# Periprosthetic joint infection

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*Lancet* 2016; 387: 386–94
Published Online June 29, 2015
http://dx.doi.org/10.1016/S0140-6736(14)61798-0

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**Periprosthetic joint infections are a devastating complication after arthroplasty and are associated with substantial patient morbidity. More than 25% of revisions are attributed to these infections, which are expected to increase. The increased prevalence of obesity, diabetes, and other comorbidities are some of the reasons for this increase. Recognition of the challenge of surgical site infections in general, and periprosthetic joint infections particularly, has prompted implementation of enhanced prevention measures preoperatively (glycaemic control, skin decontamination, decolonisation, etc), intraoperatively (ultraclean operative environment, blood conservation, etc), and postoperatively (refined anticoagulation, improved wound dressings, etc). Additionally, indications for surgical management have been refined. In this Review, we assess risk factors, preventive measures, diagnoses, clinical features, and treatment options for prosthetic joint infection. An international consensus meeting about such infections identified the best practices and further research needs. Orthopaedics could benefit from enhanced preventive, diagnostic, and treatment methods.**

## Introduction

Hip and knee arthroplasties are successful elective surgical procedures, with greater than 95% survivorship at 10-year follow-up.[1] In the UK and USA, about 800 000 joint arthroplasties are done annually, with projections to greater than 4 million by 2030.[1,2] Periprosthetic infection is estimated at 1% for hip arthroplasties and ranges between 1% and 2% after knee arthroplasties every year.[3,4] However, results from a review[5] of patients undergoing primary arthroplasty from 2006 to 2009 showed that infection rates might be higher (greater than 2%) than previously reported. Also, infections accounted for 14·8% of revisions after hip arthroplasty and were the most common revision cause (25·2%) after knee arthroplasty.[6,7]

Most early infections are postulated to occur during implantation and are attributed to endogenous skin flora or exogenous sources from the operating theatre. In addition to needing further procedures, patients who develop periprosthetic joint infections often require extended antibiotic courses. However, the development of antimicrobial resistance is a concern. During past decades, the development of new antimicrobials has slowed, which has restricted options to combat resistant organisms.[8] On the basis of one study,[9] the most common isolated organisms are meticillin-resistant and meticillin-sensitive *Staphylococcus aureus*, and meticillin-resistant and meticillin-sensitive *Staphylococcus epidermidis*. Researchers from other studies noted a decreased prevalence of infections with Gram-negative and coagulase-negative staphylococci bacteria.[10] In the USA, up to 46·7% of *S aureus* strains are meticillin resistant, and up to 23% of *Enterococci* spp are vancomycin resistant.[11] In Europe, 12% of *Streptococcus pneumoniae* strains have decreased penicillin susceptibility, more than 15% of *S aureus* strains are meticillin resistant, and nearly 9% of *Enterococci* spp are vancomycin resistant.[12] A meticillin-resistant *S aureus* (MRSA) subgroup, which emerged in 2001, has shown reduced vancomycin susceptibility. The emergence of these resistant organisms is alarming and needs new drugs with novel mechanisms of action. These infections can result in increased patient morbidity and mortality.[6] These issues underscore the importance of the problem and its increasing burden to health-care systems.

### Search strategy and selection criteria

We searched PubMed, Embase, Ovid, and Web of Science between Jan 1, 1960, and May 1, 2014 with medical subject heading terms and Boolean search queries for the following search terms: "joint", hip", "knee", "periprosthetic infection", "arthroplasty", "replacement", "revision", "prevention", "prophylaxis", risk factors", "diagnosis", "staging", "treatment", "epidemiology", "diabetes", "nutrition", "obesity", "smoking", "alcohol", "HIV", "hepatitis", "antibiotics", "hair removal", "surgical drapes", "body exhaust suit", "laminar flow", "blood management", "drains", "irrigation and débridement", and "fungal infection". Preference was given to articles published in the English language.

## Pathogenesis

Infections can occur through various mechanisms: first, direct seeding from external contaminants or contiguous spread; second, haematogenous spread from other body sites; and third, recurrent infection. Infection susceptibility is increased in settings of foreign bodies, and might result in biofilm formation, which is a bacterial adaptation in implant-associated infections. Initially, bacteria attach to the prosthesis, and work in animal models shows that the bacteria concentration needed to induce an infection is reduced by more than 100 000 times in the presence of a foreign body.[13] Furthermore, the interaction of neutrophils with a foreign body can induce a neutrophil defect, which enhances infection susceptibility.[14] Bacteria that are adherent to the prosthesis multiply and create microcolonies, which are encased in glycocalyx (biofilms). Organisms deep within the biofilm are protected from host defences.

