

Diagnosis and management of prosthetic joint infection

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Joint replacement is safe, cost effective,¹ and widely undertaken. Most prosthetic joint replacements are hips and knees; more than 130 000 people underwent such procedures in England and Wales in the 12 months from April 2006.^{w1} Subsequent prosthetic joint infection is uncommon—the incidence varies between 0.6% and 2% per joint per year.²⁻⁵ However, this complication is associated with substantial morbidity and economic cost (\$30 000 (£20 500; €22 800) to \$50 000 per patient).^{3,4,6,w2} The diagnosis of prosthetic joint infection is difficult,^{w2} because symptoms, signs, and investigations may all be non-specific.^{7,w3} Defining diagnostic criteria and optimum management is complicated by patient heterogeneity and the small numbers in many published studies.^{w4} However, prompt recognition and diagnosis of prosthetic joint infection facilitates timely intervention to salvage infected joints, preserve joint function, prevent morbidity, and reduce costs.

What are the clinical features of prosthetic joint infection?

Early prosthetic joint infection (box 1) characteristically presents with wound inflammation, joint effusion, loss of function, and pain,^{8,9,w5,w6} with or without wound dehiscence and discharge.^{8,9} Later disease is more likely to present with pain or mechanical dysfunction.^{w2} Systemic features, such as pyrexia, nausea, and malaise, are neither sensitive nor specific.^{w7} The onset of symptoms may be acute or insidious, with progressive pain or loss of function.^{7,9}

Who is at risk of prosthetic joint infection and when does it present?

Infection rates vary according to the joint replaced, indication for arthroplasty, comorbid conditions, and prophylactic strategies (box 2).^{5,15} Obesity and diabetes have been associated with early infection.^{9,15,w8} No increase in prosthetic joint infection has been reported in small cohorts of patients with kidney transplants^{w9} or HIV infection,^{w10,w11} but as arthroplasty is increasingly performed the number at risk may increase.

In publications from the Mayo Clinic, 25% of wound infections were associated with joint infection,⁶ and the

presence of any wound complication was significantly associated with deep infection.¹² In a prospective case-control study, persistence of wound drainage for longer than five days after surgery and wound haematoma were associated with prosthetic joint infection (odds ratios 1.3 and 11.8).^{w12} These studies highlight the need for careful scrutiny of all wound complications overlying an arthroplasty.

The proportion of prosthetic joints that become infected within three months of arthroplasty varies widely—from 29% to 69% in cohorts from the United Kingdom.^{2,10} Early infection is usually acquired at the time of surgery or as a consequence of wound infection, whereas later infections arise because of haematogenous spread⁸ or because the pathogens are of low virulence and slow to cause symptoms.

Which organisms commonly cause prosthetic joint infection?

Gram positive organisms, especially staphylococci (commensal skin organisms), are most common (table 1).^{2,9,10,15,17} In early infection, pathogens are usually more virulent (for example, *Staphylococcus aureus*),¹⁸ whereas more indolent organisms predominate later on (for example, coagulase negative staphylococci, *Propionibacterium acnes*).¹⁰ In a recent UK study, however, most early cases were caused by coagulase negative staphylococci.⁸ In this cohort, most antibiotic

SOURCES AND SELECTION CRITERIA

We performed Medline searches between November 2008 and January 2009 using the search terms “prosthetic joint” and “arthroplasty” combined with “infection”, “guidelines”, “septic arthritis”, “infection diagnosis”, “infection epidemiology”, and “infection revision arthroplasty”. Where possible, we focused on articles published in the past five years and restricted our search to literature published in English. We also drew from the experience of, and articles and documents published by, our multidisciplinary bone infection unit in the United Kingdom (www.noc.nhs.uk), which manages around 40 secondary and tertiary referral cases of prosthetic joint infection a year.

resistant and polymicrobial infections presented within three months of arthroplasty.¹⁰ Infection with antibiotic resistant organisms poses an increasing challenge, with meticillin resistant *S aureus* (MRSA) being more common than meticillin sensitive *S aureus* (MSSA) in some series.^{9,15}

Which laboratory investigations are needed?

