacers help to maintain proper limb length and soft tissue tension between stages. This improves patient function, preserves bone stock, prevents soft tissue contracture and facilitates reimplantation. It is difficult to measure the true antibiotic concentration however, and low levels of antibiotic release late in the life of the spacer may encourage resistant strains of bacteria. If the infecting organism is unknown the spacer may not contain suitable antibiotics. This has driven the routine use of vancomycin and now carbapenem which gives rise to further concerns about resistance to important antibiotics.

Good results have been demonstrated without using spacers. Disch et al. [10] presented a series of 32 hips treated with radical debridement and systemic antibiotics only. Thirty remained infection free at a mean follow-up time of 41 months. Nine patients did require a repeat debridement. Others have demonstrated superior outcomes with spacer use. In a level I, prospective study, Cabrita et al. [7] presented 68 infected THA treated with two-stage revision, 30 without a spacer (control group) and 38 with a vancomycin-loaded spacer (study group). At an average follow-up of seven years (5–11.5 years) the infection-free rate was 66.7% without a spacer and 89.1% with a spacer. The group treated with a spacer had better clinical results, the average Harris hip score (HHS) in the control group being 69 against 75 in the study group.

Use of a spacer does expose the patient to new potential complications. Jung et al. [22] reported complications after hip spacer implantation other than reinfection or infection persistence. The study included 88 hip spacer implantations in 82 patients. The spacer was a handmade, single sized articulating device. The mean follow-up was 54 (7–96) months. The overall complication rate was 58.5%. Spacer dislocation occurred in 17%. Spacer fractures were identified in 10.2%. Femoral fractures occurred in 13.6%. The dislocation rate after second stage reimplantation was 23%. Two patients (2.4%) had allergic reactions to the intravenous antibiotic therapy and acute renal failure occurred in five cases (6%). Increased complications can be expected with single sized spacers, especially without endoskeleton reinforcement [41, 43].

Use of articulating spacers

To overcome the complications of migration, dislocation and breakage, modern spacers have been developed to offer more choice. Off-the-shelf devices now offer a range of head sizes and lengths. Manufacturing standards in the factory ensure more mechanically reliable implants with known concentrations of antibiotics. In a large case series, Romanò et al. [31] reported on 102 consecutive patients with infected THA treated by two-stage revision: 60 received a short-stem pre-made spacer (group S) and 42 a

long-stem (group L). Systemic toxicity and spacer breakage were not observed. No difference was observed with regards to infection recurrence (one in group L, none in group S), spacer cranial dislocation (20% in group L, 14% in group S) and HHS improvement. The infection-free rate overall was 96.1% at a mean follow-up of four years.

In a retrospective review, Hsieh et al. [20] compared the use of antibiotic-loaded cement beads to a preformed spacer. The infection-free rate was 95.3% (122 of 128 patients) with the infection-free rates similar in both groups. The use of an articulating spacer was associated with a higher HHS, a shorter hospital stay and better walking capacity in the interim period. Additionally, at reimplantation the articulating spacer group demonstrated decreased operative time, less blood loss and a lower transfusion requirement. There were fewer postoperative dislocations.

Spacers using a femoral component as the endoskeleton with a metal-on-polyethylene bearing offer several proposed advantages. They are superior at restoring offset and length. Antibiotics can be tailored to the infecting organism. They may confer superior functional results and allow longer periods of use before exchange. Concerns exist about colonisation of the exposed articulating surfaces.

Several options are available. Hofmann et al. [17] described a technique in which the original femoral stem was resterilised and reimplanted with antibiotic-loaded cement. A new polyethylene liner was cemented into the acetabulum. Systemic antibiotics were administered for six weeks. Of 42 patients, eight died and three were lost to follow-up. Three refused reimplantation. The infection-free rate at two years was 94%.

Scharfenberger et al. [33] reviewed 28 patients who were treated with PROSTALAC insertion awaiting two-stage revision. They were compared to patients awaiting THA and those six months post THA. Western Ontario McMaster score and HHS were significantly better than those awaiting THA but less than early primary THA. While the long-term durability of such systems remains to be seen, this type of spacer offers superior functional performance.

