Prosthetic joint infections

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Abstract

Objectives: To review the available literature on prosthetic joint infections and provide recommendations on management particularly the importance of identifying the causative organism and starting the most appropriate antimicrobial therapy.

Methods: The medical literature was searched using PubMed, employing the key words prosthetic joint infections. There appears to be no UK consensus guidelines on the management of prosthetic joint infections or the use of prophylactic antibiotics to prevent them. There is however a number of key documents and trust policies which deal with the subject extensively. We also made use of 'The Sanford Guide to Antimicrobial therapy 2012' for the latest recommendations on the correct antimicrobial therapy.

Conclusion: Although diagnosis is often difficult, there are a number of investigations which can help us identify the organism. We recommend that the local prevalence of such infections is studied together with identification of the commonest organisms. Work is already underway between the infectious disease team and orthopaedic surgeons to devise locally adapted protocols for the identification and management of such infections. They should work in close liaison to implement the correct treatment which often involves a combination of both surgical and antimicrobial therapy.

Keywords

Prosthetic joints, infection, biofilm

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Introduction

Infections of prosthetic joints represent a devastating complication with a high morbidity and mortality and also substantial costs. Diagnosis depends on a number of clinical signs and symptoms, blood tests, histopathology, imaging and microbiological tests. It is often difficult to distinguish from aseptic failure of the joint. Treatment involves adequate antimicrobial therapy and often surgery is necessary.

The purpose of this review is to discuss the diagnosis, management and prevention of prosthetic joint infections according to current available literature and to stress the need for guidelines both for management of these infections and their prevention. Currently there appears to be no UK consensus guidelines on the management of prosthetic joint infections. There is however a number of key documents and trust policies which deal with the subject extensively and which can be combined into one main consensus guideline.

Methods

Two reviewers (CF and PF) independently performed a systematic review of the literature. The following terms were used in searches of the PubMed database: 'prosthetic joints', 'prosthetic joint infections', 'joint infections' and 'orthopaedic infections'. Publications available between the years 2000 and 2010 were considered so as to focus on the latest data available. From a total of about 2000 articles, approximately 250 relevant papers written in the English language were reviewed. Citations of key articles were also identified and reviewed. The final selected articles are cited in this document and listed as references. Additional information was obtained from the 'The Sanford Guide to Antimicrobial therapy 2012' for the latest recommendations on the correct antimicrobial therapy.

Pathogenesis

Prosthesis associated infections are caused by micro-organisms in biofilms. These are micro-organisms that grow in clusters attached to the surface, in a hydrophilic extracellular matrix.[1] Micro-organisms in this biofilm are more resistant than normal counterparts due to lack of metabolic substances and accumulation of waste products which allow them to enter a slow, non-growing state. They are in an ideal environment to resist host immunity and antibiotics. *Staphylococcus epidermidis* and *Staphylococcus aureus* usually adhere to the surface of the foreign body and rapidly accumulate to form the biofilm. The presence of a foreign body decreases the minimal infecting dose of such organisms.

Epidemiology

It is difficult to estimate the incidence rate of prosthetic infections, because of probable underestimation since some cases may be presumed to be aseptic failure. This is also true because the prosthetic joint remains always at risk to haematogenous seeding during the whole lifetime. In the first two years, the infection rate is thought to be <1% in hip and shoulder prosthesis, <2% in knee prosthesis and <9% in elbow prosthesis.[2]

This obviously depends on the centre and also if it is a revision operation where the operation risk increases up to 40%.[1]

The incidence of prosthetic joint infections has decreased due to better pre-operative prophylaxis and laminar flow in operating theatres, but it is thought that it will be increasing in the future due to better detection methods, the ageing population, increased use of prosthetic joints and the increased resistance time of these joints.

Causative organisms

Commonly identified organisms are shown in Table 1.[1] Polymicrobial infections, with MRSA and anaerobes being the most common organisms, occur more likely in patients with soft tissue defects, dehiscence and old age.[3] Polymicrobial infections tend to be found in early infections.[4] The local prevalence of prosthetic joint infections and the organisms commonly involved is not currently available because microbiology data is all grouped under 'wound swabs' or tissue biopies, which obviously include other orthopaedic wound infections. The impression of the authors is however that our rates of *S. aureus* and especially of MRSA are much higher.