Figure 1 summarises key steps in the diagnostic process. UK guidelines recommend baseline blood tests for inflammatory markers (C reactive protein, erythrocyte sedimentation rate, leucocyte count) for any case of septic arthritis.^{w5} However, these parameters are raised for up to two weeks after orthopaedic surgery so are non-specific for early infection.⁸ Serial measurements can be useful,²² because persistently or progressively high inflammatory markers may help to distinguish joint infection from an uncomplicated postoperative course. Normal results do not exclude joint infection,^{7,14} particularly infection with indolent organisms.

Blood for culture should be taken before patients with suspected acute infection are started on antibiotics, although cultures are usually negative.³⁹ Early empirical treatment reduces the diagnostic yield from cultures: more than half of culture negative cases from the Mayo Clinic had received previous antibiotics.²¹ The resulting failure to identify the causative pathogen(s) and the antimicrobial sensitivity profile may jeopardise outcomes. However, it may be impossible to take deep cultures before starting antibiotics in

Box 1 Definitions of prosthetic joint infection

No uniform case definitions exist for prosthetic joint infection, but widely accepted definitions include any of the following^{6,7,9-12,w6,w14}:

- Purulence around a prosthesis at arthrotomy or arthroscopy
- Presence of one or more sinus tract communicating with the joint
- Histological features of infection
- Isolation of an indistinguishable organism from at least two deep culture samples ("indistinguishable" refers to widely performed laboratory characterisation of an organism; in most cases this will be identification of the genus and species, plus antibiotic susceptibilities¹³). Isolation of a virulent organism, such as *Staphylococcus aureus*, *Escherichia coli*, or *Candida* spp, in one deep tissue sample is regarded by some as sufficient to confirm the diagnosis.⁷

Early prosthetic joint infection

Early prosthetic joint infection is most widely defined as deep infection of an arthroplasty occurring within three months of joint replacement. Subsequent presentation is divided into delayed (3-12 months after index surgery) or late (>12 months).^{8,9,11,14}

patients with systemic sepsis or rapidly evolving local infection.

Superficial swabs reflect colonising flora only, and results must therefore be interpreted with caution. Occasionally, swab results may help to inform empirical antibiotic choices^{w13}—for example, by identifying carriage of resistant organisms. However, deep samples of synovial fluid and tissue taken at arthrotomy, arthroscopy, or by aspiration are needed for definitive diagnosis. Such cultures were positive in 85% of 297 patients undergoing revision arthroplasty who had prosthetic joint infection.¹³ In this study, the identification of indistinguishable organisms from at least three culture samples was highly predictive of infection; to optimise diagnostic sensitivity and specificity, the authors therefore recommended that five or six samples are sent for culture.¹³

Histopathology can be a crucial adjunct to microbiology in the diagnosis of infection.^{7,13} This test has 94-98% sensitivity and adds significantly to the number of cases diagnosed by cultures alone.^{7,w14} Multicentre analysis suggests that a white cell count and neutrophil differential of the synovial fluid are also sensitive markers.²³

Which imaging modalities are useful?

Plain radiography is often non-specific in early infection but may be useful to monitor serial changes. Loosening or bone loss around a previously well fixed implant is associated with chronic prosthetic joint infection (fig 2).^{3,7,8,w14} Ultrasound is useful to confirm effusion and to facilitate aseptic aspiration. One series reported abnormalities on ⁹⁹Tc labelled scintigraphy in