Antibiotic use in spacers

To maintain the mechanical integrity of the cement the ratio of antibiotics to cement should not exceed 10% of the total cement used, i.e. 4 g total antibiotic in 40 g of cement. The most commonly added antibiotics include tobramycin, gentamicin and vancomycin. Combining antibiotics results in a synergistic elution effect. This has been measured for tobramycin/vancomycin [30] and vancomycin/meropenem [3].

In many countries, gentamicin is now only available in liquid form. Seldes et al. [35] reported that liquid gentamicin was still potent and bactericidal when used in cement. However, the study showed a near 50% decrease in both the ultimate compression and tensile strengths when 480 mg of gentamicin was added to 40 mg of cement. Hsieh et al. [19] followed 42 patients undergoing two-stage revision arthroplasty for periprosthetic infection and concluded that incorporation of liquid gentamicin in bone cement spacers led to effective drug delivery with systemic safety.

With the rise of resistant gram-negative bacteria there has been increasing use of carbapenems. Baleani et al. [3] found that 0.5 g of meropenem with 0.5 g of vancomycin in 40 g cement was mechanically acceptable. This became unacceptable when the vancomycin dose was increased to 1 g. Andollina et al. [1] conducted an in vitro study with antibiotic-impregnated cement exposed to colonies of bacteria. They showed that 1 g of both vancomycin and meropenem were needed to eliminate pseudomonas. This concentration showed delayed effect against enterococcus. Interestingly a mixture of 0.5 g of each antibiotic showed a rapid response against enterococcus but pseudomonas preparations showed growth colonies that were not eradicated. Currently there is no optimal concentration of meropenem with vancomycin that maintains the integrity of cement while providing adequate antibiotic cover.

Linezolid, an oxazolidinone, is an effective agent against MRSA, vancomycin-resistant enterococci (VRE), resistant coagulase-negative staphylococci and macrolide-resistant streptococci. An in vitro study [2] found that when mixed with gentamicin, linezolid demonstrated acceptable elution from bone cement. Further in vivo studies are required however to clarify the possible side effect profiles of linezolid-loaded cement before its widespread use.

Duration of antibiotic therapy between stages

There is no consensus regarding duration of antibiotic therapy prior to second stage reimplantation. The literature demonstrates a variety of protocols ranging from no antibiotics postoperatively to prolonged intravenous antibiotics. Most units consider four to six weeks of intravenous antibiotics with or without a course of oral antibiotics. Reducing unnecessary antibiotic use slows the development of bacterial resistance, decreases the risk of complications and lowers cost considerably.

Successful outcomes have been reported with no systemic antibiotics therapy. Stockley et al. [37] reported on 114 patients who underwent radical debridement and removal of all cement and components. Antibiotic-impregnated beads were used with three doses of antibiotic postoperatively. An 87.7% infection-free rate was reported at a mean follow-up of 74 months.

Whittaker et al. [41] reviewed 43 patients (44 spacers) who received systemic vancomycin only for two weeks in combination with a vancomycin- and gentamicin-eluting spacer system. The infection-free rate was 92.7% at a mean follow-up of 49 months.

McKenna et al. [28] presented a retrospective review of 30 patients with type II infection. An antibiotic-impregnated spacer was employed with a five day course of intravenous antibiotics after the first and second stage. When cultures dictated, an oral adjuvant was also used, either rifampicin or linezolid. Successful eradication of infection in all patients was achieved at a mean follow-up of 35 months (minimum two years).

Hsieh el al. [18] published a retrospective study of 99 patients who underwent two-stage revision with an articulating spacer. One group received antibiotic therapy for four weeks plus two weeks orally if available in oral form. The other group received one week of intravenous antibiotics. The infection-free rate was 92% after the initial surgery and antibiotic therapy. A further three patients had additional debridement and spacer exchange. There was no significant difference in infection-free rate between groups, 91% in the long-term group and 89% in the short-term group. The short-term treatment resulted in significantly shorter hospital stay (18 versus 43 days) and a significantly lower direct medical cost (US $13,732 versus US $21,756).

The rationale for using an abridged course of intravenous antibiotic is due to the effective and sustained elution of antibiotic from the cement spacer into local tissues. A number of studies have demonstrated maintenance of antibiotic levels above the minimum inhibitory concentration of common pathogens for several months following implantation [4, 27]. The rationale for a short course of antibiotics is to eliminate any bacteria displaced from the surgical area.

