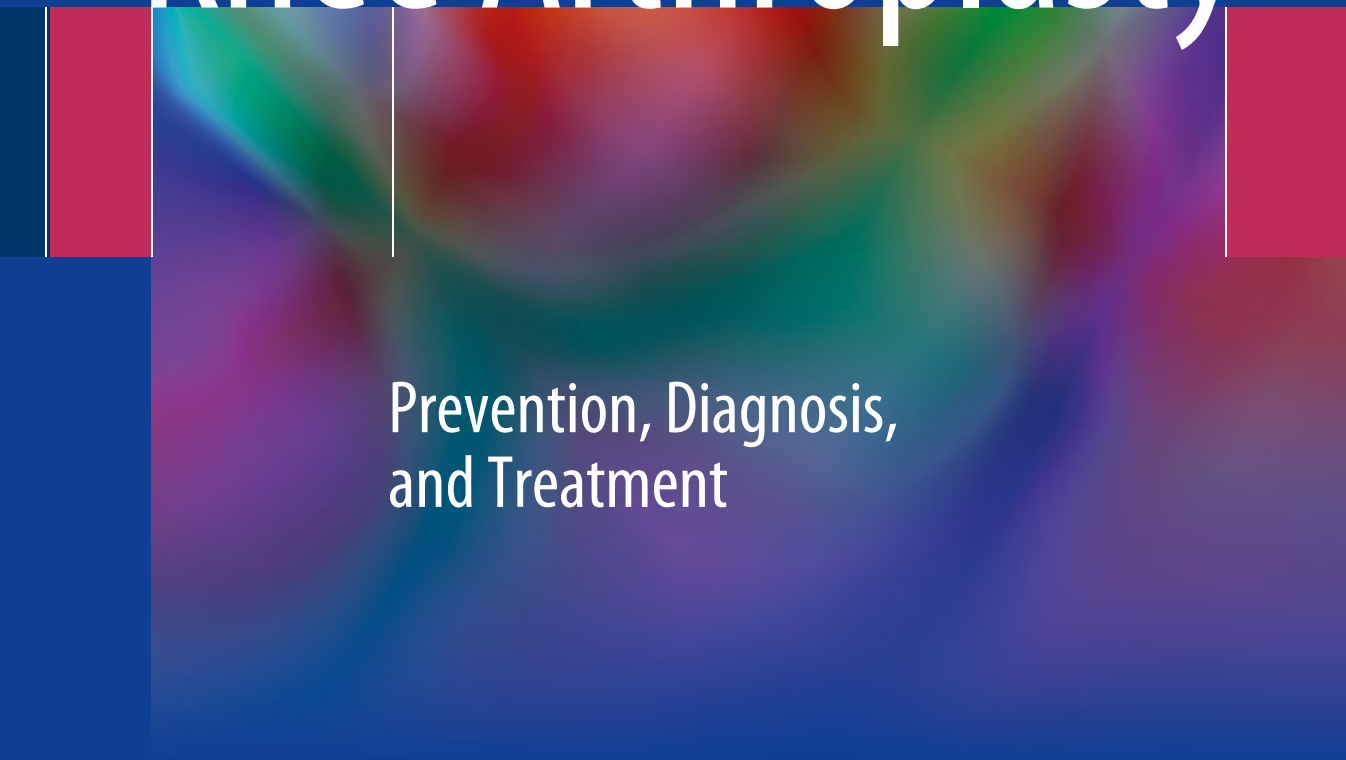
E. Carlos Rodríguez-Merchán
Sam Oussedik
Editors

The Infected Total Knee Arthroplasty



Prevention, Diagnosis, and Treatment

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Preface

Patients presenting for total knee arthroplasty (TKA) have one goal in mind—to return to "normal" knee function, however they choose to define this. Postoperative complications are understood to be a risk, but one worth taking for all patients who consent to undergo the procedure.

The diagnosis of infection following TKA is devastating and represents the most cruel betrayal of this dream of normal knee function. Both patients and clinicians alike may experience the classical grief response, journeying from denial through anger and guilt to acceptance.

Differentiating periprosthetic joint infection (PJI) from other causes of postoperative pain is the surgeon's first challenge. Infection does not always declare itself overtly and so a knowledge of the latest diagnostic strategies is vital.

From this diagnosis flows the appropriate treatment strategy. Here again, risk of failure must be navigated, both in terms of recurrent infection and poor knee function. Unfortunately, while offering the possibility of retaining good function, less invasive procedures also run a greater risk of failing to clear the infection.

As with many medical conditions, the key to obtaining a good outcome is rapid diagnosis which then enables the timely deployment of the correct treatment strategy.

In the chapters of this book we have collected the current evidence regarding the best management of PJI, drawing on the most experienced clinicians in the field from Europe and the United States. It is our hope that our readers will gain the information they need to help their patients achieve their goals.

Madrid, Spain — E. Carlos Rodríguez-Merchán
London, UK — Sam Oussedik

Contents

1 Epidemiology of the Infected Total Knee Arthroplasty: Incidence, Causes, and the Burden of Disease

E. Carlos Rodríguez-Merchán
and Alexander D. Liddle

Abstract

Periprosthetic joint infection (PJI) after total knee arthroplasty (TKA) is a severe complication. The purpose of this chapter is to review the incidence, causes, and burden of PJI after TKA. At 30 days, the overall rate of surgical site infection (SSI) is 1.1%, while the reported rate of deep infection is 0.1%. The lifetime incidence of PJI after TKA ranges from 0.7 to 4.6%. Many related and predisposing factors have been identified. These can be classified as preoperative, intraoperative, postoperative, and late infections. The preoperative factors are previous knee surgery, inflammatory arthritis, and the use of glucocorticoids and immunosuppressants. The intraoperative factors are prolonged surgical time, inadequate antibiotic prophylaxis, and intraoperative fractures. The postoperative factors are wound drainage for longer than 10 days, reoperation and deep venous thrombosis. Factors related to late infections include cutaneous infections, urinary tract infections, lower respiratory tract infections, abdominal infections, and generalized sepsis. Patients with PJIs have significantly longer hospitalizations (5.3 vs. 3 days), more readmissions (3.6 vs. 0.1), and more clinic visits (6.5 vs. 1.3) when compared to a matched control group. The mean annual cost is significantly higher in patients who have PJIs ($116,383 on average) when compared to the matched control group ($28,249 on average). Hospital costs are between 2- and 24-fold higher in patients with PJI than in those without PJI. PJIs following TKA represent a huge burden for the patient, for the surgeon, and for the health-care economy.

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1.1 Introduction

Periprosthetic joint infection (PJI) after total knee arthroplasty (TKA) is a severe complication which has significant personal and financial costs [1]. In this chapter, we discuss the burden of PJI worldwide and aim to define the risk factors for the development of PJI following TKA.

1.2 Incidence

The development of institutional and national joint registries has allowed us to define the incidence and prevalence of PJI with greater accuracy than was previously possible. Pugely et al. [2], in a study of 23,128 joint replacements (primary and revision total knee and hip arthroplasty), estimated that the rate of surgical site infection (SSI) at 30 days was 1.1%, with the rate of deep infection being 0.1% at the same time point. Infection is now the most common reason for revision in the National Joint Registry for England, Wales, and Northern Ireland, reporting a patient-time incidence rate (PTIR) of 1.05 revisions for infection per 1000 patient years [3]. While improvements in implant design, materials, and instrumentation have reduced the rate of aseptic loosening and other "technical" complications, no such improvement has been demonstrated in the rate of infection. As a result, the rate of revision for infection is increasing relative to other reasons for revision. It is not clear whether the absolute rate of PJI is increasing; Dale et al. studied the rate of revision in four Nordic arthroplasty registers and reported that the risk of PJI increased between 1995 and 2009 in all countries [4]. There were no significant changes in risk factors during that time period, but the increase may simply indicate improvements in diagnosis and reporting.

Overall, however, it is likely that the reported rates of infection represent an underestimate. Zhu et al. cross-referenced 4009 records from the New Zealand Joint Registry with records from three tertiary hospitals, finding that the rate of revision for infection was 1.1%, compared to the reported rate of 0.67%, meaning that the rate was underestimated by over a third [5]. Similar findings were reported by audits of the Danish and Swedish joint registries with the rates being underestimated by 40% and 33%, respectively [6, 7]. Reasons for underreporting may include the fact that some reoperations do not class as revision surgery (such as debridement and exchange of modular components) or that revisions for infection are not recognized and are therefore not reported.

The most common causative organisms for PJI are staphylococci [8, 9], although gram-negative organisms are becoming more common as are multidrug resistant organisms. The incidence of infection with lower virulence organisms such as propionibacteria may be underreported as they require prolonged incubation periods for cultures to be isolated [10, 11].

1.3 Risk Factors for Prosthetic Joint Infection Following TKA

Several authors have attempted to delineate the principal risk factors for PJI after TKA. Kunutsor et al. [12] conducted a meta-analysis examining risk factors for infection after primary hip and knee replacement and reported a higher risk of PJI in men compared to women and in smokers compared to nonsmokers. Diabetes, rheumatoid arthritis, corticosteroids, and previous surgery to the joint in question were all reported to increase the risk of PJI as did frailty, but alcohol intake, age, hypertension, or previous intra-articular steroid injection was not found to be associated with PJI.

Tayton et al. analyzed data on 64,566 cases from the New Zealand Joint Registry, using revision surgery for PJI at 6 and 12 months after surgery as primary outcome measures [13]. Again, male gender was a significant risk factor for infection. Other factors included previous surgery (osteotomy, ligament reconstruction), the use of laminar flow, and the use of antibiotic-laden cement. There was a trend toward signifi-

cance at 6 months with the use of surgical helmet systems. These findings showed that patient factors remain the most important in terms of predicting early PJI following TKA and suggested that some factors previously identified as being protective (such as laminar flow and exhaust systems) may in fact increase the risk of PJI. Jamsen et al. [14] analyzed 7181 TKAs and total hip arthroplasties (THAs) from a single center, finding an increased risk of PJI with diabetes (odds ratio, OR, 2.3 compared to nondiabetics) and obesity (OR 6.4 in the morbidly obese). Patients with both diabetes and morbid obesity had a 10% rate of PJI. In the study of Pugely et al., risk factors were body mass index (BMI) > 40, hypertension, prolonged operative time, electrolyte disturbance, and previous infection [2].

A number of smaller studies have supported these findings and identified further risk factors. De Dios and Cordero [15] performed a case-control study comparing 32 consecutive knee infections with 100 matched controls. The significant factors were classified as pre-, intra-, or postoperative. Preoperative factors included previous knee surgery, use of glucocorticoids, immunosuppressants, and a diagnosis of inflammatory arthropathy. Intraoperative factors included prolonged surgical time, inadequate antibiotic prophylaxis, and intraoperative fracture. Postoperative factors included wound drainage longer than 10 days, the presence of a hematoma, the need for early reoperations, a diagnosis of deep vein thrombosis (DVT), and the presence of distant infections in the skin, respiratory, or urinary tract. In the cohort study of Lee et al. [9], significant risk factors included young age and comorbidities such as diabetes, anemia, thyroid disease, heart disease, lung disease, and prolonged operating time.

1.3.1 Superficial Wound Infection

Properly treated, a superficial postoperative infection should not lead to later deep PJI. Guirro et al. [16] reviewed a cohort of 3000 TKAs, 63 of whom were diagnosed with an acute infection. While 18 of these were considered to be acute deep infections, the remaining 45 were superficial and were treated successfully with antibiotics with or without surgical debridement. Six patients required superficial debridement (in all cases the infection was superficial to the fascia); the mean duration of antibiotic treatment was 16.5 days. At almost 6 years, 6 patients had died of unrelated causes, and 3 were revised for other causes; none of the 45 patients had a deep infection [16].

1.3.2 Previous Arthroscopy and Intra-articular Injection

Werner et al. [17] found that the incidence of infection was higher in patients who underwent TKA within 6 months after knee arthroscopy compared to controls. There was no increase in infection when TKA was performed more than 6 months after knee arthroscopy.

Cancienne et al. [18] investigated the association between intra-articular injection of glucocorticoids and infection in subsequent ipsilateral TKA. In patients who had undergone steroid injections less than 3 months prior to surgery, the rate of infection was higher than controls at both 3 and 6 months post-TKA (with infection being twice as likely as controls at 3 months and 50% more likely than in controls at 6). If more than 3 months had elapsed between injection and TKA, there was no increased risk of infection compared to controls.

This association was supported by a study of 83,684 patients, of whom 35% had previously had an ipsilateral injection of corticosteroid [15]. Those patients who had undergone injection were stratified into 12 groups on the basis of the number of months prior to TKA that the injection was performed. The proportion of TKAs who went on to develop PJI was higher in knees that received an injection before TKA than in controls (4.4% vs. 3.6%; OR = 1.2, $p < 0.001$), as were the proportion who required further surgery for infection (1.49% vs. 1.04%; OR 1.4, $p < 0.001$). Time to TKA analysis suggested that the effect of injection remained significant up to 6 months with respect to any infection and 7 months with

respect to infections requiring return to theater. Above 7 months, there was no significant association between previous steroid injection and subsequent PJI.

1.3.3 Preoperative Diagnosis

As suggested by the meta-analysis of Kunutsor et al., compared to TKA performed for osteoarthritis (OA), those performed for post-traumatic or rheumatoid arthritis (RA) have a higher rate of infection [12]. Ravi et al. [19] investigated a cohort of 71,793 TKAs, of which 4% had a diagnosis of RA. After adjusting for confounders, patients with RA had a significantly higher rate of infection than patients with OA at 2 years (adjusted hazard ratio 1.47, $p = 0.03$). These findings are supported by a separate database study of 351,103 knees (3.4% of which were for RA), where the infection rate in patients with RA was 4.5%, compared to 3.8% in patients with OA.

Bala et al. [20] evaluated the impact of post-traumatic arthritis (PTA) versus primary OA on postoperative outcomes after TKA. A total of 3509 patients undergoing TKA for PTA were compared to 257,611 patients undergoing TKA for OA. Patients had similar levels of comorbidities (as measured using the Charlson index), but patients with PTA patients were younger overall. Patients undergoing TKA for PTA had a higher incidence of periprosthetic infection, cellulitis or seroma, wound complications, overall rate of revision, and need for arthrotomy or incision and drainage.

1.3.4 Anesthetic Type

Kopp et al. [21] found no difference in the incidence of SSI in patients undergoing TKA under general versus neuraxial anesthesia. They concluded that the use of peripheral nerve blocks does not influence the incidence of SSI. In common with other studies, they found a higher rate of PJI in those with high BMI and current smokers.

1.3.5 Tobacco Use

Tobacco use has been demonstrated to be a risk factor for PJI in several of the previously quoted studies [9, 12, 13]. Singh et al. [22] performed a database study to examine the relationship between tobacco use and infection. Tobacco use status was available for 7926 patients (95% of the cohort); 565 (7%) were current tobacco users. Compared to nonusers, current tobacco users were more likely to be male and have comorbidities and were younger and less likely to be obese. Both deep infection and revision were more likely in current tobacco users than in nonusers. No significant differences were noted for periprosthetic fractures or superficial infections.

Tischler et al. [23] reviewed their institutional database, identifying 15,264 patients of whom 9% were current smokers and 34% were ex-smokers. Current smokers had an OR of 1.82 (95% CI 1.03–3.23, $p = 0.04$) for infection in the first 90 days compared to nonsmokers. Again, former smokers had no increased risk of infection compared to lifelong nonsmokers, suggesting that smoking represents a modifiable risk factor for infection [23].

1.3.6 Anticoagulation

Brimmo et al. [24] compared 159 patients who had received rivaroxaban to 480 control patients who had received alternative thromboprophylactic agents. They determined that the use of rivaroxaban for thromboprophylaxis leads to a significantly increased incidence of deep SSI in patients undergoing primary TKA. Incidence of early deep SSI in the rivaroxaban group was higher than in the control group (2.5% vs. 0.2%).

Other forms of anticoagulation have also been found to correlate with the risk of PJI. Patients with a high risk of thromboembolism who are bridged with therapeutic low molecular weight heparin have a higher rate of infection compared

to those who are not [25]; likewise, patients on regular warfarin undergoing TKA have a significantly higher risk of wound complications and deep infection than those not using warfarin [26].

1.3.7 Obesity

Several authors have determined a link between obesity and infection following TKA [2, 12, 14]. Meller et al. [27] investigated the risk and cost of postoperative complications associated with morbid and super obesity after TKA using Medicare hospital claims data. Morbidly obese patients (BMI $\geq$ 40 kg/m^2) and superobese patients (BMI $\geq$ 50 kg/m^2) were compared to controls of a healthy weight, with outcomes being 12 complications including DVT, reoperation, and PJI. A multivariable Cox model was used to calculate hazard ratios. Morbidly obese patients were at significantly higher risk of complications; the hazard ratio (HR) for infection was 1.95 (95% CI 1.70–2.23, $p < 0.001$) compared to those of a healthy weight. In superobese patients, this hazard ratio increased to 3.14 (95% CI 2.33–4.22, $p < 0.001$).

1.3.8 Component Choice

In THA, there is increasing debate as to whether bearing surface changes the risk of infection [28]. There is little variation available in bearing surface in TKA, but Houdek et al. [29] reported, in a retrospective, single-center registry study, that all-polyethylene tibial components are associated with a lower rate of infection compared to metal-backed tibial components, although the mechanism is unclear.

1.3.9 Psychiatric Disorders

Klement et al. [30] observed that patients with psychiatric disorders who undergo elective primary TKA have significant increase in PJI.

1.3.10 Oral Bacteremia

Oral bacteremia has been presumed to be an important risk factor for TKA infection. Tai et al. [31] investigated whether dental scaling could reduce the risk of TKA infection. They found that the risk for TKA infection was 20% lower for patients who received dental scaling at least once within a 3-year period than for patients who never received dental scaling. Moreover, the risk of TKA infection was reduced by 31% among patients who underwent more frequent dental scaling (5–6 times within 3 years).

1.3.11 Concurrent Viral Infection

Boylan et al. [32] observed that patients with human immunodeficiency virus (HIV) were at an increased risk for perioperative wound infections after TKA. Kuo et al. [33] aimed to determine whether hepatitis B virus (HBV) infection was a risk factor for PJI. All TKAs performed in Taiwan between 2001 and 2010 were analyzed. Males with HBV infection had a 4.32-fold risk of PJI compared to males without HBV, but this was not replicated in females.

1.3.12 Cirrhosis

Deleuran et al. [34] compared outcomes following total hip and knee replacement in 363 patients with cirrhosis to a control group of over 100,000 patients from the Danish arthroplasty registries. They report a significantly higher risk of PJI in patients with cirrhosis with an adjusted HR of 2.1 (95% CI 1.3–3.7).

Jiang et al. [35] studied a cohort of 573,840 TKAs, 0.2% of whom had cirrhosis and reported a longer length of hospital stay, increased costs, and higher rates of mortality, readmission, and reoperation in patients with cirrhosis. The hazard ratio for infection was 3.4 in patients with cirrhosis compared to those without ($p < 0.001$).

1.3.13 Modification of Risk Factors

While many risk factors have been defined for PJI, many are not modifiable (such as age and gender), and there is little evidence that modifying risk factors materially reduces the risk of infection in most cases. Smith et al. [36] performed a systematic review of five studies (comprising 23,348 patients) to determine whether bariatric surgery reduces the obesity-related risk of PJI in hip and knee arthroplasty. They found no statistically significant change in the risk of PJI (or any other complication) in patients who had lost weight through bariatric surgery compared to those who remained obese [36].

Two factors which do appear to reduce the rate of infection are giving up tobacco use and the eradication of *Staphylococcus aureus* colonization prior to surgery. Crowe et al. [37] found both factors to decrease the incidence of PJI after primary TKA, thereby reducing morbidity and the costs associated with treating those infections. Stambough et al. [38] supported this finding reporting a reduction in the rate of PJI from 0.8 to 0.2% following the introduction of an eradication protocol. They calculated that in the 2205 cases performed after the introduction of universal eradication, savings of over $700,000 were made compared to the previous cohort who were only treated if they were found to be positive for *S. aureus* on screening [38]. Singh et al. examined the effect of tobacco use on PJI rate and found that smokers were 41% more likely to have a PJI but that the risk of PJI for ex-smokers returned to the risk of lifelong nonsmokers, suggesting that discontinuation of smoking has an effect on the rate of PJI [22]. Table 1.1 summarizes the main factors related to PJI following TKA.

1.4 The Burden of TKA Infection

Kapadia et al. [39] measured the impact of PJIs on the length of hospitalization, readmissions, and the associated costs. Between 2007 and 2011, their prospectively collected infection database was reviewed to identify PJIs that occurred following primary TKA, which required a two-stage revision. They identified 21 consecutive patients and matched them to 21 noninfected patients who underwent uncomplicated primary TKA. The patients who had PJIs had significantly longer hospitalizations (5.3 vs. 3.0 days), more readmissions (3.6 vs. 0.1), and more clinic visits (6.5 vs. 1.3) when compared to the matched group, respectively. The mean annual cost was significantly higher in the infected cohort ($116,383; range, $44,416–$269,914) when compared to the matched group ($28,249; range, $20,454–$47,957). Periprosthetic infections following TKA represented a tremendous economic burden for tertiary care centers and to patients.

Alp et al. [40] evaluated the economic burden of PJIs following TKA. The median total length of the hospital stay was seven times higher in PJI patients than patients without PJI (49 vs. 7 days). All hospital costs were 2- to 24-fold higher in patients with PJI than in those without PJI. In conclusion, the economic burden of PJI was high. Gow et al. [41] calculated the excess costs attributable to PJI following TKA at $40,121, not including the opportunity cost associated with reoperating on such patients when other patients could be receiving their primary joint replacement. Table 1.2 summarizes the burden of PJI following TKA.

Conclusions

Periprosthetic joint infection (PJI) is a severe complication of total knee arthroplasty (TKA) and occurs in between 0.7 and 4.6% of cases. It is associated with significant costs. A number of risk factors have been determined, including gender, diagnosis, comorbidities, and previous surgery. In some cases these are modifiable; with the evidence available, surgeons should be able to decrease their rate of PJI. In some cases, these risk factors are non-modifiable but knowledge of them allows the surgeon to appraise patients of their risk of infection preoperatively.

Table 1.1 Factors related to periprosthetic joint infection (PJI) after total knee arthroplasty (TKA) in recent literature

Crowe et al. [37]	Optimization of modifiable risk factors such as *Staphylococcus aureus* colonization, and tobacco use prior to primary TKA may decrease the incidence of PJI after primary TKA
De Dios and Cordero [15]	Preoperative factors: previous knee surgery, glucocorticoids, immunosuppressants, inflammatory arthritis. Intraoperative factors: prolonged surgical time, inadequate antibiotic prophylaxis, intraoperative fractures. Postoperative factors: secretion of the wound longer than 10 days, deep palpable hematoma, need for a new surgery, and deep venous thrombosis in lower limbs. Distant infections: cutaneous, generalized sepsis, urinary tract, pneumonia, abdominal
Lee et al. [9]	Factors related to PJI after TKA were young age, comorbidities such as diabetes, anemia, thyroid disease, heart disease, lung disease, and long operating time
Pugely et al. [2]	Independent risk factors associated with 30-day SSIs were BMI > 40, hypertension, prolonged operative time, electrolyte disturbance, and previous infection
Tayton et al. [13]	Multivariate analysis showed statistically significant associations with revision for PJI between male gender, previous surgery (osteotomy, ligament reconstruction), the use of laminar flow and the use of antibiotic-laden cement. There was a trend toward significance with the use of surgical helmet systems at 6 months
Ravi et al. [19]	Patients with rheumatoid arthritis were at higher risk of infection (1.26%, compared with 0.84%) that patients with osteoarthritis following TKA
Guirro et al. [16]	A successfully treated superficial wound infection did not result in a chronic deep TKA infection
Werner et al. [17]	The incidence of infection was higher in patients who underwent TKA within 6 months after knee arthroscopy compared to controls. There was no increase in infection when TKA was performed more than 6 months after knee arthroscopy
Boylan et al. [32]	Patients with HIV were at an increased risk for perioperative wound infections after TKA
Kuo et al. [33]	Males with HBV infection had a 4.32-fold risk of PJI compared with males without HBV. HBV infection and diabetes were the risk factors for PJI among males. The incidence of PJI was 58.8 among females with HBV infection and 75.2 among females without HBV (per 10,000 person-years). The risk of PJI was higher for males with HBV infection than for males without 0.5–1 year after TKA and >1 year after TKA. HBV infection was a risk factor for PJI after TKA among males
Cancienne et al. [18]	The incidence of infection within 3 months (2.6%) and 6 months (3.41%) after TKA within 3 months of knee injection was significantly higher than the control cohort. There was no significant difference in patients who underwent TKA more than 3 months after injection. Ipsilateral knee injection within 3 months prior to TKA was associated with a significant increase in infection
Deleuran et al. [34]	Cirrhosis patients had a higher risk (3.1% vs. 1.4%) of postoperative deep prosthetic infection after TKA for primary osteoarthritis than patients without cirrhosis
Jiang et al. [35]	PJIs were more common among patients with cirrhosis who had TKA
Bala et al. [20]	Post-traumatic arthritis patients had higher incidence of periprosthetic infection
Kopp et al. [21]	Increasing BMI and current smoking were found to significantly increase the incidence of SSI in patients undergoing TKA
Singh et al. [22]	The hazard ratios for deep infection and implant revision were higher in current tobacco users than in nonusers
Brimmo et al. [24]	The use of rivaroxaban for thromboprophylaxis leads to a significantly increased incidence of deep SSI in patients undergoing primary TKA. Incidence of early deep SSI in the rivaroxaban group was higher than in the control group (2.5% vs. 0.2%)
Houdek et al. [29]	All-polyethylene tibial components had reduced rates of postoperative infection. That is why the authors stated that all polyethylene should be considered for most of the patients, regardless of age and BMI
Klement et al. [30]	Patients with psychiatric disorders who underwent elective primary TKA had significant increase in PJI
Tai et al. [31]	The risk for TKA infection was 20% lower for patients who received dental scaling at least once within a 3-year period than for patients who never received dental scaling. Moreover, the risk of TKA infection was reduced by 31% among patients who underwent more frequent dental scaling (5–6 times within 3 years)

SSI surgical site infection, *BMI* body mass index, *HIV* human immunodeficiency virus, *HBV* hepatitis B virus

Table 1.2 Burden of periprosthetic joint infection (PJI) following total knee arthroplasty (TKA)

Kapadia et al. [39]	PJI following TKA represented a tremendous economic burden. The patients who had PJIs had significantly longer hospitalizations (5.3 vs. 3 days), more readmissions (3.6 vs. 0.1), and more clinic visits (6.5 vs. 1.3) when compared to the matched group, respectively. The mean annual cost was significantly higher in the infected group ($116,383; range, $44,416–$269,914) when compared to the matched group ($28,249; range, $20,454–$47,957)
Alp et al. [40]	The economic burden of PJI was high. The median total length of the hospital stay was seven times higher in PJI patients than patients without PJI (49 vs. 7 days). All hospital costs were 2- to 24-fold higher in patients with PJI than in those without PJI
Meller et al. [27]	High demand on resources presented a severe challenge for providing treatment for superobese patients. Controlling for patient and institutional factors, each TKA had an average total hospital charges of $75,884 among superobese (BMI $\geq$ 40 kg/m^2) patients, compared to $65,118 for the control group, a difference of $10,767. Medicare payment for the superobese patients was also higher, but only by $2703
Gow et al. [41]	There was a significant increase in cost associated with SSI following primary TKA. Compared to the control patients, SSIs were associated with an excess mean cost of $40,121. In addition to the excess cost associated with SSI, there were also opportunity costs resulting from their impact on elective surgical waiting lists

BMI body mass index, *SSI* surgical site infection

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2 Microbiological Concepts of the Infected Total Knee Arthroplasty

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Abstract

The microbiology of the infected joint replacement is now well established. Causative organisms are generally gram positive, principally staphylococci and streptococci, but many organisms may cause periprosthetic joint infection (PJI), particularly in the presence of immunosuppression. Infections following total knee arthroplasty (TKA) are difficult to treat due to the formation of biofilms, which protect the causative bacteria from antibiotics and host defenses. Adequate prevention, diagnosis, and management schemes for biofilm-based PJIs are still lacking. The current approach to biofilms centers on prevention, with the use of local and systemic antibiotics. Future strategies for the prevention and treatment of biofilms include the use of surface coatings (including surface-tethered antibiotics and metal oxide nanoparticle coatings) and disruption of the established biofilm by mechanical or pharmacological means.