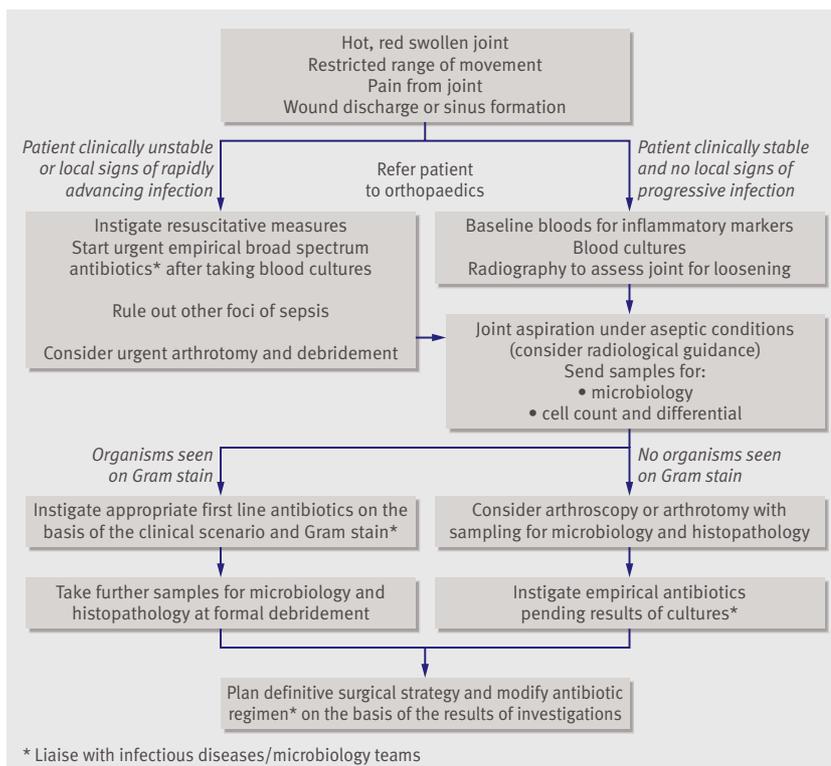


Fig 1 | Algorithm outlining diagnostic and therapeutic interventions in the management of early prosthetic joint infection

patients with early prosthetic infections,⁹ but the study did not discuss the low specificity of this test.^{8 w2} Computed tomography and magnetic resonance imaging may be useful in the evaluation of complex cases, but metal inserts interfere with these tests,^{w15} and abnormalities may be non-specific.^{14 w15}

What management challenges does prosthetic joint infection pose?

Management of infection in arthroplasty poses the dual challenge of eradicating infection while preserving mechanical joint function. Biofilm is almost universally associated with infection of prosthetic material (table 2), particularly in chronic cases, and this underpins the need for thorough debridement and prolonged treatment with a combination of antibiotics.^{3 11 w16 w17}