Second stage reconstruction options

Two-stage revision also has the benefit of allowing assessment of bone and soft tissue deficits and thus planning of reconstruction. Authors have reported outcomes for cemented and cementless fixation as well as techniques involving bone graft.

The use of cemented implants at the second stage allows the surgeon to add antibiotics to the cement to aid in the prevention of recurrent infection. Rates of eradication have been reported from 84 to 100% using this method [8, 12, 18, 25, 26, 45]. Adequate bone stock is required to ensure durability of this approach.

Early studies of cementless revision prostheses reported an infection recurrence rate of up to 18% and stem subsistence of up to 30% [23, 29]. Improvements in technology, especially modularity, has produced outcomes at least equal to cemented implants. Masri et al. [27] retrospectively reviewed 29 patients who underwent two-stage revision using cementless components for the second stage and PROSTALAC as a spacer. The infection-free rate was 89.7% at a minimum of two years follow-up. Kraay et al. [24] retrospectively reviewed 33 patients with cementless second stage reconstruction. The infection-free rate was 93% at a minimum two-year follow-up. No subsidence of the femoral component was identified. Three patients with severe pelvic bone loss needed acetabular revision. Fink et al. [13] in a prospective study of 36 patients found no infection recurrence with a mean follow-up of 35 months. A uniform protocol of a six-week spacer interval, specific local and systemic antibiotics, and a cementless modular revision stem was used. There was no implant loosening and 94% bone-ingrowth fixation of stems. Subsidence occurred in two patients. The HHS increased from a preoperative mean of 41 to 90 at 12 months post reimplantation.

Remaining large bony defects pose a complex surgical dilemma. Both bulk allograft and particulate graft may be required. The theoretical disadvantage is the risk of colonisation of avascular grafts. Early reports of allograft use have shown excellent results [5].

Hsieh et al. [18] reported on their series of 24 patients who underwent second stage reconstruction with impaction grafting. Antibiotic-loaded cement was used in revision components when a cemented prosthesis was used. No recurrence of infection had occurred at a mean follow-up of 4.2 years. They found allograft incorporated into the host bone in all patients.

Buttaro et al. [5] reported 30 cases who received vancomycin-supplemented impaction bone grafting. Antibiotics were not added to cement used in the revision prosthetics. The infection-free rate was 96.7% at a mean follow-up of 32.4 months.

Several reconstruction techniques have proved durable as second stage options. Modular cementless implants have increased the ability to reconstruct complex bone loss in conjunction with allograft. Surgical experience in dealing with bone loss with or without infection is essential.

Salvage procedures

In cases where it is difficult to obtain control of infection, excision arthroplasty may be considered. This procedure is associated with control of pain but lower functional scores [34]. A recent study by Ganse et al. [15] reviewed 17 patients at an average of 52 months post surgery for infected THA; five were managed with excision arthroplasty and 12 with two-stage revision. There were no differences in HHS between groups, both with an average score of 60. Patients should be made aware of limb length discrepancy and the likely need for a walking aid.

Summary

Infection remains an important complication of THA. The complex interaction of patient comorbidity, microbiology, local tissue deficiency and surgeon experience make management a specialised, multidisciplinary problem. Attempts at implant retention may be warranted in patients with type I and type III infections and in situations where multiple operations will not be tolerated. Promising results have been demonstrated with one-stage direct exchange protocols using cemented and cementless implants. Long-term results are needed to establish the true durability of this approach. Use of spacers has assisted in clearance of infection and in improved function during two-stage treatment. Modern articulating spacers allow closer matching of anatomy to reduce some complications associated with static models. Speculative use of vancomycin in spacers is common and there are concerns about increasing bacterial resistance. Ertapenem is now being used in spacers but ideally should be used for cases of known gram-negative infection. Surgeons should continue to use cultures to direct antibiotic therapy. There is no direct evidence that inferior results occur when using shorter courses of antibiotic therapy between stages. Reports of second stage reconstruction with cemented and cementless systems show favourable short-term outcomes, with positive results when using bulk and particulate graft. Regardless of the question, research into infection management needs to shift from retrospective cohort studies to longer-term prospective investigations. While such studies are difficult to design for patients with multiple variables, the question of antibiotic duration for instance fits this model and is of great clinical and economic importance.

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