2.1 Introduction

Periprosthetic joint infection (PJI) is a challenging problem as a result of the adaptations made by the causative bacteria to avoid destruction by the host organism, in particular the formation of biofilms [1]. The common causative bacteria in PJI have a high attraction for adhering to the components of joint replacement, including cobalt-chromium, titanium, polyethylene, and polymethyl methacrylate (PMMA) cement, and tend to be strong formers of biofilms.

In this chapter, we discuss the microbiology of the infected total knee arthroplasty (TKA),

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focusing on the nature of bacterial biofilms and the current and future strategies for their detection, prevention, and treatment.

2.2 Microbiology of the Infected Total Knee Arthroplasty (TKA)

2.2.1 Common Causative Agents of Infection Following TKA

Most prosthetic joint infections are caused by gram-positive bacteria, predominantly staphylococci [2]. In Nickinson et al.'s study of 121 patients undergoing revision TKA for infection over 15 years, coagulase-negative *Staphylococcus* and *Staphylococcus aureus* accounted for 62% of organisms cultured [3]. Holleyman et al. cross-referenced data on septic revisions from the National Joint Registry for England and Wales with microbiology data held by Public Health England [4]. They reported on 275 patients; again, staphylococci were the commonest organisms, and gram-positive organisms accounted for 241 of 275 patients (88% of the total).

Matthews et al. published a review of the literature regarding prosthetic joint infection (both hip and knee), reporting the relative frequency of bacteria in PJI reported by previous studies [5]. They estimated the rate of infection with coagulase-negative staphylococci at between 13 and 37%; *Staphylococcus aureus* accounted for 20–62%, *Streptococcus* between 4 and 27%, enterococci between 6 and 13%, and other gram positives between 6 and 20%. Gram negatives were rare, with enteric gram negatives accounting for 2–15% and pseudomonas being present in 1–4% of samples. No pathogen was identified in up to a quarter of PJIs reported in this review. More recently, Benito et al. reported on the microbiological diagnosis of 2288 cases over 15 years (again, both the hip and knee), in which gram-positive cocci were present in 78% of infections, gram-negative organisms were present in 28%, and anaerobes were present in 7% [2].

Methicillin-resistant *Staphylococcus aureus* (MRSA) presents a particular problem. It is harder to eradicate and associated with inferior outcomes compared to sensitive bacteria in terms of function and rate of reoperation [6]. The rate of MRSA bacteremia and surgical site infection increased markedly during the 1990s and early 2000s [7]. Benito et al. report that the rate of MRSA PJI increased over the first decade of this century but appears to be declining [2]. The rate of MRSA increased from less than 5% in 2003–2004 to 9.5% in 2009–2010 but fell to 7.6% in 2011–2012. This mirrors the rate of MRSA isolation overall in epidemiological datasets which have fallen as awareness has increased and programs have been introduced to screen, isolate, and treat patients who carry MRSA (see Chap. 6) [8, 9].

2.2.2 Rare and Atypical Agents of Infection Following TKA

Many other bacterial and fungal species have been reported to cause PJI in very small numbers. Most are only evidenced by case reports and are extremely rare. Rare causative agents have been described in cases involving contact with cats and dogs, vigorous dental flossing, and intravesical bacillus Calmette-Guerin [10–13]. Some organisms have particular implications—for instance, isolation of *Streptococcus bovis*/*Streptococcus equinus* species can suggest the presence of undiagnosed colonic malignancy [14]. Surgeons should be vigilant when patients present in the setting of immunosuppression where unusual organisms may present [15].

Mycobacterium tuberculosis is a rare cause of prosthetic joint infection. In 2013 Kim et al. reported a systematic review on *Mycobacterium tuberculosis* infections [16]. Only 15 patients were identified from 13 studies. Tuberculosis was confirmed in all cases by histological examination and positive culture or histochemical stain/PCR. Treatment consisted of antituberculosis medication therapy (AMT) only in two patients, AMT plus debridement and retention of the arthroplasty in five patients, and AMT plus removal/exchange of the arthroplasty in eight patients. Three patients in the cohort died; results were favorable in the surviving patients.

Fungal PJI is a rare but devastating complication following TKA. In a systematic review, Jakobs et al. found that *Candida* spp. accounted for about 80% (36 out of 45 cases) of fungal PJIs and was therefore the most frequently reported pathogen [17]. Cobo et al. performed a literature review and identified 73 cases of *Candida* PJI [18]. Of the 73 cases, 50 had a documented cause of immunosuppression; most were treated with medication and surgery, most commonly two-stage revision. Cure was obtained in three quarters of patients, but 32 of the 73 cases had to undergo definitive excision arthroplasty. Antifungals were used for long durations—courses lasted from 6 weeks to over 1 year.

2.3 Delivery of Antimicrobial Agents

In PJI, antimicrobials may be delivered systemically, either orally or intravenously, or directly via antibiotic-eluting cement or cement spacers or via intra-articular catheter.

Intravenous antibiotics demonstrate good systemic bioavailability, and the use of standard doses of cephalosporins results in therapeutic concentrations within the knee joint [19, 20]. Antibiotic-containing bone cement has been used for many years and is both effective and cost-effective in the prevention of PJI [21]. When used as a spacer in two-stage revisions, it has been shown to continue eluting antibiotics to an effective local dose over 6 weeks following implantation and, provided a sufficient dose is used, may be effective at a mean of up to 4 months following implantation [22, 23].

Whiteside et al. have described the use of intra-articular infusion for the delivery of antibiotics in revision hip and knee replacement [24]. They describe a protocol involving single-stage revision with the insertion of intra-articular Hickman lines to deliver a once daily infusion of antibiotics for up to 6 weeks. After an initial loading dose, no intravenous antibiotics are given; their pharmacokinetic study has demonstrated maintenance of therapeutic local levels of antibiotic with minimal systemic absorption. Excellent results are reported, even in difficult groups such as those with previous failed two-stage revisions and resistant organisms [24].

2.4 The Biofilm

The main challenge to the prevention and treatment of PJI is the behavior of causative bacteria in the presence of implants. Bacteria, either introduced at the time of surgery or by later hematogenous spread, adhere to the surface of the implant and form a complex glycocalyx known as a biofilm [25, 26]. The biofilm protects the bacteria from the antibiotics which are effective against them in the planktonic form. As a result, our principal pharmacological strategies for treatment of bacterial infection are ineffective; our efforts instead focus on prevention of biofilm formation by reducing the number of bacteria present in the surgical field (see Chap. 4) and by treating the planktonic form of bacteria before they are able to adhere to the implant—this forms the basis of antibiotic prophylaxis regimens (covered in more detail in Chap. 5).

The first stage of biofilm formation is adhesion; planktonic bacteria produce adhesins which allow them to bond to the surface of the implant, after which the bacteria divide and start to secrete the complex combination of proteins, polysaccharides, and phospholipids which form the acellular structure of the biofilm; these are known as extracellular polymeric substances or EPS [27]. The structure of the biofilm confers protection, nutrition, and communication, through a process known as quorum sensing [28]. This communication can involve the control of the population of bacteria and the transmission of plasmids to spread antibiotic resistance within the population of bacteria within the biofilm.

In a biofilm, bacteria comprise 10% of the overall mass, and EPS comprises 90%. The bacteria can be a single species or multiple species can exist within the same biofilm [28]. The precise contents of the EPS vary from species to species and are poorly understood [29]. Components include polysaccharides (which are involved in adhesion, aggregation, and protection of bacteria), enzymes (which are involved in turnover of the biofilm and degradation of

structural biofilm components, either to liberate bacteria to create new biofilms or to provide nutrition to bacteria within the existing biofilm), extracellular deoxyribonucleic acid (DNA), lipids (which contribute to adhesion), and biosurfactants. The largest component of the EPS is water, which is retained due to the hydrophilic components of the EPS, allowing bacteria to survive in otherwise inhospitable conditions.

2.5 Targets for the Prevention and Treatment of Biofilms

Recent research has focused on the detection of biofilms, the prevention of biofilm formation, and the disruption of biofilms which are present.

2.5.1 Improvements in Detection of Biofilms

Bacteria are generally detected and characterized on the basis of culture growth; however, bacteria in biofilm form are difficult to culture and diagnosis may be elusive. Suda et al. reported a moderate increase in yields of bacteria from PJI using the polymerase chain reaction (PCR) for bacterial ribonucleic acid (RNA), although other authors have debated the usefulness of this technology [30, 31]. Sonication of implants is performed with the aim of liberating bacteria from the biofilm into their planktonic form to allow a higher yield from culture [32]. Other methods for detection include fluorescence in situ hybridization (FISH) and DNA microarrays [33, 34].

An emerging field is the use of imaging technology to detect biofilms on orthopedic implants. Stoodley has used confocal laser scanning microscopy to image the biofilm in a retrieved specimen; others have examined biofilms using scanning electron microscopy [35, 36].

2.5.2 Prevention of Biofilm Formation

While the use of antibiotic-eluting cement is an established and evidence-based implant-based approach to the prevention of biofilm formation [37], there is increasing evidence that strategies based on the surface properties of implants may have a role to play in preventing biofilm formation. Surface properties of implants affect the ability of bacteria to adhere and form biofilms [38]. There is some evidence from basic science studies that current implant materials such as vitamin E—impregnated polyethylene and ceramic—may confer a degree of protection against biofilm formation, but studies are contradictory and clinical evidence is lacking [39–42].

Various groups have attempted to develop anti-biofilm coatings for implants. A number of strategies have been investigated, including the manipulation of surface topography of materials, the use of materials' intrinsic antimicrobial properties (such as in the use of silver or copper coatings), and the tethering of antibiotics to the implant surface [43]. Silver, when coated on the surfaces of titanium alloys, can impede biofilm infections against *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [44, 45].

2.5.3 Treatment of the Established Biofilm

Treatment of established biofilms can be mechanical—methods to disrupt the biofilm—or pharmacological. Sonication in vitro has the potential to disrupt biofilms, liberating bacteria into their planktonic form and allowing antibiotic therapy, although doubts exist as to the effectiveness of this technique and there are concerns regarding the effect on the topography of the implant and subsequent implant longevity [46]. Urish et al. have investigated the use of pulsatile lavage for disruption of biofilms during debridement, antibiotics, and implant retention (DAIR) procedures and have found it to be ineffective in removing biofilms from implants in TKA [47].

Pharmacological therapies include antibiotics, quorum quenching agents, and chemotherapeutic agents. Two antibiotics exist with anti-biofilm activity: rifampicin (which inhibits transcription) and meropenem (which inhibits cell wall biosynthesis) [48, 49]. Species including *Pseudomonas*,

Staphylococcus, *Acinetobacter*, *E. coli*, *Vibrio*, and *Candida* have the ability to disrupt quorum sensing from other bacteria, a property which may be of use in disrupting biofilms [1]. Acyl homoserine lactone (AHL), which is derived from *Pseudomonas*, has been demonstrated in early phase studies to be useful in disrupting quorum sensing within biofilms. Titania nanotubes and zinc oxide nanoparticles may also be of use [1]. Some agents used in oncological chemotherapy have demonstrated anti-biofilm activity. Cisplatin, 5-fluorocytosine, and mitomycin C have been shown to clear biofilms of embedded bacteria and may represent a future target for research [50].

Conclusions

The difficulty of treating PJI is a result of the formation of biofilms by causative organisms. The common organisms which cause PJI (particularly staphylococci and streptococci) are prodigious formers of biofilms. Biofilms are protective against antibiotics and host defenses and facilitate bacterial nutrition, allow interaction between bacteria (quorum sensing), and allow the spreading of resistance.

The approach to the biofilm in current practice centers on prevention, including the use of prophylactic antibiotics and methods to decrease bacterial colonization of surgical wounds. Future approaches are in development for the prevention (for instance, the use of coatings and new materials to discourage biofilm formation) and treatment of biofilms. Treatment of the established biofilm represents a holy grail in the management of PJI, and many approaches are under investigation.

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3 Preoperative Optimization to Prevent an Infected Total Knee Arthroplasty: Host Factors

Sven E. Putnis and Sam Oussedik

Abstract

A large number of host risk factors have been identified with an increasing number of papers demonstrating many times higher PJI rates in these patients. Some may be easier and faster to address than others. Patients who present with multiple risk factors need to have a clear understanding of the morbidity involved with PJI, and as clinicians there needs to be a planned approach in how to identify which of these conditions can be optimized and an appropriate time frame set to achieve this.

With a rise in obesity and diabetes, we may start to see an associated increase in PJI. Without good evidence to support bariatric surgery and many patients struggling with weight loss, it may be that the additional risk needs to be accepted. Identification of an early arthritic group who could be targeted for weight loss would seem logical.

When presented with an obese, diabetic patient with multiple other risk factors, there may be a point when optimization has been achieved, but the considerable increased risk of PJI remains. Further research will need to better quantify this risk in order to educate and consent patients, better prepare health services for the likelihood of complications arising, and ensure registry data is appropriately adjusted for risk.

3.1 Introduction

Preoperative assessment of patients to identify groups at higher risk of knee prosthetic joint infection (PJI) is essential. Joint registry data looking at 56,216 total knee arthroplasties (TKAs) recorded deep surgical site infection (SSI) in 0.72% (404/56,216) and associated these with a body mass index (BMI) of ≥ 35 kg/m^2 (hazard ratio (HR) = 1.47), diabetes mellitus

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(DM) (HR = 1.28), and American Society of Anesthesiologists (ASA) score of > – 3 (HR = 1.65) [1]. When using data from a meta-analysis, similar findings are seen; of 12 cohorts or case-control studies which included 548 infected patients in 57,223 cases, BMI (BMI > 30: odds ratio (OR) = 2.53, 95% CI 1.25, 5.13; BMI > 40: OR = 4.00, 95% CI 1.23, 12.98), DM (OR = 3.72, 95% CI 2.30, 6.01), hypertension (OR = 2.53, 95% CI 1.07, 5.99), steroid therapy (OR = 2.04, 95% CI 1.11, 3.74), and rheumatoid arthritis (OR = 1.83; 95% CI 1.42, 2.36) were identified risk factors [2]. These conditions and diseases, as well as others, are well known to affect tissue viability and healing; they need to be diagnosed, treated, and optimized as part of the preparation for joint replacement. This allows their effect to be minimized and the patient to be appropriately counseled.

3.2 Obesity

Patient weight is a significant factor in the progression of knee osteoarthritis; it is therefore not surprising that a substantial number of patient undergoing TKA are obese [3]. For clinical and research purposes, patients are grouped into weight categories based on their BMI. Those with BMI over 30 kg/m^2 are termed obese and those over 40 kg/m^2 are morbidly obese. Health economic studies now indicate that there is a worldwide increase in obesity levels [3], and this is reflected in TKA patients, with over 50% obese [4, 5].

Authors have broadly chosen two ways to look at obesity in TKA: reviewing all PJIs and looking at their demographic or looking at BMI and following these groups to see if they have a higher infection rate than a matched group.

A 2012 meta-analysis and systematic literature review identified 14 studies and 15,276 patients; overall infection occurred more in obese patients (OR = 1.90, 95% CI 1.46–2.47), and deep infection requiring surgical debridement was reported as increased in 9 studies including 5061 patients (OR = 2.38, 95% CI 1.28–4.55) [6].

Numerous studies have shown a link between obese patients experiencing longer operative times [7], worse knee score outcomes [8], increased overall complication rates [9, 10], and significantly both superficial and deep postoperative infections [4–6].

An association between an even higher risk of PJI relative to an increase in BMI from >30 to >40 (morbidly obese) has also been demonstrated [11, 12].

A single-center study from Finland saw an overall infection rate of 0.79% in 3915 knee replacements; infected patients had a significantly higher median BMI (31.5 compared with 28.7 kg/m^2; $p = 0.001$). Six of the 156 (3.85%) morbidly obese patients developed PJI [12]. The same unit published a review of their experience [13]. A further database review of 48 PJIs from a cohort of 4185 (1.1%) found that a BMI >40 kg/m^2 was an independent predisposing factor for PJI (OR = 3.23 95%, CI 1.6–6.5 $p = 0.001$) [14]. Findings from 41 consecutive TKAs in morbidly obese compared with a matched group with BMI <30 resulted in seven superficial infections and two deep versus no infections [15].

There is evidence to suggest that the higher the BMI, the greater your increased risk, with a complication rate including wound healing and infection higher in patients with a BMI >45, and with the risk rising for every 5 unit increase in BMI up to 70 [16]. A number of studies have looked at this "super" obese category; from a group of 8494 total joint arthroplasty (TJA) patients, 30 deep infections were identified and found that a BMI > –50 had a massively increased odds ratio of infection of 21.3 ($p = 0.001$) [17], and 29 PJIs from a cohort of 1846 (1.5%) also found that a BMI > 50 was an independent risk factor (OR = 5.28, CI 1.38–17.1) [18]. A study following the outcome of 101 matched TKAs in patients with a BMI of at least 50 found a variety of wound problems: 6 patients with wound necrosis, 1 superficial infection and 2 wound hematomas, and overall a 3.1 times higher odds ratio (95% CI 1.07–8.9) of complications compared with the matched group ($p = 0.037$) [19].

With such a large number of patients undergoing TKA, providing some evidence that they can experience good outcomes is essential. Survivorship of implants when comparing patients with either a BMI < 30 or > 30 was equivalent in a group of 535 [20]. A large database review of over 90,000 patients with a BMI > 40 who underwent TKR found that there was an independent association with a higher risk of a small number of select in-hospital postoperative complications and mortality after matching with comorbid medical conditions linked to obesity, such as type 2 diabetes and hypertension. However, the independent impact of obesity appeared to be fairly modest [21].

3.2.1 Preoperative Weight Loss and Bariatric Surgery

With the increased rate of PJI seen, it would seem logical to recommend that patients undergo weight loss during the period of knee arthritis prior to TKA. How far this should be taken, and whether this should be a prerequisite to offering surgery is currently unknown. A study looking at 10,718 obese patients undergoing TKA over a 3-year period found no difference in SSI between those who gained or lost weight (decrease in 5% body weight) preoperatively [22].

The medical and social indications for bariatric surgery are broad and need to be taken into consideration when a patient is also indicated for TKA. A computer-based model reviewing outcomes from studies and registry data and using quality-adjusted life years and cost-effectiveness as an endpoint supported bariatric surgery prior to knee arthroplasty in obese patients [23].

Clinical studies however have resulted in conflicting conclusions [24–28]. A systematic review and meta-analysis concluded that, based on this moderate quality of evidence, an improvement in clinical outcome with pre-arthroplasty bariatric surgery needs to be questioned [29]. After bariatric surgery, patients are at risk of nutritional deficiencies [30] which subsequently may also alter their susceptibility to PJI.

3.3 Malnutrition

Malnutrition is a deficiency, excess, or imbalance of body protein and other nutrients. It causes adverse effects on tissue, function, and clinical outcome, with prolonged inflammation by reducing collagen synthesis and fibroblast proliferation. It may additionally impair the immune system through lymphocyte proliferation, antibody responses, interleukin-2, and interferon-gamma, as well as delayed hypersensitivity reactions [31]. It can be seen in patients with different body weights and be related to an underlying condition or chronic disease. It has been seen to be prevalent in patients undergoing TJA [32].

Blood parameters that have been identified as markers of malnutrition and are subsequently studied are serum albumin (<3.5 g/dL), total lymphocyte count (<1500 cells/mm^3), and transferrin (<200 mg/dL). Several studies have shown the adverse effects malnutrition can have when undergoing TJA [32–35].

In 1991, a study found that TKA patients had a five times greater risk of developing major wound complications if their preoperative total lymphocyte count was <1500 cells/mm^3 and a seven times greater risk if their albumin was <3.5 g/dL [33]. A number of studies since then have also shown increased complication rates and PJIs. A preoperative serum albumin < 3.5 g/dL has been demonstrated to increase overall complication rate following TKA including SSI [35]. Two studies have analyzed large numbers of patient from ACS-NSQIP data. The first found significantly higher rates of SSI and pneumonia, an extended length of stay, and readmission in the 4% of patients with hypoalbuminemia [36]. The second showed higher superficial SSI, organ space SSI, and deep SSI. These patients also had a higher rate of postoperative pneumonia, acute renal failure, cardiac arrest requiring pulmonary resuscitation, septic shock, unplanned intubation, and blood transfusion. Their overall risk was calculated to be higher when compared to morbidly obese patients, and when compared to patients with normal albumin, there was a 3.19-fold increased risk of mortality [37]. A prospective study found that patients with hypoalbuminemia

also had an increased chance of unplanned intensive care admission postoperatively: 15.4 and 3.8% in patients with a serum albumin of <3.0 and <3.5 g/dL, respectively [38].

Like biochemical parameters, triceps skinfold (TSF) can be used as a marker of nutritional status. A prospective study of 213 TKAs where 11 patients subsequently became infected (5 deep and 6 superficial) found this to be the only significant risk factor for postoperative infection risk [38].

These findings have been seen in studies on revision TKA, with malnutrition independently associated with chronic septic failure requiring further surgery [39–42].

Malnutrition can be seen in underweight patients but is also common in obese patients and is likely more significant [43]. When looking at low patient BMI, a study which included 1315 TKA patients found that while there was an increase rate of wound hematomas and seromas, and postoperative anemia was more frequent, this patient group had in fact demonstrated a lower rate of PJI [44].

Given the findings of the studies described, it would be logical to identify malnourished patients and correct this preoperatively. Benefits of perioperative nutritional support have been seen in an elderly fracture neck of femur population [45, 46], but there are no studies to date specifically looking at the benefit of this in TJA patients. Nutritional optimization is an area of future research with a recent randomized pilot study demonstrating a decreased length of stay and postoperative C-reactive protein (CRP) in total hip arthroplasty (THA) patients who received multimodal perioperative care and immunonutrition [47].

3.4 Anemia

Preoperative anemia is reported to occur in 15–33% of patients undergoing TJA [48]. Anemia is associated with a large number of comorbid disorders and it is therefore unsuprising that, when present preoperatively, there is also an association with postoperative complications following TJA [49].

A review of 6371 TKA patients found 1249 to be anemic. This study also included 7230 THA patients with 1286 anemic in this group. The results combined both arthroplasty groups and subsequently demonstrated an increase in PJI when compared to a matched group with normal hemoglobin levels preoperatively (4.3 versus 2%) [50].

There is a decrease in the rate of postoperative allogenic blood transfusion if anemia is corrected [14, 51], and with an association between transfusion and SSI, this may also be a relevant factor [52]. Preoperative correction will depend on the cause of the anemia, with iron replacement and recombinant human erythropoietin therapy proven to be useful options after discussion with a hematologist [53–55].

3.5 Diabetes Mellitus

The rise in obesity levels has also seen an associated increase in type 2 DM [56, 57]. With this rise comes a projected increase in PJI [58]. The effect of DM in wound healing is well known, and more focused research into patients with DM undergoing TJA has shown in general that these patients are at increased risk of wound complications and deep infection [58, 59], as well as a variety of other complications such as deep vein thrombosis, hospital cost, readmission, and mortality [60–66].

Analysis of 3915 TKA patients saw an infection rate increase (from 0.66%, 95% CI 0.43–0.99% to 1.59%, 95% CI 0.84–2.99%) in those diagnosed with DM in comparison with those without. This was independent of obesity. When combined with morbid obesity, that figure rose to a PJI in 5 out of 51 patients (9.8%, 95% CI, 4.26–20.98%). Patients not diagnosed with diabetes but presenting with a blood glucose of >6.9 nmol/L also had a higher PJI rate (1.15%, 95% CI, 0.56–2.35% compared with 0.28%, 95% CI 0.15–0.53%) suggesting that this is an important part of the preoperative assessment [12]. A retrospective review of 167 TKAs in type 2 DM patients found an overall wound complication rate of 6.6% (n = 11), and logistic regression

revealed an HbA1c > –8 as an independent risk factor [67]. A prospective review of 1214 TKAs found an overall infection rate of 1.5% with an increase in diabetic patients (OR = 6.87; 95% CI 2.42–19.56), and significantly in this study, there were no PJIs in patients with diabetes who were not also obese [68]. In a Korean study comparing 222 TKAs in patients with DM versus a matched group, a wound complication rate of 9.5% compared to 5% ($p < 0.05$) was seen, and the 1 superficial infection and 2 deep infections did not reach significance [69].

The view that all DM patients are at an increased risk of PJI is not universal, however. In a large multicenter retrospective cohort study, 7567 (18.7%) DM patients were identified from a joint registry cohort of 40,491 TKAs. From the 287 patients who developed deep infection, there was no significant increased risk in the DM group, even when adjusting for BMI. The study went on to look at patient's diabetic control; no significant difference could be found when subdividing DM patients into uncontrolled (HbA1c <7%) and controlled (HbA1c >7%) [70].

Analysis of HbA1c gives a long-term record of a patient's diabetic control. Whether it is a useful marker in TKA and subsequent PJI is unclear. A study found no correlation between HbA1c and infection rates although in this study the overall deep PJI was higher in the DM group versus normal controls: 2.6 versus 0.87% [71].

With a large number of patients with DM undergoing TJA, perioperative control of blood glucose levels has also been studied. In 1565 TKAs, a rate of PJI during the 1-year follow-up of 0.44, 0.93, and 2.42% was recorded in groups with preoperative plasma glucose of <6.1 mmol/L, 6.1–6.9 mmol/L, and >–7.0 mmol/L, respectively. The patients with highest glucose levels had a fourfold risk for infection when compared to patients with the lowest glucose [72]. A further study demonstrated a twofold increase in PJI in patients with DM who had postoperative hyperglycemia and interestingly a rate three times higher in non-DM patients with hyperglycemia representing a physiological response to surgery [73].

3.6 Other Comorbidities

This chapter has highlighted a number of specific conditions that have been studied and subsequently identified as risk factors for PJI. It is often the combination of risk factors that place a patient at the highest risk. It is therefore useful to try and quantify the significance of comorbidities. A review of 83,011 patients undergoing TKR looked at a broad range of disorders and found (in decreasing order of significance) congestive heart failure, chronic pulmonary disease, preoperative anemia, DM, depression, renal disease, pulmonary circulation disorders, obesity, rheumatologic disease, psychoses, metastatic tumor, peripheral vascular disease, and valvular disease as risk factors for PJI [74]. In a 2001 single-center study of 6489 TKAs, 116 PJIs became infected. Of the 12 identified significant comorbidities, prior open surgical procedure, immunosuppressive therapy, hypopotassemia, and poor nutrition were the 4 most significant factors (each $p < 0.001$) [75].

The American Society of Anesthesiologists (ASA) is accepted as an overall summary of patient's preoperative risk and encompasses all comorbidities. A review of 4185 TKAs identified 48 (1.1%) PJIs and after univariate analysis found ASA > 2 to be an independent factor ($p = 0.002$) and a more significant one than morbid obesity ($p = 0.03$) [14].

3.6.1 Inflammatory Joint Disease and Immunosuppression

Patients with inflammatory joint disease may have a number of different reasons to have an increased rate of PJI including overall disability, disease activity, and the use of disease-modifying antirheumatic drugs (DMARDs). With over 80% of rheumatoid arthritis (RA) patients now prescribed with DMARDs [76] and 24% undergoing large joint replacement [77], optimal perioperative management of these medications will become an increasing challenge.

In a health insurance database case-control study of 2212 patients identified with a PJI, risk

factors were established; those with a diagnosis of RA (OR = 1.47, $p = 0.031$) while identified were not as significant as obesity (OR = 1.66, $p < 0.001$) or DM (OR = 1.38, $p = 0.001$). A prescription for prednisolone had a significantly increased risk (OR = 1.59, $p < 0.001$), while no significant difference was found for the use of DMARDs including tumor necrosis factor-alpha (anti-TNFa) inhibitors [78].

The decision to stop any DMARDs needs to be a balance between the risk of a perioperative disease flare and risk of PJI, and there is no current consensus on the safety of perioperative continuation of these medications [79]. A 2009 systematic review on the perioperative use of methotrexate concluded that low doses seem to be safe without a significant increase risk of PJI and an avoidance of disease flare [80]. A further controlled study with a 10-year follow-up again found no PJIs in either a group taking perioperative methotrexate or one which stopped ($n = 65$) [81].