Table 1 | Organisms that commonly cause prosthetic joint infection

Infesting organism	Frequency of pathogen	Suggested intravenous antibiotic*	Suggested oral antibiotic*
Gram positive			
Coagulase negative staphylococci	13-37% ^{2 7 10 15 17 19 w2 w28}	Glycopeptide ^{9 10 w27}	Rifampicin plus another agent, such as ciprofloxacin, fusidic acid, trimethoprim, or doxycycline, according to sensitivities ^{8 9 15 18 20 w4}
Meticillin sensitive <i>Staphylococcus aureus</i>	20-62% ^{7 9 10 17-19 w2 w28}	Flucloxacillin or ceftriaxone ^{8 10 12}	Rifampicin combinations as above, according to sensitivities ^{8 9 15 18 20 w4}
Meticillin resistant <i>S aureus</i>	2-49% ^{4 7 9 10}	Glycopeptide ^{9 10 w27}	Rifampicin combinations as above, according to sensitivities Linezolid ^{w36 w37 †}
<i>Streptococcus</i> spp	4-27% ^{4 7 10 17 w2}	Penicillin or ceftriaxone ^{8 10 w19}	Amoxicillin or cefalexin ^{10 19 w19}
<i>Enterococcus</i> spp	6-13% ^{7 9 10 w3}	Penicillin or glycopeptide with or without an aminoglycoside ^{10 w40}	Amoxicillin ^{8 10} or linezolid ^{w36 w37 †}
Diphtheroids (<i>Corynebacteria</i> spp, <i>Propionibacteria</i> spp)	6-20% ^{7 10}	Glycopeptide ¹⁰	Rifampicin combinations as above, or ampicillin ¹⁰
Gram negative			
Enteric Gram negative bacilli	2-15% ^{4 7 10 17}	Ceftriaxone ¹⁰ ; carbapenem with or without aminoglycoside ¹⁰	Ciprofloxacin ^{8 10}
<i>Pseudomonas</i> spp	1-4% ^{7 12}	Ceftazidime, ^{8 10} carbapenem, or ticarcillin with or without aminoglycoside	Ciprofloxacin ^{8 10}
Others			
Anaerobes	1-8% ^{10 17}	Carbapenem ¹⁰	Clindamycin ⁸ or metronidazole ¹⁰
Mycobacteria	<1%-6% ^{14 w7}	A combination of agents (usually including rifampicin) on the basis of the antimicrobial susceptibility profile of the organism; seek microbiology advice	
Fungi	<1% ¹⁰	Common approaches include amphotericin or fluconazole, but seek microbiology advice	Common approaches include fluconazole or itraconazole, but seek microbiology advice
Polymicrobial infections			
≥2 organisms	4-56% ^{9 10 17 w2 w25}	Consider co-amoxiclav ⁸ ; select treatment on the basis of the combination of pathogens and sensitivities ^{w25}	
Culture negative infections			
No pathogen identified	11-26% ^{8 9 18 w2}	Glycopeptide with or without carbapenem or cephalosporin ²¹	Consider standard combination, such as rifampicin plus ciprofloxacin

*All suggested regimens should be tailored according to sensitivities obtained from the microbiology laboratory and should be prescribed after consideration of comorbidities (such as renal or hepatic dysfunction), potential hypersensitivity or side effects (such as rash, nausea, nephrotoxicity), and drug interactions (such as rifampicin and warfarin). Oral therapy generally requires combination regimens; rifampicin should never be used as monotherapy, owing to a high rate of selection for resistance.

†Patients receiving linezolid should be monitored with regular full blood counts and advised about the risk of peripheral or optic neuropathy.

Box 2 Common risk factors for prosthetic joint infection

Patient factors

Systemic

Advanced age⁹

Obesity^{5 9 15 w8}

Diabetes mellitus^{9 15}

Steroids⁹

Malignancy⁶

Rheumatoid arthritis⁵

Local

Previous arthroplasty on the same joint^{5 9 w38}

Arthroplasty undertaken to treat a fracture⁵

Type of joint replaced (for example, risk is greater for the knee than the hip)²

Perioperative wound complications,⁹ including superficial wound infection,^{6 w12} haematoma, or persistent wound drainage¹⁶

Operative factors

A score ≥36 on the American Society of Anesthesiologists score^{w39}

Duration of operation >75th centile for the procedure or longer than three hours^{6 w39}

Wound classed as contaminated or dirty^{w39}

No systemic antibiotic prophylaxis

No antibiotic cement⁵

Patients with the first three operative factors are at greatest risk of developing infection at the surgical site

As with all iatrogenic complications after an elective intervention, a diagnosis of prosthetic joint infection can be difficult to accept, for both patients and clinical teams. Management often necessitates prolonged inpatient stays, repeated surgical procedures, and long term antibiotics, all of which may be associated with further morbidity, pain, and anxiety.^{w6} Although these aspects of prosthetic joint infection have not been formally studied, it is important to provide a multidisciplinary environment in which patients are supported and informed throughout their management.

What are the principles of management?

Long term outcomes are significantly better when management adheres to guidelines.^{10 24} Major considerations are whether the implant should be retained, what surgical strategy should be used, and which antimicrobial treatment to choose. The decision is influenced by disease duration, causative pathogen(s), extent of bone and soft tissue involvement, comorbid conditions, technical abilities of the surgical team, and the wishes of the patient (table 3).

What surgical options are available?

