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Peri-Prosthetic Joint Infection: Prevention, Diagnosis and Management

Adrian J. Cassar Gheiti and Kevin J. Mulhall

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1. Introduction

Total Joint Arthroplasty (TJA) is a safe and effective procedure that improves the quality of life and restores function in most patients suffering from joint arthritis. Post-operative peri-prosthetic joint infections (PJI) are an uncommon and difficult complication of joint replacement surgery.

PJI affects 1-3% total joint replacements and is the most common indication for revision in total knee arthroplasty (TKA) and third most common indication for revision total hip arthroplasty (THA)[1-4]. PJI can be difficult to diagnose and can present at any time from the primary procedure[5, 6]. PJI is painful, disabling, costly and often requires multiple procedures[7], prolonged periods of rehabilitation, antibiotic treatment and poor functional outcome. It places a considerable burden on hospital and surgeon resources with an estimated annual cost of infected revisions in US hospitals increasing from $320 million in 2001 to $566 million in 2009, with a projected cost exceeding $1.62 billion by 2020[8]. Consistent efforts at prevention are mandatory, and treatment of infection requires appropriate assessment of its chronicity and causative factors, the status of the wound and the overall health of the patient.

We will first provide an overview on peri-prosthetic joint infection and the possible risk factors involved. Finally, we will provide an overview of the current evidence available in preventing, diagnosis and managing peri-prosthetic joint infection.

2. Pathophysiology

Peri-prosthetic joint infections are a result of an intricate interaction between the host, the pathogen and the implant[9-11]. There is a multitude of host factors, ranging from medical comorbidities to social economic status, which increase the risk of PJI[9, 10, 12-15].

2.1. Host and environmental factors

Predisposing factors for PJI can be sub classified into preoperative, intraoperative and post-operative factors (Table 1). Preoperative predisposing factors include medical conditions such as diabetes, inflammatory arthropathies, preoperative anemia, congestive heart disease and chronic pulmonary disease to mention few[9, 10, 12, 14]. Intraoperative predisposing factors include simultaneous bilateral joint arthroplasty, longer operative time, knee arthroplasty, increased operating room traffic and contamination by the surgical team during preparation and draping[12, 16-19].

Post-operative predisposing factors to PJI include immunosuppressive medications, allogenic blood transfusion, post-operative atrial fibrillation, myocardial infarction, urinary tract infection and longer hospital stay[9, 10, 12].

Peri-prosthetic joint infections are typically caused by microorganisms that grow in biofilms[36]. Within biofilms, microorganisms in a polymetric matrix and develop into organized complex communities resembling a multicellular organism[37]. In a biofilm, microbes are protected from antimicrobial agents and host immune responses. This may be related to the reduced growth rate of biofilm microorganisms, which enter a stationary phase of growth[38]. Different microbes have different interactions with the host and the prosthetic. Some have specific adhesion molecules which help them adhere to the implant until a biofilm is formed, which is mediated in part by intracellular adhesion molecules[39]. Initially, adherent microorganisms and early biofilms are relatively unstable and still susceptible to host defense and antimicrobial agents. In contrast, mature biofilms are more stable and resist to elimination[40]. Furthermore, implants are devoid of microcirculation, which is crucial for the immune system and antibiotics to interact with microbes. Implants also tend to activate neutrophils which release peptides that deactivate granulocytes, impairing the removal of microbes[41]. This effect on granulocytes reduces the minimal amount of microbes that are required to cause an infection[41]. Inoculation of implants, not only occurs during the time of surgery, but can occur in the presence of a bacteremia from any source in the human body during the entire lifetime of the implant[42].

2.2. Microbial profile in PJI

A multitude of organisms mostly bacteria and fungi are reported to cause PJI (Table.2). The most reported organisms responsible for PJI are Gram positive *cocci*, most commonly *Staphylococcus Aureus* and *Staphylococcus Epidermidis* as reported by various authors[12, 20, 22, 31, 43-45]. On certain occasions, Gram negative bacteria and Fungi can also be responsible for periprosthetic joint infections[46, 47]. In a recent study published by Buller et al., Methicillin Resistant *Staph. Aureus* (MRSA) and Methicillin Resistant *Staph. Epidermidis* (MRSE) account for about 15.5% of all PJIs[20] and according to other studies up to 19% of PJIs can be poly microbial[12, 22, 48]. These microorganisms can all be part of normal skin flora; hence, direct inoculation at the time of the operation as well as airborne contamination are the most likely causes of these infections.

Predisposing Factors	Studies
Preoperative	
Male sex	Buller et al.[20], Jämsen et al.[21]
Socioeconomic status	Pulido et al.[12], Berbari et al.[22]
ASA > 2	Pulido et al.[12], Buller et al.[20], Bozic et al.[9], Saleh et al.[23],
Diabetes and elevated blood sugars	Buller et al.[20], Bozic et al.[9], Jämsen et al.[24], Berbari et al[22]., Saleh et al.[23]
Inflammatory Arthropathy	Pulido et al.[12], Bozic et al.[9], Wilson et al.[10], Jämsen et al.[21] , Berbari et al.[22]
Immunosuppressant medication	Wilson et al.[10], Berbari et al.[22], Saleh et al.[23]
Preoperative Anaemia	Pulido et al.[12], Greenky et al.[14], Bozic et al.[9]
Poor Nutrition	Berbari et al.[22]
Higher BMI	Pulido et al.[12], Bozic et al.[9]
Other infected Joint Arthroplasty	Buller et al.[20], Jafari et al.[15], Berbari et al.[22]
History of malignancy/metastasis	Bozic et al.[9], Berbari et al.[22]
Skin ulcers/PVD	Bozic et al.[9], Wilson et al.[10], Berbari et al.[22], Poss et al.[25]
Intraoperative	
Knee arthroplasty	Pulido et al.[12], Buller et al.[20]
Simultaneous bilateral	Pulido et al.[12]
Longer operative time	Pulido et al.[12], Muilwijk et al.[26], Ong et al.[27], Berbari et al.[22], Saleh et al.[23]
No prophylactic antibiotic	Fogelberg et al.[28], Pavel et al.[29], Meehan et al.[30], Al-Maiyah et al.[31]
Cement with no antibiotics	Hanssen AD.[32], Jämsen et al.[21]
Skin Preparation and Draping	Johnson et al.[33], Katthagen et al.[16]
Contamination by operating room personnel	Ayers et al.[34], Rao et al.[35]
Operating Room Traffic	Panahi et al.[18]
Postoperative	
Renal impairment	Pulido et al.[12], Saleh et al.[23], Bozic et al.[9]
Allogenic blood transfusion	Pulido et al.[12], Berbari et al.[22], Saleh et al.[23]
Myocardial Infarction	Pulido et al.[12]
Atrial fibrillation	Pulido et al.[12], Berbari et al.[22]
Urinary tract infection	Pulido et al.[12], Wilson et al.[10], Poss et al.[25]
Haematoma	Pulido et al.[12], Jämsen et al.[21], Berbari et al.[22], Saleh et al.[23]
Continuous wound discharge	Pulido et al.[12], Jämsen et al.[21], Berbari et al.[22]
Prolonged Hospital stay	Pulido et al,[12]. Berbari et al.[22]

