Title: Prosthetic Joint Infection in the Hip and Knee

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Abstract:

Prosthetic joint infection (PJI) is a devastating complication of joint arthroplasty with an incidence of around 1% following a primary arthroplasty, 3% following aseptic revision and 20% following septic revision. It can occur following direct inoculation, haematogenous or contiguous spread.

The majority of PJI are secondary to bacterial infection although fungal PJI may be seen in multiply operated or immune compromised patients. Risk factors for PJI include patient, pathology and procedure related factors which, where possible, should be optimised prior to surgery.

The diagnosis of PJI remains a challenge and is based on patient history, clinical examination together with laboratory and radiological testing. No diagnostic assessment is 100% accurate with various diagnostic criteria used clinically. Once confirmed PJI should be treated by a multi-disciplinary team.

Surgical treatment remains the gold standard with the surgical management aiming to identify the causative agent, through a rigorous standardised tissue sampling framework, and eradicate the infection. Surgical approaches including Debridement Antibiotics and Implant Retention (DAIR), single stage revision, two stage revision, arthrodesis and amputation. The approach used is tailored to the individual patient with the optimum surgical strategy being one that successfully eradicates the infection, but at the same time minimises morbidity to the patient.

Keywords: Knee arthroplasty; Hip Arthroplasty; Revision Arthroplasty; Prosthetic Joint Infection; Patient Outcomes.

Introduction

Epidemiology

Prosthetic joint infection (PJI) is a devastating complication of joint arthroplasty. Despite the incidence being relatively low, at around 1% following a primary arthroplasty, it is the most common indication for early revision[1]. The incidence following revision surgery is markedly higher, at around 3% following aseptic revision and 20% following septic revision. The incidence of PJI appears to be increasing. This is thought to be in part through better diagnosis but the increased complexity of primary arthroplasty, both patient and procedural, as well as the increase in the number of revision arthroplasty performed likely also has a role.

PJI can occur following direct inoculation at the time of surgery (or interventional procedure or trauma) or via haematogenous or contiguous spread. The majority of PJI presents in the first two years following surgery, and is attributed to direct inoculation at the time of surgery. Around a quarter of PJI is attributed to haematogenous spread, characterised by an initial asymptomatic postoperative period before the onset of symptoms, typically more than two years after surgery, and typically within a month of infective symptoms at a distant site. PJI in one joint is a risk factor for PJI at another site in patients with multiple prosthesis with up to a fifth of patients with PJI and multiple joint prostheses developing PJI at another site, one third of these synchronous with the index PJI[2].

The most common infective organisms are bacterial, typically *Staphylococcus aureus*, *Staphylococcus epidermis* and *Coagulase negative Staphylococcus*[3]. Fungal PJI is relatively rare, but may be seen in the multiply operated or immune compromised patient with *Candida* species being the causative pathogen. In around a fifth of PJI the infective organism is not identified, so called culture negative infection.

Once established infective organisms form a structured aggregation of microbial cells encased in a self-produced matrix on the surface of the prosthesis known as a biofilm. There are four phases to biofilm development: cell adhesion, cell aggregation, maturation, and cellular detachment. Antibiotics have poor activity against biofilms which, whilst incompletely understood, is thought to be due the physical protection that the extracellular matrix provides, in combination with the presence of bacterial subpopulations with different phenotypic levels of antibiotic resistance. The presence and maturity of the biofilm is thought

to influence the likelihood of success of Debridement Antibiotics and Implant Retention (DAIR) which will be discussed later.

Risk Factors and Clinical Presentation

Risk factors for PJI include patient, pathology and procedure related factors. Patient factors include high body mass index (BMI), poorly controlled diabetes and anaemia. Additionally pre-operative colonisation with Staphylococcus, both methicillin sensitive staphylococcus aureus (MSSA) and methicillin resistant staphylococcus aureus (MRSA), is thought to be associated with an increased risk of PJI and as such selective, or universal decolonisation may be used pre-operatively. Patients undergoing arthroplasty for inflammatory arthritis, post-traumatic and post native joint septic arthritis are at increased risk of infection. Where metal work is present, or post septic arthritis a staged procedure may be indicated and these cases should be discussed at MDT prior to proceeding with consideration made for intra-operative sampling and local antibiotic delivery. Finally revision procedures, patients being managed with endoprosthesis or and those in whom additional procedures are performed in combination with arthroplasty, for example extensor mechanism reconstruction, may be at increased risk due to prolonged operative times.