Review articles also looking at anti-TNFa and other biologics have concluded that despite inconclusive data, the trend was to an increased risk of PJI. The advice currently is to withhold anti-TNFa and other biologics prior to surgery based on the dosing interval and continue methotrexate and hydroxychloroquine through the perioperative period. There was no consensus regarding medications such as leflunomide and rituximab [82–84]. Without compelling evidence and with new medications and drug combinations being prescribed, a perioperative plan needs to be made with guidance from local rheumatologists.

3.6.2 Glucocorticoid Steroids

There is a strong association between systemic glucocorticoid therapy and the risk of infection, demonstrated in a 2011 systematic review and meta-analysis [85] with higher doses conferring greater risk. There is evidence that perioperative supplemental doses to counter the adrenal insufficiency precipitated by surgical stress are not required [86–88].

Intra-articular injection of steroids prior to TKA was not shown to increase either deep or superficial infection in systematic review and meta-analyses [89, 90]. A review of a national database of TKAs found a significant difference in PJI between patients administered with intra-articular steroid within 3 months (2.6%, OR = 1.6–2.5, $p < 0.0001$) and 6 months (3.41%, OR = 1.2–1.8, $p < 0.0001$) of TKA [91], suggesting that there is a period of time where steroid concentration is high enough to be a risk factor.

3.6.3 Human Immunodeficiency Virus (HIV)

With the advent of antiretroviral medication, patients with HIV can mount an immune response. A 2001 study of 28 patients with HIV saw 4 (14%) develop a PJI, 2 of these patients also had a history of intravenous drug use [92].

3.6.4 Renal, Gastrointestinal, and Hepatic Disorders

Optimization of organ function with particular emphasis on how function may be affecting anemia and nutritional status has been recommended [93]. Using data from the Scottish Arthroplasty Project, an analysis of 59,288 TKAs found 652 PJI infections within 90 days. There was a significant association with those diagnosed with renal failure ($p = 0.002$), and dialysis prior to TKA appeared to eliminate this risk [94].

3.7 Smoking

There are numerous studies linking smoking with wound healing and infection rates in surgery. A 2012 systematic review and meta-analysis found 140 cohort studies including 479,150 patients on the subject. The conclusion was that postoperative healing complications occur significantly more often in smokers compared with nonsmokers and in former smokers compared with those who never smoked. Perioperative

smoking cessation intervention reduces surgical site infections, but not other healing complications [95].

A 2011 systematic review looking at outcomes in smokers after TKA and THA found they had a significantly higher rate of reoperation or revision, implant loosening, deep infection, and mortality compared to those who did not smoke [96]. When focusing on TKA patients, studies have shown an increase in hospital length of stay and intensive care unit admissions [97] and revision rates, including PJI [98]. A history of smoking was one of the significant risk factors identified of the 116 infected knees from a cohort of 6489 [75], and analysis from ACS-NSQIP data showed a substantially higher risk of morbidity and mortality with an increase in complications as a dose-dependent relationship with the number of pack-years [99].

A Cochrane meta-analysis concluded that smoking cessation before planned surgery reduced morbidity and mortality with intensive behavioral therapy, defined as weekly face-to-face encounters, combined with nicotine replacement therapy—the most successful approach [100]. Evidence would suggest that a benefit of abstinence is conferred in the period 4–8 weeks prior to surgery [101, 102]. A prospective randomized trial of 120 active smokers showed a significant reduction in wound complications and the need for additional surgery for the group who underwent a successful pre-arthroplasty cessation program (5 vs. 30% and 3.6 vs. 15%) [101]. Studies have however found that former smokers are still at increased risk [96, 99].

Conclusions

Preoperative patient optimization is a key part of modern arthroplasty pathways. While many risk factors for the development of PJI have been identified, not all can be mitigated. Once these comorbidities have been addressed, the residual risk to the patient must be quantified and clearly discussed in order to obtain informed consent.

Modern arthroplasty registers must make use of this knowledge to allow risk stratification of outcome data and avoid penalizing surgeons for taking on this higher risk cohort. A failure to do so may ultimately result in life-changing surgery being refused to an increasingly large proportion of our populations.

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4 Depilation and Skin Preparation to Prevent an Infected Total Knee Arthroplasty

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Abstract

Depilation and skin preparation before total knee arthroplasty (TKA) and any other surgery are well known but frequently underestimated as a potential source of contamination. The patient's skin is a major source of pathogens that may cause surgical site infection. Optimizing the methods employed may reduce the burden of infections.

4.1 Introduction

Skin care and depilation before total knee arthroplasty (TKA) should be considered one of the key steps in clinical guidelines for lower-limb arthroplasty. There are many questions and considerations that we have to review before a surgical incision.

One question is when to perform preoperative hair removal (PHR). Many authors consider that there is no difference in complications whether this occurs the evening before or the same day as the surgery [1] and neither does the method appear important—shaving, clipping, or chemical depilation.

Common sense and the evidence support that if there is hair in the surgical site, depilation should be performed [1].

The Cochrane review of 2011 about skin care and depilation arises from the idea that traditionally preparation included removal of hair from the incision site, but some studies claim that PHR is harmful, causes surgical site infections (SSIs), and should be avoided.

The purpose of this chapter is to review the literature in order to know if we can optimize preoperative skin preparation.

4.2 General Recommendations

- Patients should take a bath or shower before surgery with either soap or an antiseptic solution.
- Hair at the surgical site should be removed only when the hair interferes with the surgical procedure.
- Safe effective preoperative antiseptics should be selected for the individual patient.

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4.3 Preoperative Hair Removal (PHR): Shaving, Clipping, or Depilatory Creams

During the process of shaving, the skin may experience microscopic cuts and abrasions. It is believed that saprophytic skin flora is able to enter and colonize these cuts, therefore contaminating the surgical incision site leading to SSIs and potentially to periprosthetic joint infections (PJI) [1].

It is important to remember that PHR should not take place in the operating room because this may contaminate the sterile surgical field [2].

Another important recommendation is that PHR should be carried out by skilled personnel in order to prevent abrasion injuries.

The Centers for Disease Control (CDC) strongly recommends that PHR should not be performed unless the hair at or around the incision site will interfere with the surgery [1].

The Norwegian Center for Health Technology Assessment found that strong evidence does not exit either in favor of or against PHR, while the British Hospital Infection Society Working Party guidelines recommend that "only the area to be incised need hair removal" and that shaving should be avoided if possible. The CDC guidelines recommend removal of hair immediately before surgery, and preferably with clippers [2].

Although hair may be considered a source of bacterial infection, the process of removing hair may cause primary infection because of microscopic cuts to the skin. One alternative is using depilatory creams, although it is important to remember that a patch test is mandatory to avoid irritation or allergic reaction at the site of incision [1].

Clippers are recommended on the day of surgery and always outside the operation room.

4.4 Local Antiseptics (Iodine vs. Chlorhexidine)

The two most commonly used antiseptic solutions are iodine and chlorhexidine combined with isopropyl alcohol. Chlorhexidine is a broad-spectrum biocide effective against Gram-positive bacteria, Gram-negative bacteria, and fungi [3]. Iodine can penetrate the cell wall of microorganisms, and the lethal effects are believed to result from disruption of protein and nucleic acid structure and synthesis [4].

Chlorhexidine inactivates microorganisms with a broader spectrum than other antimicrobials (e.g., antibiotics) and has a quicker kill rate than other antimicrobials (e.g., povidone/iodine). It has both bacteriostatic (inhibits bacterial growth) and bactericidal (kills bacteria) mechanisms of action, depending on its concentration [4]. Chlorhexidine kills by disrupting the cell membrane. Upon application in vitro, chlorhexidine can kill almost 100% of Gram-positive and Gram-negative bacteria within 30 s. Since chlorhexidine formulations can destroy the majority of categories of microbes, there is a limited risk of developing an opportunistic infection.

Recently, some studies have demonstrated the benefits of chlorhexidine-soaked dressings applied in the hours before surgery [5, 6]. In 2010, a randomized study [6] described that the overall rate of SSI was significantly lower with chlorhexidine than with iodine (9.5 vs. 16.1%; $P = 0.004$). Chlorhexidine was significantly more protective than iodine against both superficial incisional infections (4.2 vs. 8.6%; $P = 0.008$) and deep incisional infections (1 vs. 3%; $P = 0.05$). Based on the evidence, chlorhexidine is preferred to other antiseptics.

4.5 Skin Closure

There is a recent meta-analysis [7] that compared sutures versus staples for skin closure in orthopedic surgery and demonstrated that there is no difference of developing a wound infection when the wound is closed with staples rather than sutures.

4.6 Suction Drains

Currently with the tranexamic acid protocols [8–13], suction drains are rarely used. Suction drains should be used only in patients with

coagulation deficiencies to avoid hematomas, potential dehiscence, and PJI [3].

Conclusions

Current existing evidence suggests that clippers are associated with fewer surgical site infections (SSIs) than razors. Preoperative hair removal (PHR) should not be carried out unless the hair at or around the incision site will interfere with the surgery. If it is considered that PHR is required, it must be performed the on day of surgery, preferably with clippers. In the case of using depilatory creams, remember to carry out the patch test before applying the depilatory cream at the surgical site. Regarding skin preparation, chlorhexidine is better than iodine antiseptic solutions.

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Antibiotic Prophylaxis to Prevent Infection in Total Knee Arthroplasty

5

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Abstract

Total knee arthroplasty (TKA) is one of the most frequent and successful procedures performed in orthopedic surgery. Despite its safety, complications are still present. Infection is one of the more devastating complications in TKA as it places a significant burden on patients, surgeons, and health systems. Surgical site infection in non-contaminated surgery still affects 2–5% of patients. These data highlight the importance of prophylactic measures in preventing infection following TKA. The key point on choosing antibiotic prophylaxis is the spectrum of action and the penetration into the bone and periarticular tissues. Antibiotics should cover the most frequent microorganisms causing postoperative infection. It should achieve a high enough concentration (at least the minimum inhibitory concentration) in the serum and bone and maintain this over time. For standard antibiotic prophylaxis, drug administration should be done during the hour before incision. Cephalosporins are the most widely used antibiotics for periprosthetic joint infection prophylaxis during the last decades in the USA and Europe. They are effective against gram-positive organisms, aerobic gram-negative bacilli, and anaerobes. Despite the great advantages, cefazolin (1–3 g depending on body weight every 2–5 h) is not effective against methicillin-resistant *Staphylococcus aureus* (*MRSA*). For this, increased prevalence of MRSA should be taken into account to decide if cefazolin is the best option. However, clindamycin (90 mg every 3–6 h) and vancomycin (15/kg every 6–12 h) are appropriate options when cephalosporins are contraindicated (i.e., allergy) or when risk factors for antibiotic-resistant organism are present.

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5.1 Introduction

Infection is one of the more devastating complications of total knee arthroplasty (TKA) as it places a significant burden on patients, surgeons, and health systems [1]. Surgical site infection in non-contaminated surgery still affects 2–5% of patients [2]. Increasing numbers of replacements are performed every year, while the infection rate remains constant affecting approximately 2% of cases within the first 2 years after the operation [3].

It is estimated that each case of infection costs about $50,000 ($100,000 in case of drug-resistant microorganism) [3]. There has been a small incremental rise in the incidence of infections after TKA, and it is estimated that it will be almost 50,000 cases of infected TKA in the USA by 2020 [3]. This emphasizes both the importance of the topic and adherence to prophylactic measures.

Several factors should be taken into account in order to prevent periprosthetic joint infection (PJI); some of them are covered in other chapters of this book. These include optimizing host factors, improvement of operating room and surgical technique, adequate skin preparation, and antibiotic prophylaxis [4–6]. In this chapter, we will focus on antibiotic prophylaxis, examining both classical concepts and new trends.

5.2 What Is Antibiotic Prophylaxis?

Prophylactic parenteral antibiotics have critically contributed to reducing infection rates in TKA. Infections are considered to result from the index surgery if they are diagnosed within the first year after the index surgery. Prophylactic antibiotics are given to avoid infection when there is a significant risk of perioperative infection. In order to be effective, serum and bone concentrations during surgery should be higher than minimum inhibitory concentration for the likely causative organisms [7].

Every time we use antibiotics, we should consider the local flora in order to select the appropriate antibiotic type and dose. Regular use of broad-spectrum antibiotics leads to resistant microorganism infections, which are associated with worse outcomes and higher costs [8].

An ideal antibiotic for periprosthetic joint infection (PJI) prophylaxis should prevent surgical site infection (SSI), prevent SSI-related morbidity and mortality, reduce the duration and cost of healthcare, produce no adverse effects, and have no adverse consequences for the microbial flora of the patient or the center [9].

5.3 Historical Perspective

Fleming's discovery of penicillin in 1928 established the start of the "antibiotic era." The use of antibiotics became commonplace during the Second World War for treating infected wounds of Allied armies. Despite its effectiveness and the thousands of lives saved, antibiotic use was not studied and generalized as preoperative prophylaxis until the 1950s.

Early studies [10, 11] reported controversial results on infection rate in the postoperative period if preoperative prophylaxis was used. The beneficial effect of antibiotic prophylaxis (diminishing up to four times the infection rate) was overshadowed by the critical development of antimicrobial resistance [12]. This microorganism selection was patent in a study conducted by Peel et al. where, in 163 patients with PJI, up to 63% of cases were caused by a microorganism resistant to the antibiotic used on index procedure. Up to 26% of patient samples grew positive cultures for methicillin-resistant *Staphylococcus aureus* (MRSA) [13].

Even if with increased incidence of resistance and infection complexity, antibiotic prophylaxis continued to be used as its benefits in reducing infection rates in TKA were enormous.

5.4 Know Your Enemy

It is paramount to know which are the most frequent microorganisms causing SSI when selecting the appropriate antibiotic prophylaxis. As TKA is a clean surgery (articular cavity content is

sterile), many infections will be caused by skin flora. Contamination by air is also present, and all the personnel in the operating room can be implicated in PJI [14].

Most infections are caused by gram-positive organism present in the skin [15]. In this group, *Staphylococcus aureus* (including methicillin-sensitive and methicillin-resistant forms) and coagulase-negative staphylococci as *Staphylococcus epidermidis* are the most frequent species involved [1]. *Staphylococcus aureus* remains the most frequent pathogen leading to PJI [6]. About two-thirds of PJI are caused by different species of staphylococci [16].

Staphylococcus epidermidis has the ability to adhere to implants, creating biofilm [17, 18], an ideal environment to reproduce and resist host defenses and antibiotic penetration [19]. This biofilm is difficult to eradicate and creates serious difficulties in treating PJI. While antibiotics can control and suppress the clinical symptoms of infection, it is usually not enough to eradicate it; it is necessary to remove associated biofilm [18].

Other gram-positive agents, as *Streptococcus* spp. and *Enterococcus* spp., can be involved in a PJI, especially in association with *Staphylococcus* spp. Of the gram-negative group, *Escherichia coli*, *Enterobacter* spp., *Pseudomonas* spp., and *Klebsiella* spp. are frequently involved [8]. All of them can be part of the skin flora of the patient.

In a study related to incidence of PJI in the UK in the first postoperative year, *Staphylococcus aureus* represents up to 44% of infections (9% of total incidence of MRSA species), *Staphylococcus epidermidis* 31%, *Enterococcus* spp. 12%, *Escherichia coli* 7%, *Enterobacter* spp. 7%, *Pseudomonas* spp. 7%, and *Streptococcus* spp. 7%. Up to 28% of infections were polymicrobial [6].

The great majority of these pathogens are present in skin flora, and the fact that most of PJI arise within the first 2 years after the index procedure suggests that direct inoculation from the skin is the most frequent route of acquisition.

Even if most of infections are caused by *Staphylococcus aureus*, special attention should be paid to nosocomial agents, as MRSA and *Clostridium difficile* [20], as these microorganisms are usually resistant to classical antibiotics. Patients undergoing revision TKA have more risk for *Clostridium difficile* infection in comparison to primary arthroplasty, due to aging, longer stay, and, in many cases, prolonged antibiotic treatment [21].

5.5 The Effectiveness of Antibiotic Prophylaxis

The vast majority of antibiotics used for TKA prophylaxis are bactericidal. This means that they kill the bacteria, in contrast with bacteriostatic antibiotics, which inhibit bacterial growth and reproduction. The bactericidal group includes beta-lactams (penicillins, cephalosporins), vancomycin, and aminoglycosides. Example of a bacteriostatic is clindamycin.

Beta-lactams inhibit the cross-linking process of peptidoglycan structure of the cell wall of gram-positive organism, leading to bacterial death. Beta-lactamases arose in microorganisms in response to counteract beta-lactam action. To compensate for the selection pressure leading to a high prevalence of beta-lactamase-producing staphylococci, methicillin was introduced. Increasing use of methicillin has led to further selection with the rise of MRSA.

The key point on choosing antibiotic prophylaxis is the spectrum of action. Antibiotics should cover the most frequently encountered microorganisms causing postoperative infection. It should achieve high enough concentrations (at least the minimum inhibitory concentration) in the serum and bone for an appropriate length of time.

5.6 Antibiotic Selection and Dosage

There are no data supporting superiority of one class of antimicrobials over another for antimicrobial prophylaxis in TKA [9].

Laboratory tests and cultures of many patients could lead to determining the sensitivity of the

most frequent local flora affecting patients undergoing TKA [22] in an institution. This could lead to algorithms for diagnostic tests and prophylactic antibiotics.

Antimicrobials should be given in appropriate dosage and time to achieve adequate tissue concentrations during the surgery. A minimum duration of prophylaxis should be employed to minimize adverse effects; resistance development and costs should also be taken into account [9].

In recent years, antibiotic stewardship programs (ASPs) developed by multidisciplinary teams have been developed in several institutions, in order to define the local flora and incidence of infections, proper antibiotic, dosage, and duration, minimizing complications and costs [23]. Implementation of these programs has demonstrated a decrease in complications, costs, and imaging techniques [23].

Dosage should be weight adjusted, especially in obese patients. Many studies have demonstrated that standard dose administration in obese patients could fall short of the minimum inhibitory concentration of antibiotic in serum or tissues [9]. As many patients undergoing TKA are obese, administration of weight-adjusted antibiotic doses should be emphasized.

The most frequently recommended and used for prophylaxis are first- or second-generation cephalosporin (as cefazolin or cefuroxime). Isoxazolyl penicillin is an appropriate alternative, while vancomycin is not recommended for routinely use as basic prophylaxis [24]. Some authors do not recommend routine use of dual antibiotics [25–27]. In 2012 Sewick et al. [26] analyzed whether dual antibiotic prophylaxis reduced the rate of SSI compared to single antibiotic prophylaxis in total joint arthroplasty. The addition of vancomycin as a prophylactic antibiotic agent apparently did not reduce the rate of SSI compared to cefazolin alone. The use of vancomycin in addition to cefazolin appeared to reduce the incidence of MRSA infections. Doses and intervals of application for different antibiotics are detailed on Table 5.1.

Table 5.1 Most frequently used antibiotics and dose for prophylaxis

Antimicrobial	Recommended dose
Cefazolin	2 g (3 g for patients over 120 kg)
Cefotaxime	1.5 g
Ceftriaxone	2 g
Ciprofloxacin	400 mg
Clindamycin	900 mg
Gentamicin	5 mg/kg
Levofloxacin	500 mg
Vancomycin	15 mg/kg

Cefazolin is the most widely used antibiotic for PJI prophylaxis during the last decades in the USA and Europe [8]. It is effective against gram-positive, aerobic gram-negative bacilli, and anaerobes. It also shows an excellent tissue availability within first minutes after its administration [28]. Inhibitory concentrations are reached with doses as low as 1 g by intravenous (IV) administration. In 2015, Angthong et al. [28] reported that IV cefazolin at a dose of 2 g produced greater intraosseous concentrations overall than a dose of 1 g. However, higher intraosseous concentrations did not correlate with higher inhibitory effects. Despite its great advantages, cefazolin it is not effective against MRSA. For this, increased prevalence of MRSA should be taken into account to decide if cefazolin is the best option in our case. This is especially important as most of early PJI are caused by microorganism resistant to cefazolin [29].

However, clindamycin and vancomycin are appropriate options when cephalosporins are contraindicated (i.e., allergy) or when risk factors for antibiotic-resistant organism are present. Clindamycin adequately covers *Staphylococcus* spp. and *Streptococcus* spp. and is effective against many MRSA species as well, but vancomycin confers better coverage of MRSA. It is recommended for patients with known sensitivity to beta-lactams in regions with low prevalence of MRSA, when vancomycin would be indicated.

Vancomycin is also effective against streptococci, enterococci, and *Clostridium* and reaches good tissue concentration within the first minutes after its administration [30].

Quinolones are another alternative, with excellent cover against gram-positive and gram-negative bacteria. However, ciprofloxacin is not

the best option, as resistance may develop relatively rapidly and because it favors *Clostridium difficile* colonization [31].

Gentamicin is also active against gram-negative and gram-positive bacteria. It is active against MRSA also. It can be used mixed with bone cement because it is heat stable. It can be also used in dual antibiotic prophylaxis [31].

Local microorganism resistance should be assessed to determine the proper prophylaxis. Microbiological and infectious diseases departments should continuously monitor the prevalence and resistance of different microorganisms. This is especially important with the cases of high prevalence of MRSA. Regarding this, even if vancomycin is not recommended for routine use in healthy people, its use should be considered when a TKA is performed in patients colonized by MRSA and penicillin allergies or when a high risk of MRSA infection exists [24]. However, no clear evidence supporting routine dual antibiotic prophylaxis (i.e., cefazolin + vancomycin) in no high-risk patients exists, while complications (especially nephrotoxicity) are significantly increased [16]. In 2003 Lazzarini et al. [32] found that TKA bone and soft tissue penetration of teicoplanin after regional prophylaxis with 200 mg was at least comparable with that achieved after systemic prophylaxis with 800 mg. Regional prophylaxis in TKA appeared to be safe and valuable. Higher dosages of teicoplanin seemed to be required to ensure coverage against coagulase-negative staphylococci.

As with other antibiotics, vancomycin use to treat pseudomembranous colitis has encouraged the development of vancomycin-resistant bacteria, including *Staphylococcus* spp. New antibiotics have been introduced to treat these bacteria, such as linezolid, daptomycin, and tigecycline. However, it seems to be reasonable to optimize antibiotic use and other methods of PJI prophylaxis to avoid increasing resistances.

This is especially important when treating nosocomial pathogens such as *Escherichia coli*, *Klebsiella pneumonia,* and *Enterococcus* spp. New resistances against third-generation cephalosporins, fluoroquinolones, or both have recently been reported [33]. This is likely to jeopardize future effective prophylaxis as well as PJI treatment.

It is difficult to select an adequate prophylaxis for patients colonized or recently infected with multidrug-resistant pathogens. It is probably sufficient to cover pathogens, but other factors such as the immune status of the host and the proximity of the reservoir of the pathogen to the incision should be considered. In contrast to MRSA-colonized patients, where prophylaxis against MRSA is standard and evidence based, the ideal antibiotic for gram-negative pathogen-colonized patients is not well established [9]. Patients must be covered on a case-by-case basis, considering the factors mentioned above.

In the special case of patients receiving therapeutic antimicrobials for a remote infection before surgery, elective TKA should be postponed.

5.7 Drug Administration

Some issues pertaining to administration should be considered. Classically, systemic administration should be done within the hour before the incision or the tourniquet inflation [7, 34]. In a study conducted by Steinberg et al., a decrease of 0.8% was seen if the antibiotic was administered within 30 min before incision or tourniquet inflation, in comparison when it was administered 30–60 min before [35]. No differences were found when antibiotic administration was done 30 min before tourniquet inflation in comparison with 10 min before inflation [36]. Classen et al. demonstrated that antibiotics administered during anesthetic induction were more effective than early administration (between 24 and 2 h before incision) or administration after surgery [37]. So, for standard antibiotic prophylaxis, drug administration should be done within the hour before incision [9].

However, vancomycin should be administered over 60–120 min, in order to avoid a histaminergic reaction (red man syndrome), which can develop if the infusion is more rapid. Vancomycin should also be administered earlier as its penetration into the bone, synovium, and soft tissue is slower in comparison with cefazolin

[1]. Relating to administration, it is important to adjust doses to the patient's weight. It has been noted that the standard 1 g of vancomycin could be insufficient for preventing MRSA infections in up to 69% of patients [38]. Up to 69% of patients are underdosed with 1 g of vancomycin, and doses of 15 mg/kg are appropriated. It has also been recommended to start fluoroquinolone infusion within 2 h before incision [9].

It should be emphasized that prophylactic antibiotics should not be administered before incision or tourniquet inflation when a PJI is suspected and a TKA revision is encountered. Antibiotic prophylaxis should be delayed until intra-articular cultures are obtained in such cases.

In order to maintain adequate systemic concentration, administration should be repeated 4 h after the incision or when high blood loss (>2000 mL) is observed [24, 39, 40]. Antibiotic prophylaxis should be maintained until 24 h [41]. Current evidence does not support any benefit of antibiotic prophylaxis beyond 24 h [9]. Several studies have demonstrated no improvement on infection rates when the prophylaxis is maintained further than 24 h in clean surgery [42, 43], and, in fact, complications such as toxicity, *Clostridium difficile* infections, and development of resistances are consequences of unnecessary, prolonged prophylaxis [44, 45], increasing iatrogenia and costs [46, 47].

Topical administration of antibiotics in the surgical incision is superior to placebo but not superior to parenteral administration, and it does not increase parenteral-administered antibiotic efficacy [9, 48].

5.8 *Staphylococcus aureus* Screening and Decolonization

Staphylococcus aureus colonization is a known risk factor for PJI [49]. Kalmeijer et al. demonstrated that nasal colonization was an independent risk factor for PJI [50]. A recent study [51] showed an almost full individual concordance between *Staphylococcus aureus* genotypes in carriers who developed a deep SSI. This fact firmly supports transmission from the nose, skin surfaces, and other endogenous body areas as a possible route of infection.

Near 20% of the general population is *Staphylococcus aureus* carrier, and up to 4% of the population is colonized by MRSA [52, 53]. In the last decade, MRSA has changed from being exclusively nosocomial to community-acquired infection [8]. While nasal colonization has decreased in the last decade in the USA, MRSA colonization has increased [9]. A population may be classified according to three different patterns regarding their nasal colonization status: intermittent carriers (60%), persistent carriers (20%), and noncarriers (20%) [54].

The anterior nostrils are the main reservoir of *Staphylococcus aureus* in colonized individuals. Secondary reservoirs include the oropharynx, axillae, groin, perineum, forehead, and neck. These other sites should be encountered especially in the context of low-prevalent MRSA colonized population, where nasal cultures could not be sensitive enough for detection [55].

Given the consequences of infection, many studies regarding the management and decolonization of *Staphylococcus aureus* and MRSA carriers have been developed in recent years [49, 52]. Increased resistance to vancomycin has encouraged the development of screening programs and the change of antimicrobials as a consequence.

It has been demonstrated that preoperative screening of carrier condition and decolonization is effective [56] and a cost-effective procedure to decrease PJI rates [57–59].

Regarding the preoperative diagnosis of *Staphylococcus aureus*, cultures are still the standard method. Anterior nasal swab cultures are the most common sampling method, but as remarked before, other sites, such as the pharynx, groin, or wounds, could be more suitable in enhancing detection in low-prevalent carrier populations [60].

In recent years, polymerase chain reaction (PCR) has gained importance as an alternative to preoperative cultures in diagnosing carriers. It is also useful and effective in detecting MRSA [52, 59, 61]. It has been demonstrated to

be sensitive, specific, and cost-effective in the diagnosis of carrier status and seems to be the best test in comparison to others [61]. It is more sensitive and faster than traditional cultures and currently constitutes the gold standard for *Staphylococcus aureus* detection [16].

Decolonization has been done classically with intranasal mupirocin. It is applied on colonized high-risk patients for perioperative PJI, decreasing perioperative infection rates [62]. But this is controversial, as other well-designed studies do not demonstrate differences between mupirocin administration or not [63]. Therefore, as it is an antibiotic, and, even if resistances have been rarely reported [62], its overuse could lead to resistance development [64]. This is why it is not recommended as empiric preoperative prophylaxis in patients without surveillance [16]. It has been estimated that prior mupirocin exposure increase nasal colonization ninefold in MRSA carriers [65].