Causal factors affecting periprosthetic joint infections include those that are related to patients (such as male sex and previous surgery) and operating environment. Although pathogen type is dependent on the patient, risk factors, and comorbidities, organism characteristics and

infection timing are also important in causation. For example, *S aureus* small-colony variants have been identified in failed treatment of periprosthetic joint infection with standard antibiotics. These strains are slow-growing subpopulations with distinct phenotypes.[15] Furthermore, some patients with infections are culture-negative and might need empirical antibiotic treatment; however, this treatment should be avoided until a microbiological diagnosis has been established, except in cases of severe sepsis.

## Epidemiology

Microbiological and resistance epidemiology of periprosthetic joint infections varies between countries. In the USA, the most common organisms are meticillin-resistant and meticillin-sensitive *S aureus*, and meticillin-resistant and meticillin-sensitive *S epidermidis*.[9] Europe has shown the highest prevalence of coagulase-negative *Staphylococcus* spp, followed by *S aureus*, streptococcus, and enterococcus organisms.[16] Organism trends that might affect antibiotic prophylaxis and treatment regimens should be followed.

Infection costs in the USA alone exceeded US$900 million in 2012 and future projections are to exceed $1·6 billion by 2020.[17] Revision procedures continue to impose substantial economic burdens, which have been estimated to be as high as €80 000 per case.[6] One study[18] noted a cost of €95 000 per periprosthetic joint infection, which is five times higher than a primary arthroplasty. These costs have been attributed to re-operations, lengthened rehabilitation time, and extended use of antibiotics and analgesics. The projected increase in revision procedures is an economic burden that might overwhelm the worldwide health-care system.

Infected patients have poor satisfaction with their procedure; up to 23% are satisfied and 18% report complete dissatisfaction. Health-related quality of life is lower for patients with periprosthetic joint infections than for those with uncomplicated arthroplasty. Infected patients do not return to the functionality experienced by equivalent matched populations. Infections lead to high mortality; two-stage hip revisions for infection have up to 25·8% all-cause mortality within 2 years.[19] Mortality as high as 45% at a mean of 4·7 years was reported for recurrent infections.[20]

## Risk factors

Various patient-specific comorbidities and demographic factors increase risk of periprosthetic joint infection.[21] Any joint infections, septicaemia, active cutaneous or deep tissue infections, or blood transfusions are important risk factors.[22] Patient-specific factors consist of uncontrolled diabetes,[23] malnutrition,[24] morbid obesity,[25] smoking[26] and alcohol consumption,[27] immunocompromising diseases,[28] drug use,[29] and nasal carriage of *S aureus*.[30]

Diabetes is a risk factor for infection after general surgical and orthopaedic procedures; however, total joint arthroplasty findings are varied. Some researchers have shown that infection rates for diabetic patients are seven times higher than for non-diabetic patients.[31] A study[32] of 101 infected and 1847 non-infected patients had more patients with diabetes in the infected cohort (22% *vs* 9%; p<0·001) than in the non-infected group. Although glycosylated haemoglobin ($HbA_{1c}$) is used as a glycaemic control indicator, it has not been predictive of infection.[33] Preoperative identification of diabetic control should be assessed.

Poor nutritional status preoperatively resulted in adverse outcomes after arthroplasties, which include poor wound healing and a seven-times increase in infections. Malnutrition is diagnosed if serum albumin is less than 34 g/L (healthy range is 34–54 g/L), or total lymphocyte count is less than 1200 cells per µL (healthy range is 3900–10 000 cells per µL).[34] Proper nutritional optimisation can decrease periprosthetic joint infections.[35]

WHO estimated that 10% of the world population (more than 400 million adults) is obese (body mass index [BMI] >30·0 kg/m²). Frequently reported outcomes after arthroplasty in obese patients are poor wound healing, long-term wound drainage, and high infection rates.[36] Increased risks are attributed to long operative times, increased allogeneic blood transfusions, and additional comorbidities.[31] Also, obese patients have impaired tissue antibiotic penetration, which can be below minimum inhibitory thresholds, leading to increased infection risk.[37] Difficulties with antibiotic dosing in obese patients are the basis for propagating weight-based perioperative antibiotic adaptation. A Nationwide Inpatient Sample database[38] showed that morbidly obese patients (BMI ≥40 kg/m²) had a higher infection risk than did non-obese patients (infection rate of 0·24% *vs* 0·17%; p=0·001). Even mildly obese patients with a BMI ≥35 kg/m² had increased risk.