The risk presented by modifiable and non-modifiable risk factors should be discussed as part of the shared decision making process prior to proceeding with primary or revision arthroplasty. Where arthroplasty can be delayed without causing harm modifiable risk factors should be optimised. Where a delay presents a risk to the patient, for example impending fracture, the risk versus benefits of delaying surgery to permit optimisation of modifiable risk factors should be discussed with the patient. In some scenarios a two-stage revision may be performed to permit optimisation of risk factors between stages.

Clinically the presentation of patients with PJI varies depending on host and infective organism characteristics. Patients can present acutely unwell with a red, hot, painful joint or there may be a more insidious onset with pain and stiffness that may worsen over time. PJI must be considered in all patients with a symptomatic joint replacement as infection may be the cause of symptoms, either in isolation, or combination with another cause.

PJI is a devastating complication for patients. Eradication rates following surgery for PJI are around 80% however as a result of deconditioning due to prolonged hospital stays, multiple surgeries, as well as due to co-exiting comorbidities in those patients where eradication is achieved joint function may be poor. The mortality rate following revision for PJI has been

reported to be around 4% at one year, and exceeding 20% at five years, well above age-adjusted mortality. In addition to the patient impact PJI is also incredibly costly and in the United States the combined annual hospital costs related to PJI of the hip and knee is expected to exceed $1.8 billion by 2030.

Where PJI is suspected or confirmed patients should managed on a well-defined pathway as outlined by the British Orthopaedic Association Standards for Trauma and Orthopaedics (BOAST) Investigation and Management of Prosthetic Joint Infection in Knee Replacement and the British Hip Society Surgical Standard Investigation & Management of Peri-prosthetic Joint Infection [4-6]. All cases of suspected and confirmed PJI should have an outpatient review within 4 weeks, or be admitted for inpatient management if acutely unwell. Where PJI is confirmed cases should be discussed in an infection MDT which should consist of orthopaedic surgeons, infectious disease physicians or microbiologists and specialist nurses. In the UK revision networks for both hip and knee have recently been implemented with revision arthroplasty for PJI centralised at regional centres as part of the Getting It Right First Time (GIRFT) mandate from NHS England.

Diagnosis and Classification

The diagnosis of PJI remains a challenge and is based on patient history, clinically examination together with laboratory and radiological testing. Serological C-reactive protein (CRP) and plain X-rays are required in all cases. Serological erythrocyte sedimentation rate (ESR), plasma viscosity and/or D-Dimer may be performed based on local policy[7]. A 3-phase isotope bone scan is not routinely recommended but, in patients more than two years following surgery, has a strong negative predictive value and may be used to rule out infection in combination with other assessments.

Where abnormal results are returned aspiration (+/- radiological guided biopsy), in a clean environment, should be performed with aspirated fluid placed in sterile pots, and when possible, also inoculated into blood culture bottles to improve culture yield. Joint fluid can also be assessed for leukocyte esterase, synovial white blood cell count, proportion of polymorphonuclear neutrophils, as well as other synovial markers of infection such as alpha-defensin based on local policy. Where aspiration or biopsy is performed antibiotics should be stopped for two weeks prior except where the patient is systemically unwell (septic).

Where diagnostic uncertainty persists arthroscopic or open biopsy can be performed with five separate surgical specimens taken for microscopy, extended culture and sensitivity with

clean instruments for each sample together with histology specimens for quantitative assessment of neutrophil infiltrates. In culture negative infection samples that are highly suspicious for PJI additional fungal or mycobacterial cultures and/or molecular testing can be performed as guided by the MDT. Where implants are removed, or exchanged, as part of a revision procedure sonication can be performed. Diagnostic tools including Next generation sequencing (NGS), where microbial deoxyribonucleic acids (DNA) from a synovial fluid samples is sequenced, can be used but at present they are not used routinely and their role in the diagnosis of PJI has yet to be fully established[8].

At present, no diagnostic assessment with 100% accuracy exists and as such various criteria have been proposed to stratify patients including the International Consensus Meeting (ICM) 2018 criteria and the European Bone and Joint Infection Society (EBJIS) criteria[9, 10].

The ICM 2018 criteria (Table 1) for PJI are based on the MusculoSkeletal Infection Society (MSIS) criteria introduced in 2011, and later modified in 2013 at the ICM. Using the ICM 2018 criteria PJI is diagnosed in the presence of a major criteria, or combination of minor criteria based on pre and intra-operative factors with cases classified as infected, inconclusive or not infected. The ICM 2018 criteria have been reported to have a sensitivity of 97.7%, with 80% of diagnosis being achieved prior to the inclusion of intraoperative factors.