Table 1. Predisposing factors to PJI

Organism	Study (number of cases)							
	Buller et al [342]	Mahmud et al [250]	Romano et al [71]	Pulido et al [63]	Berbari et al [462]	Phillips et al [75]	Al-Maiyah et al [106]	Salvati et al [2330]
Staphylococcus								
MRSA	13.5%	3.2%	31%	19%	22%	4%	6.6%	27.3%
MSSA	19.6%	16%	21.1%	19%		25%		
MRSE	2%	21.2%	22.5%	11%	19%	36%	68.9%	27.8%
MSSE	19.9%							
α-Hemolytic Streptococcus	3.8%							0.7%
β-Hemolytic Streptococcus	6.1%	2.8%	5.6%	12.7%	9%	7%		7.2%
γ-Hemolytic Streptococcus	4.1%							5.6%
Enterococcus	2.9%		5.6%	1.6%	1.2%	9%		4.5%
VRE	0.6%							
Streptococcus milleri	0.6%							
Peptostreptococcus	2.4%		2.8%				12.3%	
Gram-positive rods								
Corynebacterium	0.3%		1.4%	1.6%	0.6%			3.2%
Enterobacter	4.1%	1.6%						1%
Propionibacterium	2.9%	0.8%	2.8%			1%		1.7%
Gram negative								
Escherichia coli	3.2%	1.2%		3.2%		4%	0.9%	5.5%
Haemophilus	0.3%							
Citrobacter koseri	0.3%							0.1%
Klebsiella	1.2%			3.2%		3%		1.3%
Proteus mirabilis	2.0%			1.6%				3.1%
Pseudomonas	3.2%	0.8%	5.6%	1.6%		4%	1.9%	5.6%
Salmonella	0.9%					1%		0.3%
Serratia marcescens	0.3%	1.2%	1.4%	1.6%				0.3%
Bacteroides fragilis	0.3%	0.4%						0.5%
Yeasts								
Candida	0.3%				0.2%			0.3%
Diphteroids						1%	9.4%	0.9%
Polymicrobial		0.02%		6.3%	19%			
Culture negative	8.8%	27.2%		9.5%	12%			
No Results		22.4%						

MRSA: Methicillin Resistant *Staph. aureus*, MSSA: Methicillin Sensitive *Staph. aureus,* MRSE: Methicillin Resistant *Staph. epidermis.* MSSE: Methicillin Sensitive *Staph. epidermis.*

Table 2. Percentage of microbes in PJI [12, 20, 22, 31, 43-45, 48]

While, the patient's endogenous flora is largely held accountable for surgical site infections, the surgical team personnel and operating room environment may also contribute to disperse organisms[49] and increase the bacterial count[18, 50]. Members of the surgical team who have direct contact with sterile field have been linked to outbreaks of unusual organism such as *Serratia Marcescens*[51]. Even though anesthesiologists, are not directly involved in the operative field, they perform a variety of procedures related to the operation and have been associated with outbreaks of bloodstream and surgical site infections linked to the re-use of propofol vials and other deviations from acceptable protocols[52].

2.3. Classification of PJI

The classification of PJI is based on, either the type of pathogenesis or the time of clinical manifestation. When PJI are classified according to the pathogenesis, inoculation of the surgical site occurs either exogenously or haematogenously[11]. Exogenous infection, are infections that occur during surgery or in the early post-operative period, usually in the presence of large hematomas. Haematogenous infections are acquired through the bloodstream at any time after surgery. As discussed in section 2.1, it has been reported that implants impair the immune defenses and decrease the minimal abscess-forming dose of *Staph. aureus* at least 10 000 fold both in an animal and human model[53, 54]. Patients with prosthetic joints have a reported risk of 30 - 40% for haematogenous device–associated infection during *Staph. aureus* sepsis[13, 42]. Even though patients, are mostly susceptible to PJI early after implantation, haematogenous infection can occur at any time after surgery.

More commonly, PJI is classified according to the time of clinical manifestation after total joint replacement. This classification is divided into 4 stages or groups[11, 55, 56]:

- Stage I or Early post-operative infection, which present acutely within the first 4 to 8 weeks after the operation

- Stage II or Delayed onset PJI and occurs between the 3rd month up to 24 months after surgery

- Stage III or Late onset PJI usually occur after 2 years from the procedure, the presentation is usually sudden in an otherwise well-functioning joint.

- Stage IV or Silent infection when a positive culture is found at time of revision without any previous evidence of infection.