Initial surgical aims are to drain abscesses and remove dead tissue, to confirm the diagnosis with multiple tissue samples,¹³ and to achieve primary soft tissue closure

AREAS FOR FUTURE RESEARCH

- Further development and wider availability of molecular diagnostic techniques may help improve microbiological diagnosis in culture negative cases
- Large multicentre randomised trials are needed to establish optimum management strategies (in particular, to identify who would benefit from a “debride and retain” approach); to evaluate antibiotic regimens; and to stratify the duration of antibiotic treatment. This will allow delivery of the most cost effective care

over drains. Management options can thereafter be divided into three broad categories (table 3)^{5 8 w2}:

- Debridement and retention of a well fixed prosthesis^{12 18 20 w18 w19}
- Removal of the prosthesis, then immediate reimplantation of a new prosthesis (one stage revision)^{14 24} or delayed reimplantation, typically six to eight weeks later (two stage revision)^{21 24 w20}
- Palliative strategies are needed in a minority of cases, usually in patients with severe comorbid disease.

Debridement, antibiotics, and implant retention

This approach incorporates thorough debridement of infected tissue around the joint, exchange of replaceable parts of the prosthesis, soft tissue closure, and treatment with antibiotics.^{18-20 w18 w21} In a recent study, open arthrotomy was superior to arthroscopic washout.^{w18} Certain pathogens, such as penicillin susceptible streptococci, are associated with good outcomes.^{w19}

This management approach can eradicate infection while preserving joint function, and it is a particularly attractive option in early infection.^{8 18 24 w19}

Revision arthroplasty

Removal of an infected prosthesis together with the affected bone, soft tissues, and all cement is a demanding procedure that needs considerable surgical expertise. Preoperatively, patients need counselling and optimisation of their general health.

Two stage revision is the most common approach to chronic prosthetic joint infection in many centres,^{7 17 21 w2}



Fig 2 | Plain radiograph of a chronically infected left total hip replacement, showing loosening (arrows), cortical bone loss, and femoral migration of the prosthesis

and it offers the option of local delivery of antibiotics via antibiotic eluting cement spacers.^{5 w20} However, this approach is expensive, time consuming, and may result in further tissue damage. In our experience, many patients also find it difficult to cope with restricted mobility before reimplantation.

Although one stage revision is less common,¹⁷ it is standard in some centres and can be successful.¹⁴ Outcome is probably related to the thoroughness of surgical resection, regardless of whether one or two stage reconstruction is used.^{w22 w23}

Serious soft tissue defects can be caused by aggressive local infection or can be secondary to surgical debridement. Around the knee in particular, plastic surgery may be needed to provide soft tissue cover for exposed bone or prosthesis.^{w24}

What is the best antimicrobial strategy?

The choice of antibiotics should be based on culture results; antibiotics should achieve high concentrations in the tissue and be active against slow growing organisms and biofilms.^{12 w4 w16} Liaison with microbiology services is advisable.^{17 w4} We present an overview of commonly selected agents (table 1), but the choice of agent, route of administration, and duration of treatment varies greatly.

Empirical antibiotics

Empirical antibiotics may be needed while culture results are awaited and for the duration of treatment for culture negative infection. Local policies based on

Table 2 | Characteristics of biofilms relevant to prosthetic joint infection

Characteristic	Relevance to pathophysiology	Clinical correlates
Genetic diversity: small colony variants ^{w17}	Subpopulations of organisms exist as slow growing phenotypic variants	Organisms may look atypical in vitro, so can confound laboratory diagnosis Slow growth increases the risk of antibiotic failure and justifies the use of prolonged treatment ¹¹
Polysaccharide matrix	Extracellular slime; distributes nutrients and facilitates communication between cells	Microenvironment favours persistence of organisms and may inhibit bacterial killing and phagocytosis; justifies use of prolonged antibiotic regimens incorporating rifampicin ^{12 20}
Adherence to surfaces	Whole population of infecting organisms may be adherent to prosthetic material	Can significantly reduce yield from bacterial culture of synovial fluid; therefore, periprosthetic and tissue samples are also needed to confirm diagnosis ^{7 w14}
Quorum sensing ^{w16}	Genetic interactions between populations of cells	Antibiotic resistance is conferred by sharing of genetic resistance determinants; this characteristic is one reason for using combined oral antibiotic regimens ⁹