Clinical presentation and classification

Leading signs of joint infections include erythema, pain, limitation of movement, fever, oedema, haematomas and poor wound healing. Low grade infections can present with only some loosening of the joint with or without pain, making it difficult to distinguish from aseptic failure. Late infections usually present with systemic symptoms following unrecognised bacteraemia from teeth, skin, lung or urinary tract.

Prosthetic infections can be classified into early, delayed (or low grade infections) and late infections as shown in Table 2.[5,6]

Micro-organisms	Frequency
Coagulase negative Staphylococcus	30-43%
Staphylococcus aureus	12-23%
Streptococci	9-10%
Enterococci	3-7%
Gram negative bacilli	3-6%
Anaerobes	2-4%
Polymicrobial	10-12%
Unknown	10-11%

Table 1 *Commonly identified micro-organisms*[1]

Risk factors

Spread of infection is thought to occur in one of three ways.

1. Perioperative inoculation of micro-organisms in the wound.
2. Haematogenous spread from a distant source of infection.
3. Contiguous from a focus source e.g. infection due to penetrating trauma or previous osteomyelitis.

Rheumatoid arthritis, psoriasis, immunosuppression, steroids, poor nutrition, diabetes and old age are thought to be risk factors.[1] Some also claim malignancy, superficial infection at surgery and poor arthroplasty technique.[7] The overall risk of bacteraemia appeared low in one study at 0.3%[8] but increased to 34% if the organism is *S. aureus.* Haematogenous spread appears to affect knee more than hip prosthesis.[1]

According to S. Esposito in a recent clinical review, the most important risk factors are co-morbidities and prior joint replacements.[9] A study done in 2007 in Melbourne, Australia, assessed the risk factors for acute prosthetic joint infections and found that there was a correlation between having a Body Mass Index of >=30 with two or more co-morbidities and an increased risk of prosthetic joint infections. Diabetes was also a potential risk factor. Other factors were assessed but were not found to significantly contribute to the risk of infections. These were smoking, increasing age, prior haemoglobin levels and length of hospital stay.[10]

Early (<3months) 29-45%	Acquired during surgery or up to 4 days later. Organisms involved are highly virulent e.g. *S. aureus* or gram negative bacilli.
Delayed (3-24 months) 23-41%	Acquired during surgery Organisms less virulent e.g. coagulase negative Staphylococci.
Late (>24 months) 30-33%	Due to haematogenous seeding from remote infections

Table 2 *Classification of prosthetic joint infections*[5,6]

Investigations

There is no single test which is sensitive and specific enough to diagnose prosthetic joint infections; therefore a group of carefully chosen tests should accompany the clinical examination. These tests include: blood tests, microbiology, histological and radiological investigations:

1. **Full blood count and inflammatory markers** – can be suggestive of an infection but are definitely not at all specific. C reactive protein rises post-op and gradually decreases within weeks. A series of measurements of CRP is therefore more informative than a single value.
2. **Synovial fluid aspirate for leukocyte count and differential** – helps differentiate an infection from aseptic failure. A synovial fluid count >$1.7X10^9$/l and >65% neutrophils had a sensitivity for diagnosing prosthetic joint infections of 94% and 97% and a specificity of 88% and 98% respectively.[11]
3. **Histology** of the periprosthetic tissue has 80% sensitivity and 90% specificity but it is difficult to interpret and inflammatory changes vary between specimens and even in the same patient. Fink et al in 2008[12] compared the value of synovial biopsy, joint aspiration and CRP in diagnosing late prosthetic joint infection of total knee replacements. They found that biopsy had a sensitivity of 100% and a specificity of 98%. Aspirate had a sensitivity of 72.5% and specificity of 95.2% whilst CRP had a sensitivity of 72%%, and a specificity of 80.9%.
4. **Microbial specimens** –
   a) Culture from a sinus tract or wound often results in contaminants from the skin giving misleading results. Only if *Staphylococcus aureus* is cultured is this highly predictive of the causative organism.[13]
   b) Synovial fluid aspiration detects the infective organism in 45-100% of cases. [14]
   c) Synovial fluid PCR analysis. PCR has higher sensitivity, specificity and accuracy versus culture. It increases the utility of pre-operative aspiration for patients who require revision total joint surgery. [15]
   d) Perioperative specimens provide the most accurate specimens for detection of microorganisms with a sensitivity of 65-94%[16-18] Taking swabs should be avoided and antibiotics should be stopped for two weeks prior to surgery.
   e) If the prosthesis is removed, this too can be cultured.
   Dempsey et al in a study in 2007[19] explained that it is difficult to isolate the bacteria present on the surface of the joint by traditional methods because the bacteria are strongly adherent to the biofilm and because of antibiotic containing cement. They used mild ultrasonification to remove adherent microbes from the joint and then used molecular techniques to detect the microbial DNA from bacteria. Using PCR they managed to detect bacteria in 72% of prosthetic hip joints removed whilst there was only a 22% detection rate by conventional cultures
5. **Imaging**
   a) **Plain X-rays** – Although neither sensitive nor specific, a continuous radiolucent line >2mm or severe osteolysis within the first 12 months is suggestive of infection. Fig 1
   b) **Ultrasound** – may detect effusions and help guide aspirations
   c) **Contrast arthrography** increases the accuracy of assessment. Synovial pouches or abscesses are suggestive of infections.
   d) **Bone scintigraphy** with ^{99m}Tc has good sensitivity but low specificity. This is also because bone remodelling is normally present for the first year post op. If monoclonal antibodies are added to ^{99m}Tc accuracy is increased to 81%.
   e) **CT/MRI** – Definitely more sensitive than plain x-rays but metal implants tend to create numerous artefacts.

Treatment

The aim of successful treatment of prosthetic joint infections is to obtain a long-term pain-free and functional joint. There are 4 surgical options which together with the correct antimicrobial therapy try to achieve this.

Surgery

1. **Debridment with retention of prosthesis**. This is only advisable if symptoms are <3 weeks old, the joint is stable, there are no sinus tracts and the organisms are highly susceptible to antimicrobials. Under these conditions it is claimed to have a success rate of >70%.[2,20]
   Zimmerli et al carried out a randomized control study in 1998 [20] whereby patients underwent debridment without removal of the joint and were given ciprofloxacin and rifampicin. Cure rate for Staphylococcal infections was 100%.
2. **One-stage approach** – This involves the removal and insertion of a new prosthesis during the same operation together with antimicrobials. It is suggested if the soft tissue is intact or very minimally compromised and the organisms are not very virulent. In such cases an 86%-100% cure rate is claimed.[21-23]
3. **Two-stage approach** – This is the removal of the prostheses with insertion of a new prosthesis at a later date. It the organisms are not so virulent, a spacer (temporary, antibiotic-impregnated bone cement) is inserted and the joint replaced after 2-4 weeks.
   This method has the highest cure rate usually >90%[2,24-29] however it comes at a higher cost and a fastidious wait for the patient.
4. **Permanent removal of the prosthetic joint** is only indicated when the risk of reinfection is very high e.g. in immunosuppressed patients. Very debilitated, inoperable patients can be kept on long term antimicrobials. This obviously controls the infection but no cure occurs. 80% relapse occurs if antibiotics are stopped.

Antimicrobial therapy

Table 3 summarises the choice of antimicrobials for the most common organisms as suggested in 'The Sanford Guide to Antimicrobial Therapy 2012'.[30] The recommended treatment duration is 3 months for hip prosthesis and 6 months for knee prosthesis.[2] Intravenous treatment can be given for the first 2-4 weeks then switched to oral therapy. If a two stage surgical approach is chosen, antibiotics are stopped 2 weeks before reimplantation to obtain reliable tissue cultures and document treatment success. After reinsertion of the joint, antimicrobials are restarted. If cultures of the intraoperative specimens remain negative treatment is stopped; if still positive treatment is continued for 3 to 6 months as above.