Early (Stage I), delayed (Stage II) and silent (Stage IV) infections are commonly exogenous, while stage I infections are probably caused by virulent microorganisms such as *Staph. aureus* and *Escherichia coli*, Stage II and Stage IV are typically caused by low virulent bacteria such as coagulase negative staphylococci and *Propionbacterium acnes*[56, 57]. Stage III or Late onset PJI occur acutely in a well-functioning joint and are caused by haematogenous spread. The most common primary focus of infection is from skin and soft tissue infections, but seeding from urinary, respiratory, gastrointestinal tract and dental infections are also reported[58]. In a recent report by Sendi et al., 57.5% of cases with haematogenous PJI had no source identified either because of primary bacteremia, or because the primary infection has already healed by the time signs and symptoms of PJI present[13].

2.4. Definition of PJI

The Musculoskeletal Infection Society (MSIS) have recently analyzed the available evidenced and proposed a set of criteria to define peri-prosthetic joint infection.

Based on these criteria[59], a definite PJI exists when:

i.   there is a sinus tract communicating with the prosthesis; or

ii.   a pathogen is isolated by culture from 2 or more separate tissue or fluid samples obtained from the affected prosthetic joint; or

iii.   when 4 of the following 6 criteria exist;

   a.   elevated serum erythrocyte sedimentation rate and serum C-reactive protein (CRP) concentration,

   b.   elevated synovial white blood cell count,

   c.   elevated synovial polymorphonuclear percentage(PMN%),

   d.   presence of purulence in the affected joint

   e.   isolation of a microorganism in one culture of periprosthetic tissue or fluid, or

   f.   greater than 5 neutrophils per high-power field in 5 high-power fields observed from histologic analysis of periprosthetic tissue at ×400magnification.

PJI may be present if less than 4 of these criteria re not met and that in certain infections with low virulent organisms such as *Propionibacetium acnes,* several of these criteria may not be routinely met despite the presence of PJI.

3. Prevention of PJI

Both the host and environmental factors described previously (Table. 1) can affect the risk for developing PJI. An effective strategy in preventing PJI is to improve both host and environmental factors during the pre, intra and post-operative period (Table. 3).

There are a number of host factors that increase the risk of PJI including conditions such as diabetes, inflammatory arthropathy, preoperative anaemia, poor nutrition and obesity to mention a few(Table. 1). Patients who present for elective orthopaedics procedures are in suboptimal health. Furthermore, the impact of various risk factors appears to be accumulative, such that each factor has an individual affect to increase the risk of infection and has a synergistic potential on the risk conferred by other factors[60, 61]. Thus, identifying such risk factors and addressing them in the preoperative setting is critical in reducing PJI and other postoperative complication.

Time			Strategy
Preoperative	Early	Host optimization	Improve Diabetic control
			Treat possible site of infections
			Improve possible Medical Comorbidities
			Obesity + Improve Nutritional Status
			Pre – operative anaemia
			Smoke Cessation
			MRSA screening
	Day of Surgery	Surgical Site Optimization	Surgical Site Shaving
			Skin decolonisation (CHG wipes/showers)
Intraoperative	Surgical factors		Prophylactic antibiotics
			Skin Preparation
			Draping
			Bleeding Control
			Antibiotic impregnated cement
			Skin Closure
			Wound Dressing
	Surgical team		Decolonization: Surgical scrubbing/rubbing
			Impermeable Gowns/PPS
			Double Gloving
	OR environment		Operating Room Traffic
			Laminar Airflow
Post-operative	Immediate		Antibiotics for 24 hours
			Wound management
			Blood Transfusion only where indicated
			Management of medical complications
	Late		Antibiotic prophylaxis before invasive procedures

CHG: Chlorhexadine Gluconate, OR: Operating Room, PPS: Personal Protection System, MRSA: Methicillin Resistant Staph. aureus Adopted from Matar et al. Preventing infection in total joint arthroplasty. J Bone Joint Surg Am. 2010;92 Suppl 2:36-46. Epub 2010/12/09.

Table 3. Preoperative, Intraoperative and Post-operative Strategies in preventing PJI

3.1. Pre-operative period

3.1.1. Health optimization

Pre-operative optimization of health is of crucial importance to ensure a satisfactory out-come following total joint arthroplasty. ASA scores >2, diabetes and rheumatoid arthritis among several factors have been associated with increased rates of perioperative complications and PJI after total joint arthroplasty[9, 12, 20, 21, 24]. Lei et al. and Malinzak et al. have both reported that diabetes and the total number of comorbidities were associated with a higher risk of infection and that medical conditions have a synergistic effect on the risk of developing a PJI[60, 62].

Prior to total joint arthroplasty, all patients should be assessed and managed in a multidisciplinary pre-assessment clinic to optimize their general health. These have been shown to significantly reduce both the post-operative mortality and costs per admission in orthopaedic surgery[63]. Pre Assessment Clinics (PAC), focus on optimizing the host health in the preoperative period such as improving nutritional status, optimizing diabetic control, cardiac and respiratory comorbidities and screening for possible source of infection and MRSA decolonization. In our institution, all patients are assessed in the pre assessment clinic by a consultant anesthesiologist, specialist nurse, nutritionist and physiotherapist, and if necessary further consultation with other medical specialists such as cardiologist, rheumatologist or neurologists is available to optimize the patients' health preoperatively. The anesthetic consultant also follows the patient during hospitalization and during the post-operative period whenever possible.

3.1.2. Bacterial decolonization

The Centre for Disease Control (CDC) guidelines for prevention of surgical site infection (SSIs) has strongly recommended that patients require to shower or bathe with an antiseptic agent on at least the night before the operative day in order to reduce bacterial load[64]. While whole body bathing with antiseptic has been shown to reduce bacterial load of the skin as well as reducing the risk of infections[35, 65-67], it presents challenges in achieving entire body coverage and in maintaining sufficiently high concentrations of solution on the skin for effective antisepsis[68]. Further more patient compliance with these protocols is an issue[69]. Recent studies have addressed the effectiveness of preoperative protocols with chlorhexidine gluconate (CHG) applied twice daily by patients at home before their joint replacement[33, 70] and one study reported reduction in SSI infection from 3.19% to 1.59% after the introduction of 2% CHG in place of povidone iodine antiseptic[71]. Based on the results of these studies, home skin preparation seems to be a simple and cost effective technique in reducing PJI but patient compliance is an issue and further randomized control trials are required to fully understand the effect on preventing PJI.