Smoking and alcohol consumption result in poor postoperative outcomes.[39,40] Nicotine-mediated vaso-constriction has been postulated as the main cause for deficient wound healing.[41] Bad circulation results in tissue hypoxia and increased infection susceptibility. Several meta-analyses across several surgical subspecialties have underscored preoperative smoking cessation benefits, which decrease postoperative infections by more than 50%.[42] Alcohol misuse led to higher postoperative complications and periprosthetic joint infections after arthroplasty.[43]

Immunocompromising diseases and associated drug use are independent risk factors. Patients with HIV and hepatitis C infections might be at risk.[44] Fortunately, undetectable viral loads and CD4 cell counts of more than 400 cells per mL might result in long-term survivorship similar to that in healthy patients. Immunosuppressive drugs that negatively affect postoperative outcomes consist of glucocorticoids, cytostatics, interferon, and tumour necrosis factor inhibitors.[29]

Some patients do not have predisposing factors, but are highly prone to infection. The notion of primary immunodeficiency refers to adults with no predisposing factors who develop infections.[45] One in 1200 people are estimated to be so afflicted.[46] About 180 described disorders place adults at risk of infection. Ten clinical warning signs can be used for identification.[47] Some patients might have a reversible or treatable immunodeficiency. In a survey of 185 patients with severe periprosthetic joint infections, 27 had two or more warning signs of primary immunodeficiency.

Further developments include the recognition that all disease states have a genetic basis. Since the sequencing of the human genome, a plethora of genome-wide association studies have been done, which unravelled the genetic links to disease. There might be a genetic contribution to periprosthetic joint infection.[48] Thus, recognition of this genetic basis for infection might be a step in the right direction.

## Preventive measures

Meticillin-resistant *S aureus* accounts for 12–23% of all periprosthetic joint infections in the USA. The effectiveness of nasal and cutaneous decolonisation, which aims to lower endogenous bacterial loads and to prevent infections, has been debated. Nasal carriers of high numbers of *S aureus* have a three to six times higher infection risk than non-carriers or low-level carriers.[30] Various studies do not have a congruous application method, especially for treatment timing, which leads to varying results. A randomised, double-blinded, multicentre trial assessed the efficacy of screening and decolonisation with nasal mupirocin ointment and chlorhexidine in comparison with placebo. A higher infection rate with *S aureus* was reported in the placebo group than in the study group. Other investigations assessing mupirocin for orthopaedic and general surgical patients have not reported infection reductions.

A cost-effectiveness analysis assessed preoperative mupirocin in patients with total joint arthroplasty. The costs and benefits were assessed for three hypothetical cohorts: preoperative screening followed by mupirocin treatment for *S aureus* culture-positive patients, empirical preoperative treatment with mupirocin without screening, and no preoperative screening or treatment. Both the treat all strategy and the screen and treat all those identified as carriers strategy had lower costs than when no treatment was given. Controlled randomised trials are necessary to establish if screening with subsequent decolonisation is an efficacious method.

Use of preoperative antiseptics is supported by the Centers for Disease Control and Prevention. Various skin preparations have been studied, including bathing, antiseptic soaps, iodine-based antiseptics, and chlorhexidine gluconate-based drugs. Investigations show improved effectiveness of chlorhexidine gluconate compared with povidone–iodine-based solutions.[49] Two retrospective studies[50,51] have shown substantial infection reductions with chlorhexidine gluconate.

Intraoperative systemic antibiotics are standard of care for arthroplasties (panel 1). Antibiotic prophylaxis reduces the relative risk of an infection by up to 81% and the absolute risk by 8%.[52] The Surgical Care Improvement Project guidelines[53] recommend starting antibiotics at least 1 h before surgery with discontinuance within 24 h. Additionally, surgeons should consider using single-dose or short-term antibiotics to reduce costs, pharmacological toxicity, and development of antibiotic resistance.[54]

The Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery[55] recommend cefazolin for patients with total joint arthroplasty. Clindamycin and vancomycin are regarded as adequate alternatives. Vancomycin should be used for MRSA-colonised patients and considered in institutions with high prevalence of MRSA surgical site infections.