Organism	Antibiotic
S. pyogenes, Grp A,B or G, viridans strep	Penicillin G or Ceftriaxone 2 g dly x 4wks
MSSE/MSSA	Nafcillin or oxacillin 2g 4hrly iv + rifampicin 300mg iv bd x 6wks or Vancomycin 1g iv 12hlry + Rifampicin 300mg po bd x 6wks or Daptomycin 6mg/kg iv 24hrly + Rifampicin 300mg po bd x 6wks.
MRSE/MRSA	Vancomycin 1g iv 12hrly + Rifampicin 300mg po bd x 6wks or Ciprofloxacin 750mg iv/po bd (or Levofloxacin 750mg iv/po dly) + rifampicin or Linezolid or Daptomycin and Rifampicin x 6wks
P. aeuroginosa	Ceftriaxone 2g dly iv + Ciprofloxacin 750mg iv/po bd (or Levofloxacin 750mg iv/po dly)

Table 3 *Choice of antibiotic regime*[30]
MSSE=methicillin sensitive Staphylococcus epidermis
MSSA= methicillin sensitive Staphylococcus aureus
MRSE= methicillin resistant Staphylococcus epidermis
MRSA=methicillin resistant Staphylococcus aureus.

Treatment outcome is monitored both clinically and by taking serial blood tests mainly inflammatory markers and full blood count. The patient should be reviewed regularly with these results for at least a year after the infection

Prevention of prosthetic joint infections

The importance of prevention of late haematogenous infection is well understood but often overlooked. Haematogenous infection of a prosthetic joint replacement is a devastating complication that can lead to the loss of that joint and significant morbidity.

There seems to be some controversy in the literature whether antibiotic prophylaxis should be administered or not. The overall risk of haematogenous infection from any source is variously reported as 0.4-1.7%[8,31]

In comprehensive reviews of literature, Thyne and Ferguson in 1991[32], the American Dental Association/American Academy of Orthopaedic Surgeons in 1997[33] and Tong and Rothwell in 2000[34] have concluded that there is minimal evidence of haematological infection of prosthetic joints by oral organisms at 0.00-0.01%. They suggest that the risk of antibiotic prophylaxis outweighs the benefits.

Notwithstanding this data, the 1997 combined advisory statement of the American Dental Association recommends that patients at a potentially

increased risk of haematological spread of infection to a prosthetic joint should have antibiotic prophylaxis before dental procedures likely to cause bacteraemia.

The antibiotics chosen must be active against viridans streptococcal infections as they are the most significant oral organisms.

The Sanford 2012 guidelines[35] recommend using the same prophylaxis as in cardiac patients at risk of endocarditis. It quotes the Journal of the American Dental Association[36] in saying that most patients with prosthetic joints do not require prophylaxis for routine dental procedures but individual considerations prevail in high risk procedures.

Conclusion

- Prosthetic joint infections are caused by micro-organisms in biofilms. This makes them more resistant and difficult to eradicate.
- Coagulase negative staphylococci and *Staphylococcus aureus* are the most common organisms.
- Infections are classified into early (<3months), delayed (3-24months) and late (<24months).
- Clinical signs such as erythema, fever, pain and loosening of the joint are common but it is often difficult to distinguish infection from aseptic failure.
- Other co-morbidities present risk factors to getting prosthetic joint infections.
- There is no single investigation but a collection of blood tests, histopathological, microbiological and radiological investigations.
- The ideal treatment is surgery and antimicrobial agents tailored on the above results.
- The aim of treatment is to obtain a long-term, pain-free and functional joint.

The optimum management of implant associated infection is still a subject of debate. More randomized clinical studies which take into account the various aspects of treatment, the selection and duration of antibiotic therapy and the time and scope of surgery are necessary. Also we believe that there need to be guidelines on the use of prophylactic antibiotics in patients with prosthetic joints. Better molecular techniques will help increase the yield in identifying the organism and therefore target the antimicrobial therapy better.

We recommend that the local prevalence of such infections is studied together with identification of the commonest organisms. This can be done by labelling wound swabs and deep biopsies from such patients as possible 'prosthetic joint infections' so they can be classified separately from other wound infections. Work is already underway between the infectious disease team and orthopaedic surgeons to devise locally adapted protocols. Better liaison between the infectious diseases team, the micobiologists and orthopaedic surgeons is of paramount importance so that such infections are identified early and the correct management steps are taken.

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