3.1.3. Prophylactic antibiotics

The benefits of prophylactic antibiotics have been widely reported in orthopaedic literature [28-30, 72]. In 1970, Foldberg et al. compared a group treated prophylactically with penicillin given preoperatively, intraoperatively and up to 5 days post operatively, with a control group not treated with antibiotics; both groups underwent a mixture of mold arthroplasties and spinal fusions[28]. The prevalence of infections was 1.7% in the treated group while 8.9% in the control group[28]. Furthermore during the period of the study these authors have noticed an increase in the prevalence of MRSA in all major orthopaedic wound infections, which demonstrates a delicate balance between the use and overuse of antibiotics in the prevention and treatment of infections.

The most common organisms responsible for PJI have been already discussed in section 2.2, and prophylactic antibiotics are targeted to cover this spectrum of organisms. Cefazolin and cefuroxamine are the antibiotics of choice because of their good tissue penetration and excellent activity against Staphylococci and Streptococci. The American Association of Orthopaedic Surgeons (AAOS) published guidelines regarding prophylactic choice, dosing and optimal postoperative duration[61]. The AAOS recommendations for the use of intravenous antibiotic prophylaxis are as follows:

- **Recommendation 1:** The antibiotic used for prophylaxis should be selected carefully, consistent with current recommendations in the literature, taking into account the issue of resistance and *patient allergies*. Currently, cefazolin and cefuroxamine are the preferred antibiotics for patients undergoing orthopaedic procedures. Clindamycin and vancomycin may be used in patients with known β-lactam allergy. Vancomycin may be used in patients with known colonization with MRSA or in facilities with recent MRSA outbreaks. In multiple studies, exposure to vancomycin is reported as a risk in the development of vancomycin resistant enterococcus (VRE) colonization and infection. Vancomycin should be reserved fir the treatment of serious infection with β-lactam resistant organisms or for treatment of infection in patients with life threatening allergy to β-lactam antimicrobials.

- **Recommendation 2:** Timing and dosage of antibiotics administration should optimize the *efficiency of the therapy*. Prophylactic antibiotics should be administered within 1 hour before skin incision. Owing to an extended infusion time, vancomycin should be started within 2 hours before incision. If a proximal tourniquet is used, the antibiotic must be completely infused before the inflation of the tourniquet. Dose amount should be proportional to the patients' weight; for patients who weigh more than 80Kg, Cefazolin dose should be doubled. Additional intraoperative doses of antibiotics are advised is [1] the duration of the procedure exceeds one to two tines the antibiotic's half-life or [2] there is significant blood loss during the procedure. The general guidelines for frequency of intraoperative antibiotic administration are as follows: cefazolin every 2-5 hours, cefuroxamine every 2-4 hours, clindamycin every 2-6 hours and vancomycin every 6-12 hours.

- **Recommendation 3:** Duration of prophylactic antibiotic administration should not exceed *the 24 hour postoperative period*. Prophylactic antibiotics should be discontinued within 24 hours of the end of surgery. The medical literature does not support the continuation of antibiotics until all drains or catheters are removed and provides no evidence of benefit when they are continued past the 24 hours.

3.2. Intra-operative period

3.2.1. Pre-operative hair removal

Pre-operative hair removal is of common practice, and a meta-analysis by the Cochrane group showed that the relative risk of surgical site infection following hair removal with a razor was significantly higher than that following hair removal with clippers, but there was no difference reported in the rate of post-operative infections between procedures preceded by hair removal and those performed without hair removal[73]. It is recommended that whenever hair is removed clippers rather than a razor should be used at the time of surgery[73].

3.2.2. Pre-operative skin preparation

3.2.2.1. Patients

Three main types of skin antiseptic agents are used; mainly chlorohexidine gluconate (CHG), alcohol based solutions and povidone-iodine. Chlorohexidine is favored due to its long lasting and cumulative activity against gram-positive and gram negative organisms found on human flora. Povidone iodine it is also effective in reducing skin flora but in becomes ineffective on contact with blood and duration of activity is shorter the CHG. Alcohol is an excellent antimicrobial but its effectiveness is limited by the lack of any residual activity after drying and the risk of flammability. A Cochrane meta-analysis carried out in 2004 showed no difference in efficiency among skin antiseptics used in clean surgery[74]. Recent studies strongly suggest that CHG combined with alcohol is superior to povidone-iodine combined with alcohol in antisepsis for patients[75-77]. Ostrander et al. reported reduced bacterial count on feet prepared with Chloraprep (2% CHG and 70% isopropyl alcohol; Medi-Flex, Overland Park, Kansas) than on those prepared with Duraprep (0.7% iodin and 74% isopropyl alcohol; 3M Healthcare, St. Paul, Minnesota) or Techni-Care[3.0% chloroxylenol; Care-Tech Laboratories, St. Louis, Missouri) but there was no difference in infection rates among the 3 groups[77].

3.2.2.2. Surgeon

Antiseptic agents for surgeons can be classified into hand scrubs agents and hand rub agents. Hand scrubs are typically solutions of CHG or povidone-iodine while hand rubs are typically alcohol based solutions. Most data indicates that povidone–iodine and CHG have equal efficacy in decreasing bacterial colony forming units from the skin of surgeons; furthermore no difference was found between hand rubs and hand scrub solutions[78, 79]. Some studies report better cost effectiveness of alcoholic hand rub by saving on water consumption and better physician compliance [78].

3.2.3. Draping

There is strong evidence in the literature for the use of plastic surgical adhesive tapes and nonpermeable paper drapes for surgical site draping [16, 80-83]. Nonpermeable drapes are used to prevent bacterial penetration during surgery, which was found to increase when tra-

ditional cloth drapes got wet[80]. Iobhan iodophor-impregnated drapes (3M Health Care) have been shown a reduction in wound contamination without any decrease in wound infection rate after total joint arthroplasty[84]. In their review of 4 000 patients in seven different trials, the Cochrane Wounds Group, found no evidence that adhesive drapes (plain or impregnated with antimicrobials) reduce surgical site infection rates[85].