Clipper hair removal might decrease infection risk compared with razors because razors cause cutaneous microlesions and allow endogenous flora colonisation.[56] The consensus is that hair removal should be done immediately before surgery with clippers.[57]

Various perioperative skin preparations are used, including chlorhexidine-based, povidone–iodine-based, and alcohol-based solutions, in several comparison studies.[58] Reports show that chlorhexidine-based solutions result in lower positive skin cultures than in iodine-based groups.[58]

Surgical draping is the standard of care worldwide and includes cloth, adhesive and non-adhesive nylon, and iodine impregnation. Plastic drapes are a better barrier to microbial penetration than are cloths.[59] One study[60] reports that the addition of iodine-impregnated drapes was effective in reducing bacterial colonisation. Other investigations have recorded increased infection rates

***Panel 1:* Preventive measures**

**Preoperative methods**
- Patient-specific factor optimisation
- MRSA decolonisation
- Skin disinfection

**Intraoperative methods**
- Antibiotic prophylaxis
- Cutaneous preparation (hair removal, skin antisepsis, and surgical draping)
- Operative environment (operating theatre ventilation, body exhaust suits, gloves, and intraoperative lavage)
- Blood conservation
- Prosthesis selection

**Postoperative methods**
- Antibiotic prophylaxis
- Evacuation drains

MRSA=meticillin-resistant *Staphylococcus aureus*.

with adhesive draping, whereas iodine-impregnated drapes had no effect.[61]

Vertical-flow and horizontal-flow ventilation has been used to maintain ultraclean operating theatre air to dilute and minimise particles from wound contamination. Early studies[62] reported that laminar airflow reduced bacterial counts in operating theatres. However, an analysis[63] of the New Zealand Joint Registry showed significantly more early infections in laminar flow operating theatres than in conventional theatres. A systematic review[64] investigating laminar airflow and surgical site infections after total joint arthroplasty reported an increased infection risk. With conflicting evidence, use of laminar airflow is at the surgeon's discretion.

Body exhaust suits are commonly used for arthroplasties; however, their use has been questioned. Some investigations have shown no differences in infection rate compared with standard dress.[65] A joint registry review[63] recorded significantly higher infection rates in arthroplasties.

During arthroplasty, 50–67% of surgical gloves are estimated to be perforated, which is associated with increased infection rates.[66] To prevent this rise in infection, many surgeons have adopted double-gloving practices, although of unproven effectiveness.

Few studies have addressed intraoperative lavage during arthroplasties. A retrospective study[67] reported a six-times reduction in infection rates with dilute betadine lavage, which might be an inexpensive method.

The use of allogeneic and autologous blood transfusions in arthroplasty increases the risk of infection.[68] Risk factors for transfusions include low preoperative haemoglobin, female sex, increased surgery duration, and high Charlson comorbidity index.[69] Cell salvage systems, reinfusion drains, bipolar sealers, and tranexamic acid might help to minimise blood loss.[70] Use of tranexamic acid reduces transfusion requirements after total joint arthroplasty, which might reduce infection risk.[71]

Prosthetic selection has not affected incidence of periprosthetic joint infections. No significant difference in the frequency of infection exists for cementless versus cemented prostheses.[72] However, international joint registry data have suggested that antibiotic-laden cement can lower infection risk compared with uncemented or non-antibiotic-laden cement.[73] However, concerns about antibiotic-cement use include increased costs, allergic reactions, and antibiotic resistance. This practice might be effective in diabetic individuals and immunocompromised patients who are at increased infection risk.

### Postoperative prevention methods

The American Association of Orthopaedic Surgeons (AAOS) and the American Dental Association (ADA) recommend prophylactic antibiotics for patients thought to be at risk for procedures leading to transient bacteraemia. The AAOS guidelines recommend starting antibiotics 1 h before dental procedures and discontinuing within 24 h. For outpatient-based procedures, a single preoperative dose is recommended.[74] The ADA regards patients to be at an increased risk during the first 2 years after total joint arthroplasty or if they have an immunocompromising illness.[75] Unfortunately, these guidelines were developed through an exhaustive systematic analysis of reports, limited by evidence quality. Of note, the English and French guidelines do not recommend the use of antibiotic prophylaxis for dental care in patients with prostheses.