Table 3 | Characteristics of patients appropriate for different management approaches to prosthetic joint infection

Surgical strategy	Patient characteristics
Debridement, antibiotics, and implant retention	No loosening of prosthesis; adequately functioning joint ^{10 12 w19} Healthy soft tissue envelope ^{8 19 w18} Short duration of symptoms ^{8 19 24 w19} (although recent studies also support this approach in some patients with more chronic disease) ^{w18} Clearly characterised bacteriology, and highly antibiotic-susceptible organism(s), such as penicillin susceptible <i>Streptococcus</i> spp ^{w19}
One stage revision arthroplasty	Unstable implant but intact soft tissue ⁸ Organism susceptible to antibiotics ^{8 w19} More complex surgery contraindicated because of comorbidity
Two stage revision arthroplasty	Unstable implant ⁸ Considerable damage to soft tissue ^{8 19} Resistant or difficult to treat organism, ^{8 22} such as meticillin resistant <i>Staphylococcus aureus</i> , vancomycin resistant enterococci, and fungi Long established infection Failure of previous attempt at debridement and retention ³
Removal of prosthesis or arthrodesis	Serious comorbidity Repeat surgery unacceptable to the patient or deemed unsafe ⁸
Amputation	Last resort in the context of uncontrolled symptoms from the joint, including intractable pain or profuse discharge from sinuses that does not respond to antibiotic suppression Uncontrolled systemic sepsis Mechanical joint failure not amenable to salvage, ^{w41} or severe soft tissue damage not amenable to reconstruction Other options declined by the patient

the prevalence of resistant organisms guide the choice of agent. If prescribing parenteral treatment, a glycopeptide is often included to cover MRSA.^{3 10 22} Gram negative cover may be added by using an intravenous cephalosporin or carbapenem,¹⁰ especially if polymicrobial infection is likely.^{w25} An aminoglycoside is an alternative choice if concerns exist about *Clostridium difficile* diarrhoea.²²

Intravenous treatment

Selected patients can continue intravenous antibiotics in the community under the supervision of an outpatient parenteral antibiotic therapy programme.^{25 w26} A once daily antibiotic regimen using agents with a long

half life, such as teicoplanin or ceftriaxone, is optimum.^{9 w27}

Oral treatment

Oral antibiotics can prolong safe affordable treatment. Rifampicin has excellent biofilm activity but selects rapidly for resistance if used as monotherapy. The most robust evidence comes from a randomised controlled trial of rifampicin plus a fluoroquinolone versus fluoroquinolone alone¹²; the success of this regimen is confirmed by other studies of staphylococcal infection.^{9 12 15 18} Rifampicin and fusidic acid is an alternative combination for treating fluoroquinolone resistant organisms.²⁰ In a study of 40 episodes of prosthetic knee infection, any rifampicin containing regimen was more than 95% successful.²⁴

Duration of antibiotic treatment

The duration of antibiotic treatment varies according to surgical management. If an infected prosthesis is retained, many clinicians favour up to six weeks' parenteral treatment.^{9 17} If joint revision is undertaken some centres reduce the duration of intravenous antibiotics to two to four weeks.^{17 18} Robust data are lacking and clinical practice varies. Oral antibiotics are generally prescribed for a minimum of three to six months for a retained prosthesis and six weeks for revision arthroplasty, without prolonged parenteral treatment.¹¹

In the minority of patients in whom surgery is precluded or declined, indefinite long term oral antibiotics (≥1 year) may be given, with the aim of suppressing but not curing the infection.^{17 w21} Despite these general recommendations, antibiotic prescribing varies considerably.^{3 9 17 18 20 22 w2 w28} An American study found no relation between the duration of parenteral treatment and the risk of relapse,²² and recent UK data suggest that oral treatment beyond six months does not increase the cure rate.^{w18}

What preventive strategies exist?