3.2.4. Double gloving

Sterile surgical gloves aim to protect the patient from contamination from residual bacteria from members of the surgical team after hand scrubbing and protect the surgical team from the patient's body fluids[86]. Double gloving has been recommended because it has been shown that it reduces perforations in the innermost glove especially in orthopaedic procedures where sharp surfaces are easily formed[86-88]. Beldame et al. have reported that, 80% of glove perforations occur during surgical incision and changing the outer glove after surgical incision and before implantation of the prosthesis can reduce the risk of contamination and perforation and resulted in a sterile state in 80% of cases[89].

3.2.5. Laminar flow, operating room traffic and personal protection system

Operating theatres are designed to reduce bacterial exposure to patients during surgery. Vertical laminar airflow (LAF) provides directional airflow through a higher efficiency particulate air (HEPA) filters and positive air pressure within the surgical field. Multiple studies have reported reduced PJI rates with LAF[17, 90-92]. Brandt et al. reported no benefit from using LAF, and it was even associated with increased risk of surgical site infection after total hip arthroplasty. A recent systematic review on SSI following hip and knee arthroplasty included 8 studies over the past 10 years and showed no improvement on PJI rates and recommends against the installation of LAF systems in new operating theatres[93].

The opening of the operating room door disrupts the laminar airflow, allowing pathogens to enter the space surrounding the site of the operation with increased risk of PJI[17, 94, 95]. Panahi et al. have reported a mean rate of 0.69 door opening per minute for primary and 0.84 openings per minute for revision total joint arthroplasty. Only 8% of the traffic was determined to be due to scrubbing in and out, demonstrating a high rate of unjustifiable traffic, the authors further advise to implement strategies in reducing operating room traffic in an attempt to decrease one etiology of PJI[18].

The human exhaust system or personal protection system (PPS) was initially introduced by Sir J Charnley in the 1960s and designed to decrease airborne bacteria and intraoperative contamination in total joint arthroplasty[96]. No uniform opinion exists with regard to the use of PPS and the incidence of PJI[97-101]. One of the main issues with PPS is that, they are bulky and tend to get contaminated. In a recent study, Kearns et al. have reported that 53 out of 102 PPS tested were contaminated with staphylococcus and one with MRSA, which means that the PPS does not remain externally sterile in half of the cases[19]. These authors recommend refraining from touching the PPS during surgery and the need to change gloves if hand contact with the PPS occurs[19].

3.2.6. Operative time

Long operative times have been found to increase the risk for PJI after total joint arthroplasty[27, 102, 103]. From a cohort of 9245 patients undergoing total joint arthroplasty, Pulido et al reported longer operative time as a predisposing factor for PJI, a finding which is also supported Kurtz et al. and Peersman et al[104, 105]. Furthermore, surgeons volume seems to be inversely proportional to the rate of infection, were the higher the surgeon volume the lower the rate of infection, but this was only found to be statistically significant after total knee arthroplasty[26].

3.2.7. Addition of antibiotics to cement

In recent years antibiotic impregnated cement has become a standard for use in cemented primary arthroplasty. According to recent studies, the rate of PJI was lower when a combination of intravenous antibiotic prophylaxis and antibiotic impregnated cement was used for primary cemented arthroplasty[21, 106]. Antibiotic impregnated cement seems to be of particular use in the revision setting[107-109]. Nevertheless there is strong evidence to support the efficiency of combined regime of prophylactic antibiotic and cement impregnated antibiotic when compared to prophylactic antibiotic only in patients with other risk factors for PJI[32, 110, 111].

3.2.8. Wound closure and surgical dressing

Various methods of skin closure are used in arthroplasty surgery, ranging from skin staples, subcuticular closure with absorbable suture and recently the use of knotless barbed sutures. A recent meta-analysis by Smith et al. reported that closure with skin staples had a significant risk of wound infection when compared to traditional suturing, but out of the six studies reviewed only one study had acceptable methodology[112]. Newman et al has reviewed 181 patients after total knee arthroplasty and reported significant fewer complications after closure with skin staples when compared with absorbable subcuticular sutures[113]. A prospective randomized control trial comparing staples to subcuticular absorbable suture and tissue adhesives after TKA, showed highest superficial infection rate for subcuticular suture (26%) and the lowest for skin staples (5%), although none of them required any treatment with antibiotics[114]. Furthermore, staple based wound closure was fastest and the least expensive after TKA but had the longest hospital stay when compared to the other methods[114]. Recently there has been increased interest in knotless barbed sutures for wound closure after total joint arthroplasty[115-117]. Most studies reported faster closure times for the barbed sutures when compared to traditional methods[116, 117]. Patell et al. have reported a significant increase risk of major wound complications especially after TKA, when barbed sutures (4.3%) were used compared to staples 1.1% and standard absorbable subcuticular closure (4.2%)[115]. However, debate still exists on which is the optimal method of closure.

Surgical technique with careful tissue handling and wound closure is important in wound healing, as well as the type of dressing that is applied postoperatively[118, 119]. Wound

dressing assist with healing by acting as a physical barrier to bacteria, splinting the wound to protect it from subsequent injury, helping with haemostasis, reducing dead space and minimizing pain. The use of occlusive dressings is well known to improve re-epithelisation and subsequent collagen synthesis when compared to wound exposed to air[120, 121]. In a recent Cochrane review, Dumville et al. reported no evidence to suggest that one dressing is better than any other in preventing surgical site infection and advised that the choice of dressing should be based on costs and the need for management of specific symptoms[122]. After total joint arthroplasty, a hydrofiber/hydrocolloid dressing using the jubilee method has been shown to reduce the rate of blister formation but no significant reduction in surgical site infection[118]. Burke et al. have carried out a prospective randomized study comparing the jubilee dressing method with standard adhesive dressing after total joint arthroplasty and reported a significant reduction in blister formation, leakage and dressing changes in the group treated with the jubilee method but no significant reduction in SSI. The authors of this study recommend the use of the hydrofiber/hydrocolloid dressing combination after total joint arthroplasty due to the associated lower complication rate[123].