Evacuation drain use has controversial effectiveness and has been implicated as a factor in infection risk. Retrograde infection can occur through the drain tract; therefore, early drain removal (between 24 h and 48 h) is recommended.[21] Wound irrigation and debridement should be used for persistent wound drainage (greater than 1 week). For patients with an early wound infection, local wound care and oral antibiotics result in resolution of early drainage and only 28% need further management.[24] However, drainage and superficial infections are known risk factors for development of periprosthetic joint infections. Therefore, careful assessment and adequate follow-up for superficial infections is necessary. Use of microbial cultures of drain fluid during the first postoperative days is not generally recommended.[76]

## Diagnosis and staging

Various diagnostic criteria and algorithms have been proposed, including at an international consensus meeting about definition of periprosthetic joint infections (panel 2).[77] Some infections might present without meeting these criteria, especially less virulent organisms, such as *Propionibacterium acnes*. The minor criteria identified in the algorithm cannot be pathognomonic for infections. Joint aspirations are the single most important method to establish a diagnosis. Histopathology is sensitive in predicting culture-positive infections, but is moderately accurate in ruling out a diagnosis.[79] Frozen sections should be considered for patients undergoing revisions. The assessment of such samples is surgeon dependent, and there should be agreement between the surgeon and pathologist about diagnostic criteria. Frozen sections of periprosthetic tissue are effective for detection of acute inflammation, but have poor chronic infection sensitivity.[80] At least three to five periprosthetic specimen cultures should be taken, and incubated in both anaerobic and aerobic environments.

Plain radiographs should be the first imaging method used for diagnosis. A wide band of radiolucency at the metal–bone interface (or cement–bone interface) with bone destruction suggests that infection is present. Plain radiographs have low diagnostic sensitivity and specificity for differentiating between septic and aseptic osteolysis.

*Panel 2:* **Diagnostic criteria for periprosthetic joint infection**

**Major**

- Two positive periprosthetic cultures with phenotypically identical organisms
- Sinus tract communicating with the joint

**Minor**

- Raised serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
- Raised synovial fluid white blood cell (WBC) count change on leucocyte esterase test strip*
- Raised synovial fluid polymorphonuclear neutrophil percentage (PMN%)†
- Positive histological analysis of periprosthetic tissue
- A single positive culture

Developed by the International Consensus Meeting on Periprosthetic Joint Infections.[77] Periprosthetic joint infection=either one major criterion or three minor criteria. *WBC count cutoff value of 1100–1700 cells per µL. †PMN cutoff value of more than 65% neutrophilia.[78]

CT scans might assist because the presence of a periosteal reaction or soft tissue accumulation near osteolysis is suggestive of infection. MRI has a high accuracy for the detection of purulent infection and periprosthetic osteolysis.[81] Nuclear imaging techniques could also be used; bone scintigraphy with technetium has high sensitivity, but low specificity, because areas of increased uptake can suggest aseptic or septic loosening, or simply healthy bone. However, combined $^{111}$Indium-labeled white blood cell and bone marrow scintigraphy has shown superior accuracy for diagnosing infection.[82] The use of $^{18}$F-fluorodeoxyglucose (FDG) PET has emerged for detection of infection.[83] Some studies have reported up to 90% sensitivity and 89·3% specificity for hip arthroplasty and 90·9% sensitivity and 72% specificity for knee arthroplasty.[83] By contrast, some have noted low sensitivity and poor accuracy for detecting infections.

## Clinical features

Early post-interventional infections arise within 3 months of surgery and are postulated to occur during implantation. Patients present with pain, induration or oedema, wound drainage, surgical site erythema, and effusion. Infections can occur in the setting of wound dehiscence, with spread from the cutaneous sites to deeper tissue. Early post-interventional infections should be managed without delay and time cannot be lost in undertaking of imaging and diagnostic tests.

These infections occur from 3 to 12 months post-operatively and are thought to arise during implantation. Infecting organisms are generally less virulent, such as *Propionibacterium acnes*, enterococci, and coagulase-negative staphylococci.[84] Most delayed-onset infections present with persistent joint pain, and less than 50% of patients have fever.[85] Delayed infections might present similarly to aseptic failures, but persistent pain is associated with infection and weight-bearing pain, and motion is indicative of aseptic failure.