Although optimal timing and duration of administration are not standardized, it is thought that 5 days of treatment are required to be effective. Treatment compliance in this situation can be low [66]. Multiple colonization sites are another risk factor for decolonization failure.

In recent years, povidone-iodine has emerged as an alternative to decolonization with intranasal mupirocin [67]. It is effective to eradicate mupirocin-resistant *Staphylococcus aureus* [68]. It can be applied on the day of the surgery and does not develop resistances, being at least as effective as mupirocin is [66].

Other alternatives to mupirocin decolonization have been proposed. Two percent chlorhexidine body shower has demonstrated mixed results. While it seems to be effective as monotherapy, better results have been observed when used as adjunct to mupirocin protocols [69]. An advantage is that a shower covers other sites of *Staphylococcus aureus* colonization. None of them have been as extensively studied as mupirocin, and further studies are needed.

To date, PCR has gained importance in *Staphylococcus aureus* carrier screening, as well as decolonization of carriers with nasal povidone-iodine.

Decolonization is not permanent [70]. When a patient has been colonized, a high risk of recolonization exists, and, if mupirocin was used, increased risk of resistances exists [64]. So if a patient is undergoing subsequent procedures, screening for carrier status and, eventually, decolonization, should be done.

5.9 Antibiotic-Loaded Bone Cement

Polymethyl methacrylate (PMMA) bone cement is widely used and represents the standard for TKA fixation to bone. Bone cement has the capacity to release antibiotic molecules during hours or even days. This capacity is increased as the porosity is increased [71]. In recent years, adding antibiotics into bone cement has been encouraged as a way to increase bone and surgical site antibiotic concentration and liberation, especially in the revision setting, where cement spacers and antibiotic-loaded bone cement are widely used [71, 72]. However, although the evidence for the use of antibiotic-loaded bone cement in TKA looks favorable, it has not been confirmed by recent studies [73], and available data from different national registries remain controversial [71].

Added antibiotics can alter bone cement properties and should comply with several criteria [74]. They should be heat stable, water-soluble, and bactericide allowing for gradual elution and avoiding allergic reaction [1].

Aminoglycosides (e.g., gentamicin, tobramycin) fit these criteria. Other antibiotics such as vancomycin, erythromycin, or colistin have been also used. The association of tobramycin and vancomycin is of interest, as its elution is improved if they are associated [75].

Adding further doses of antibiotics to cement should be considered carefully, in order to not alter the mechanical properties of PMMA. In a classical study by Lautenschlager et al. [76], 10 g of gentamicin added to 60 g of cement resulted in decreased strength and mechanical properties. As a general principle, the higher the dose, the higher the elution of the antibiotic from the cement while the worse the mechanical resistance [77, 78].

It is not clear what is the ideal concentration of antibiotic with no repercussion on mechanical strength and microbiological effectiveness [78]. However, increased risk of mechanical failure with the use of antibiotic cement has not been demonstrated in the clinical setting [79]. No differences between prepackaged cement with antibiotic and manual blended cement powder with antibiotic in the operating room have been demonstrated [80].

Toxicity and selection pressure of flora and development of resistances are also potential adverse effects of antibiotic load bone cement [71]. While adverse effects such as local bone cell toxicity and nephrotoxicity have been reported, these remain rare, as the dose of antibiotics is usually low.

In a study from the Canadian joint registry [81], no differences in 2-year revision rates for TKA were observed between patients with antibiotic-loaded bone cement and conventional bone cement. This has been also observed in other studies [71].

Antibiotic loading of bone cement increases the overall cost of TKA. In a study conducted by Gutowski et al. [82], they investigated the clinical and cost-effectiveness of the use of antibiotic-loaded cement for primary TKA by comparing the rate of infection in 3048 TKAs performed without loaded cement over a 3-year period versus the incidence of infection after 4830 TKAs performed with tobramycin-loaded cement over a later period of time of a similar duration. Depending on the type of antibiotic-loaded cement that was used, its cost in all primary TKAs ranged between USD $2112.72 and USD $112606.67 per case of infection that was prevented. It has been estimated that the treatment of one case of PJI varies from 50,000 to 100,000$ [3]. Taking into account that antibiotic-loaded cements are more economical than managing PJI, we could use them especially when we are facing a case with high risk of infection [24].

5.10 Complications

Antibiotic prophylaxis is not a cost-free action. As with all medicines, antibiotics can result in adverse effects. Antibiotic administration under the adequate dosage/levels could lead to increasing resistances and partial treatment of infections [23]. As we have described before, increasing microbial resistance is one of the main problems we face.

Antibiotic overuse could also result in *Clostridium difficile* infection. In a study reported by Campbell et al. on inpatient hospitalization, antibiotics for urinary tract infections and the use of proton pump inhibitors were identified as risk factors for *Clostridium difficile* infection in orthopedic patients [83]. Longer duration of prophylaxis and the usage of multiple agents have also been identified as risk factors [84].

Even rare, anaphylactic reactions to cephalosporins can occur (beta-lactams are the most frequent antibiotics causing anaphylactic reactions), as with other beta-lactam antibiotics.

Type 1 (immunoglobulin E (IgE)-mediated) allergic reactions to beta-lactams are uncommon. They usually occur within 30–60 min after administration and can pose a life-threatening emergency. In this situation, cephalosporins, penicillins, or carbapenems should be avoided.

However in other non-IgE-mediated allergic reactions against penicillins such as anaphylaxis, urticarial, bronchospasm, Stevens-Johnson syndrome, or toxic epidermal necrolysis, cephalosporin and carbapenem use could be safe [9]. Patients should be questioned about their history of allergies before drug administration. It is also important to determine whether an antibiotic allergy is true or not, to avoid wrong administration of other drugs and possible resistance development.

Other more common reactions with beta-lactam administration include skin rash, eosinophilia, diarrhea, or *Clostridium difficile* infection. As previously stated, clindamycin is a good alternative when beta-lactams are not indicated. The typical and most severe adverse effect of clindamycin is *Clostridium difficile* diarrhea. Other adverse effects are skin rash or abdominal pain.

Regarding vancomycin, a histamine release can occur with fast infusion. This reaction includes pruritus, erythema, and hypotension (red man syndrome). It can be avoided with slow

infusion. Nephrotoxicity and ototoxicity are other side effects of vancomycin but rare (<1%). If anaphylaxis or intolerance to vancomycin is present, daptomycin constitutes a good alternative.

Conclusions

Prophylactic antibiotics should cover at least the most prevalent bacteria-producing postoperative infection. They should reach high enough concentrations (at least the minimum inhibitory concentration) in the serum and bone and maintain this over time. Doses should be repeated to keep appropriate concentrations. For standard antibiotic prophylaxis, drug administration should be done within the first hour before incision. Cefazolin (1–3 g depending on body weight every 2–5 h) is the most widely used antibiotic for PJI prophylaxis during the last decades in the USA and Europe. It is effective against gram-positive, aerobic gram-negative bacilli, and anaerobes. In spite of its great advantages, cefazolin is not effective against MRSA. For this reason, a high prevalence of MRSA should be kept in mind to determine if cefazolin is the best option in our case. However, clindamycin (90 mg every 3–6 h) and vancomycin (15/kg every 6–12 h) are adequate alternatives when cefazolin is contraindicated (i.e., allergy) or when risk factors for antibiotic-resistant organisms are present.

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Preoperative Screening and Eradication of Infection

6

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Abstract

The screening for and treatment of asymptomatic bacterial colonization of the skin, mucus membranes and urinary tract are established orthopaedic practice. Eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) from the nose and perineum prior to arthroplasty is common in the healthcare systems of most developed countries, and there is a substantial base of good-quality evidence to support this practice. Extending screening and eradication to encompass methicillin-sensitive staphylococcal strains (which cause PJI more commonly than MRSA) has been proposed, and studies exist which demonstrate significant reductions in PJI when sensitive strains are screened for. By contrast, the routine screening for and eradication of asymptomatic bacteriuria appear not to be effective on the basis of the current evidence, and there is increasing expert opinion against continued screening. Rationalization and standardization of preoperative screening policies have the potential to improve outcomes by reducing the incidence of PJI whilst minimizing the complications of the unnecessary use of antibiotics.

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6.1 Introduction

Since the advent of arthroplasty surgery in the 1960s, great efforts have been made to prevent infection by reducing the exposure of patients to causative bacteria before, during and after surgery. The importance of reducing the patient's exposure to pathogens in the operating theatre was recognized by Charnley, who noted that the introduction of various techniques to reduce the volume of circulating airborne bacteria reduced the rate of infection following hip

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arthroplasty from between 7 and 9% to less than 1% over a 10-year period between 1960 and 1970 [1]. Subsequently Lidwell, in his series of studies of the operating theatre, reported that the rate of infection approximately halved with the use of ultraclean airflow systems and halved again if body exhaust suits were used [2].

When reducing the burden of bacteria present in the operating theatre, one important factor is bacteria associated with the patient themselves. Whilst the surgical site is prepared with antiseptic to remove bacteria present on the skin, the patient may harbour bacterial commensals within the nose, axilla, groin or other sites, and bacteria may also be present within the urinary tract without causing symptoms. Preoperative screening for asymptomatic colonization may reduce the chance of infection by direct contamination or haematogenous spread and is widely practiced. This chapter aims to present the evidence for such screening procedures and to recommend best practice on the basis of this evidence.

6.2 Screening and Eradication of Staphylococci on Skin and Mucus Membranes

Methicillin-resistant *Staphylococcus aureus* (MRSA) became increasingly prevalent within hospitals in the 1990s and by the turn of the century accounted for a substantial proportion of prosthetic joint infections (PJIs) in orthopaedic surgery [3]. Kalmeijer et al. in 2000 reported on a cohort study of 272 patients undergoing elective orthopaedic surgery which aimed to determine preoperative risk factors for PJI [4]. Of the surgeon and patient factors explored, only one, the presence of nasal colonization with *Staphylococcus aureus*, was an independent predictor of subsequent PJI. At a similar time, von Eiff et al. reported a link between nasal colonization with *S. aureus* and subsequent bacteraemia [5]. In 2003, Wilcox et al. reported a significant decline in the number of PJIs after elective orthopaedic surgery following the introduction of a program of screening and eradication of nasal carriage of MRSA [6]. Subsequently, a policy of screening and eradication of MRSA colonization has been adopted by healthcare organizations around the world [7, 8].

The introduction of such programs, together with other mechanisms for the control and treatment of resistant organisms, has coincided with a marked decline in cases of MRSA. In the United Kingdom, between 2004 and 2006, over a quarter of cases of surgical site infection (all specialties) were attributed to MRSA, whilst in 2011/2012, this had fallen to 4% [9]. A study from France has reported a decline in the burden of MRSA by 35% following the introduction of a multimodal program including screening and eradication [10]. A nationwide initiative in Veterans Affairs hospitals in the United States reported that rates of MRSA infection in hospital fell from 1.64 per 1000 patient days in the intensive care setting and 0.47 per 1000 patient days in general inpatients to 0.62 and 0.26 cases per 1000 patient days, respectively, having stayed stable for 2 years prior to the introduction of the screening program [11].

6.2.1 Current Recommendations for Preoperative Screening

Different healthcare systems adopt different policies for screening of patients prior to TKA. In the United Kingdom, the Department of Health recommends that all patients being admitted for elective orthopaedic surgery should be screened for MRSA by way of nasal, axillary and perineal swabs, with those exhibiting colonization being treated with topical antiseptic ointment; they recommend against routine treatment without screening and do not give guidance on treatment of staff [7]. The situation in the United States is less straightforward; a 2015 current concepts review recommended that screening and eradication should be performed, as a cost-effective, low-risk intervention, although further evidence was needed [12]. In Europe, practice varies between countries, but most jurisdictions have policies for routine screening of high-risk patients or those admitted for high-risk procedures such as arthroplasty [8].

6.2.2 Screening and Eradication Methods

The introduction of MRSA screening programs has led to the establishment of standardized protocols for the detection and eradication of colonizing organisms. Whilst these vary between countries, the principles are broadly similar. No country has a national program by which every patient is screened; in most cases, patients deemed 'at risk' (including all orthopaedic patients) are screened with low-risk patients such as those presenting for day-case general surgery being excluded [8].

Various methods of screening are used. Typically, culture swabs are taken from the nose and perineum; other sites may be screened if of importance for the procedure being performed (such as the axilla in shoulder arthroplasty) or if of particularly high risk of colonization (such as indwelling lines and wounds) [13]. Both conventional culture and molecular techniques (polymerase chain reaction, PCR) are used for detection of organisms. PCR provides a rapid result within 2–4 h and so may be used for emergency admissions; however, it is more expensive than conventional culture and has little benefit over culture methods if performed prior to elective admission [14, 15]. For conventional culture, MRSA chromogenic agar is generally used—on this medium, MRSA grows as blue colonies which allows rapid visual identification without specialist equipment. However, this does not allow the identification of methicillin-sensitive staphylococcal strains (see Sect. 6.2.4) [16].

Patients identified as carriers of MRSA then go on to decolonization which is normally performed using mupirocin, which is a naturally occurring antibiotic. The use of mupirocin is advocated by the World Health Organization and the International Consensus Meeting on Prosthetic Joint Infection [17, 18]. Concerns exist as to resistance to the development of bacterial strains which are resistant to mupirocin [19]. Mupirocin resistance can be classified as low level (which occurs as a consequence of spontaneous chromosomal mutations) or high level (which is plasmid-mediated), and the prevalence of resistance by either mode may be as high as 95% [20]. The majority of these are the low-level type, which is of uncertain clinical significance, but the high prevalence of resistant strains is important to bear in mind, indicating the need for mupirocin to be part of antimicrobial stewardship arrangements like any other antibiotic. Other protocols, including the addition of chlorhexidine or the use of povidone iodine, have been developed and are advocated by some groups [21, 22].

6.2.3 Evidence for MRSA Screening and Eradication

The effectiveness of an MRSA screening and eradication program have been demonstrated by multiple studies, but the literature is not homogenous. A recent systematic review demonstrated significant falls in MRSA infection once screening programs were introduced [23]. A meta-analysis of ten studies across different specialties was more guarded demonstrating a relative risk of surgical site infections of 0.69 (95% CI 0.46–1.01) in screened patients [24]. Within orthopaedic surgery, the literature is strongly in favour of screening and decolonization, and this, together with the population-level data, suggests that this practice should continue [9–11, 15, 25].

The cost-effectiveness of screening and eradication is dependent on the prevalence of MRSA within the population concerned. In the UK National Health Service, procedures or practices are considered to be cost-effective if they result in a cost per quality-adjusted life year (QALY) of less than £30,000; whilst screening and eradication of high-risk patients is the most cost-effective strategy, even this only reaches the threshold for cost-effectiveness if the prevalence of MRSA was three times the current level [9]. This was supported by the study of de Wouters et al. who found that conventional criteria for designating a patient at high risk of MRSA were not effective in a population with a low level of colonization overall [26]. A Markov decision analysis performed by Slover et al. reported that in order to be cost

saving, screening had to result in a reduction in the rate of revision of arthroplasty cases by 35% to be cost-effective [27]. However, this assumed that the cost of treating an infected arthroplasty was the same as the cost of a primary arthroplasty, which would appear to be a substantial underestimate [28]. A study of the Veterans Affairs program found the cost per QALY to be between $28,000 and $57,000, which was considered to be cost-effective [29]. The huge financial and personal costs associated with PJI would appear to render screening and eradication to be a proportionate and pragmatic course of action.

6.2.4 Sensitive Strains of *Staphylococcus aureus*

Whilst most screening and eradication programs focus on MRSA, susceptible strains of *S. aureus* (methicillin-sensitive *Staphylococcus aureus*, MSSA) are much more common agents of PJI, and up to a third of people are colonized with such bacteria [16]. Dancer et al. compared the rates of PJI in 6 months before and after extending their preoperative screening program to include MSSA, reporting that rates of deep *S. aureus* infection fell from 15/213 (6.5%) to 1/307 (0.3%, with that one case being in a patient with a negative screen). The change in policy involved a small change in laboratory procedures and was inexpensive; the authors estimated that the change in infection rates led to an overall saving of £812,559 after taking into account the cost of screening and eradication [16].

These results were supported by the study of Sporer et al. who introduced a combined MRSA/MSSA screening program in 1999 (having not previously screened for either); their retrospective study of 9690 patients demonstrated a reduction in the overall rate of infection from 1.1 to 0.3% after the introduction of the combined screening program [30]. Prior to screening, two thirds of cases of PJI isolated *Staphylococcus aureus*; this fell to one third following the introduction of screening. Likewise, the study of Malcolm et al. reported a 50% fall in cases of PJI after a combined MRSA/MSSA screening and eradication program was introduced [31].

6.2.5 Routine Eradication Without Screening

Some authors have proposed the universal provision of eradication without screening [32]. This has the advantage of being effective against all bacteria, and it does not generate the costs associated with laboratory testing and transport of samples. In the acute setting, it has the advantage of avoiding a lead time for the screening result to become available; it was in this context that Huang et al. recommended routine decolonization for admissions to ITU, where universal decolonization resulted in a significant decrease in the rate of MRSA bacteraemia [32]. In planned orthopaedic surgery, the benefits are more limited, and to our knowledge, there is no study in the literature comparing universal decolonization to screening and decolonization in orthopaedics [9].

6.2.6 Screening of Staff

Amongst healthcare workers, the rate of nasal carriage of MRSA has been estimated at 4.5% [33]. It seems reasonable that if patients are to be screened prior to surgery, then there is a case to be made for the healthcare professionals treating them to be screened as well. This would be a significant undertaking given the number of staff involved and the potential for recolonization requiring regular rescreening. As a result, robust evidence is needed before such programs could be undertaken. Systematic reviews are consistent in reporting a lack of high-quality evidence with which to answer this question [34, 35]. A systematic review has estimated that nasal colonization rates amongst staff are no different in units with MRSA outbreaks than in those without [34]. Whilst case reports and small case series have been published to associate outbreaks of MRSA with a single colonized member of staff, there is little high-quality

evidence available to support routine screening and decolonization of staff members [36].

6.3 Preoperative Screening for Asymptomatic Bacteriuria

Up to 19% of patients undergoing arthroplasty and 20% of women over the age of 80 have bacteria present in their urine at any given time without symptoms of a urinary tract infection [37]. The routine preoperative screening of midstream urine (MSU) samples has been practiced since the 1970s and continues to be recommended by several national and international societies including the British Orthopaedic Association [38].

However, the utility of screening and treatment of asymptomatic bacteriuria is unclear, and there is little evidence to support this practice [37, 39]. It is 30 years since Ritter and Fechtman published their study of 277 patients in which they found no evidence that bacteriuria caused PJI [40], and several studies have since been published demonstrating no evidence of a link [41, 42]. As a result, the International Consensus Meeting on Periprosthetic Joint Infection has advised that routine urinalysis need not be undertaken prior to arthroplasty surgery [18].

Others have found that patients with asymptomatic bacteriuria are more likely to develop a PJI, but only because they are older, more frail and by definition more susceptible to bacterial infection; the increased risk disappears once these factors are adjusted for [43]. This explains the finding in the large study by Souza et al. that patients with asymptomatic bacteriuria were indeed at higher risk of PJI but that eradicating the bacteriuria made no difference to that risk [44]. Similar findings were reported in the randomized, controlled trial of Cordero-Ampuero et al. who found no difference in the rate of PJI amongst patients treated with antibiotics for asymptomatic bacteriuria compared to those in whom it was ignored [45] and in the study of Lamb et al. where preoperative urinalysis was discontinued in asymptomatic patients [46]. In this latter study, the rate of prosthetic joint infection and the rate of antibiotic use were recorded in 3523 patients who underwent elective arthroplasty with routine screening compared to 1891 patients who underwent their procedure without screening. In the first group, 11.5% had positive urine cultures, and 12.2% of these received antibiotics. No significant increase in PJI was recorded after the discontinuation of screening, and the use of antibiotics fell from 1.2 courses per 100 arthroplasties to zero [46].

Conclusions

Preoperative screening and eradication of colonizing organisms has a place in orthopaedic surgery. Whilst the cost-effectiveness of routine screening for nasal MRSA is borderline, there is strong evidence for its clinical effectiveness. Routine screening for MSSA is infrequently practiced, but the data that exists supports its increased use. Conversely, the established orthodoxy of screening for and treating asymptomatic bacteriuria is supported by little evidence, and it appears unlikely to be effective. The rationalization of preoperative screening has the potential to improve outcomes by decreasing the number of PJIs significantly whilst reducing the risks associated with unnecessary antibiotic treatment.

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Clinical Diagnosis of the Infected Total Knee Arthroplasty

7

Stephen M. Petis and Matthew P. Abdel

Abstract

Periprosthetic joint infection following total knee arthroplasty (TKA) is a devastating complication. The reported incidence of infection following a primary TKA is 1–3% and 8–10% following revision surgery. This diagnosis is associated with poor patient-reported outcomes, high complication rates, and increased mortality. Treatment of an infected TKA costs anywhere from $25,000 to $100,000 and requires a tremendous amount of healthcare resource allocation for successful eradication of the disease. By the year 2020, diagnosis and treatment of periprosthetic joint infection (PJI) is projected to cost the American healthcare system $1.6 billion.

It is critical to make the diagnosis of PJI in a timely manner, as delayed treatment has been associated with poor infection-free survival following reimplantation. The diagnosis is made when careful consideration is given to patient history, physical examination, imaging studies, serologic and synovial fluid analysis, microbiologic studies, histologic evaluation of periprosthetic tissue, implant sonication, and molecular testing. Although the diagnostic armamentarium continues to become more sophisticated, a concise history and physical examination can diagnose the majority of PJIs following TKA. This chapter will review the critical elements of the clinical diagnosis of an infected TKA.

7.1 Introduction

As the number of total knee arthroplasty (TKA) procedures performed annually continues to rise, the burden of periprosthetic joint infection (PJI) following TKA will increase concomitantly [1]. The incidence of PJI following TKA varies between 1–3% for primary TKA and 8–10% for revision cases [2, 3]. Imaging studies, serologic

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and synovial fluid analyses, microbiologic and histologic studies, implant sonication, and molecular studies can help make the diagnosis of PJI [4–6]. However, these modalities should never substitute for a concise patient history and detailed physical examination when diagnosing PJI following TKA.

7.2 Patient History

A concise patient history is mandatory in the diagnosis of PJI following TKA. Any patient presenting with a painful TKA should have PJI as a leading working diagnosis until proven otherwise. Although the differential diagnosis of a painful TKA is extensive (Table 7.1), failing to diagnose a PJI can have marked consequences in terms of implant survivorship and patient morbidity.

Unexplained pain following TKA should be evaluated for an infection until proven otherwise. It is important to gauge whether the TKA has always been painful, or if the pain started suddenly. Patients will often report pain at rest, as well as nighttime pain. The pain may also have insidious onset, as is often the case with more indolent, chronic PJIs. The pain may be global around the knee and is often worsened by range of motion and weight bearing on the involved extremity. Careful questioning should elicit whether there is concomitant hip or lumbar back pain referring to the knee.

Table 7.1 Differential diagnosis of a painful total knee arthroplasty

Prosthetic etiologies	• Periprosthetic infection • Aseptic loosening • Polyethylene wear • Periprosthetic fracture • Flexion instability • Anterior knee pain—unresurfaced patella, patellar maltracking
Extra-articular etiologies	• Soft tissue pain—bursitis, ligament strain, tendinitis • Complex regional pain syndrome • Periarticular neuropathy • Referred pain—ipsilateral hip, lumbar spine

7.2.1 Risk Factors

Risk factors for the development of PJI following TKA are classified as host factors and surgical factors (Table 7.2). Many of these predictive factors are supported by literature [3, 7–21]. Therefore, it is important to acquire information about past medical and surgical history and to identify which of these factors is potentially modifiable prior to further surgical intervention.

Determining the diagnosis for the index TKA (e.g. primary osteoarthritis, post-traumatic arthritis, inflammatory arthritis, post-septic arthritis) can help predict case complexity, which may contribute to an increased risk of infection [22]. Previous treatment for soft tissue erythema, wound drainage, or other concerns for PJI should be outlined. It is critical to document previous surgical attempts to eradicate infection, as well as the timing of the treatment postoperatively. A classification system exists that categorizes PJIs based on time to diagnosis (Table 7.3). Since management protocols differ based on when the PJI diagnosis is made, concise determination of the presumed onset of the infection is paramount [9].

Table 7.2 Host and surgical risk factors for periprosthetic joint infections

Host risk factors	• Obesity (body mass index >30 kg/m^2) [7] • Liver disease [8] • Renal disease [9] • Malnourishment [10] • Smoking [11] • Diabetes mellitus [12] • Inflammatory arthropathy [13] • Immuno-compromised state [14] • Corticosteroid use [15] • Excessive alcohol consumption [16] • Other systemic infections (bacteremia, urinary tract infection, etc.) [3]
Surgical risk factors	• Improper aseptic technique • Prolonged operating room time [17] • Multiple surgeries [18] • Revision TKA [19] • Previous wound complications [20] • Allogenic blood transfusion [21]

Table 7.3 Classification of periprosthetic joint infection proposed by Tsukayama et al. [23]

Categorization	Modifier	Criteria
Type 1	Positive intra-operative culture	2 positive cultures at time of revision for reasons other than infection
Type 2	Early	Infection diagnosis within 4 weeks of index operation
Type 3	Late	Infection diagnosis outside of 4 weeks of index operation
Type 4	Acute hematogenous	Infection diagnosis within 4 weeks of symptom onset with concomitant bacteremia

Table 7.4 Host staging system as proposed by Cierny III and DiPasquale [24]

Host type	Local factors	Systemic factors
A	• No healing deficiency	• Healthy
B	• Venous stasis • Chronic lymphedema • Peripheral vascular disease • Previous radiation • Extensive fibrosis • Retained foreign bodies	• Malnutrition • Immuno-compromised state • Chronic hypoxia • Malignancy • Diabetes mellitus • Chronic or current tobacco use • Major organ dysfunction
C	• Cannot withstand treatment	• Morbidity and mortality risk of proposed treatment exceeds the risks of living with current illness

7.2.2 Host Characterization

A complete history and documentation of the patient's comorbidities allows the clinician to classify the patient's host status. Different classification systems exist. The classification outlined by Cierny and DiPasquale [24] classifies patients as type A, B, or C hosts based on comorbid conditions and tissue healing potential (Table 7.4). The staging system by McPherson et al. [25] is more comprehensive, considering timing of PJI diagnosis, host comorbidities, and soft tissue condition (Table 7.5). The timing of PJI diagnosis is classified as early (type 1, diagnosis of PJI less than 4 weeks after index surgery), acute hematogenous (type 2, symptom onset within 4 weeks of bacteremia), and late (type 3, diagnosis of PJI greater than 4 weeks after index surgery). It is important to identify these local and systemic factors whenever a PJI is suspected following TKA. This information can help the surgeon educate their patients regarding the likelihood of treatment success, as well as identify factors that may be modifiable during the treatment course of the infection.

7.3 Physical Examination

The physical examination of the TKA concerning for PJI should begin with acquiring the patient's vital signs. Patients who present febrile or with hemodynamic instability require urgent surgical intervention in order to prevent sepsis and multi-organ dysfunction. Although this clinical scenario is rare, PJI has been associated with increased mortality [26]. Therefore, early recognition and treatment of a PJI with concomitant sepsis becomes one of the few life-saving interventions in orthopedic surgery [27].