3.3. Post-operative period

Most medical complications in the post-operative period have been to increased rates of PJI, mainly elevated blood creatinine levels, allogenic blood transfusion, myocardial infarction, atrial fibrillation and urinary tract infections[9, 10, 12, 21, 22, 25]. Adequate hydration is critical in post-operative period and allogenic blood transfusion is indicated in the presence of symptomatic anaemia, a haemoglobin level <8g/dL, or when it is medically indicated[124]. Control and monitoring of blood sugar levels is important in diabetic patients and should follow the same principles used in the preoperative period. Persistent wound drainage has been has been found as a contributing factor in the development of PJI[12, 21, 22], however there is little or no supportive evidence for the continues use of antibiotics[61] or antimicrobial impregnated dressings[122]. Furthermore, post-operative complication can result in delayed rehabilitation after a total joint arthroplasty with resultant delay in discharge from hospital, which has been reported by various studies as a risk factor for the development of PJI[12, 22].

4. Diagnosing PJI

Currently there is no diagnostic modality, which is 100% reliable in diagnosis PJI. An assessment using a combination of clinical findings and investigations is necessary.

4.1. Clinical

A careful history and physical examination are crucial in making a diagnosis of PJI. Although the diagnosis of early postoperative or acute haematogenous infection is not difficult, late infections can be challenging to distinguish from other causes of pain in a patient with previous total joint arthroplasty. Clinically, early or acute infections are characterized

by pain, fever, wound drainage or erythema. While the only feature of chronic infection, can be pain unrelieved by a seemingly well-functioning arthroplasty. Loosening during the first year post implantation or a consistently painful arthroplasty should be considered infected until proven otherwise.

4.2. Diagnostic investigations

4.2.1. Serology

Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) are baseline screening tests for any patient planned for revision arthroplasty regardless of the cause of failure[5]. Diagnostic value of ESR and CRP has been widely reported, and their combined use is a very good 'rule out' test [125, 126]. When both ESR and CRP are negative, periprosthetic infection is unlikely, however when both tests are positive PJI must be considered, and this warrants further investigations [5]. Ghanem et al. have reported that values higher than an ESR of 30 mm/h and CRP 10 mg/l combined to gather had 97.6% sensitivity for a positive diagnosis of PJI[127].

A full blood count including a white blood cell (WBC) count is part of the routine workout for patients with suspected PJI, however recent evidence suggests that serum WBC and differential carries a very low sensitivity (55% and 52% respectively) and specificity (66% and 75% respectively)[128]. Accordingly, routine serum WBC count and differential have no role in the diagnosis of PJI..

4.2.2. Joint aspiration

Joint aspiration is recommended as part of the work up in diagnosing PJI in patients with combined elevation of ESR and CRP levels in the hip and elevation of ESR and/or CRP levels in the knee joint[5]. Joint aspiration is usually carried out under sterile conditions, and synovial fluid should be for culture and sensitivity, WBC count and neutrophil percentage. Some patients with abnormal ESR and CRP may require more than one aspiration. A WBC count higher than 1700 cell/µl or a neutrophil percentage greater than 65% is highly suggestive of chronic PJI, however these values are not applicable when diagnosis acute PJI[129, 130]

4.2.3. Imaging studies

Imaging studies such as plain radiographs, computed tomography (CT) or magnetic resonance imaging (MRI) scans are useful in sub classifying patient into high and low probability of PJI. Radiolucent lines, focal osteolysis, periosteal bone formation or early loosening may all suggest PJI[131], however differentiating between PJI and aseptic loosening may not be possible using imaging modalities on their own. Nuclear scintigraphy detects inflammation in peri-prosthetic tissue, and although technetium-99m bone scintigraphy has very high sensitivity, it lacks specificity for infection[132]. A technetium bone scan can remain positive more than a year after implantation because of increased periprosthetic bone remodelling.

Love et al. reported increased sensitivity (96%), specificity (87%) and accuracy (91%) when a leukocyte/marrow scintigraphy was used to identify PJI. The test was significantly more accurate than bone (50%), bone/gallium (66%) and leuckocyte/bone (70%) scintigraphy in diagnosing PJI[133]. It seems that a Leukocyte/marrow scintigraphy will remain the procedure of choice in diagnosing PJI until agents capable of differentiating infection from aseptic inflammation are developed[133].

Figure 1. Plain AnteroPosterior and Lateral Radiographs showing focal areas of osteolysis, suspicious of PJI.

4.2.4. Intraoperative techniques

Various techniques can be used intraoperatively during revision arthroplasty to diagnose infection. These techniques include synovial fluid biomarkers, cultures and frozen sections.

4.2.4.1. Cultures and Gram stain

Cultures of periprosthetic tissues provide the most reliable means of detecting that pathogen and are often used as a reference standard in diagnosing PJI. Multiple samples should be taken at the time of the procedure from various regions, at least 3 samples for culture are recommended[134-136]. Cultures may be negative because prior antibiotic exposure, low number of organisms, an inappropriate culture medium, fastidious organisms or prolonged

transport time to the laboratory[11]. Grams stains have high specificity (97%) but extreme low sensitivity (less than 26%)[137, 138]. The AAOS guidelines recommend against the routine use of intraoperative gram stain for the diagnosis of PJI[5].

4.2.4.2. Frozen sections

A meta-analysis by Della Valle et al reported that frozen sections are very good in ruling in but have low value in ruling out and infection[5]. These studies have more than 80% sensitivity and more than 90% specificity, but they also have high interobserver variability. The degree of inflammatory cells infiltrations varies among specimens from the same patient, sometimes even within individual tissue samples[11].