Table 1: International Consensus Meeting 2018 Criteria [9]

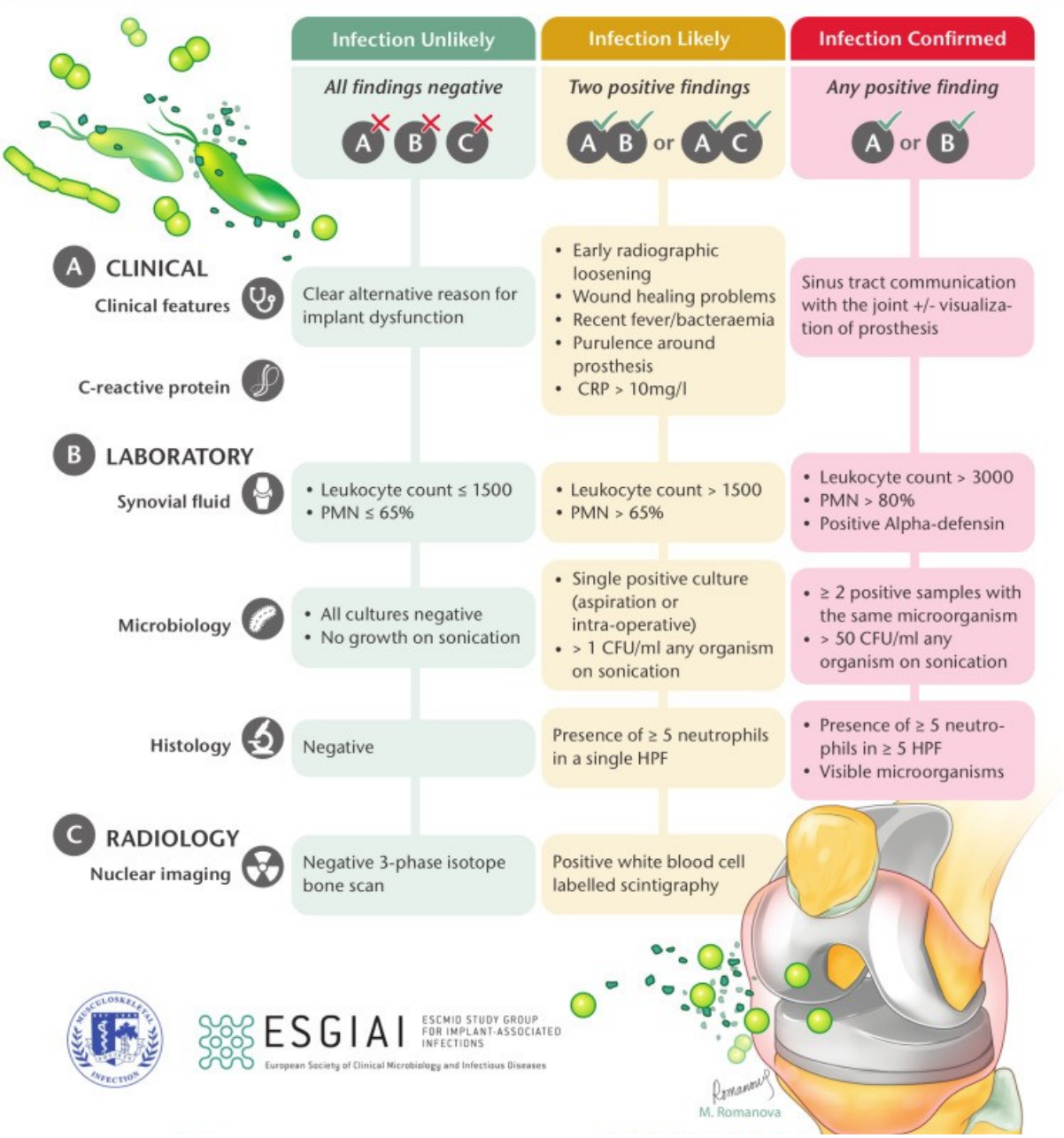
Major Criteria (at least one of the following)	**Decision**
Two positive growths of the same organism using standard culture methods	Infected
Sinus tract with evidence of communication with the joint or visualization of the prosthesis	