The focused knee examination begins by identifying the presence of an antalgic gait. The knee should be inspected for erythema and asymmetric swelling suggestive of a knee effusion or synovitis (Fig. 7.1). In the absence of diagnostic testing, soft tissue erythema and worsening joint swelling are the most common physical exam findings used to diagnose PJI following TKA [28]. Multiple surgical scars around the knee can suggest multiple previous surgeries. Skin grafting and soft tissue flaps or transfers can suggest prior wound healing issues (Fig. 7.2). Finally,

Table 7.5 Host staging system as proposed by McPherson et al. [25]

Grade of host/tissue	Definition	Compromising factors
Systemic factors		
A B C	No compromising factors 1–2 compromising factors >3 compromising factors	• Age >80 years • Alcohol abuse • Nicotine use • Chronic indwelling catheters • Chronic malnutrition • Diabetes mellitus • Liver/pulmonary/renal insufficiency • Inflammatory disease • Malignancy • Immuno-compromised state
Local tissue factors		
1 2 3	No compromising factors 1–2 compromising factors >3 compromising factors	• Active infection • Multiple previous incisions • Soft tissue loss • Large subcutaneous abscess • Sinus tract • Previous crush injury • Previous radiation • Peripheral vascular disease

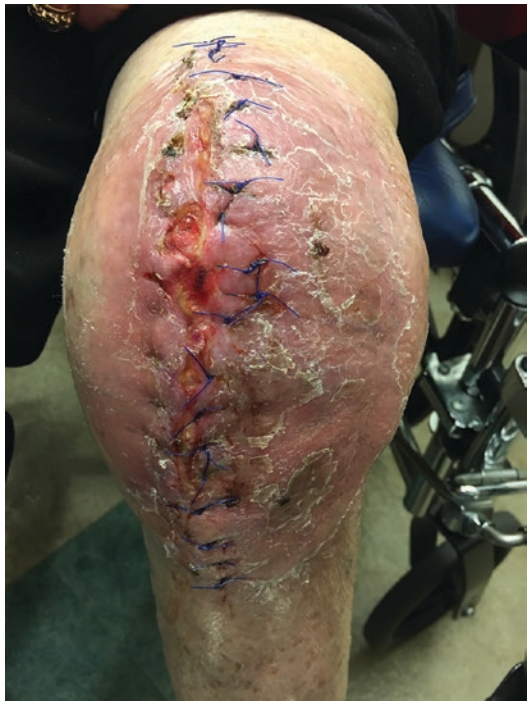

Fig. 7.1 Clinical photograph demonstrated knee swelling, erythema, and poor wound healing in the setting of an infected TKA

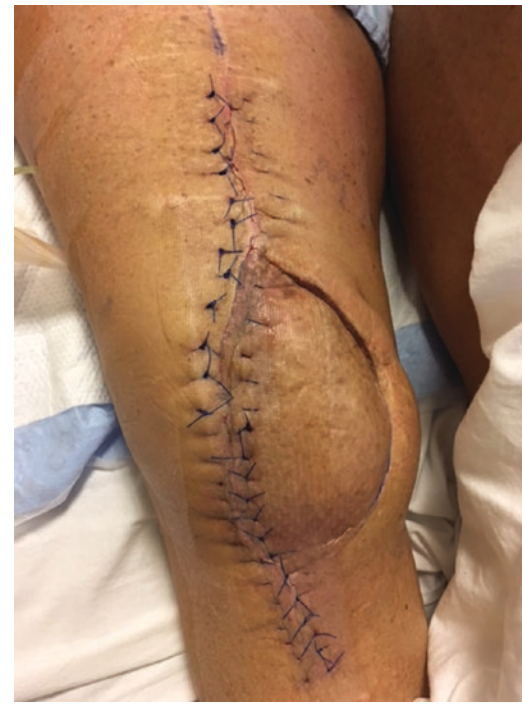

Fig. 7.2 Clinical photograph of a treated PJI following TKA. Note the medial gastrocnemius rotation flap that was used to address soft tissue loss following multiple surgical attempts to eradicate infection

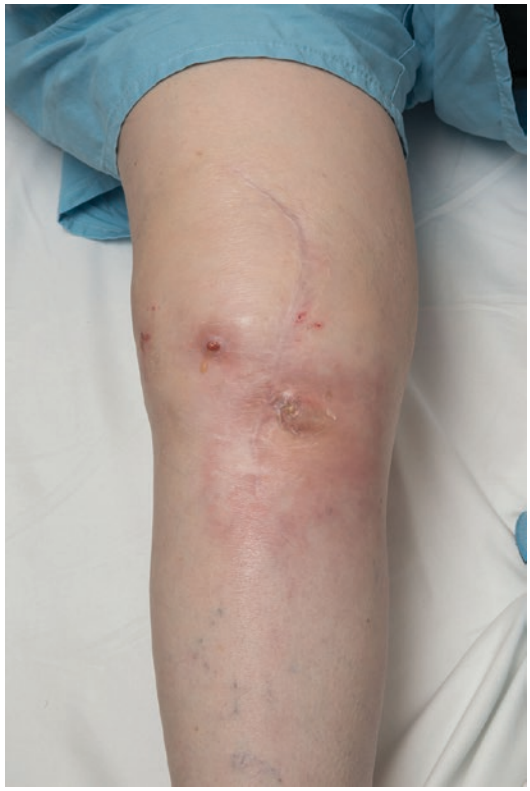

Fig. 7.3 Clinical photograph of an infected TKA. Note the egress of fluid from the sinus tract lateral to the skin incision

and most importantly, the clinician should identify any sinus tracts around the knee (Fig. 7.3). Sinus tracts are a major diagnostic criterion for PJI [29].

Next, palpation of the knee should determine focal areas of tenderness, looking for fluctuance that may represent an underlying abscess. Patellar ballottement can help identify an underlying knee effusion. Reduced knee range of motion is a hallmark feature of PJI following TKA. Many patients will complain of an abrupt loss of motion with increasing pain in the context of an infection. A detailed peripheral vascular examination should identify venous or arterial insufficiency, lymphedema, or any stigmata of vascular disease that will compromise soft tissue healing and chance of eradicating the infection. Finally, it is important to examine the ipsilateral hip and lumbar spine to ensure that the pain is not referred from either of these sites.

There is no substitute for concise history taking and a detailed physical examination when diagnosing an infected TKA. The history can identify risk factors for developing PJIs, the timing of the infection relative to the index surgery, and previous attempts to treat a PJI. This information can predict the likelihood of successful eradication of the disease. The physical examination helps to confirm the diagnosis and identify local tissue and systemic factors that can complicate the treatment of the PJI. Despite ongoing advances in serologic and molecular diagnostic testing for infection, the majority of cases of infected PJI should be made with clinical acumen.

Conclusions

It is critical to make the diagnosis of PJI in a timely manner, as delayed treatment has been associated with poor infection-free survival following reimplantation. The diagnosis is made when careful consideration is given to patient history, physical examination, imaging studies, serologic and synovial fluid analysis, microbiologic studies, histologic evaluation of periprosthetic tissue, implant sonication, and molecular testing. Although the diagnostic armamentarium continues to become more sophisticated, a concise history and physical examination can diagnose the majority of PJIs following TKA. This chapter will review the critical elements of the clinical diagnosis of an infected TKA.

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8 Diagnosis by Imaging of the Infected Total Knee Arthroplasty

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Abstract

Several complementary imaging modalities can be used to confirm or refute the diagnosis of prosthetic joint infection (PJI). These include plain films, fistulography, ultrasound, bone scintigraphy, computerized tomography scan (CT scan), magnetic resonance imaging (MRI), and positron electron tomography (PET). Plain radiographs and ultrasound are neither sensitive nor specific, and CT scan and MRI can be limited by hardware-induced artifacts. Bone scintigraphy is not affected by orthopedic hardware and is the current imaging modality of choice for suspected total knee arthroplasty (TKA) infection. Bone scintigraphy is sensitive for identifying the failed TKA but cannot be used to determine the cause of failure. SPECT/CT should be part of the routine diagnostic algorithm for patients with pain after TKA. The presence of lamellated hyperintense synovitis on MRI has a high sensitivity and specificity for infection. The current role of PET is still controversial, but it could be an appropriate alternative.

8.1 Introduction

Several imaging modalities can be employed to diagnose PJI [1]. This chapter will review the role of imaging tests in the assessment of patients with a potential total knee arthroplasty (TKA)-associated infection. The role of plain films, fistulography, ultrasound, bone scintigraphy, computerized tomography scan (CT scan), magnetic resonance imaging (MRI), and positron electron tomography (PET) will be analyzed in turn.

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8.2 Plain Films

Conventional radiographs (X-ray) are employed in the initial diagnosis of most suspected knee disorders.

Periodic X-ray review is used in the standard postoperative follow-up of TKR patients. The appearance of rapidly progressing radiolucent lines around the implant should raise the suspicion of infection. The resorption of subchondral bone and patchy osteoporosis can also be signs of PJI. PJI-associated osteolysis is commonly seen, although the type of osteolysis found is normally fairly unspecific (Fig. 8.1).

8.3 Fistulography

In cases where a suppurating fistula is present, fistulography could demonstrate continuity between the fistulous tract and the deep tissues and prostheses (Fig. 8.2a). It is very useful in the assessment of a periprosthetic abscess with fistulous tract (Fig. 8.2b–d).

8.4 Ultrasonography (US)

In revision TKR planning, a presurgical US can be useful to visualize the relationship between the prosthesis and the popliteal vascular bundle (Fig. 8.3a). US can also evaluate the bone-prosthesis interface in the marginal areas related to subluxations and/or sustentation defects (Fig. 8.3b).

US can be used to assess joint effusions. US is a diagnostic technique that permits the differentiation between effusion and synovial thickening (Fig. 8.3c). The normal synovium is a thin membrane. When it becomes inflamed, diffuse or nodular thickening of the membrane is seen, which may show increased vascular flow on Doppler US. US is very useful for the diagnosis of soft tissue swelling, to follow its progression or regression and to make the diagnosis of a periprosthetic abscess (Fig. 8.3d).

US Doppler can also be used to evaluate vascular and neurological complications (Fig. 8.3e, f).

8.5 Bone Scintigraphy

Bone scintigraphy is not affected by orthopedic hardware and is the current imaging modality of choice for suspected joint replacement infection (Fig. 8.4). Bone scintigraphy is sensitive for identifying the failed TKA but cannot be used to determine the cause of failure.

In 1990 Rand et al. [2] reported that indium 111 (111 In) leukocyte scanning had an accuracy of 84%, a sensitivity of 83%, and a specificity of 85%. In 1997 Nijhof et al. [3] found that the

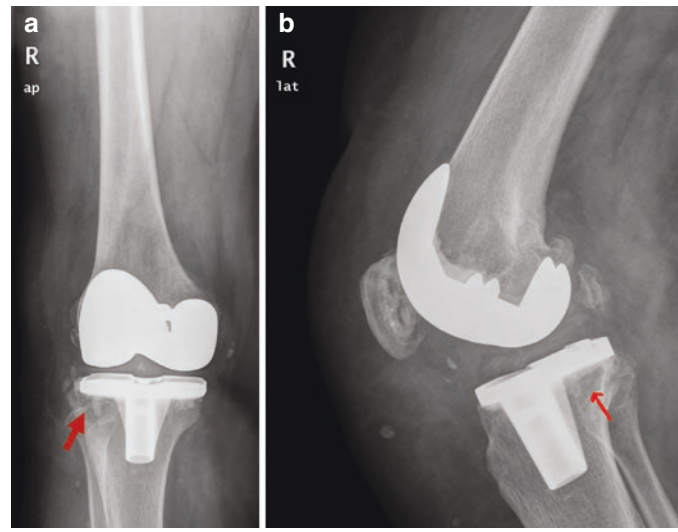

Fig. 8.1 Plain radiographs: (**a**) Anteroposterior and (**b**) lateral radiographs of a TKA demonstrating unspecific osteolysis and subchondral sclerosis (*arrows*). These findings made us suspect an infection

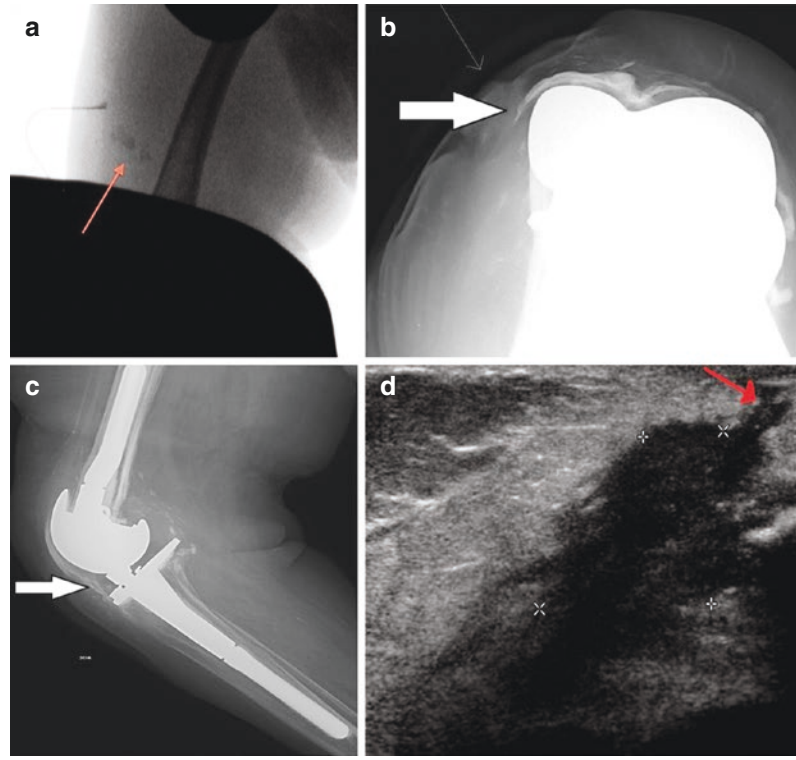

Fig. 8.2 Fistulography: (**a**) The introduction of low-osmolar nonionic radiographic contrast media in a suppurating fistula demonstrated continuity between the fistulous tract and the deep soft tissues (*arrow*). (**b**) Axial radiograph with contrast media showing a suppurating fistula in the lateral compartment of a TKA (*arrow*). (**c**) Lateral radiograph of a TKA with contrast media (*arrow*) showing the same findings. (**d**) US longitudinal view showing a periprosthetic abscess (*cross*) with a fistulous tract (*arrow*)

sensitivity of indium-111-labeled immunoglobulin G (In-111-IgG) scintigraphy for infection was 1.0; for TKA the specificity was 0.5. In-111-IgG was shown to be a highly sensitive and fairly specific tool for detecting late infections of TKAs.

In 2001 Van Acker et al. [4] compared fluorine-18 fluorodeoxyglucose PET (FDG-PET), technetium-99m hexamethylpropylene amine oxime (HMPAO)-labeled white blood cell (WBC) scintigraphy, and bone scintigraphy in the assessment of painful TKAs. It was concluded that WBC scintigraphy in combination with bone scintigraphy had a high specificity in the detection of infected TKAs. FDG-PET seemed to offer no additional benefit.

In 2000 Teller et al. [5] compared preoperative sequential imaging with joint aspiration and clinical assessment during revision TKA. Sequential technetium-99-hydroxymethyl diphosphonate and indium-111 leukocyte imaging were 64% sensitive and 78% specific. Positive scintigraphy increased the likelihood of finding infection intraoperatively from 14% to 30%, although negative scintigraphy decreased this likelihood to 7%. Based on this study, the routine use of sequential technetium-99-hydroxymethyl diphosphonate and indium-111 leukocyte imaging was not recommended for differentiating occult infection from mechanical failure in painful, loose TKA.

In 2000 Scher et al. [6] analyzed the predictive value of indium-111 leukocyte scans in the diagnosis of infected TKA. The results of this study suggested limited indications for the use of the indium-111 scan in the evaluation of painful TKA. A negative indium scan may be helpful in ruling out infection in cases in which the diagnosis is not otherwise evident. Indium scans were found to have a 77% sensitivity, 86% specificity, 54% and 95% positive and negative predictive values, and 84% accuracy for the prediction of infection.

In 2001 Joseph et al. [7] investigated the reliability of combined indium-111 leukocyte/technetium-99m sulfur colloid scans, with and without the addition of blood pooling and blood flow studies, in the diagnosis of infected TKA. Routine use of these radionuclide scans

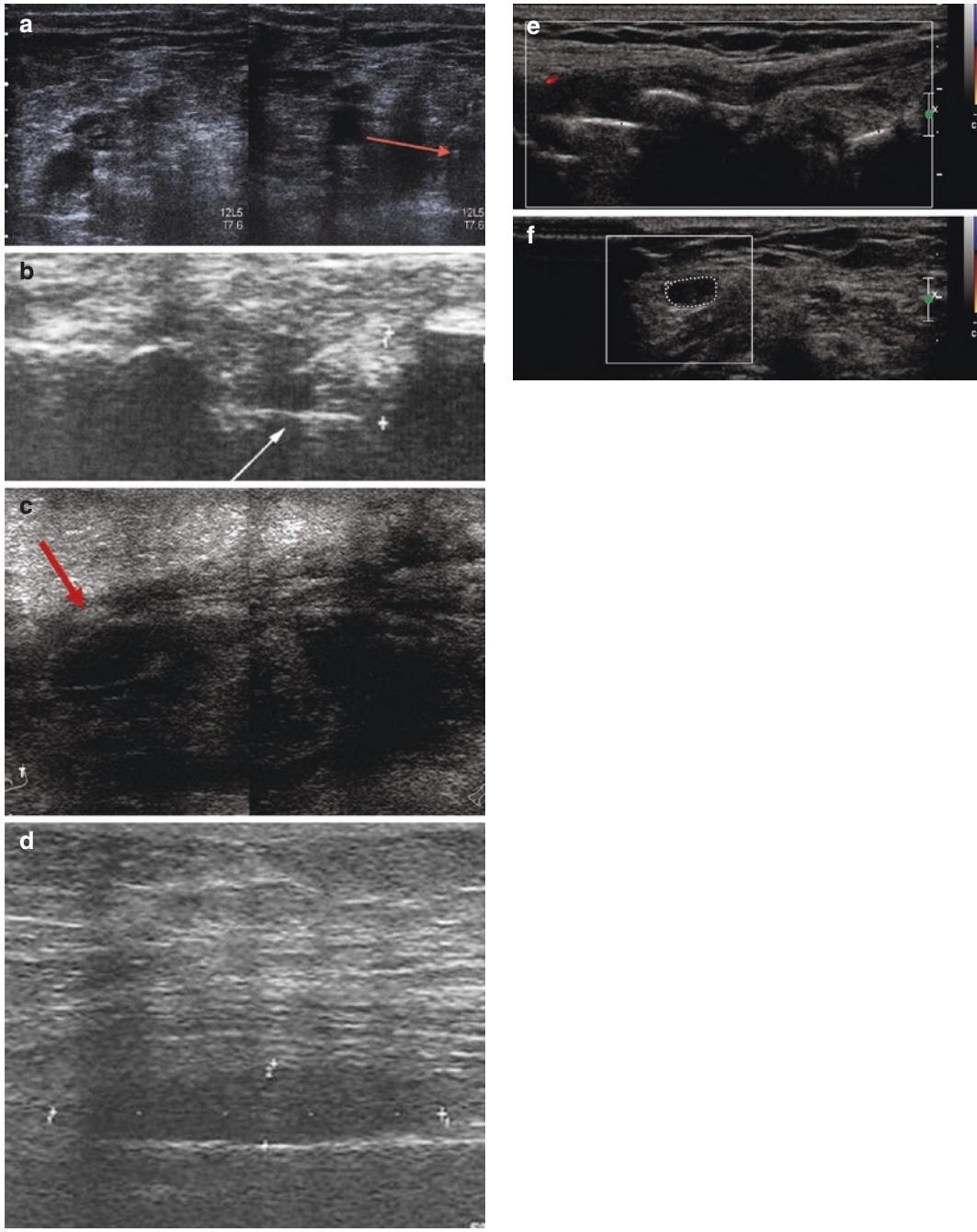

Fig. 8.3 Ultrasonography (US): (**a**) US Doppler can help us visualize the normal relationship between a TKA and the popliteal vascular bundle. (**b**) The US longitudinal view let us evaluate the bone-prosthesis interface (*arrow*). (**c**) Note effusion and synovial hypertrophy (*arrow*). (**d**) A little periprosthetic abscess was also found. (**e**) Longitudinal US Doppler view showing a neurological complication (the peroneal nerve is thickened and with hypoechogenicity; (**f**) US Doppler view in axial, showing the same neurological complication

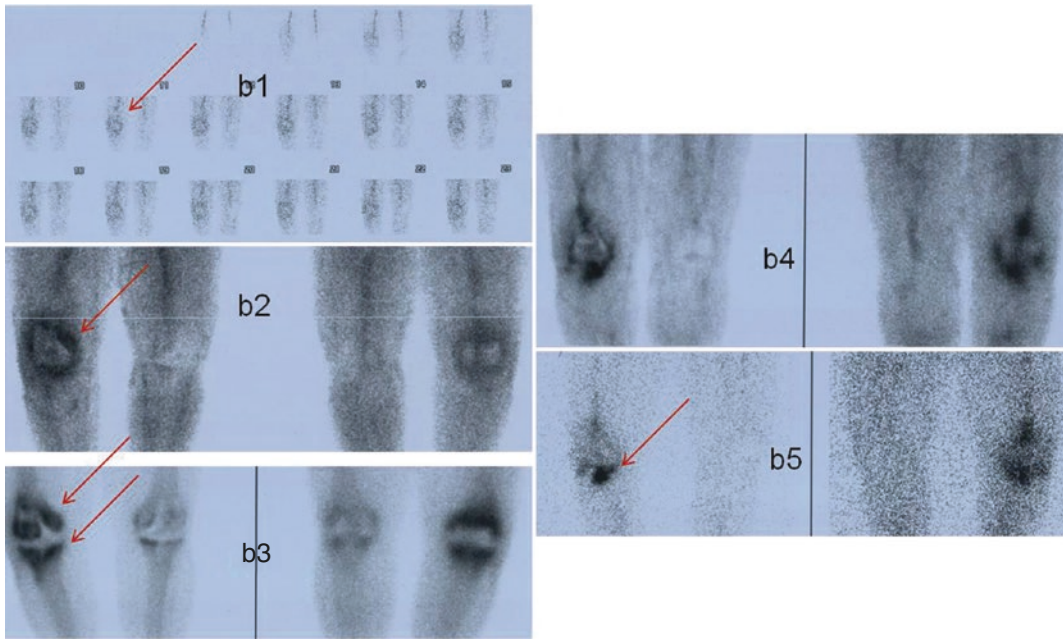

Fig. 8.4 Positive bone scintigraphy in three phases (*b1–b3*) and leukocyte scans (*b4–b5*) made us suspect an infection of the tibial component

was not supported by this study. Results for imaging alone included 100% specificity, 46% sensitivity, 100% positive predictive value, 84% negative predictive value, and 88% accuracy. Inclusion of blood pooling and flow phase data improved results to 66% sensitivity, 89% negative predictive value, and 90% accuracy, with reductions in specificity (98%) and positive predictive value (91%).

In 2002 Larikka et al. [8] evaluated the usefulness of 99mTc-labeled ciprofloxacin imaging in detecting the presence of infection in patients with symptomatic TKAs. 99mTc-ciprofloxacin imaging showed diagnostic sensitivity of 86% and a specificity of 78% for correctly diagnosing the presence of infection.

In 2004 von Rothenburg et al. [9] evaluated the diagnostic accuracy of 99mTc-labeled antigranulocyte antibody Fab' fragments in infected TKA. They found a sensitivity of 93%, a specificity of 65%, and a positive predictive accuracy of 63%. There was a negative predictive accuracy of 94%. The high negative predictive accuracy in the whole group suggested that the scan can be used to exclude infection.

In 2008 Rubello et al. [10] evaluated the clinical efficacy of a dual-time acquisition protocol consisting of early 4 hours and delayed 20–24-h imaging with antigranulocyte scintigraphy (LeukoScan) in the diagnosis of infection in painful TKA. The results of this study suggested that delayed LeukoScan imaging was important in identifying false-positive results detected on early imaging. Thus, a dual-time, 4-h early and 20–24-h delayed LeukoScan imaging approach should be recommended to increase the diagnostic accuracy of the scintigraphy, with the exception of patients with a negative early LeukoScan examination, in whom the acquisition of delayed imaging appears unnecessary. Concomitant antibiotic therapy did not influence the diagnostic value of LeukoScan.

In 2012 Gratz et al. [11] compared the diagnostic accuracy of imaging using an intact murine

antigranulocyte antibody 99mTc-besilesomab and a murine antibody Fab fragment 99mTc-sulesomab, in patients with suspected septically loosened TKA. At 4 and 24 h after intravenous injection, absolute uptake of 99mTc-besilesomab was significantly higher than 99mTc-sulesomab in infected knee joints. Infected-to-healthy knee activity ratios were similar at 4 and 24 h for 99mTc-besilesomab and 99mTc-sulesomab. Both 99mTc-besilesomab and 99mTc-sulesomab had similar diagnostic accuracy for the detection of septic arthroplasty. If repeated use of immunoscintigraphy is needed for follow-up, 99mTc-sulesomab should be preferred over 99mTc-besilesomab since it is known to be well tolerated and without side effects or incompatibility reactions.

In 2014 Ouyang et al. [12] investigated the diagnostic validity of three-phase bone scintigraphy (TPBS) for diagnosing prosthetic joint infection (PJI) in cases of suspected infected TKA. They performed a systematic review and meta-analysis to define pool sensitivity, specificity, diagnostic odds ratios (DORs), positive likelihood ratios (PLR), negative likelihood ratios (NLR), the area under the receiver-operating characteristic curve (AUC), and posttest probability. Heterogeneity and publication bias were assessed, and subgroup and meta-regression analyses were conducted. The pooled sensitivity and specificity for using TPBS to detect PJI were 0.83 and 0.73, respectively. The AUC, PLR, NLR, and DOR were 0.85, 3.1, 0.23, and 14, respectively. Low clinical scenario-negative posttest probabilities were 7%, and high clinical scenario-positive posttest probabilities were 90%. Subgroup analyses indicated that the sensitivity and specificity of TPBS for detecting infected arthroplasty of the hip (0.81 and 0.78, respectively) were significantly higher than those of the knee (0.75 and 0.55, respectively). There was no significant evidence of publication bias. The main conclusion was that TPBS had reasonable diagnostic value for detecting PJI and could be performed as a screening test or part of preoperative testing and analyzed in conjunction with other findings at the time of suspected PJI.

In 2014 Basu et al. [13] compared the value of FDG-PET with combined In-labeled leukocyte/Tc-sulfur colloid bone marrow (WBC/BM) imaging for diagnosing infection in hip and knee prostheses. The sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET in knee prostheses were 94.7%, 88.2%, 69.2%, and 98.4%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of WBC/BM imaging in knee prostheses were 33.3%, 88.5%, 25.0%, and 92.0%, respectively. The main conclusion was that the diagnostic performance of FDG-PET scan in detecting infection in painful knee prostheses is optimal for routine clinical application. Considering the complexity and costs of WBC/BM imaging and related safety issues associated with this preparation, FDG-PET seems to be an appropriate alternative for assessing these patients.