4.2.4.3. Synovial fluid biomarkers

Synovial fluid can used to analyse for various biomarkers such as leukocyte esterase, synovial CRP and white blood cell count, interleukin 6 (IL-6) and interleukin 8 (IL-8). Leukocyte esterase is an enzyme secreted by activated neutrophils that migrate at the site of infections. This enzyme is usually found on colorimetric dipsticks to diagnose urinary tract infections. Potential advantages of this diagnostic tool include wide availability, low cost and potential of an accurate diagnosis within minutes. Parvizi et al. have initially reported preliminary data on using leukocyte esterase as a diagnostic tool. These authors reported 80.6% sensitivity and 100% specificity in diagnosing PJI, with 100% positive predictive value and 93.3% negative predictive value[139]. Wetters et al also reported similar results when they used leukocyte esterase for diagnosis PJI[140]. In both studies, the leukocyte esterase strip was unreadable in on third off cases due to synovial blood or debris. Even though, these results are promising, both of these studies have their limitations in the methodology used, and further on, none of studies identifies whether the leukocyte esterase strip is able to differentiate between inflammation and infection.

Measurement of synovial CRP has been shown to be a sensitive (85%) and specific (95%) marker in diagnosis PJI[141, 142]. Recent studies report IL-6 levels to be more accurate in diagnosis PJI than ESR, CRP level, or synovial fluid WBC count and can be useful in diagnosis of PJI in patients with confounding systemic variables. Jacovides et al. have also reported higher specificity and sensitivity for both IL-6 (100% and 87.1%) and IL-8 (97.7% and 90.3%) when compared to synovial CRP (97.7% and 87.1%)[143]. Based on these studies synovial fluid biomarkers could provide an additional valuable resource for the diagnosis of PJI, but further studies are required.

4.3. AAOS guidelines

The American Academy of Orthopaedic Surgeons (AAOS), based on the current clinical evidence, has proposed clinical guidelines in the diagnosis of peri-prosthetic joint infection[144]. On the bases of the clinical features, the patients are classified into those who have a high or low probability of PJI (Table 4). The guidelines consist of 15 recommendations, with the majority being supported strongly in the literature. The guidelines advocate an al-

gorithmic approach to the diagnosis of PJI, beginning with baseline investigations such the Erythrocyte Sedimentation Rate (ESR) and the C Reactive Protein (CRP) that carry high sensitivity and specificity when combined together[125, 126].

	One or more symptoms, AND at least one or more:
Higher Probability of Infection	• risk factor* OR
	• physical exam finding; OR
	• early implant loosening/osteolysis (as detected by x-ray)
Lower Probability of Infection	Pain or joint stiffness only and none of the following:
	• risk factors;* OR
	• physical exam findings; OR
	• early implant loosening/osteolysis (as detected by x-ray)

*risk factor supported by evidence or expert opinion. Adopted from the AAOS clinical practice guidelines for the diagnosis of periprosthetic infections[144]

Table 4. Stratification of patients into High or low probability of infection[144]

Further investigations, such as joint aspiration, are recommended in a stepwise manner depending on the ESR and CRP levels. The AAOS clinical guidelines and algorithms for the diagnosis peri-prosthetic infections, are available free to download from http://www.aaos.org/research/guidelines/guide.asp.

5. Management of PJI

The management of total joint arthroplasty consists of one or more of the following techniques:

i.   Antibiotic therapy

ii.   Debridement and Irrigation of the joint with component retention or linear exchange

iii.   Single Stage Revision Arthroplasty (SSRA)

iv.   Two Stage Revision Arthroplasty (TSRA)

v.   Arthrodesis

vi.   Amputation

Management decisions are made on severity, chronicity of the infection, virulence of the infecting organism, status of surrounding soft tissue and physiological status of the patient.

5.1. Unexpected positive intraoperative cultures

Unexpected positive intraoperative cultures are found in cases where pre-operative assessment fails to show infection, these cases usually undergo revision for aseptic loosening. Tsukayama eta al. reported up to 11% of cases were infection was diagnosed with positive intraoperative cultures and were all treated with 6 weeks of antibiotics without additional operation. Antibiotic therapy failed in 3 of these cases, and the patients required further surgical treatment with 2 patient showing evidence of recurrent infection at 2 year follow up[56]. In another study, 15 patients with positive intraoperative cultures were not treated with antibiotics, recurrence of infection was reported in 6 patients[145]. Based on these studies, patients with unexpected positive cultures should be treated with antibiotics for 6 weeks while monitoring their ESR and CRP values to assess response to treatment under the supervision of a specialist microbiologist[146].

5.2. Antibiotic suppression

When patients have poor state of health, have a high risk of complications after surgery and the infective organism is of low virulence and susceptible to antibiotic therapy, suppression by antibiotic alone may be the best option. Rao et al. investigated the rates of eradication of antibiotic resistant organisms with suppression therapy and noted eradication in 86% at mean follow up of five years, with five recurrent infections all within the first 3 years[147]. Antibiotic suppression is also indicated in patient with persistent PJI following surgical intervention if they decline or cannot tolerate further surgery[6, 11, 148, 149]. The literature on antibiotic suppressive therapy without any surgical intervention is poor; despite this, patients who cannot tolerate surgery have no other option than suppressive therapy.

5.3. Debridement and Irrigation with component retention or linear exchange

Operative debridement and irrigation with component retention should be reserved of acute infections (Stage II and occasionally stage III). Early infections may range in severity from superficial cellulitis to deep infections. Superficial infections associated with wound dehiscence or purulent drainage and infections with wound necrosis or infected haematomas often require surgical debridement. Reported eradication rate has been between 24% to 71 % following open debridement and irrigation[56, 150, 151]. Even though, some case reports show excellent results from irrigation and debridement[152], a recent multicentre retrospective study showed that irrigation and debridement with component retention is not affected by organism type and that this technique had a failure rate as high as 70%, with the authors questioning the actual role of irrigation and debridement in the treatment of PJI[151]. Prostheses retention is also contraindicated in those with multiple joint arthroplasty or when the duration of symptoms is more than 1 month[7, 15].