The incidence of prosthetic joint infection has been progressively reduced by improvements in ultraclean air, preoperative preparation, surgical technique, theatre design, prophylactic antibiotics, wound care, and hand hygiene.^{w2} Ring fencing of beds for elective orthopaedic patients reduced the rate of MRSA infection by 70% in one UK centre.^{w29} Decolonising patients who are colonised with MRSA before elective surgery reduced the risk of implant infection in some centres,^{w30 w31} but local guidelines vary. Many orthopaedic surgeons advocate the use of antibiotic prophylaxis for patients with arthroplasties who are undergoing invasive dental procedures,^{w32} although this practice is not supported by clear evidence. Rigorous protocols (including surgical site infection care bundles)^{w33} are essential if infection rates are to be reduced.

What are the current developments in this field?

Further multicentre collaborations and randomised trials are needed to answer key questions about

TIPS FOR NON-SPECIALISTS

- Patients with arthroplasty who present with wound discharge or erythema over the joint, or who report swelling, pain, or restriction of joint movement, should be promptly investigated for prosthetic joint infection^{8 11}
- Refer such patients immediately to an orthopaedic team. In hospital, take baseline bloods (for inflammatory markers and cultures)^{w5} and have the joint imaged and aspirated. Plain radiographs may be normal, but loosening of the prosthesis raises suspicion of infection
- Collaborate with a microbiologist or infectious diseases doctor early in the course of management¹⁷
- Avoid giving empirical antibiotics until samples have been taken for culture unless the patient is systemically unwell or has local signs of rapidly advancing infection²¹
- If an attempt is made to retain the prosthesis, surgical debridement of infected soft tissues around the joint plus 3-6 months of antibiotics, using rifampicin based regimens for staphylococcal infection is recommended^{9 12 15 18 20}

SUMMARY POINTS

Early diagnosis of prosthetic joint infection reduces morbidity and improves outcomes

Infection is eradicated and joint function is preserved in most patients who receive appropriate combined surgical and medical treatment

A multidisciplinary team is often needed for optimal diagnosis, treatment, and rehabilitation; specialist referral may be required.

Well fixed implants can be salvaged by aggressive debridement, antibiotics, and implant retention

Antibiotics are usually needed for three to six months if the prosthesis is retained, or for up to six weeks after revision arthroplasty

optimum diagnosis and management of these challenging infections. For now, attention to sound surgical and antimicrobial principles in the context of a coordinated multidisciplinary team offer the best treatment options.

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ADDITIONAL EDUCATIONAL RESOURCES

For healthcare professionals

- UpToDate (www.uptodate.com)— This evidence based, peer reviewed resource for clinicians includes information on prevention, diagnosis, and management of prosthetic joint infection. Follow the link to infectious diseases then contents, then see the section on skin, soft tissue, and bone infection
- Infectious Diseases Society of America (www.idsociety.org)—Guidelines on the diagnosis and management of prosthetic joint infection will be available online later this year
- For guidelines, drug regimens, and management algorithms, see Zimmerli et al⁸ and Trampuz and Zimmerli¹¹
- Coakley G, Mathews C, Field M, Jones A, Kingsley G, Walker D, et al. BSR & BHPR, BOA, RCGP and BSAC guidelines for management of the hot swollen joint in adults. *Rheumatology (Oxford)* 2006;45:1039-41
- UK Guidelines are currently being drafted for the British Orthopaedic Association, British Infection Society, and Association of Medical Microbiologists (projected date of publication is late 2009)

For patients

- Oxford Bone Infection Unit (www.noc.nhs.uk/ourservices/bone_infection.aspx)—Patient information leaflets on prosthetic joint infection, use of antibiotics in bone and joint infection, and central venous access devices for parenteral treatment at home
- Uptodate for Patients (www.uptodate.com/patients)—Additional information can be found using the search term “prosthetic joint infection”

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