Update on the diagnosis and management of the periprosthetic knee joint infection

Philip Pastides

Dinesh Nathwani

Abstract

A periprosthetic joint infection is an uncommon and unwanted complication following knee arthroplasty surgery. Its management can involve a considerable time period of both surgical and non-surgical intervention, which is both costly and distressing for both the patient and the treating surgeon. Obtaining an accurate diagnosis in a timely fashion can also be difficult and delay in treatment may have a detrimental affect. This paper outlines the up-to-date guidance for diagnosing, managing, surveying and treating this undesired complication, making special reference to findings and recommendations made from the International Consensus meeting on periprosthetic joint infection in 2013.

Keywords arthroplasty; diagnosis; infection; knee; periprosthetic

Introduction

Although not the commonest complication of knee replacement surgery, a periprosthetic joint infection (PJI) is considered one of the most feared, with potentially devastating consequences.

Using the Nationwide Inpatient Sample, the annual PJI incidence rate in the United States, expressed as a percentage of the total number of arthroplasties performed, increased from 1.99 to 2.18% for hip arthroplasties and from 2.05 to 2.18% for knee arthroplasties from 2001 to 2009.[1] UK National Joint Registry data from the 12th annual report show a revision rate of knee replacement surgery due to infection of around 1.6% within the first year of surgery, which reduces to 0.37% by 7–11 years.[2]

The difficulties and challenges facing clinicians to detect, manage and eradicate PJI are immense and highly complex. To address this, an International Consensus meeting on periprosthetic joint infection was organized in 2013. Delegates from disciplines including orthopaedic surgery, infectious disease and many others participated. The process of generating the consensus has spanned 10 months. 400 delegates from 60 countries and numerous societies evaluated over 3500 relevant publications. Covered topics included: mitigation and education on comorbidities associated with increased Surgical Site Infection (SSI)/PJI, perioperative skin preparation, perioperative antibiotics, operative environment, blood conservation, prosthesis selection, diagnosis of PJI, wound management, spacers, irrigation and debridement, antibiotic treatment, timing of reimplantation, one-stage *versus* two-stage exchange arthroplasty, management of fungal or atypical PJI, oral antibiotic therapy and prevention of late PJI. It is regarded as the cornerstone in the holistic management of PJI and it is highly recommended that clinicians dealing with patients suspected or diagnosed with PJI should be well aware of it. Consisting of a series of statements, each and every one of them has undergone careful scrutiny by both subject matter experts and generalists.[3]

Philip Pastides *MRCS MSc(Orth Eng) MBBS BSc(Hons) ST6 Trauma and Orthopaedic Registrar, Charing Cross Hospital, Imperial College NHS Healthcare, London, UK. Conflict of interest: none.*

Dinesh Nathwani *FRCS (Tr&Orth) MBChB MSc Consultant Knee Surgeon, Charing Cross Hospital, Imperial College NHS Healthcare, London, UK. Conflict of interest: none.*

How do you define a periprosthetic joint infection?

What constitutes a periprosthetic joint infection? How does one define it? The lay person's definition is, reasonably, the presence of a pathogenic organism in or around a prosthesis. However, it is more complicated than this, as detection of the organism is often impossible.[4] As a result, a workgroup convened by the Musculoskeletal Infection Society (MSIS) analysed the available evidence and proposed a new set of criteria in order to define a PJI.[5]

Based on the agreed criteria, a PJI can confidently assumed to be present if:

- there is a sinus tract communicating with the prosthesis; or
- a pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected joint; or
- at least four of the following six criteria exist:
  - elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration,
  - elevated synovial leucocyte count,
  - elevated synovial neutrophil percentage (PMN%),
  - presence of purulence in the affected joint,
  - isolation of a microorganism in one culture of periprosthetic tissue/fluid,
  - greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification.

Pathogenesis

The pathogenesis is that of a microbe within or around the prosthesis that affects either the soft tissue envelope around the joint and/or the interface between the replaced components and the bone. A biofilm tends to develop, which forms an ideal medium to harbour the microbe. The biofilm is an accumulation of microorganisms embedded in a self-produced polysaccharide matrix that can then adhere to a solid biological or non-biological surface. Once formed, organisms within the film are protected from host immune responses and may demonstrate a reduced susceptibility to antibiotics as a result of changes in metabolic processes. This can therefore make the potential infection extremely difficult to eradicate and thus develop into a more chronic problem. Furthermore, these biofilms are less inflammatory in nature and thus harder to detect clinically (hence the non-suitability of the 'lay definition' for PJI mentioned above).[6,7]

Classification

Prosthetic joint infections can be classified as early, delayed and late, as shown in Table 1.[8,9]

Please cite this article in press as: Pastides P, Nathwani D, Update on the diagnosis and management of the periprosthetic knee joint infection, Orthopaedics and Trauma (2016), http://dx.doi.org/10.1016/j.mporth.2016.09.008

Classification and likely sources of PJI

	Time interval post surgery	Likely source
Early	<3 months	Probably at time of surgery
Delayed	Between 3 and 12 months	Probably at time of surgery
Late	>12 months	Probably haematogenous

Table 1

In terms of the actual pathogens that tend to cause PJI, there is a little variation in rates. However, Gram-positive cocci appear to be involved in the majority of PJI involving the knee (and hip) joint. *Staphylococcus aureus* and *coagulase negative staphylococcus* species are fairly similar in incidence, constituting more than half of the cases. *Streptococci, enterococci* and *diphtheroids* each account for around 10% of cases. Gram-negative organisms are much less common than Gram-positive, causing around 8% of cases.[10]

Diagnosis of a PJI

As in all medical specialities, history and examination form the cornerstone of making the correct diagnosis. The knee joint has the benefit of being relatively superficial and subcutaneous and thus easy to inspect and palpate. The classical mantra of the 'painful, red, hot joint' certainly is valid in extreme cases; however, low-grade infections are often subtle and harder to detect. Following replacement surgery, the knee joint may remain swollen for many months and so this is not a reliable sign.