8.6 Computerized Tomography (CT Scan)

CT scan can play a role in the diagnosis of the infected TKA (Fig. 8.5). Bone single photon emission computed tomography (SPECT)/CT is considered as useful in unhappy patients with pain, stiffness, or swelling after total knee arthroplasty (TKA). In 2015 Hirschmann et al. [14] reported typical patterns of bone tracer uptake (BTU), distribution, and intensity values in patients after TKA. SPECT/CT changed the clinical diagnosis and final treatment in 85/100 (85%) knees. Intraoperative findings confirmed the preoperative SPECT/CT diagnosis in 32/33 knees (97%). TKA loosening as well as progression of patellofemoral osteoarthritis (OA) was correctly diagnosed in 100% of knees. Typical patterns of BTU for specific pathologies were identified. Loose femoral components significantly correlated with increased BTU at the lateral femoral regions. Loose tibial TKA components significantly correlated with increased BTU at all tibial regions and around the tibial peg. The diagnostic benefits of SPECT/CT

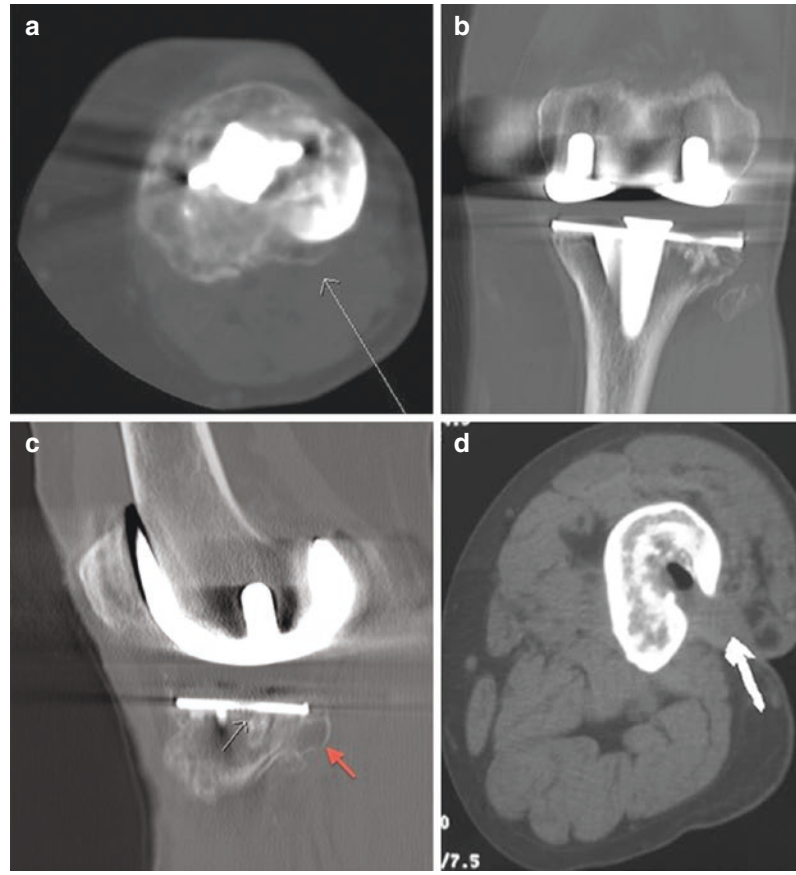

Fig. 8.5 Painful and loose TKA: (**a**) CT scan (axial view); (**b**) CT scan (coronal view); (**c**) CT scan (sagittal view). Note osteolysis in lateral compartment. The CT scan helped us evaluate the bone-prosthesis interface and detected marginal areas related to sustentation defects on the posterior tibial region (*arrows*). (**d**) Chronic occult infection. Axial CT scan demonstrated continuity between the femoral fistulous tract, the superficial tissues, and the skin (*arrow*)

in patients after TKA were proven. Typical pathology-related BTU patterns were identified.

8.7 Magnetic Resonance Imaging (MRI)

In MRI studies, the initial synovial reaction is associated with synovial hypertrophy. The metallic prostheses and debris produce additional magnetic susceptibility artifacts (Fig. 8.6).

Synovial hypertrophy is usually intermediate signal on T1- and T2-weighted images, enabling differentiation from fluid within the joint. However, active synovitis may show signal characteristics similar to that of fluid. Enhancement of the synovium with intravenous contrast media may help distinguish active synovitis from fibrotic synovium.

In 2013 Plodkowski et al. [15] investigated the sensitivity and specificity of lamellated hyperintense synovitis for infection following TKA and determined the inter- and intra-observer variability of this sign on MRI. Images from 28 patients with proven infected TKA and 28 patients with noninfected TKA were reviewed by two musculoskeletal radiologists for the presence of lamellated hyperintense synovitis. Cases were reviewed once more 2 weeks later by each reader. The sensitivity and specificity were calculated with the initial reports. κ values were used to assess inter- and intra-observer reliability. The sensitivity of lamellated hyperintense synovitis for infection was 0.86–0.92, and the specificity was 0.85–0.87. There was almost perfect inter- and intra-observer agreement in the classification of the synovial pattern.

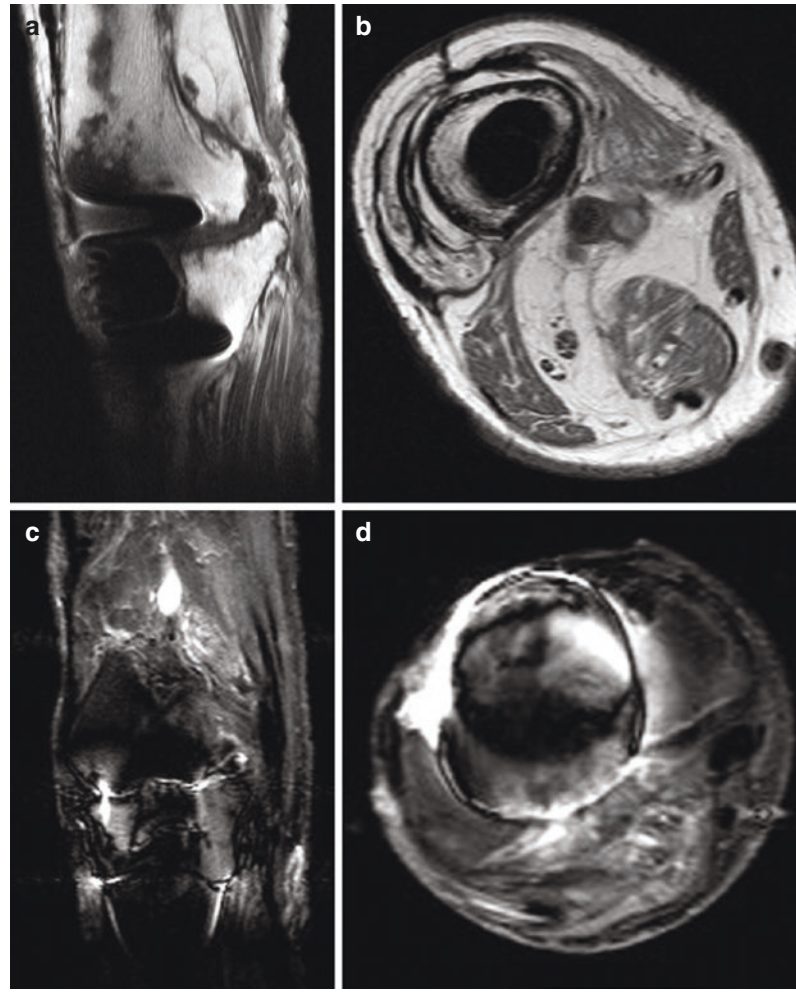

Fig. 8.6 MRI of the knee of a patient with rheumatoid arthritis and an infected TKA: (**a**) Sagittal T1-weighted image; (**b**) axial T1-weighted image; (**c**) coronal T2 fat sat image; (**d**) axial T2 fat sat image. Note the magnetic artifacts

8.8 Positron Electron Tomography (PET)

FDG-PET is an alternative method of assessing patients with a painful TKA. As mentioned above, Van Acker et al. [4] compared FDG-PET, 99mtc-HMPAO white blood cell SPET, and bone scintigraphy in the evaluation of painful TKAs. It was concluded that WBC scintigraphy in combination with bone scintigraphy had a high specificity in the detection of infected TKAs and that FDG-PET seemed to offer no additional benefit (Fig. 8.7).

As previously mentioned, Basu et al. [13] analyzed the role of FDG-PET for diagnosing infection in hip and knee prostheses and compared FDG-PET with combined (111)In-labeled leukocyte/99 mTc-sulfur colloid bone marrow imaging. It was concluded that the diagnostic performance of FDG-PET scan in detecting infection in painful knee prostheses was optimal for routine clinical application. Considering the complexity and costs of WBC/BM imaging and related safety issues associated with this preparation, FDG-PET seemed to be an appropriate alternative for assessing these patients.

Conclusions

Differentiating aseptic loosening, the most common cause of TKA failure, from infection, is important because their treatments are very different. However, differentiating between these two entities is often difficult.

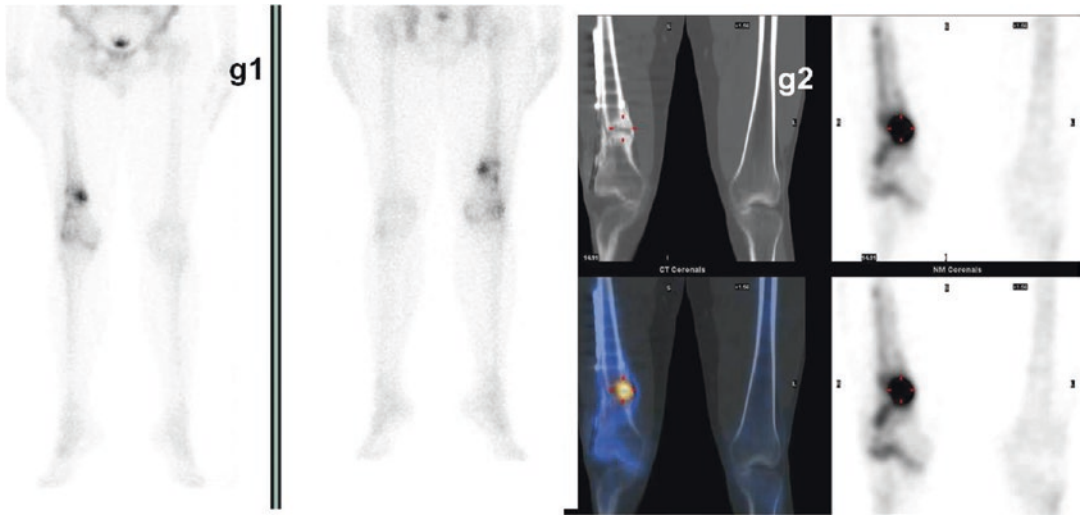

Fig. 8.7 SPECT/CT coronal view with enhancement made us suspect infection at the distal femoral region (femoral component)

Plain radiographs and ultrasonography (US) are neither sensitive nor specific, and CT scan and MRI can be limited by hardware-induced artifacts. Bone scintigraphy is not affected by orthopedic hardware and is the current imaging modality of choice for suspected PJI. Bone scintigraphy is sensitive for identifying the failed TKA but cannot be used to determine the cause of failure. SPECT/CT should be part of the routine diagnostic algorithm for patients with pain after TKA. The presence of lamellated hyperintense synovitis on MRI had a high sensitivity and specificity for infection. The current role of FDG-PET is still controversial but could be an appropriate alternative for assessing these patients.

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9 Serological Markers of Infection in the Infected Total Knee Arthroplasty

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Abstract

Diagnosis of periprosthetic joint infection (PJI) is challenging as no perfect test for it exists. Often a combination of serological, synovial, microbiological, histological, and radiological investigations is performed that are expensive, invasive, and imperfect. Serum biomarkers are dependable diagnostic tools given the low-risk nature and ease of collecting blood that aid in the diagnosis of PJI. However, it must be noted they are not without limitations. This chapter will focus on current serological markers and their efficacy in diagnosing PJI. Routine workup for PJI involves the measurements of serum white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The combination of ESR and CRP is very effective to "rule out" PJI. Additional biomarkers such as IL-6, IL-4, TNF-alpha, procalcitonin, and siCAM1 have also shown value in the diagnosis of PJI. Scientific investigation continues to work toward a "gold standard" serum test for the diagnosis of PJI.

9.1 Introduction

Periprosthetic joint infection (PJI) is the most devastating complication in joint arthroplasty surgery [1, 2]. Suspicion for PJI should be high when encountering a patient with a painful TJA given the marked morbidity and mortality associated with this condition [3]. Currently, there is no "gold standard" test for the diagnosis of PJI, and thus the current American Academy of Orthopaedic Surgeons (AAOS) guidelines recommend a combination of tests. Taking into account the benefits, costs, and risks of different diagnostic strategies for PJI, the use of serum markers has proven to be a highly effective strategy [3]. In the AAOS clinical practice guidelines, serum markers, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) remain the first-line tests to rule out PJI due to their high

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sensitivity. However, as we will discuss in this chapter, all serum markers have their limitations, and there is currently no perfect biomarker. Nevertheless, serum markers are still appealing because they are noninvasive and much more practical than synovial tests, particularly when synovial fluid cannot be obtained, a frequent occurrence in the aspiration of spacers. This chapter will focus on current and developing serological markers and their efficacy in diagnosing PJI.

9.1.1 Current Diagnostic Method for PJI

PJI often involves biofilm-related infections, in which bacteria adhere to the surfaces of the prosthesis, contributing to their persistent nature and difficulty in diagnosis. Traditional microbiological tests are optimized to detect free-floating bacteria, not bacteria embedded on biofilm [4]. Diagnosis of PJI involves a combination of serological, microbiological, histological, and radiological investigations that are expensive, invasive, and imperfect.

In recent years, efforts to standardize a definition for PJI have been made by MSIS and the International Consensus Meeting. These definitions are listed below in Tables 9.1 and 9.2, respectively [5, 6]. Ideal diagnostic tests are minimally invasive, sensitive, specific, and inexpensive. Serum biomarkers are dependable diagnostic tools given the low-risk nature and ease of collecting blood that aid in the diagnosis of PJI; however, it must be noted they are not without limitations [7].

9.2 Serum Biomarkers

In 1998, the National Institutes of Health defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention." Biomarkers represent the most objective reproducible medical signs [8]. Serum markers can be used as screening tools, in combination with other serum markers to support a diagnosis, to monitor response to therapy. The following section will examine the serum biomarkers involved with PJI diagnosis. Each serum marker will be discussed individually to explain their genesis, purpose, power, and limitations.

9.2.1 Traditional Serum Biomarkers

Routine workup for PJI involves the measurements of serum white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

9.2.1.1 WBC Count

Serum white blood cell (WBC) count is used as a proxy to measure a host response to infection [9]. Serum WBC count and neutrophil differential are frequently ordered in the workup of suspected PJI; however, several studies have shown limited efficacy (minimal role) in the diagnosis of PJI [10–12]. A meta-analysis that pooled studies related to serum WBC count found its sensitivity to be 45% and specificity to be 87% in diagnosis of PJI [13]. Furthermore, WBC count is influenced by antibiotic use and can be low in patients

Table 9.1 MSIS definition of PJI [5]

MSIS definition of PJI	
	PJI exists when:
1.	There is a sinus tract communicating with the prosthesis
2.	A pathogen is isolated by culture from two or more separate tissue or fluid samples obtained from the affected prosthetic joint
3.	When four of the following six 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 (f) Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification

Table 9.2 ICM definition of PJI [6]

ICM definition of PJI			
	PJI is present if one of the two major criteria or three of five minor criteria exists		
Major criteria	1. There is a sinus tract communicating with the prosthesis		
	2. Two positive periprosthetic cultures with phenotypically identical organisms		
Minor criteria	Having three of the following minor criteria:	Acute PJI (<90 days)	Chronic PJI (>90 days)
	1. Elevated ESR or CRP	ESR: no threshold	ESR: >30 mm/h
		CRP > 100 mg/L	CRP > 10 mg/L
	2. Elevated SF WBC count	10,000 cells/μL	3000 cells/μL
	Changes in leukocyte esterase strip	+ or ++	+ or ++
	3. Elevated SF PMN %	90%	80%
	4. Positive histologic analysis of the periprosthetic tissue	>5 neutrophil per high-power field in 5 high-power fields (×400)	>5 neutrophil per high-power field in 5 high-power fields (×400)
	5. A single positive culture		

who are immunosuppressed or high in patients with hematologic malignancies.

Recommendation: Due to its low sensitivity, WBC count is not recommended for the diagnosis of PJI.

9.2.1.2 Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate (ESR) is the time at which red blood cells (RBCs) in a test tube separate from blood serum and settle at the bottom of the tube. The sedimentation rate increases with inflammation. ESR is a nonspecific measurement of inflammation and tissue injury and has been found to be elevated from 3 to 12 months following surgery, but on average remains elevated for the acute postoperative period (6 weeks) [14, 15].

Current guidelines recommend the use of ESR in conjunction with CRP as a first-line screening test for the diagnosis of PJI. At the international consensus meeting (ICM) in 2013, no threshold was established for ESR during the acute postoperative period as ESR is not useful in the diagnosis of acute PJI [6]. However, ESR can be used for patients with chronic PJI. For chronic PJI (greater than 6 weeks), the ICM did deem an ESR of greater than 30 mm/h as an appropriate threshold to aid in the diagnosis of chronic PJI [4–6]. A meta-analysis showed a pooled sensitivity of 75% and specificity of 70% for ESR in diagnosis of PJI [13]. ESR is a marker for inflammation and thus can be elevated by other concomitant systemic diseases such as: renal disease, malignancy, chronic inflammatory conditions, advanced age, gender, and others [16]. In addition, ESR can be influenced by immunosuppression and premature antibiotic therapy as with many of the serum biomarkers discussed below. Lastly, the method by which ESR is measured, manual versus automated, also affects the results [17–19]. In recent years the manual method of ESR measurement (Westergren method) has been abandoned in favor of automated count, making reference to the threshold to the ESR value in the old literature less relevant.

9.2.1.3 C-Reactive Protein

C-reactive protein (CRP) is an acute-phase protein synthesized in the liver that functions to activate the complement system. CRP levels rise rapidly in the postoperative period, normalizing by 2–4 weeks [20]. Unlike ESR, CRP can be used for the diagnosis of both acute and chronic PJI. At the ICM in 2013, a threshold of greater than 100 mg/L (for the knee and hip) was recommended for CRP during the acute postoperative period for the diagnosis of acute PJI [6, 21]. For chronic PJI (greater than 6 weeks), the ICM did deem a CRP threshold of greater than

10 mg/L as appropriate to aid in the diagnosis of chronic PJI [4–6].

A meta-analysis showed a sensitivity of 88% and specificity of 74% for CRP in diagnosis of PJI. Although more specific than ESR, CRP can also be found to be elevated in any inflammatory condition such as inflammatory arthropathies, infections, and neoplasia [13]. Further, the level of serum CRP may be affected by premature antimicrobial therapy and immunosuppression [22].

It should be noted that the ICM has come to a consensus on the diagnostic threshold values of PJI for ESR and CRP in both the acute and chronic postoperative period; however, individual studies have reported differing threshold values, particularly in the setting of acute infections. One study reported thresholds for acute postoperative period of 54 mm/h for ESR and 23.5 mg/L for CRP. The same study reported on thresholds of 46.5 mm/h for ESR and 23.5 mg/L for the chronic postoperative period [23].

9.2.1.4 Erythrocyte Sedimentation Rate and C-Reactive Protein

ESR and CRP are inexpensive, widely available, and noninvasive diagnostic tests. In combination, ESR and CRP have proven to be a valuable screening test with a combined sensitivity of 98% for the diagnosis of PJI [24, 25].

In 2010, the AAOS issued several guidelines with respect to the diagnosis of PJI. The AAOS strongly recommended ESR and CRP testing for patients assessed for PJI. Following abnormal ESR and/or CRP results, the AAOS also strongly recommends that the knee be aspirated, with aspirated fluid to be sent for microbial culture and synovial fluid WBC count and differential. For abnormal ESR and/or CRP results in the hip, AAOS strongly recommends a selective approach toward aspiration based on the probability of PJI and planned reoperation status [26].

More recently, the AAOS has recommended the combination of ESR and CRP tests to "rule out" infection. When both ESR and CRP are negative, PJI is unlikely (negative likelihood ratio 0–0.06). When both ESR and CRP are positive, PJI must be considered (positive likelihood ratio 4.3–12.1). Through the analysis of several level I studies that examined the use of ESR, CRP, and the combined use of ESR and CRP, the AAOS has concluded that the use of either test alone is less reliable in "ruling out" or "ruling in" infection as compared to when both tests are combined. Given the "rule out" reliability of the combined use of ESR and CRP, aspiration should be considered if ESR and CRP values are abnormal or if clinical suspicion is very high [26].

While ESR and CRP are currently the "gold standard" in the diagnosis of PJI, they are not without limitations. Following revision surgery, both ESR and CRP cannot reliably predict the persistence or elimination of infection [27, 28]. Several studies have reported that ESR and CRP have limited efficacy in predicting eradication of infection and determining the optimal timing for reimplantations. Furthermore, because ESR and CRP are affected by systemic diseases, they have limited efficacy in diagnosing PJI in patients with inflammatory arthropathies, a common etiology for end-stage arthritis requiring arthroplasty. Additionally, both tests have a limited ability in the setting of premature antimicrobial administration and low sensitivity for detecting low-virulence organisms such as coagulase-negative *Staphylococcus*, *Propionibacterium acnes*, *Candida*, *Corynebacterium*, *Mycobacterium*, and *Actinomyces* [29].

Recommendation: The combination of ESR and CRP is an effective diagnostic tool to "rule out" PJI (Table 9.3).

9.2.2 Ancillary Serum Biomarkers

9.2.2.1 IL-6

Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced by stimulated monocytes and macrophages. IL-6 is a major regulator of the acute-phase response, stimulating the secretion of other acute-phase proteins including CRP. This means that IL-6 has a faster response to infection and provides an opportunity for early detection of PJI [30]. In normal individuals, serum IL-6 level is approximately 1 pg/mL but can increase to

Table 9.3 This table shows the effectiveness of combination of ESR and CRP to rule out PJI

Biomarker	Sensitivity, %	Specificity, %	Threshold	Recommendation
WBC count	45	87	N/A	Not recommended
ESR	75	70	Acute PJI: none Chronic PJI: >30 mm/h	Recommended as screening test
CRP	88	74	Acute PJI: > 100 mg/L Chronic PJI: >10 mg/L	Recommended as screening test
ESR and CRP	98			Recommended as screening test

30–430 pg/mL for up to 3 days following total joint arthroplasty [10, 31]. IL-6 values peak at two days after uncomplicated arthroplasty before rapidly returning to normal values [13].

Studies have shown IL-6 to have a PJI diagnostic odds ratio of 28.6 compared with 7.1 for CRP. The combination of IL-6 and CRP improved the diagnostic odds ratio to 168 [32]. One study reported IL-6 to have a sensitivity of 46.7% and specificity of 95% for the diagnosis of PJI [33]. A meta-analysis showed a pooled sensitivity of 97% and specificity of 91% [13].

Recommendation: IL-6 has shown promise in the early detection of PJI with its faster response to infection. IL-6 is currently not used widely or part of consensus guidelines, but the literature supports its efficacy in the diagnosis of PJI. More investigation is required to validate routine use of IL-6.

9.2.2.2 IL-4

Interleukin-4 (IL-4) is a pro-inflammatory cytokine. IL-4 plays an important role in the immune response, stimulating the activation of B-cell and T-cell proliferation, as well as the differentiation of B cells into plasma cells. Serum levels have been found to be significantly higher in infected TJA revisions as opposed to aseptic TJA revisions [34]. IL-4 has a sensitivity of 60% and specificity of 90% [13].

Recommendation: Although IL-4 has shown promise in the diagnosis of PJI, it is not currently used widely or part of consensus guidelines. More investigation is required to validate routine use of IL-4.

9.2.2.3 Tumor Necrosis Factor-Alpha

Tumor necrosis factor-alpha (TNF-alpha) is a pro-inflammatory cytokine released by monocytes in response to infection. It has been found to have a sensitivity of 43% and specificity of 94% in the diagnosis of PJI [31]. The primary limitation of TNF-alpha is that it must be analyzed within 1 h of sampling along with a very long processing time.

Recommendation: TNF-alpha has shown promise in confirming the diagnosis of PJI; however, its use is restricted by its low sensitivity and timing restraints for analysis. TNF-alpha is not currently widely used or part of consensus guidelines. More investigation is required to validate routine use of TNF-alpha.

9.2.2.4 sICAM-1

Soluble intercellular adhesion molecule 1 (siCAM-1) is found on endothelial cells and on leukocytes. sICAM-1 can be found at significantly high levels in PJI [35]. Drago et al. demonstrated that the absence of high sICAM-1 levels is extremely useful in confirming the eradication of PJI [36].

Recommendation: siCAM-1 has shown promise in showing eradication of infection, but is not currently used widely or part of consensus guidelines. More investigation is required to validate routine use of sICAM-1.

9.2.2.5 Procalcitonin

Procalcitonin (PCT) is secreted by the mononuclear phagocyte system. Blood concentrations of PCT have been shown to be elevated in systemic

Table 9.4 This table shows how PCT can be used as adjunct serum marker to distinguish between inflammatory and septic conditions

Biomarker	Sensitivity, %	Specificity, %	Threshold	Recommendation
IL-6	97	91	10 pg/ml	IL-6 has shown promise in the early detection of PJI with its faster response to infection. Further investigation is required
IL-4	60	90		Further investigation is required
TNF-α	43	94		Further investigation is required. Restricted by low sensitivity and time limitations of test
PCT	80–98	33–37	0.3 ng/ml	PCT can be used as adjunct serum marker to distinguish between inflammatory and septic conditions
sICAM-1				Shows promise in showing eradication of infection; however, further investigation is required to validate routine use of sICAM-1

inflammation, especially when caused by bacterial infection [37]. PCT has shown utility in other infections, but has been investigated only in a limited basis for the diagnosis of PJI [33]. Recently, PCT has received significant attention as a serum biomarker for sepsis [37–39]. Additionally, PCT is able to distinguish between inflammatory and septic conditions.

Studies to determine the sensitivity and specificity for PCT have yet to be formed. Proponents for PCT have advocated its use in diagnosing PJI as PCT does not rise following routine TJA. PCT has demonstrated a very high specificity of 98% for the diagnosis of PJI, however remains insensitive with a low sensitivity of 33% [40]. Other studies have found no role for PCT in the diagnosis of PJI [35]. A more recent study demonstrated contrasting findings for PCT that demonstrated a sensitivity of 80% and specificity of 37% [41].

Recommendation: PCT can be used as adjunct serum marker to distinguish between inflammatory and septic conditions (Table 9.4).

9.2.3 Developing Serum Biomarkers

9.2.3.1 Serum D-Dimer

D-Dimer is a fibrin degradation product present in the blood following the breakup of a blood clot via fibrinolysis. D-Dimer has been used to aid in the diagnosis of venous thrombotic events (VTE), but recently has shown promise as a biomarker for PJI. A recent pilot study examining the role of D-dimer has demonstrated a high sensitivity for the diagnosis of PJI and found D-dimer to reflect inflammation of the synovium within an infected joint. Preliminary results of this pilot study encourage the future investigation toward establishing D-dimer as screening tool for PJI [42, 43].

Recommendation: D-dimer has shown promise in the diagnosis of PJI; however, future investigation is required to determine D-dimer's role in both the diagnosis of PJI and when reimplantation of a two-stage exchange can be performed.

Conclusions

Serum markers remain valuable noninvasive diagnostic tools to screen for and diagnose PJI. However, there is no widely accepted serum biomarker that can be used in isolation with good sensitivity and specificity. Thus, serum biomarkers, e.g., ESR and CRP, are used in conjunction with more invasive synovial tests. Diagnosis of PJI relies on a variety of tests with more information allowing the surgeon to make a more informed decision on the likelihood of PJI. Clinical suspicion and understanding of the biomarkers available are vital for successful diagnosis and treatment of PJI. Scientific investigation continues to work toward a "gold standard" serum test for the diagnosis of PJI.

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10 The Role of Knee Aspiration in the Infected Total Knee Arthroplasty

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Abstract

Diagnosis of periprosthetic joint infection (PJI) in total knee arthroplasty (TKA) remains challenging. Although several algorithms have been reported, a combination of multiple tests and clinical suspicion continues to form the basis of diagnosis. Knee aspiration is a valuable tool, and it should be performed routinely if inflammatory biological markers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)] are elevated. Samples should be cultured for 14 days. Synovial fluid analysis [white blood cell and PMN (polymorphonuclear) cell percentage] has gained popularity. Leukocyte esterase, alpha-defensin, and methods of genetic diagnosis could play a decisive role in the future.

10.1 Introduction

Multiple algorithms have been established to investigate the painful total knee arthroplasty (TKA), and although the culture of the intraoperative samples could be considered the gold standard, controversy still exists, with up to 5–37% of false positives and 2–18% of false negatives [1].

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Clinical suspicion of septic failure of TKA should be based on clinical history and examination findings together with complementary tests: conventional radiography, CT (computed tomography), FDG-PET scan [fluorodeoxyglucose (FDG)-positron emission tomography (PET)], scintigraphy, and analysis with CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate).

Knee aspiration is one of the most valuable tools and adjuvants for the preoperative diagnosis of PJI. Some authors have discouraged its use, although MSIS (Musculoskeletal Infection Society) [2], IDSA (Infectious Diseases Society of America) [3], and AAOS (American Academy of Orthopedic Surgeons) [4] defend this technique with a strong recommendation if the clinical suspicion of the septic failure is high.