Minor Criteria	**Threshold**		**Score**	**Decision**
	Acute	**Chronic**		
Serum CRP (mg/L) *Or* D-Dimer (μg/L)	100 Unknown	10 860	2	Combined preoperative and postoperative score: ≥6 Infected 3-5 Inconclusive <3 Not infected
Elevated Serum ESR (mm/hr)	No role	30	1	
Elevated Synovial WBC (cells/μL) *Or* Leukocyte esterase *Or* Positive Alpha-defensin (signal/cutoff)	10,000 ++ 1.0	3,000 ++ 1.0	3	
Elevated Synovial PMN (%)	90	70	2	
Single positive culture			2	
Positive histology			3	
Positive intraoperative purulence			3	

The EBJIS criteria are supported by the Musculoskeletal Infection Society (MSIS) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (Figure 1). Using the EBJIS criteria cases are classified based on clinical, laboratory and radiological findings as infection confirmed, infection likely or infection unlikely. In a comparative study assessing the performance of the ICM 2018, EBJIS and the Infectious Diseases Society of America (IDSA) 2013 criteria in a cohort of 206 patients the EBJIS criteria classified as 'infection confirmed' all cases of PJI diagnosed by either of the other two criteria, classified fewer cases as inconclusive and had a better performance based on pre-operative data than the other two systems[11]. Further work is required to define the gold standard criteria for diagnosing PJI.

Once PJI has been confirmed it can be further classified by: time of onset (acute vs chronic (typically regarded as >90days), source of infection (direct vs contiguous spread from adjacent infected vs haematogenous spread) or causative organism. In addition several composite scoring systems, including the Joint-Specific, Bone involvement, Anti-microbial options, Coverage of the soft tissues, Host status (JS-BACH) classification of prosthetic joint infection, have been published that have been reported to assist in predicting likelihood of recurrence and quality of life following surgery for PJI[12].

Figure 1: The EBJIS definition of periprosthetic joint infection [10]


Infection Unlikely
All findings negative
A B C
Infection Likely
Two positive findings
A B or A C
Infection Confirmed
Any positive finding
A or B
A CLINICAL
Clinical features
Clear alternative reason for implant dysfunction
C-reactive protein
• Early radiographic loosening
• Wound healing problems
• Recent fever/bacteraemia
• Purulence around prosthesis
• CRP > 10mg/l
Sinus tract communication with the joint +/- visualization of prosthesis
B LABORATORY
Synovial fluid
• Leukocyte count ≤ 1500
• PMN ≤ 65%
• Leukocyte count > 1500
• PMN > 65%
• Leukocyte count > 3000
• PMN > 80%
• Positive Alpha-defensin
Microbiology
• All cultures negative
• No growth on sonication
• Single positive culture (aspiration or intra-operative)
• > 1 CFU/ml any organism on sonication
• ≥ 2 positive samples with the same microorganism
• > 50 CFU/ml any organism on sonication
Histology
Negative
Presence of ≥ 5 neutrophils in a single HPF
• Presence of ≥ 5 neutrophils in ≥ 5 HPF
• Visible microorganisms
C RADIOLOGY
Nuclear imaging
Negative 3-phase isotope bone scan
Positive white blood cell labelled scintigraphy
ESGIAI
ESCMID STUDY GROUP FOR IMPLANT-ASSOCIATED INFECTIONS
European Society of Clinical Microbiology and Infectious Diseases
M. Romanova

Management

Surgical treatment of PJI remains the gold standard. Whilst long-term antibiotic suppression is used in select patients, this is often not tolerated and there are concerns about the development of resistance in the longer term. Surgical management of PJI has two goals:

- Identify the causative agent
- Eradicate the infection

To identify the causative agent a rigorous standardised tissue sampling framework should be used for all revision cases, and in primary cases where there is potential for infection. Preoperative prophylactic antibiotics should be held until deep surgical samples have been obtained with surgical samples taken as soon as possible after the skin incision, and prior to significant manipulation of the surgical wound to minimise contamination. A minimum of five (paired) deep samples should be sent for microbiology and for histopathology. Each sample should be taken with a clean set of surgical instruments so that each sample is totally independent from the others and labelled separately labelled as to its anatomical source. For the knee the joint is aspirated after skin incision, but before arthrotomy, to minimise skin contamination with samples taken systemically from the suprapatellar recess, medial and lateral gutters, fat pad, posterior capsule and bone-implant interface of the tibial and femoral components. For the hip the joint is aspirated after dissection down to the capsule but prior to arthrotomy. Following arthrotomy samples are then taken from the posterior capsule, anterior capsule and the bone-implant interface of the femoral and acetabular components. The hip is then dislocated and the modular femoral head and acetabular liner are removed to permit a fifth sample to be taken from behind the removed liner for modular cementless components.