Late infections arise 12 months after surgery and are generally due to haematogenous spread from another site.[86] Presentation is acute onset of symptoms in a previously asymptomatic joint. The origin of infection is not always known, with some reports of only 50% of cases identified.[87] Most of these cases are due to *S aureus*, Gram-negative bacilli, and β-haemolytic streptococci.[87]

## Treatment options

A potential surgical management option for early postoperative or late haematogenous periprosthetic joint infections is irrigation and debridement. Success rates range from 0% to 89%, with highest success for early treatment (within 30 days of onset) with low virulence organisms and healthy patients.[88] Irrigation and debridement should not be done if the wound cannot be closed. Treatment of highly virulent organisms, such as MRSA, has lowered the success rates.[89] Some studies reported that exchange of the polyethylene liner reduced the failure risk by 33%.[90] One institution study[91] compared infection control rate in patients with component retention (32 knees) with a cohort with component removal and two-stage revision (32 knees). Final results at mean 36 months of follow-up showed no difference in rates of component retention. Polyethylene non-exchange and *S aureus* infections were contributing factors for failure.

Two-stage exchange arthroplasty is the most common operation for management of periprosthetic joint infections. Patients infected with antibiotic-resistant organisms, the presence of a sinus tract or non-viable soft tissue coverage might benefit from two-stage revisions. Intervals of more than 6 months between revisions often result in inadequate infection eradication. Although the duration of antibiotic treatment is debatable, data suggest that a 6-week course might be sufficient in most cases.[92]

Patients are generally managed with an antibiotic-free period before reimplantation to verify that the infection was successfully treated. Although little evidence exists about the precise interval, a period of 2–4 weeks is recommended before reimplantation is appropriate.[92] A minimum of 2 weeks seems to be important because tissue-culture sensitivity was less than 50% if antibiotics were discontinued less than 2 weeks before sampling.[93] Other reports have suggested that this interval might not have a major role in recurrent infections, since many pathogens can be dormant for years in the absence of an implant and then re-emerge as an infection.[93] Success rates range from 65% to 100%, but the reasons for this range and the particular factors that affect outcomes are unknown. Some researchers have suggested that positive reimplantation cultures are associated with poor outcomes. However, in a study of 97 reimplantations, five cases were culture positive, and of these only one failed.[13]

Few reports favour the use of one-stage exchange over two-stage exchange. One-stage exchange is regarded as a reasonable option when effective antibiotics are available for the organism. It can cost up to 1·7 times less than a two-stage revision.[94] Fewer procedures are generally accepted to have decreased patient morbidity, duration of operating theatre time, medical management use, and subsequently a lower economic burden. However, reinfection rates might be higher with one-stage exchange, and could ultimately result in high costs.

The use of long-term suppressive oral antibiotics is an option when prosthesis removal is inappropriate. Possible indications include poor general health, when removal would result in poor functional outcomes, and patient preferences. The goal of suppressive treatment is an asymptomatic functioning prosthesis, but not necessarily infection eradication. Favourable outcomes in 86% of patients at mid-term follow-up were reported.[95] Another study noted that 15 of 18 patients given antibiotic suppression for a mean of 48·9 months had retention of functional prostheses.[96] Antibiotic-related complications occurred in 22% of patients, but did not require discontinuation.[96] Another study reported 2-year survival rate free of treatment failure to be 60%.[97] Lengthening of antibiotic suppression might also delay rather than prevent failure, since studies have reported that failure risk rises after antibiotic cessation.[98] Prospective investigations in suppressed patients will be informative.

Switching from intravenous to oral antibiotic treatment might be appropriate because it can reduce the length of stay in hospital and lower health-care expenditures. The availability of oral formulations (which achieve similar serum concentrations as intravenous antibiotics) can decrease infusion-related adverse events, making this option appealing. Few data exist about the effectiveness of intravenous-to-oral antibiotic step-down treatment. However, a study of patients with *S aureus* osteomyelitis did not show differences between those treated with intravenous versus intravenous-to-oral antibiotics.[99] Use of intravenous-to-oral step down is at the discretion of the surgeon until more studies adequately assess this treatment. Interdisciplinary management teams are likely to further improve clinical outcomes after periprosthetic joint infection.