How useful is a CRP level and when do you perform it?

Sometimes considered a 'tick box' blood test, there is a role for the CRP level, or more specifically the trend in the level. It is part of the diagnostic criteria set out by the MSIS. Several authors have looked at the trend and factors involved in the CRP trend. Overall, it has been noted that there is a bigger rise in the CRP level in TKR compared to THR. Furthermore, it appears to peak at around day three post-operatively for the former and around day two post-operatively for the latter. More interesting is that whilst CRP seems to normalize by around the third week post-operatively for hip replacement surgery, it can take up to 2–3 months for the levels to normalize following a knee replacement. A large haematoma has also been shown to prolong the elevated CRP level for joint replacement surgery.[11–13]

Aspiration of the possible infected TKR

Gram staining and culturing of joint aspirates are known to have a relatively low sensitivity and specificity and thus cannot be comfortably relied on in isolation to either confirm or exclude a PJI.[14] They should be obtained under strict aseptic conditions within the operating room, to help minimize the effect of contamination. Aspirates should also be sampled when the patient has been off antibiotics for at a number of weeks (see guidance below).

A somewhat overlooked diagnostic criterion is that of the cut-off values for both the fluid leucocyte count and the neutrophil percentage obtained from the aspirate to help diagnose a PJI. This is what Ghanem et al.[15] evaluated, using 161/429 TKR found to be infected at the time of revision surgery. They set cut-off values for fluid leucocyte levels at >1100 cells/10^{-3} cm^3 and >64% for the neutrophil differential. When both tests yielded results below their cut-off values, the negative predictive value of the combination increased to 98.2% (95% confidence interval, 95.5%–99.5%); whereas when both tests yielded results greater than their cut-off values, infection was confirmed in 98.6% (95% confidence interval, 94.9%–99.8%).

What other investigations are thought to be useful?

In 2010, the American Association of Orthopedic Surgeons and their clinical practice guidelines unit produced a key document based on a systematic review of the available literature to discuss treatment and diagnosis of PJI.[16] This was one of the many documents reviewed in the key Consensus meeting in 2013.[3]

Specifically, for a possible knee PJI, they strongly recommend the monitoring of ESR and CRP levels (not making reference of timing of tests), diagnostic aspiration of the joint, ideally with the patient off antibiotics for at least two weeks, with the aspirate being sent for microbiological culture, synovial fluid white blood cell count and differential. Furthermore, they strongly recommend against the use of intra-operative Gram stain to exclude PJI, instead opting for frozen sectioning of peri-implant tissues in patients who are undergoing revision procedures in whom the diagnosis of PJI has not been established or excluded.

In cases of equivocal initial aspiration cultures, a repeat sample is recommended. In terms of imaging to help make a diagnosis, they found limited evidence for the use of nuclear imaging and inconclusive evidence for conventional scans such as CT, CT Spect or MRI.

New bedside testing

In order to help diagnose a PJI, synovial fluid biomarkers would present an ideal method, as fluid taken directly from around the prosthesis tends to be easily accessible. Several promising markers have been found[17] but one in particular seems to be very promising indeed.[18]

Synovasure™ (Zimmer) is a validated bedside test that the manufacturers claim has 97% sensitivity and 96% specificity in diagnosis a PJI.[19] It functions by measuring alpha-defensin, which is an antimicrobial peptide that is released by neutrophils in response to pathogens. In a follow-up study, the same group of authors compared the results of this test to frozen section. The bedside device has a positive predictive value of 80% (95% CI 44%–96%) and a negative predictive value of 87% (95% CI 68%–96%), and showed a sensitivity of 67% (95% CI 35%–89%) and specificity of 93% (95% CI 75%–99%). Frozen section had a lower sensitivity (58% [95% CI 29%–84%]) but a higher specificity (96% [95% CI 80%–100%]). The authors thereby concluded that the test is at least equivalent to intra-operative frozen section and is a useful tool to confirm the absence of PJI.[20] Bonanzinga et al.[21] have since performed another prospective study using alpha-defensin levels. Using a cohort of 156 patients (65 knees, 91 hips), alpha-defensin immunoassays from the joint fluid were compared to tissue samples sent for culture and histological assessment taken during surgical debridement. Samples were cultured until positive or until negative at 14 days. A diagnosis of PJI was confirmed in 29 patients according to the International Consensus Group on PJI described above.

They found that the sensitivity of the immunoassay was 97% (95% confidence interval [CI], 92%–99%), the specificity was

Please cite this article in press as: Pastides P, Nathwani D, Update on the diagnosis and management of the periprosthetic knee joint infection, Orthopaedics and Trauma (2016), http://dx.doi.org/10.1016/j.mporth.2016.09.008