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MSIS [2] and IDSA [3] established several criteria (Tables 10.1 and 10.2).

There is conflicting evidence to support the use of aspiration for microbial culture before the second stage of revision knee arthroplasty. The test's low sensitivity suggests that it should not be performed routinely. However, given its high specificity, it may be useful in select cases [5].

The role of knee aspiration is obtaining samples for preoperative culture (sensitivity of 72% and specificity of 95%) and evaluation of the presence of purulence, elevated synovial fluid leukocyte count, and neutrophil percentage. We may conclude the definition of PJI is constantly evolving as new tools are incorporated in the diagnosis supported by the scientific evidence. The purpose of this chapter is to review the role of knee aspiration in the infected TKA.

Table 10.1 MSIS (Musculoskeletal Infection Society) criteria of periprosthetic joint infection (PJI) [2]

1. Sinus tract communicating with the prosthesis
2. Pathogen isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint
3. Four of following six criteria exist:
(a) Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration
(b) Elevated synovial leukocyte count
(c) Elevated synovial neutrophil percentage (PMN%)
(d) Presence of purulence in the affected joint
(e) Isolation of a microorganism in one culture of periprosthetic tissue or fluid
(f) Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification

Table 10.2 IDSA (Infectious Diseases Society of America) guidelines for the diagnosis of periprosthetic joint infection (PJI) [3]. The presence of PJI is possible even if the below criteria are not met

1. Sinus tract that communicates with the prosthesis
2. Acute inflammation as seen on histopathologic examination of the periprosthetic tissue at the time of surgical debridement or prosthesis removal
3. Purulence without another known etiology surrounding the prosthesis
4. Two or more intraoperative cultures or combination of preoperative aspiration and intraoperative cultures that yield the same organism

10.2 Approach Considerations, Technique, and Alternatives

Knee aspiration is a useful tool and safely performed under maximum aseptic conditions. However, in certain circumstances (morbid obesity, infection, and cellulitis near the joint line), arthrocentesis can be considered a real challenge [6]. Several different approaches have been described to obtain synovial fluid of the knee [7] (Figs. 10.1 and 10.2).

The lateral midpatellar approach is the most commonly used. The needle is directed at a 45° angle toward intra-articular space. A superolateral approach (2 cm above and 1 cm lateral to patellar surface) may be used, especially in large effusion cases. A 15 ml of joint fluid should be sufficient for the analysis. Aspiration in the supine position yields more fluid and is recommended for suspected infection [8].

Many reviews have shown ultrasound-guided aspiration as an alternative to traditional joint aspiration. Radiologists have described the success of several techniques of USG (ultrasound-guided) joint and soft tissue injection. Several clinical studies suggested that ultrasound could be used as an adjuvant tool for intra-articular injections in the knee joint via the suprapatellar bursa [9].

One of the drawbacks of this technique is dry aspiration which has an incidence of up to 30% of the cases in the hip. Other limitations include the inability to identify microorganisms that have formed biofilms or have been internalized by osteoblasts [10].

Fink et al. [11] demonstrated that preoperative synovial biopsy with samples obtained at arthroscopy increased sensitivity (100%) and specificity (98.2%) compared with knee aspiration (72.5% and 95.2%, respectively). Williams [12] considered that this practice is not recommended

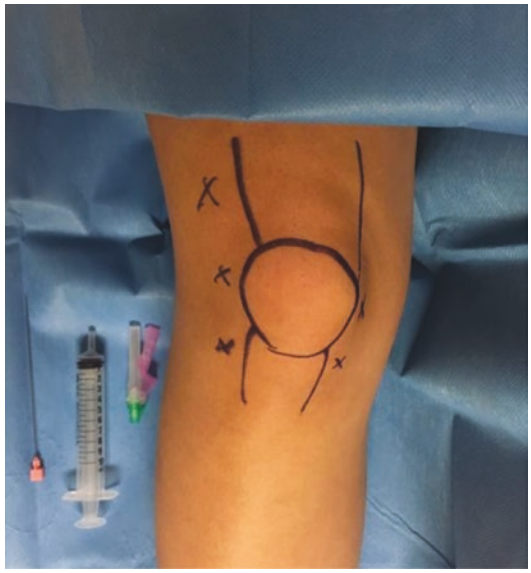

Fig. 10.1 Landmarks for knee aspiration

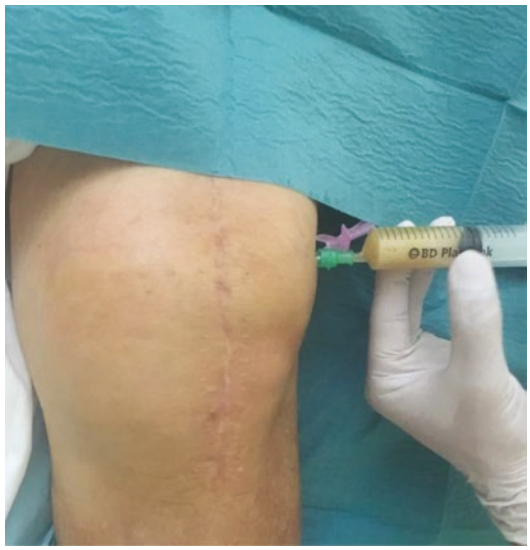

Fig. 10.2 Superolateral approach

because of its more invasive nature. Other techniques have been described such as the percutaneous interface biopsy with a sensitivity of 88.2% and specificity of 100% based on the hypothesis that a sample interface of the periprosthetic membrane could complement the results of the knee aspiration [10].

10.3 Analysis of Synovial Fluid and Culture

The role of arthrocentesis in the evaluation of the painful TKA has evolved over past decades. Aspiration is not only useful in diagnosing but also in analyzing the sensitivity profile and antibiogram of the microorganism causing the infection.

Most authors seem to agree with the fact that in the clinical suspicion of infection and high and inflammatory parameters (CRP and ESR), the practice of aspiration should be mandatory [13]. Gredianus et al. [14] found ESR with a cutoff point of 30 mm/h had a sensitivity of 93% and specificity of 84%. Similarly, CRP had a sensitivity of 91% and specificity of 86% (10 mg/dl). In a level 1 study of 207 consecutive TKA revisions, if both ESR and CRP were normal, the probability of periprosthetic joint infection was 3%. Sensitivity of combined ESR, CRP, and aspiration was 99.7% [15]. After considering the benefits, opportunities, costs, and risks of the different available alternatives, preclinical models support the AAOS recommendations regarding the use of serum markers (ESR/CRP) before arthrodesis as the best diagnostic strategy for periprosthetic joint infection (PJI) [16].

A recent literature review of Meermans et al. [17] including 29 studies of joint infection in hip and knee prostheses reported a mean sensitivity of cultures of 71%. Joint aspiration should be performed 2 weeks after any antibiotic treatment has been discontinued. The odds of a negative culture increase 4.7-fold if the patient has received antibiotics in the last 3 months [18].

White blood cell (WBC) count with analysis of polymorphonuclear (PMN) percentage has gained popularity for differentiating periprosthetic joint infection from aseptic total knee arthroplasty. Normal joint fluid contains <200 white blood cells and <25% segmented cells. In patients with inflammatory and degenerative diseases, this figure can rise to 1000 WBC/ml. WBC counts lower than 1100 WBC/μl containing less than 64% PMNs resulted in 99.6% negative predictive value for excluding periprosthetic joint infection [19].

Similarly, a synovial fluid WBC count greater than 9000 WBC/μl combined with elevation of either the ESR or CRP resulted in a 100% positive predictor value and 98% accuracy for identifying PJI [20].

Some studies have focused on analyzing the WBC count and PMN %. AAOS establishes a cutoff point of 1760/ml white blood cells and 73% PMN if performed after 6 weeks from surgery and 10,700 cells/ml and 89% PMN if earlier [21]. Ghanem argues that the finding in the joint aspiration of >1100 ml^{-1} cells and 64% PMN confirms the diagnosis [22]. Other reports raise this figure up to 2382 ml^{-1} [23]. Synovial fluid WBC count and PMN percentage are both elevated during the early postoperative period. The two markers behave differently, with synovial fluid WBC counts demonstrating an earlier return to baseline levels. WBC and PMN percentage may not be reliable for a patient with inflammatory arthropathy [24].

Gram staining has a low sensitivity of 10–67% [25]. In most cases, 5 days of culture should be enough, although it recommended that cultures remain incubated for 14 days to allow the identification of other less virulent microorganisms (propionibacterium species, aerobic gram-positive bacilli, and *Peptostreptococcus*); otherwise, up to 30% of infections would go undetected [18].

Additional mycobacterial and fungal cultures can be obtained for at-risk patients or when clinical suspicion dictates such action. It is unclear if anaerobic, fungal, or acid-fast bacilli cultures should be routinely sent because of the additional cost [26].

Blood culture bottles (BCBs) have proven to be more effective than the conventional swabs in transporting samples to the lab. BCB is a low-cost, easy-access method that significantly improves the ability to positively identify bacterial cultures in PJI [27]. Hughes et al. [28] have shown the use of BCB is superior to conventional methods in the setting of native joint infection. Furthermore, Minassian et al. [29] showed that BCBs had comparable sensitivity, specificity, and shorter time to positivity than cooked meat enrichment broth methods.

Synovial fluid should be stored in tubes containing ethylenediaminetetraacetic acid (EDTA) and kept at 4 °C before analysis [30]. Synovial fluid white cell count decreases by 47% after 48 h when stored in heparin, compared with 5.1% when stored in EDTA. EDTA is a much more suitable preservative than heparin [31].

10.4 Other Biological Markers and Future Development

10.4.1 Leukocyte Esterase

In recent years, the use of leukocyte esterase (LE) has become popular (Fig. 10.3).

Leukocyte esterase is an enzyme present in activated PMNs, often found in infected body fluids. Leukocyte esterase reagent (LER) strips are commonly used for the diagnosis of urinary tract infections as well as peritonitis and chorioamnionitis. The strips apply different biochemical reactions to yield a purple color. In theory, the intensity of purple should directly correlate with the PMN count. An LE of ++ has a sensitivity of 81%, specificity of 100%, positive predictive value of 100%, negative predictive value of 93%, and strong correlation with ESR, CRP, synovial WBC count, and synovial PMN% [32].

A multicenter study showed that the LER strips are a quick, inexpensive, and sensitive tool for the diagnosis of PJI [33]. McNabb [34] found that if the LE strip test is negative, the patient is 99.3% likely to not have a periprosthetic infection. Recently, the MSIS has included LE test as a minor criteria for joint infection.

Fig. 10.3 Leukocyte esterase positive test

10.4.2 ELISA of Synovial CRP

An enzyme-linked immunosorbent assay (ELISA) of synovial CRP test improves the diagnostic accuracy relative to the traditional serum CRP assay (sensitivity of 85% and specificity of 97%) [35].

10.4.3 Alpha-Defensin

Alpha-defensin is a protein naturally released by neutrophils in response to synovial fluid pathogens with a specificity test of 96% and above [36]. If the result is positive, the likelihood of PJI is very high, but other reasons for elevated alpha-defensin level should be excluded. Metallosis may offer a false-positive test. Alpha-defensin levels are not influenced by systemic inflammation and remain unaffected by antimicrobial therapy [37]. Bingham et al. [38] have reported even better results for the alpha-defensin assay (sensitivity of 100% and specificity of 95%). Alpha-defensin assay has a role to play in the complex scenario of PJI diagnosis and when using the established threshold value of 5.2 mg/L. The test has shown a sensitivity and specificity of 100% [38].

10.4.4 Sonication

The ultrasonic treatment of the removed prosthetic components and the subsequent culture of the resulting liquid (especially in cases with concomitant antibiotic treatment) show promising results, but the technique is not routine in most laboratories at present [39].

10.4.5 PCR (Polymerase Chain Reaction)

Molecular diagnostic methods (bacterial genetic information) have been promulgated as the future gold standard for implant-related infections. PCR is specific only for a single microorganism or broad range (16S ribosomal DNA) for unknown organisms although it has a high incidence of false-positive results, and it is not a reliable test for polymicrobial infection [40].

Conclusions

Knee aspiration is one of the most relevant tools and adjuvants for the preoperative diagnosis of periprosthetic joint infection (PJI). There is contradictory evidence to support the use of aspiration for microbial culture before the second stage of revision knee arthroplasty. The test's low sensitivity suggests that it should not be performed routinely. However, given its high specificity, it may be helpful in selected cases. Knee aspiration is crucial in obtaining samples for preoperative culture (sensitivity of 72% and specificity of 95%) and assessment of the presence of purulence, raised synovial leukocyte count, and neutrophil percentage. Leukocyte esterase, alpha-defensin, and methods of genetic diagnosis could play an important role in the future.

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11 Polymerase Chain Reaction (PCR) in the Infected Total Knee Arthroplasty

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Abstract

The diagnosis of periprosthetic joint infection (PJI) continues to be a widely debated and researched topic worldwide. Several diagnostic tools are currently available for PJI, and new ones continue to be added to the available options to the clinician. The polymerase chain reaction (PCR) is a molecular biology technique that is used as a diagnostic modality in periprosthetic joint infection. In this chapter, we discuss indications, advantages and limitations of this molecular diagnostic technology.

11.1 Introduction: The Problem and Burden of Periprosthetic Joint Infection

The clinical challenges encompassing PJI are complex [1, 2]: firstly, the diagnosis itself may be uncertain [3]; secondly, several confounding variables such as the presence of metal or polyethylene debris may mask the presentation; finally, when managing infection, a single, staged or partial exchange with chronic suppression may have to be used depending on the type of host, pathogen and surgeon experience [4].

PJI has a significant effect on the long-term quality of life of the affected population, with treatment associated with prolonged hospital stay and multiple surgical procedures and side effects of prolonged antibiotic treatment [5].

Several patient factors have been associated with higher risk of infection including comorbidities such as high body mass index (BMI), diabetes mellitus, renal failure, rheumatoid arthritis, neoplasms and haemophilia [6]. Patients, on regular immunosuppressive medications such as cortisone and anti-rheumatoid medications, are also more susceptible to infection [6].

It is also not uncommon that the majority of patients, who require revision surgery, are elderly and frail with high medical comorbidities, and they may present acutely unwell due to the infected joint.

In addition to these clinical concerns about the patient, there are also technical aspects connected to the complexity of the surgery when dealing with PJI such as bone loss, deformity and instability. All these factors add to the burden of

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heightened perioperative workup, operating time, blood transfusions, surgical instrumentations and implants and intra- and perioperative complications [7, 8].

The economic impact of PJI to the healthcare systems is significant, and the additional costs of PJI to hospitals have been estimated to be huge worldwide.

There are about 100,000 orthopaedic prosthesis infections annually reported in the United States alone, with each costing an additional average of $15,000–30,000 per patient [9].

In an evaluation of the economic burden of PJI in knee arthroplasty, Kurtz et al. [10] reviewed data from the United States National Inpatient Survey. He noted that the mean length of inpatient stay for total knee arthroplasty (TKA) increased from 3.9 days in the average patient to 7.6 days for those diagnosed with PJI, with an increase in cost from $35,769 in the former group to $56,275 in the latter group.

Another key issue that needs to be highlighted in this scenario is the discrepancy between the costs and reimbursement for treatment in both primary and revision TKA [11].

In the United Kingdom, the cost of some knee revision surgery procedures for PJI has now reached £75,000 per patient, while the current reimbursement from the National Health Service (NHS) tariff lies between 38,795 and 12,490 per case [12].

Kallala et al. [12] analysed the differences in costs and expenses between revision TKA for infection and revision surgery for other causes like pain, instability, aseptic loosening and fracture. Reviewing 168 consecutive cases at a tertiary referral centre, they reported that revision surgery for infection was associated with a mean length of stay more than twice that of aseptic cases (21.5 vs 9.5 days, $p < 0.0001$), and the mean cost of a revision for infection was more than three times that of an aseptic revision (£30,011 (SD 4514) vs £9655 (SD 599.7), $p < 0.0001$). The burden of PJI and its cost implications is currently huge and is expected to rise over the years. This has to be taken into consideration by clinicians when considering the clinically available strategies for diagnosis of PJI.

11.2 Results of Other Strategies for Diagnosis of PJI and Their Shortcomings

The diagnosis of PJI is challenging due to the difficulty of isolating the precise causative microorganism(s) [1]. In low-grade infections, the presenting history and symptoms can be nonspecific, and often a severe inflammatory response is lacking [1]. Clinicians may encounter this as subclinical infection with symptoms of pain and discomfort.

It is hence not uncommon to encounter cases of "aseptic loosening" to those who were actually infected and were not investigated rigorously or had escaped detection despite the use of the available methods for diagnosis of PJI [13].

Microorganisms are known to exist in biofilms on the surface of implants, and this inherently imparts resistance to diagnosis as well as treatment with the conventional antibiotic delivery methods [1]. This biofilm theory is considered to play a significant role in the pathogenies of PJI and makes it more difficult to control already established infections [14].

The orthopaedic prosthesis provides a platform for the initial adherence and growth of the bacteria. The biofilm that is found on the surface of the prosthesis consists of a complex network of sessile bacteria organized in microcolonies, within a highly hydrated polymeric matrix in which microorganisms can survive and be protected by the host immune response [14].

The bacteria receive nutritional support from the surrounding matrix, and moreover, it can survive in a quiescent state communicating with each other and regulating expression and production of virulence factors. Using this phenomenon of quorum sensing, the bacteria can avoid detection and in doing so result in culture-negative and antibiotic-resistant PJI [14].

Laboratory markers like white cell count and differential, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can help with making a diagnosis of PJI. However, there is no reliable gold standard with a reproducible sensitivity and specificity for establishing diagnosis of PJI, short of identifying the infective bacteria by culture [15].

CRP and ESR as a combination test have a high sensitivity (96%) but a low specificity (56%) [16]. They can be elevated for reasons other than infection, such as autoimmune disorders, recent surgery, concurrent infections debris from metal articulations or tumours. However, due to their low cost, they remain clinically invaluable as screening tests for PJI [14, 16].

Recent studies [17, 18] have shown that the synovial CRP is increased in PJI patients, and it is a better and more accurate marker than serum CRP with reported sensitivity of 84% and specificity of 97.1%.

Cultures from intraoperative tissue or fluid samples remain the gold standard for diagnosis.

However, it is possible to have falsely negative results especially when few samples are analysed [19] or samples are not representative. The sensitivity in periprosthetic tissue cultures ranges from 61% to 73% for PJI diagnosis [20] and from 43% to 75% in synovial fluid culture [20, 21].

Prior to antibiotic exposure and the inability to isolate microorganisms from biofilms, both influence positive predictive value of tissue cultures when diagnosing PJI [22]. Not surprisingly, improving culture methods is becoming the new area of interest for more accurate diagnosis of PJI.

Sonication of the removed prosthesis or components is one technique that improves area of the bacterial mass attached to the implants, and so it increases the specificity and sensitivity of the conventional cultures methods [20].

Recent studies have shown that samples obtained through sonication and then incubated in enriched blood culture can lead to growing of the majority of microorganisms in less than 3 days [23, 24].

In further attempts to improve accuracy of identifying pathogens, molecular diagnostic techniques have been introduced into the diagnostic armamentarium of PJI, trying to improve the accuracy of pathogens. Although not available in all hospital laboratories, molecular diagnostic techniques may have a niche role to play in diagnosis of PJI.

In the following discussion, we have focused on presenting the current evidence around the use of polymerase chain reaction (PCR) in PJI diagnosis.

11.3 The Basic Science of PCR Technology and How That Can Be Used to Help in the Infection Scenario

PCR is a molecular biology technique that in simple terms is a method of amplifying a single copy of a piece of DNA and creating millions of copies of it for easily identification [25] (Fig. 11.1). Target gene sequences are processed and amplified by DNA polymerase using known pair of primers complementary to the sequence of interest.

Both bacterial DNA and RNA are amenable targets for amplification and detection.

This technique has routine clinical applications in genetic testing analysis and also in detecting infectious agents such as human immunodeficiency virus and also *Mycobacterium tuberculosis* [26].

The PCR assay can be divided in two main groups: specific PCR, that are real-time PCR which target a single bacterial species or a group of closely related species, and broad-range PCR, that could detect the DNA from any bacterium. These broad-range PCR are based on the gene coding for a small subunit of the bacterial ribosome (16S rDNA) (Fig. 11.2).

The 16S rRNA gene is the most common amplification target; it has highly conserved and hypervariable regions: the conserved regions serve as binding sites for universal bacteria primers, while the hypervariable regions can be probed by specific primers to identify specific microorganisms.

PCR-based techniques are typically real-time PCR assays, meaning that the process happens in real time while the amplified DNA is detected. This is accomplished by the use of non-specific fluorescent dyes that intercalate with any double-stranded DNA and/or sequence-specific DNA probes that consist of oligonucleotides that are labelled with a fluorescent reporter detected as a function of hybridization of the probe with its complementary sequence [27, 28].

The amplified bacterial DNA is usually analysed in an agarose gel electrophoresis and Southern hybridization, producing an initial result within

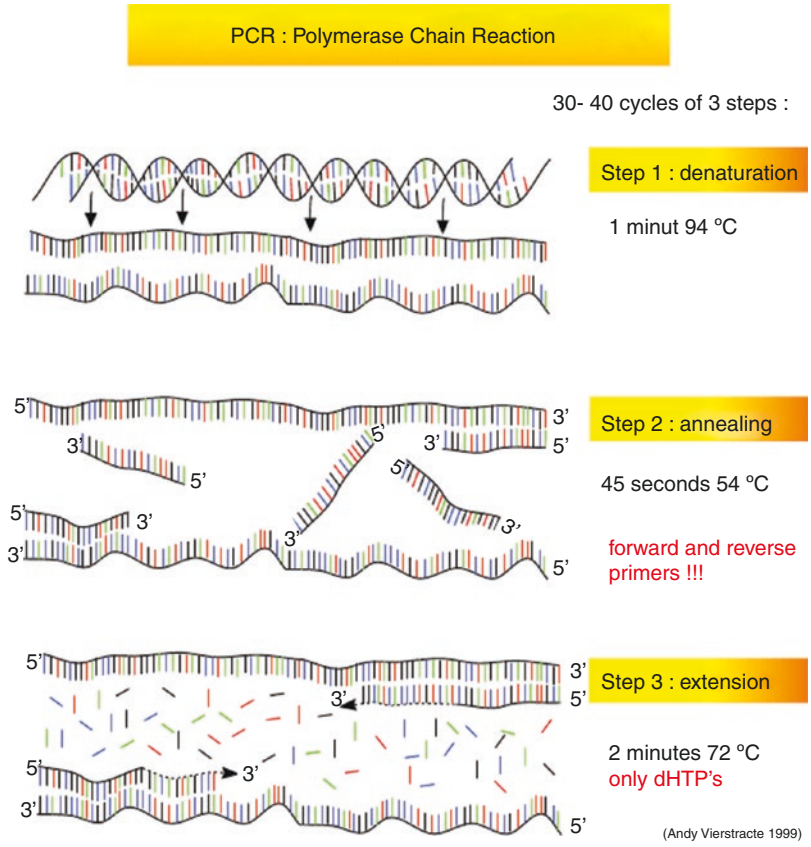

Fig. 11.1 Basics of polymerase chain reaction (PCR) cycling (original image from "Kavya SR. PCR Technique with its Application. Research & Reviews: Journal of Microbiology and Biotechnology. 2015; 4–1")

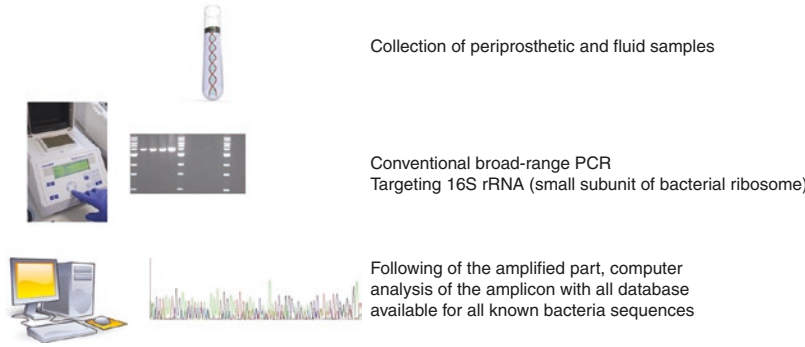

Fig. 11.2 Schematic representation of the conventional broad-range polymerase chain reaction (PCR) technology

4–6 h. This time scale is significantly less than the 2–3 days required for routine cultures [29].

In the investigation of PJI, broad-range PCR has been extensively used compared to specific PCR.

PCR can also be used to identify specific resistance genes such as *mecA* in particular in methicillin-resistant staphylococci in PJI [30]. It can also be used in the quantitative variant (qPCR), which shows the total quantity of antibiotic-resistant bacteria in the patient samples and also the bacterial load of each species in multi-microbial infections [31].

11.4 The Tips and Tricks of How to Collect Samples, How to Store and How to Interpret

It is recommended that the PCR assays be used on at least three samples collected from fluids by needle aspiration or periprosthetic tissue following a surgical biopsy [32, 33].

Ideally, samples should be sent immediately to the laboratory for analyzation. In case direct transport of fresh specimens to laboratory is not possible, PCR should be performed on paraffin-embedded biopsy samples. However, clinicians should be aware that PCR techniques on paraffin-embedded biopsy samples have shown comparatively less specificity and sensitivity [34].

Before the molecular amplification as per protocol, the specimens are left overnight in a lysis buffer and proteinase K [35].

One of the main disadvantages of the PCR technique is the possibility of false-positive results in the setting of contamination of the samples by DNA from dead or contaminating environmental bacteria, or from primer cross-reactivity with human tissue [36]. For this reason, it is essential to follow standard laboratory precautions that avoid any source of contaminations when collecting and transporting microbiology samples.

Superficial wounds and swabs are not ideal for sample collection when considering PCR techniques for diagnosis because of the frequent colonization by the skin flora that can contaminate the samples and lead to false positives as described above.

False-positive results can be reduced by performing PCR on several independent samples from each patient and by using specific genes primers for the specific bacteria alongside the 16S rRNA gene primers.

The interpretation of the PCR-tested samples is another crucial step, and both positive and negative controls have to be correctly established.

An original sequence observed for the first time in a laboratory can usually be considered to be a true positive [35], while the same sequence found in two samples of two patients may suggest a potential contamination.

Care must be given to sequences from microorganisms that are usually present in water or reagents (*Pseudomonas* spp. and *Acinetobacter* spp.) and those from skin (coagulase-negative staphylococci and *Propionibacterium acnes*), which could contribute to contamination [37].

When a result obtained by PCR testing is doubtful, it is possible to target a second gene using the same DNA, and another sample from the patient is needed for the confirmation.

11.5 Perceived Advantages and Limitations

The first studies of using PCR methods for targeting common prosthesis-related pathogens by targeting the 16S rRNA bacterial gene were performed by Mariani et al. [38, 39].

They demonstrated that the positive predictive value in a cohort of 20 revision TKAs was 100% [38], and in a subsequent series of 50 revision TKAs, they found a concordance between all the culture positive specimens and PCR with no false-positive results [39].

A recent meta-analysis [40] has shown that the specificity and the sensitivity of the PCR technique for diagnosis of PJI varied based on the study design, sample type, PCR type and reference standards. They estimated the sensitivity and specificity of PCR technique on the tissue synovial fluid samples were 0.95 and 0.81 and 0.84 and 0.89, respectively.

In a prospective study Gallo et al. [21] compared PCR and culture techniques in the diagnosis of PJI, they included joint fluid samples from 115 patients, and PCR was positive in 71% of PJI cases resulting in an improved sensitivity, specificity and accuracy.

In another study, Portillo et al. [23] demonstrated that multiplex PCR had better sensitivity and specificity compared to culture from periprosthetic tissue or sonication fluid culture, especially in patients who previously received antibiotics.

Similarly, Achermann et al. [24], in a study comparing PCR techniques versus sonication for improving diagnostic yield in PJI, reported that among 19 cases that received antibiotics, multiplex PCR was positive in all 19, while the sonication cultures grew the organisms in only eight cases.

In a recent study, Kawamura et al. [41] validated a new multiplex real-time polymerase chain reaction assay to detect methicillin-resistant *Staphylococcus* and to distinguish between gram-positive and gram-negative strains. In this series, in 8 out of 12 samples, the PCR was positive in culture-negative cases that were treated with prior antibiotics at the time of diagnosis.