5.4. Single stage revision arthroplasty

Single stage revision with removal of components, debridement, irrigation and reimplantation of new components provides removal of infected prosthesis while limiting the number of surgeries, recovery time and costs. Callaghan et al. reports 8.3% rate of recurrence after single stage revision arthroplasty with a minimum follow up of 10 years[153]. The local therapy, is achieved by adding antibiotics to the cement used for fixation of the implant, this is followed by a minimum of 6 weeks antibiotic therapy. Two studies comparing one-stage to two stage revision arthroplasty favoured the two stage technique[154, 155]. Failure rates in SSRA ranged from 10.1% to 12.4%, compared to 3.5% to 5.6% in TSRA. A recent meta-analysis comparing SSRA to TSRA reported the presence of nearly three additional reinfections per 100 revisions when performing a one stage compared to a two stage procedure[156]. However, not enough evidence is available to demonstrate that one technique is superior to the other[156].

5.5. Two stage revision arthroplasty

Two stage revision arthroplasty (TSRA) is currently the gold standard technique for the treatment of infected joint arthroplasty[107, 157-159]. TSRA involves initial removal of the infected components and all foreign material including cement, cement restrictors and cables or wires whenever possible with meticulous debridement and irrigation. All necrotic tissue is excised, and sinus tracts are debrided. After irrigation the joint should be inspected for any remaining debris. A cement spacer loaded with antibiotics is used, this is either pre-manufactured or constructed at the time of surgery[160, 161]. Various techniques described in the construction of a cement loaded spacer, the technique used depends on the joint involved and the level of bone loss encountered during the first stage[109, 161-164]. These custom spacers allow antibiotic elution locally to eradicate the infective organism and maintain soft tissue balance to accommodate the definitive implant during the second stage. A minimum course of six weeks of antibiotics is usually required, and resolution of infection is confirmed through serial ESR and CRP and repeated aspiration of the joint. A further aspiration of the joint before the second stage is recommended in one study, which reported recurrence rate of 3% among those who underwent aspiration compared with 14% in those who did not[165].

The advantages of TSRA[166] include:

i.   meticulous debridement of soft tissue, necrotic bone and cement during the first stage and during the second stage before reimplantation

ii.   identification of offending organism, sensitivities are determined and appropriate antibiotic therapy is given for a prolonged period before reimplantation

iii. evaluation of distant foci of infection and eradication of sites responsible for haematogenous spread

iv.   informed decision can be made as to whether the degree of disability from resection arthroplasty or arthrodesis would justify the risks involved in the implantation of a new prosthesis

The disadvantages[166] include:

i.   prolonged period of disability and hospital stay

ii.   increased costs

iii.   delayed rehabilitation

iv.   technically difficult second procedure due to loss soft tissue balance, loss of bone stock shortening and scarring

TSRA has been associated with lower rates of recurrent infections in most studies[6, 167, 168]. The duration of antibiotics between the two stages has not been determined, but a minimum of 6 weeks is usually standard and is guided by serial ESR and CRP levels. Management of bone stock deficiency at the time of revision is a problem. Impaction bone grafting with cemented prosthesis has been used for reconstruction during the second stage with good results. English et al. reported eradication in 49 out of 53 cases treated with impaction bone grafting during the second stage with a minimum follow up of 2 years[169] and a recurrence rate up to 7.5%[169, 170]. Use of antibiotic loaded cement for fixation of the implant during the second stage has been shown to reduce rates of reinfection. Garvin et al. reported eradication in 95% of patients at 5 year interval when gentamicin loaded cement was utilised during the second stage[171]. Highest success rates for TSRA were found for patients treated with antibiotics-eluting spacer or beads between the first and second stage, followed by a second reconstruction with an antibiotic loaded cemented reconstruction[55, 167, 172].

Data on uncemented implants has generally been less positive, with early studies reporting rates of infection as high as 18% and additional cases of loosening[43, 173]. Studies that are more recent have reported reinfection rates between 6% and 11%[174]. The decision regarding cemented or uncemented reimplantation is guided by the available bone stock, physiological age and expected longevity of the patient. To minimize loss of bone stock during the first stage, the Exeter group adopted a cement in cement revision technique for hip arthroplasty, where an excision arthroplasty with antibiotic impregnated cement beads is carried out during the first stage. In this technique if the cement mantle from the previous arthroplasty is well fixed, is left alone. During the second stage, the cement beads are removed, and the existing cement mantle is reamed to remove any membrane or microfilm and to create space for the new antibiotic augmented cement and the new implant. Sixteen patients with at least three years follow up underwent this procedure with one patient requiring revision due to recurrent infection[175].

5.6. Arthrodesis and amputation

Salvage procedures are reserved for patients whose medical condition such as immunocompromised patients or in patients where successful reconstruction is impossible. Successful reconstruction is limited those patients with insufficient bone stock, inadequate muscle function and poor soft tissue coverage. Eradication of infection after salvage procedures is reported between 86% to 96% although they are usually associated with poor functional outcomes[176-178]. Above knee amputation provides good return to function with a fitted pros-

thesis, especially in patients who cannot tolerate multiple procedures. Arthrodesis allows the patient to retain the extremity at the cost of reducing ambulation especially in patients with a fused knee.

6. Conclusion

Infection of a total Joint arthroplasty is considered a major complication in orthopaedic surgery with significant morbidity and places a considerable burden on hospitals and surgeons. Prevention is better than treatment and improving the patients' health prior to surgery is important in reducing the risk of infection. Furthermore, prompt diagnosis, permits early treatment that is important in acute infections. In the absence of a perfect test, the evidence based algorithmic approach brought forward by the AAOS guidelines should enable diagnosis of infection to be made with a high degree of confidence. There is clearly a role for surgical intervention, and so far a two-stage revision arthroplasty demonstrates the lowest rates of recurrent infection and as such is regarded as the 'gold standard'.

Author details

Adrian J. Cassar Gheiti and Kevin J. Mulhall

Orthopaedic Research and Innovation Foundation, Republic of Ireland

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