Patients should be monitored clinically for infection signs and with weekly serum C-reactive protein and erythrocyte sedimentation rate.[100] Marker monitoring is controversial because it is not always indicative of infection resolution; however, serial trends are important predictors of treatment success.

## Miscellaneous topics

Fungal organisms or atypical bacterial infections have been postulated to occur with a patient history of immunosuppression, diabetes, autoimmune diseases, malignant diseases, and longlasting antibiotic treatment. They are infections in which the dominant organism is fungal or atypical bacteria. Two-stage revision is regarded as the treatment of choice; however, it is not as successful as treatment of bacteria. The use of antifungal agents, such as azoles and amphotericin, is recommended for 6 weeks minimum.[101]

Oral antibiotics might have equal effectiveness for treating infections when compared with intravenous antibiotics. For example, linezolid is 100% bioavailable in oral and intravenous formulations. A multicentre, prospective, randomised, phase 4 clinical trial of skin and soft tissue infections caused by MRSA reported favourable cure rates with oral linezolid compared with intravenous vancomycin.[102] Additionally, oral antibiotics confer some advantages such as earlier hospital discharge, reduction in labour requirements for drug administration, and cost savings.[103] A randomised, placebo-controlled, double-blinded trial assessed the efficacy of an oral rifampin-containing regimen in staphylococcal infections associated with orthopaedic implants.[104] Patients who received a ciprofloxacin–rifampin combination achieved a significantly higher cure rate than the ciprofloxacin–placebo group. Additionally, one study noted that failure risk after staphylococcal periprosthetic joint infection was lower when debridement and retention were combined with a rifampin regimen than for a patient cohort treated without rifampin.[105] Similar studies have since validated that rifampin combination regimens result in more favourable outcomes than seen in patients given other antibiotics.[90,106] Of note, the interest of rifampicin-combinations is not limited to the possibility of considering early switch to oral therapy, but more importantly the use of these combinations is associated with improved outcomes in patients treated for staphylococcal periprosthetic joint infection or even for *Enterococcus* spp, as suggested by the European Society Group of Infections on Artificial Implants.[107]

Various organisms play a part in periprosthetic joint infections, which need different antibiotics. Quinopristin and dalfopristin in combination are effective against *S aureus,* including MRSA, and *Enterococcus faecium*, including vancomycin-resistant enterococci (VRE), but not against *E faecalis*.[108] Daptomycin is effective for many Gram-positive bacteria, including vancomycin-resistant *S aureus*, MRSA, and VRE. Penicillin and ceftriaxone are effective against *Streptococcus* spp, except *S agalactiae*. Clindamycin is recommended for anaerobes.

## Conclusions

Periprosthetic infections are a tremendous burden to patients and health-care institutions worldwide. In the past several decades, many innovations in the prevention, diagnosis, and treatment of patients with periprosthetic joint infections have been seen. However, the incidence of this problem is increasing in conjunction with increased arthroplasty procedures and the development of a raised number of drug-resistant organisms. Additionally, there is a shift in patient demographics and a rising prevalence of

comorbid conditions, such as obesity and diabetes, which will continue to negatively affect patients undergoing arthroplasties in the leg. To meet this challenge, novel diagnostic and treatment measures are necessary. However, for the benefit of patients, infection prevention methods should be improved, and health-care workers need to adhere to the best established practices.

#### Contributors

All authors contributed equally in the preparation of this Review.

#### Declaration of interests

BHK is on the Speakers bureau and is a paid consultant for Sage Products. MAM receives royalties from Stryker and Microport and is a paid consultant for DJ Orthopaedics, Janssen, Joint Active Systems, Medtronic, Sage Products, Stryker, TissueGene, and Microport. He has received research support from DJ Orthopaedics, Joint Active Systems, National Institutes of Health (NIAMS and NICHD), Sage Products, Stryker, Tissue Gene, and Microport, is on the editorial or governing board of *American Journal of Orthopaedics*; *Journal of Arthroplasty*; *Journal of Bone and Joint Surgery—American*; and *Journal of Knee Surgery*; *Surgical Techniques International*, and is a board member for the American Association of Orthopaedic Surgeons. JAD is on the Speakers bureau for 3M and Sage Products. AB receives royalties from Guardian and is a paid consultant for Ongoing Care Solutions, DJO Global, and Orthosensor. JF has received research support from Siemens AG. RAB declares no competing interests.

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