Following sampling, antibiotics can be given and a formal radical synovectomy performed which improves access to the joint. Following radical synovectomy, debridement and removal of prosthesis/modular components pulsatile lavage of the joint is performed with a minimum of 5 litres of 0.05% chlorhexidine gluconate followed by a three minute soak in dilute, sterile, povidone-iodine. The exception to this is where Debridement, Antibiotics and Implant Retention (DAIR) of unicompartmental knee replacement where 0.9% saline is used for lavage, delivered by syringe, to avoid damage to the retained compartments.

The surgical strategy to eradicate infection is planned pre-operatively at MDT and is based on host factors, infecting organism factors as well as surgical history. Management options, listed in order from the least to most invasive, include:

- Debridement Antibiotics and Implant Retention (DAIR)
- Single Stage Revision
- Two Stage Revision
- Arthrodesis
- Amputation

The optimum surgical strategy is one that successfully eradicates infection eradication, but at the same time minimises morbidity to the patient. In unselected patients DAIR and single stage revision have a higher chance of failure, as compared to two stage revision. However, through appropriate patient selection DAIR and single stage can have similar success rates to two-stage revision but with lower morbidity to the patient, better function and lower hospital costs. In our centre the preference is to perform DAIR and single stage revision where possible.

Debridement Antibiotics and Implant Retention

Debridement Antibiotics and Implant Retention (DAIR) where debridement, irrigation and exchange of modular implants is performed is indicated for acute infections where there is a well-fixed, well-functioning implant. It is contra-indicated in the presence of a sinus, loose implant and in infections caused by fungal, multi-drug resistant or atypical organisms. Caution is recommended in immunocompromised patients or those with multiple comorbidities. We do not consider the absence of, or negative, pre-operative cultures a contra-indication to DAIR.

DAIR should be performed by an experienced arthroplasty surgeon with the success of DAIR declines with time from onset of infection. There is controversy over whether a maximum time from onset exists with some authors suggesting that DAIR should only be performed before 3 or 6 weeks due to concerns about biofilm formation. In our centre we do not have a maximum time from onset of symptoms. Arthroscopic washout and debridement has no place in the definitive treatment of PJI and should only be performed as a temporising / life-saving measure to reduce the septic load and allow patient optimisation prior to a formal DAIR or revision procedure.

Single Stage Revision

Single stage revision, where all components (including the patella implant in the knee) and cement are removed, the joint formally debrided, irrigated and new definitive components is

the most common treatment for PJI in Europe. Single stage revision is contra-indicated in the septic patient, cases of previous failed single stage revision, fungal, atypical or multi-drug resistant infection and where radical debridement is not possible such as where there is involvement of the neurovascular bundles. Additionally, where primary wound closure is not possible our preference is to perform a two-stage procedure, with a muscle flap performed during the first stage. Whilst the absence of, or negative, pre-operative cultures is a contra-indications to single stage revision caution should be taken in this cohort of patients. In rare cases single stage revision can be used in patients who the MDT views would not tolerate two stage revision, typically due to medical comorbidity, following a sharded decision making process.

Two Stage Revision

Two stage revision, involves a minimum of two operations and is the most common treatment for PJI in North America. During the first-stage all components (including the patella implant in the knee) and cement are removed, the joint is formally debrided, irrigated and an antibiotic spacer inserted. Following the first-stage procedure the patient is placed on broad spectrum antibiotics which are then tailored to the causative agent with the antibiotic choice and duration decided in collaboration with the infectious disease team. When the treating team considers the infection to be controlled, based on clinical judgement, laboratory, and radiological findings a second-stage procedure is performed. The second-stage procedure, where definitive components are implanted, is scheduled at least two-weeks after the planned cessation of antibiotics to permit sampling for microbiology and histology as described above. We routinely perform a further debridement at second-stage and place the patient on broad spectrum antibiotics post-operatively until initial cultures are returned. We do not routinely perform aspiration of the joint prior to second stage as culture of synovial fluid from a joint with an antibiotic-loaded cement spacer in situ has been shown to have low sensitivity for demonstrating persistence of infection.

Two-stage revision can be used in cases where DAIR and single-stage revision are contra-indicated provided the patient can tolerate multiple operations, the joint can be reconstructed and the soft-tissue envelope can be closed, either primarily or through the use of a pedicled or free-muscle flap. In cases where two-stage revision cannot be performed salvage options must be considered including: resection arthroplasty, arthrodesis or amputation.

Resection arthroplasty

Resection arthroplasty, where all components and cement are removed followed by debridement, irrigation and antibiotics can be used in the hip, Girdlestone Procedure. Once the wound has healed patients are permitted to weight bear as pain permits. In the knee it is rarely used in the knee due to concerns about instability.

Arthrodesis

Arthrodesis can be performed for the knee, but is rarely performed in the hip. Arthrodesis can be achieved by external fixation, internal plate fixation or intra-medullary nail fixation. It can be performed as a single-or two stage procedure with antibiotics as advised by the infectious disease team.

Amputation

Amputation is used as a last resort for the management of PJI. Where amputation is considered patients are pre-operatively counselled as to these risks by an doctor specialising in rehabilitation medicine. Whilst prosthesis can be fitted for both above knee (knee arthroplasty) and hindquarter (hip arthroplasty) amputations mobilisation with a prosthetic limb (as compared to native limb) requires considerably more energy and may patients are wheelchair bound.

General Surgical Considerations

Patients undergoing surgery for PJI frequently have had multiple previous operations and may have multiple scars. Careful consideration of the methods for wound closure should be considered pre-operatively and the surgical incision should not put at risk the vascular supply to the local skin or ‘burn bridges’ for later reconstruction. Plastic surgical advice and formal involvement in the surgical procedure should be sought for almost all cases other than the simplest wounds.

In addition to systemic antibiotics local antibiotics/antifungals can be used, either delivered locally through antibiotic loaded cement and/or by way of an absorbable antibiotic carriers. Local antimicrobial therapy permits high local antibiotic concentrations to be achieved whilst minimising systemic side effects. For interstage cement spacers, large concentrations of antibiotics, up to 20% of total spacer mass, may be used. Additionally hand mixing the cement (i.e. non-vacuum mix) incorporates air bubbles which increase the surface area and lead to greater antibiotic elution. Both of these methods however weaken the mechanical

strength of the spacer and should not be used for definitive implant fixation. The antibiotic choice for carriers should be discussed pre-operatively discussed with the infectious disease team.

The type and duration of systemic antibiotics should be discussed with the infection diseases team. In our unit immediately after completion of surgical sampling, patients are usually given intravenous meropenem and vancomycin as this combination has previously been shown to provide the most effective empiric cover. Meropenem is normally discontinued after 48 hours of incubation if no gram negative organisms have been identified with the vancomycin continuing until final culture results are available. The most important variable governing the choice of antibiotic is the susceptibility of the infecting organism and therefore optimisation of a microbiological diagnosis is a priority. Once the infecting organism is identified the type, dose and duration of antimicrobial treatment is determined by the infection disease team taking into account procedure performed, sensitivities, pharmacokinetics, history of drug allergy or intolerance, potential drug interactions, cost and convenience.

Conclusion

Prosthetic joint infection (PJI) is a devastating complication of joint arthroplasty with an incidence of around 1% following a primary arthroplasty, 3% following aseptic revision and 20% following septic revision. It is the most common indication for early revision and its incidence is increasing.

PJI can occur following direct inoculation, haematogenous or contiguous spread and once established forms a biofilm limiting the activity of antibiotics. The majority of PJI are secondary to bacterial infection, commonly staphylococcal species, although fungal PJI may be seen in multiply operated or immune compromised patients. Risk factors for PJI include patient, pathology and procedure related factors which may be modifiable or non-modifiable with modifiable risk factors, where possible, optimised prior to surgery.

The diagnosis of PJI remains a challenge and is based on patient history, clinical examination together with laboratory and radiological testing. No diagnostic assessment is 100% accurate and therefore various diagnostic criteria are used clinically to confirm PJI including the International Consensus Meeting (ICM) 2018 criteria and the European Bone and Joint Infection Society (EBJIS) criteria.

Once confirmed PJI should be treated by a multi-disciplinary team including orthopaedic surgeons, infection disease physicians, plastic surgeons and specialist nurses. Surgical treatment remains the gold standard with the surgical management of PJI having two goals: identify the causative agent and eradicate the infection. These goals can be achieved using different approaches including DAIR, single stage revision, two stage revision, arthrodesis and amputation. The approach used is tailored to the individual patient with the optimum surgical strategy being one that successfully eradicates the infection, but at the same time minimises morbidity to the patient.

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