Jacovides et al. [42] showed that the Ibis T500 biosensor system can improve the utility of PCR in detecting pathogen in culture-negative cases. In this technique, the spectral signals from the mass spectrometer are used to determine the mass of each PCR amplicon and therefore the base pair compositions. This can be used to identify the bacterial species and the abundance of PCR amplicons that are present in the analysed sample [42].

The Ibis device, that is a DNA-based amplification and analysis system, revealed that 88% of cases that were initially considered to have aseptic loosening had a subclinical infection [42].

The PCR has shown another promising application in the intraoperative decision-making pathway in revision surgery. Kobayashi et al. [43] demonstrated in a prospective study that the PCR revealed methicillin-resistant *Staphylococcus* infection in specimens from 6 of the 30 operations analysed, and the 16S rRNA gene universal polymerase chain reaction analysis was positive for specimens from 13 operations with an overall sensitivity of 0.87 and a specificity of 0.8.

In another study, Bergin et al. [44] showed how the rRNA RT-qPCR assay was able to detect as few as 590 colony forming units/mL of *Staphylococcus aureus* and 2900 colony forming units/mL of *Escherichia coli*, demonstrating 100% specificity and positive predictive value with a sensitivity equivalent to that of intraoperative culture that was influenced by antibiotic administration.

Because RNA rapidly degrades upon cell death, rRNA RT-qPCR assay system is useful only to detect living bacteria and the viable bacterial load.

Greenwood-Quaintance et al. [45] compared the PCR-electrospray ionization mass spectrometry to culture using sonication fluid from 152 subjects with PJI and found that the sensitivities for detecting PJI were 77.6% for PCR and 69.7% for culture ($p = 0.0105$). This difference was even more marked among the patients who had received antimicrobials before surgery, the specificities being 93.5 and 99.3%, respectively, ($p = 0.0002$).

The same group of researchers [46] published another study in which PCR together with electrospray ionization mass spectrometry applied to synovial fluid specimens had 81% sensitivity and 95% specificity for the diagnosis of PJI.

Alraddadi et al. [47] reported 16S rRNA PCR was a valuable tool in the antimicrobial management and on how clinicians made important therapeutic antimicrobial choices based on the PCR results. In this study, 19 patients, previously considered clinically infected by infectious disease consultants, successfully discontinued their antibiotic therapy based on negative PCR assay.

Despite its high sensitivity, the validity of PCR technique is still limited by the number of false-positive results due to both the high magnification power of DNA amplification and the persistence of bacterial DNA following the bacterial death [48] (Table 11.1).

When universal primers are used to amplify the 16S rRNA genes of all bacteria present, the resulting PCR amplicons must be sequenced and compared to known sequences, and this is a

Table 11.1 Main limitations and drawbacks for the use of PCR (polymerase chain reaction) in diagnosis of PJI (periprosthetic joint infections)

Limitations for the use of PCR
• Expensive technology
• Availability of nearby laboratory
• Lacking of international protocols for standardized methods for PCR optimization
• Possibilities of false-positive results
• Contamination

lengthy and costly process that requires quality databases.

Other limitations at the moment of a wider application of PCR are its unavailability in many centres and the costs associated with routine use of this technique.

Widespread use of PCR diagnostic tests is also challenging because they need an operating theatre with direct access to a molecular diagnostics laboratory to efficiently process the samples.

Furthermore, as reported by Saeed and Ahmad-Saeed [49] in their review article, no study has looked at the real cost-effectiveness and the overall burden of the routine use of PCR in the diagnosis of PJI.

11.6 Unique Scenarios Where This Technique May Be Beneficial

The main indication for the use of PCR is when there is a lack of microorganism culture or in a case of suspicious multi-bacterial infection, particularly in the presence of open wounds.

A broad-range PCR is able to detect mixed polymicrobial agents allowing the identification of the main organism. Usually this is not possible with routine tissue culture, where overgrowth of different species can mask the result.

Identification of resistant genes in clinical samples using PCR allows modifying the antibiotic regimens for the most effective treatment. Specific primers for PCR detection have been validated for erythromycin resistance-associated methylase genes ermA, *ermB* and *ermC*, macrolide transporter protein gene *mefA*, ATP-dependent macrolide efflux pump gene *msrA*, aminoglycoside modifying enzyme gene *Aac*(6′)-*aph*(2″), oxacillin resistance gene *mecA* coding a penicillin-binding protein 2a, penicillin resistance gene *blaZ* coding beta-lactamase, IMP-1 metallo-beta-lactamase gene (bla_{IMP}) and vancomycin resistance gene (*vanA*, *vanB*) [50].

The other main advantages of the PCR are in cases that have been exposed to a previous antibiotic therapy or prophylaxis and where antibiotic therapy hasn't been discontinued for at least 2 weeks prior to surgery [20, 22, 23] (Table 11.2).

Table 11.2 Main indications for the usefulness of PCR (polymerase chain reaction) in diagnosis of PJI (periprosthetic joint infections)

Indications for the use of PCR
• Failure of etiological diagnosis of PJI with traditional methods
• Clinically suspicious cases that remain culture negative
• Prior administration of antibiotics and culture-negative biopsy
• Reduced growth rate due to biofilm microorganisms
• Identification of small-colony variant infection and difficult to culture bacteria
• Identification of resistance genes
• Identify the main pathogen in the presence of mixed polymicrobial infections

11.7 Future Work in PCR

The future of PCR technology in PJI diagnosis lies in a full demonstration of accuracy and sensitivity of the technique and further clinical validation of its use in the diagnosis of PJI.

Moreover, in the future, following the improvement and the availability of a large number of bacterial genomes, it would be possible to target an increased number of bacteria with better accuracy to make the diagnosis of the infecting pathogen.

With the refinement of the PCR technologies and also the advances in the sequencing tools, this method will not only have determined the true positive or true negative results but also the antimicrobial susceptibilities of the detected strains.

Formal studies are also needed to look at the cost-effectiveness of PCR in avoiding unnecessary operation/revision surgery or unnecessary antibiotics therapy to assess the overall impact of this technology on health economy.

Conclusions

As demand for total knee arthroplasty increases, there is also an increase in the incidence of PJI. These infections are difficult to diagnose, and once diagnosed, they are difficult to eradicate. The consequence of that is a significant financial burden to the healthcare system and also considerable morbidity to the patients.

The introduction of molecular methods like PCR in PJI diagnostics has seen an exponential increase in the recent years showing a promising quicker diagnostic method compared to the traditional routine culture of bacteria, particularly in challenging clinical scenarios.

PCR technology may be a step towards better decision-making in those controversial situations where a correct diagnosis/treatment can prevent unnecessary operations, prolonged use of antibiotics and reduced morbidity to the patient, ultimately reducing healthcare costs.

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12 Histological Diagnosis in the Infected Total Knee Arthroplasty

Paddy Subramanian and Rahul Patel

Abstract

Histology is a valuable part of the armamentarium of investigations and workup for diagnosing infection following total knee arthroplasty. It is the last tool available to the surgeon in diagnosing the periprosthetic joint infection (PJI) at the time of surgery particularly when the preoperative investigations have been unable to adequately exclude PJI. It is a relatively cheap and simple modality that is universally available.

The literature supports that a diagnosis of infection correlates with the presence of raised number of polymorphonuclear neutrophils (PMNs) per high-power field (HPF) in periprosthetic tissue collected at the time of surgery. However, the exact number and criteria for this is still debated in the literature. There is clearly a balance to be made between the diagnostic sensitivity, specificity and accuracy. Using higher PMNs per HPF or more HPF will improve specificity at the expense of sensitivity.

12.1 Introduction

There are a multitude of investigations available to aid diagnosis of a PJI. However, the limited sensitivity and specificity of these tests pose difficulties in differentiating PJI from other causes of failure. An important diagnostic tool remains histological analysis of the periprosthetic joint tissue, in particular intraoperative frozen section analysis. It is a relatively cheap and simple test. Frozen section histology is particularly useful in diagnosing PJI when such diagnosis cannot be made preoperatively. Histology forms part of the criteria used in the joint AAOS (American Academy of Orthopaedic Surgeons) and Musculoskeletal Infection Society (MIS) guidelines [1]. These guidelines were produced to aid surgeons in the diagnosis of PJI, which may not be straightforward, particularly in the context of low-virulence organisms. These guidelines are summarised in Table 12.1. A positive diagnosis of PJI can be made if there are one major criteria or three or more minor criteria.

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Table 12.1 The diagnosis of PJI based on the Musculoskeletal Infection Society (MSIS) criteria [1]

Major criteria
1. Two positive periprosthetic (tissue or fluid) cultures with matching organisms
2. A sinus tract communicating with the joint
Minor criteria
1. Having three of the following five minor criteria:
(a) Increased C-reactive protein (>100 mg/L in acute PJI[a], >10 mg/L in chronic PJI) and an erythrocyte sedimentation rate of >30 mm/h in chronic PJI
(b) Increased synovial fluid white blood cell count (>10,000 cells/μL in acute PJI[a], >3000 cells/μL in chronic PJI) or ++ change on leukocyte esterase test strip of synovial fluid
(c) Increased synovial fluid PMN % (>90% in acute PJI[a], >80% in chronic PJI)
(d) Positive histological analysis of periprosthetic tissue (>5 PMNs per HPF in 5 HPFs at ×400)
(e) A single positive periprosthetic (tissue or fluid) culture

PJI periprosthetic joint infection, *PMNs* polymorphonuclear cells, *HPF* high-power field
[a]Acute infection is taken to be less than 6 weeks following implantation surgery and chronic more than 6 weeks

It is of prime importance that the diagnosis of a PJI is made if infection is present as failure to diagnose the joint infection will lead to lack of appropriate debridement and customised systemic antibiotic therapy, ultimately risking early failure of the revision arthroplasty. On the other hand, incorrectly diagnosing a PJI exposes the patient to more radical surgery with potentially staged procedures and the risks associated with prolonged systemic antibiotics.

The surgeon needs to use a combination of clinical history, examination and investigations. Newer studies show promising results with novel serological markers including interleukin-6 (IL-6) and alpha defensin [2]. None of the tests however have the ability to exclude joint infection with certainty. When equivocal preoperative workup is present, surgery is the last opportunity to differentiate the cause of failure. Intraoperative cultures are not available immediately and the results can be affected by the antibiotic-loaded spacers or systemic antibiotics. Furthermore, studies have shown that a surgeon's intraoperative evaluation for the presence of infection has a low sensitivity and specificity, 70% and 87%, respectively, with an accuracy of 82% [3], thus fuelling the drive to obtain histology in selected cases.

12.2 Role of Histology

1. *Preoperative*: using biopsies obtained percutaneously or arthroscopically
2. *Intraoperative*: using frozen sections during revision arthroplasty
3. *Postoperative*: using paraffin sections from samples sent at revision surgery

12.3 Preoperative Histology Assessment

Preoperative synovial tissue biopsy can be useful in determining the diagnosis. A number of techniques have been published for obtaining these tissue samples. These should be done in an aseptic manner in the operating room, preferably in an anaesthetised patient. These range from percutaneously using a Tru-Cut needle (Tru-Cut; Cardinal Health, Galway, UK) or arthroscopic biopsy forceps during a formal arthroscopy [4, 5]. It should be noted that if taking the tissue samples blind and percutaneously, caution should be exercised as there is a risk of damaging the arthroplasty components to the extent that one group has recommended this blind technique should be avoided in the well-fixed arthroplasty. In these cases, a formal arthroscopy may be more appropriate with a saline-filled joint at the expense of diluting the microbiology counts in the samples taken. However, these tissue samples can still be investigated for signs of inflammation in addition to culture and microbiology. These techniques have been shown to have a higher sensitivity and specificity compared to aspiration of the synovial fluid alone and C-reactive protein (CRP), particularly in the context of late PJI [5]. A further advantage of preoperative tissue sampling is in the analysis of antibiotic sensitivity of the organisms and therefore being able to tailor perioperative and postoperative antibiotic therapy to the individual patient and microorganism.

12.4 Intraoperative Histology Assessment

During revision arthroplasty surgery, an intraoperative frozen section histology sample can provide some useful information to the surgeon. Gram staining techniques from this tissue can be carried out. This test however has a very low-sensitivity [6, 7], poor negative predictive value, and its results did not alter the treatment of patients undergoing revision arthroplasty due to infection. It does however have high specificity, although it is recognised that the gram-positive samples are often found in those patients where the diagnosis of PJI is not in question. Frozen section analysis for a rapid intraoperative diagnosis of PJI, on the other hand, has better diagnostic accuracy than gram staining.

Histological samples are usually assessed by the pathologist on the following day after the specimen is fixed in formalin. However, occasionally the results are required more rapidly and thus a frozen section may be performed. The pathologist has to arrive at a correct decision in a time-sensitive manner. Historically, these techniques began with De Riemer in 1818, who used frozen sections in a diagnostic manner [8]. The technique continued to evolve from the 1950s with a cumbersome long process to the use of the modern-day cryomicrotome (cryostat) [9]. The cryostat is a refrigerated box containing a rotatory microtome. The tissue is frozen with an aerosol spray and is left in the cryostat for sectioning. The tissues are then stained, typically with haematoxylin and eosin (H&E). This tissue is then analysed under a light-powered microscope. The whole process with a report from the pathologist occurs usually within 20 min [10].

Although the AAOS and the Musculoskeletal Infection Society have produced guidelines which include histology in the diagnostic criteria, many still believe that intraoperative frozen section histology is of little value.

A recent meta-analysis by Tsaras et al. [11] involving 26 studies with more than 3000 patients confirmed that intraoperative frozen sections of periprosthetic tissues performed well in predicting a diagnosis of culture-positive PJI, despite having different criteria for the histological diagnosis of infection [variable number of polymorphonuclear neutrophil (PMN) per high-power field (HPF)]. This meta-analysis illustrated that the threshold of five PMNs had a diagnostic odds ratio of 52.6 compared to threshold of ten PMNs with an odds ratio of 69.8. The authors of this meta-analysis have emphasised the importance of frozen section histology in PJI, but at the same time, note further research is required to define the threshold number of PMNs per HPFs that is most predictive of PJI. They showed that the presence of acute inflammation provided a high positive likelihood ratio of 12. The absence of acute inflammation had a negative likelihood ratio of 0.23. This meta-analysis supports that frozen section analysis is a helpful investigation for supporting a diagnosis of PJI in patients with an intermediate pretest probability of PJI. For the patient with a low pretest probability of PJI, a negative frozen section result may be sufficient to exclude the diagnosis. In summary, they conclude that intraoperative frozen sections of periprosthetic tissues performed well for diagnosing PJI but only moderate accuracy for ruling out the diagnosis.

One group from the Cleveland Clinic has carried out a study supporting the use of both frozen section and the MSIS criteria at the time of second stage revision arthroplasty [12]. Although the MSIS criteria were originally developed to aid diagnosis of PJI before revision, the Cleveland group has tried to confirm the validity of using frozen sections and the MSIS criteria to diagnose ongoing infection and thus predicting failure of second stage reimplantation. The group accepts there are limitations in their study, but note that frozen section analysis at second stage revision had a high diagnostic specificity although a low sensitivity. In 2017, the same group has further assessed the value of intraoperative histology and has concluded that frozen section yields a high specificity, positive predictive value and negative predictive value and accuracy, with moderate sensitivity [13].

12.5 Postoperative Histology Assessment

At the time of revision surgery, apart from the frozen section samples (a diagnostic service which may or may not be available), formal histology can and should be sent at the time of revision to aid in the diagnosis of PJI. The Cleveland Clinic group as above has shown that the discrepancy between frozen section and permanent sections is low and they are both useful adjuncts.

12.6 Histological Classification of Periprosthetic Tissue

Histological analysis in providing evidence of infection will demonstrate acute inflammation, namely, the presence of neutrophil infiltration at the site of infection (Table 12.2). This can be seen on both frozen and paraffin-fixed samples.

Contamination during the primary procedure and secondary haematogenous invasion into the periprosthetic tissue are the most likely reasons to develop a deep-seated PJI [14]. Acute infections are usually caused by a virulent organism and show a typical histological picture of acute inflammation. In contrast, bacterial contamination with a low-virulence organism may have minimal symptoms. These low-virulence organisms are typically caused by small colony variants of staphylococcus [15]. These low-virulence organisms may contribute to the false negative results associated with frozen section analysis [16].

Based on the histomorphological criteria, four types of periprosthetic membrane were defined by Morawietz et al. in 2006 [17]. This classification has been validated [18]. This classification was based on the detection of foreign body particles, granulation tissue and PMNs (Table 12.2).

Table 12.2 Morawietz histological classification of periprosthetic tissue [17]

Type 1: Wear particle-induced type (foreign body particles, macrophages and multinucleated giant cells occupy at least 20% of the area)
Type 2: Infectious type (granulation tissue with neutrophilic granulocytes, plasma cells and few, if any, wear particles)
Type 3: Combined type (aspects of types 1 and 2 simultaneously)
Type 4: Indeterminate—neither criteria for types 1 or 2 and strongly resembles scarring connective tissue

It is generally accepted that types 1 and 4 are aseptic loosening and types 2 and 3 are septic loosening.

This classification was expanded upon by including criteria for particle identification. Type 4 has been modified to include fibrous type [19]. Further revision of the consensus classification includes the following types:

Type 5: Arthrofibrotic type

Type 6: Allergic/immunological/toxic adverse reactions

Type 7: Bone pathologies—when evidence of perivascular/interstitial lymphocytic CD20 and CD3+ve infiltrate, presence of mast cells and eosinophils and tissue necrosis associated with implant wear material [20].

12.7 Methods of Biopsy for Tissue

Tissue samples should be obtained using sharp dissection rather than electrocautery due to the associated thermal damage [21, 22]. It should be taken before the administration of antibiotics intraoperatively.

The histological specimens should be obtained from the interface membrane, pseudocapsule and other periprosthetic tissue. In both infected and aseptic loosening, a small layer of tissue forms between the bone and the prosthesis known as the periprosthetic interface membrane. There is associated bony lysis around the implant due to micromotion of the implant and cellular enzymolytic processes. The pseudocapsule is the tissue surrounding the effective joint space. Feldman originally described taking two tissue samples from inflamed pseudocapsule and the interface membrane [3]. However, it is the periprosthetic interface membrane that provides the most useful diagnostic information for the pathologist, yielding a sensitivity of 85% compared to pseudocapsule 42% with similar specificities [23–25]. If the surgeon is taking histology preoperatively, the

more readily accessible tissue would be the joint pseudocapsule/neosynovium, which has been described above. A minimum of three different sites of biopsy are recommended in the literature [24] and confirmed more recently in the context of frozen sections [26]. The tissue samples can then be sectioned for the microscopic examination.

Conventionally the staining of leucocytes is with H&E. Some studies have shown the use of other stains to increase the sensitivity of diagnosing infection on histology such as the use of naphthol-AS-D-chloroacetate-esterase (NACE and myeloperoxidase (MPOX), though these techniques are more time consuming as they require embedding in paraffin, which means that the results will not be available during the surgery [27]. Other groups have recommended the use of CD15 immunohistochemistry top aid in the identification of PMN identification [28].

Once stained, the H&E slides are evaluated under low magnification and the areas suspicious of inflammation are identified. Then, the number of PMN in one HPF (×400 magnification, with a visual field diameter 0.625 mm) is counted in these areas. It should be noted that the PMN with fibrinous exudate is excluded and the pathologist will cease counting at ten PMNs in that HPF. Finally, a total of ten HPFs are evaluated in this manner and the number of PMNs is summed. This sum has to be between 0 and 100. Assessment of other cell types such as plasma cells and lymphocytes has not been shown to be useful in the diagnosis of PJI [29].

12.8 Defining Infection via Histopathology

The literature supports that a diagnosis of infection correlates with the presence of raised number of PMN per HPF in periprosthetic tissue collected at the time of surgery. However, the exact number and criteria for this is vehemently debated in the literature [1, 3, 11, 27, 30–37].

The role of histology in diagnosing the infected arthroplasty started from Charosky's work in the early 1970s [38]. Mirra et al. [31] first described the correlation between the number of PMN per HPF and the presence of deep infection in arthroplasty. Mirra's group reviewed 36 patients with revision arthroplasty and noted that 15 had positive cultures. These 15 patients also all had positive histological findings consistent with acute inflammation. However, in the other 21 culture-negative patients, there was no evidence of acute inflammation on histology. Mirra followed up his original study with a larger group of patients [39]. Mirra concluded that infection was deemed present when one out of the five most cellular tissue regions showed more than five PMNs per HPF.

Feldman et al. in 1995 [3] on the other hand suggested that infection is present when more than five PMNs were present in all *five* HPFs in the most cellular tissue samples. This was replicated by Spangehl et al. showing a sensitivity of 80% and specificity of 94% using five PMNs per HPF [7, 40]. Athanasou increased the number of HPF to ten and diagnosed infection if there was at least one PML in all ten HPFs [32, 33]. Feldman confirmed that these criteria were accurate for frozen section analysis [3]. This was also replicated by Wu et al. who concluded that five PMNs per HPF are a suitable diagnostic threshold in frozen sections [26]. Lonner et al. felt that increasing the diagnostic cut-off to ten PML per HPF increased the specificity and accuracy of frozen sections [36]. Banit et al. diagnosed infection if there were more than ten PML in one out of the five most cellular HPFs [34]. One study combined Banit's criteria to screen for infection and Feldman's criteria to evaluate all positive tests providing an accuracy of 0.94 [27]. Morawietz et al. have suggested on a different line that there should be a threshold number per ten HPFs and this number is 23 [28]. They conclude that twenty-three neutrophils in ten HPFs is the best histopathological threshold to differentiate between aseptic and septic prosthetic loosening.

There is clearly a balance to be attained between the diagnostic sensitivity, specificity and accuracy. Using higher PMNs per HPF or more HPF will improve specificity at the expense of sensitivity [13]. A meta-analysis in 2013 comparing specifically ten versus five PMNs as a

threshold for PJI concluded that in a cohort of 1011 patients, there was no difference in sensitive or diagnostic odds ratio, but the specificity was significantly higher for ten than for five PMNs per HPF [41]. Thus, they advocated a threshold of ten PMNs per HPF is better for diagnosing PJI.

12.9 Limitations of Histology

- Does not identify the causative organism, important for tailoring antimicrobial therapy.
- Needs dedicated pathologist with interest in orthopaedic histology.
- Variation in accepted diagnostic criteria (*see above*).
- *P. acnes*, CNS and other low-virulence organisms do not always produce a PMN response [16, 42], thus lowering the diagnostic sensitivity of this investigation.
- It is open to surgical sampling errors, for example, poor or inadequate sampling of tissue numbers and sites.
- In frozen section histology, freezing artefacts can distort results and even alter the tissue structure.
- Risk of false positive frozen sections:
  - With acute periprosthetic fractures/dislocations
  - With acute periprosthetic tissue trauma with resulting inflammation

12.10 Advantages of Histology

- Universal availability and cheap.
- Frozen section can provide rapid results which can guide the surgeon intraoperatively with results being available within 30 min. Sometimes it will be last available test to guide the surgeon in equivocal cases.
- Less likely to be affected by preoperative antibiotics compared to serological or microbiological techniques.
- It has the additional ability to diagnose tumours.
- High specificity and moderate sensitivity.

Conclusions

The use of histology whether as a frozen section to get a timely diagnostic response or as formal paraffin sections has been proven in the literature to be a useful tool in the surgeon's armamentarium in the battle to diagnose the prosthetic joint infection.

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13 Intraoperative Cultures for the Suspected Total Knee Arthroplasty Infection

Antony C. Raymond and Sam Oussedik

Abstract

Infection of a total knee arthroplasty (TKA) can be difficult to accurately diagnose with multiple factors potentially affecting the result. Here we discuss factors associated with microbiological and histological sampling, transport, storage and analysis, all of which can be improved upon to maximise diagnostic accuracy. Much of this adheres to published guidelines, such as those from the Musculoskeletal Infection Society (MSIS), but also expands upon them using the most recent and relevant research studies.

13.1 Introduction

Intraoperative samplings for suspected cases of periprosthetic joint infection (PJI) are integral to its diagnosis, identification of causative pathogens and management. Intraoperative cultures can influence whether to perform a one- or two-stage revision, and it should guide the choice of antibiotic for the use intravenously and orally or for cement impregnation [1]. In this chapter, we look at the types of sampling and their indication, timing, technique and efficacy.

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13.2 Types of Sampling and General Principles

Sampling includes joint aspiration, either percutaneously or via arthrotomy; biopsy that may be percutaneous, arthroscopic or open; swab cultures as well as implant extraction and sonication covered in the following chapter.

According to the Oxford criteria, culture of a pathogen from at least three separate tissue or fluid samples is highly predictive of infection yielding a sensitivity of 66% and specificity of 99.6%. They demonstrated that isolation from two samples gave a sensitivity of 71% and specificity of 97% whereas from 1 sample, a yield of 83% and 81%, respectively [2]. More recently the Musculoskeletal Infection Society in 2011 published guidelines stating that the isolation of an organism from two separate cultures constitutes a diagnosis of infection [3]. However the isolation of a single virulent organism, such as

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S. aureus, *E. coli* or *Candida* spp., may also represent PJI [4]. This has also been incorporated into the MSIS definition for PJI. It should be noted that the majority of PJIs (65%) are caused by coagulase-negative staphylococci a group that consists of multiple species (e.g. *S. epidermidis*), followed by *S. aureus*, streptococci and enterococci. Aerobic Gram-negative bacilli that include *Enterobacteriaceae* (*E.Coli*, *Proteus mirabilis*, etc.) and *Pseudomonas aeruginosa* are less common [5].

General principles apply to all types of sampling. It should be performed under sterile conditions to minimise risk of contamination of the joint and samples taken [6–9]. Antibiotic therapy should be stopped 2 weeks prior to aspiration as failure to do so reduces culture sensitivities in one study from 76.9% to 41.2% [10]. Antibiotic therapy within the preceding 3 months of diagnosis is associated with a 4.11 odds ratio of culture-negative periprosthetic joint infection [11]. Samples should be transported to the laboratory within 2 h of collection, as recommended by the Infectious Diseases Society of America [12]. If this is not possible, refrigeration is recommended. Specimens left for over 24 h prior to analysis may cause certain fastidious bacterial species to perish, such as *N. gonorrhoea*, *S. pneumoniae* and many anaerobes [2, 12, 13].

13.3 Joint Fluid Aspiration Technique

Joint aspiration is important in both acute and chronic PJI. If performed percutaneously, it should be done under sterile conditions preferably in the operating theatre. The patient should be supine, and the area should be prepped and draped in the standard manner [7, 8, 14]. Local anaesthetic should be avoided as it has been shown to be bacteriostatic in vitro [15].

A small skin incision is made superolateral to the patella and held open with an Alms retractor. This approach can access the suprapatellar pouch of the joint cavity. The incision should then be irrigated with 0.9% saline solution prior to advancement of a 14 G spinal needle and syringe [8].

Synovial fluid should also be taken for microbiological analysis during any revision surgery and is obtained immediately after arthrotomy with a sterile syringe.

Fluid should be transferred directly into aerobic and anaerobic blood culture bottles, which are more sensitive and yield less contaminant results whilst also yielding faster culture results compared to traditional agar and broth culturing [16–18].

13.4 Open and Arthroscopic Biopsy Technique

Open biopsy requires sedation and the use of a rongeur or biopsy needle, such as a 14 G Trucut needle. The knee should be prepped and draped in the standard manner. Local anaesthetic should be avoided. Three to four biopsy samples should be taken for optimal diagnostic accuracy depending on whether tissues will be inoculated into blood culture bottle or be processed using conventional agar and broth techniques, respectively [19]. The samples should be taken with separate and sterile instruments and transferred directly into the culture receptacle without contact with gloves, gauze, drapes or other surfaces, to avoid contamination [7, 8, 20].

Fink et al. have described arthroscopic biopsy of the knee. It takes place under general anaesthetic, an anterolateral portal is made and arthroscopic biopsy forceps are introduced. Multiple samples are taken blind from different parts of the knee close to the prosthesis, without joint irrigation in order to prevent dilution. The knee is subsequently assessed arthroscopically for bleeding and damage to the components, and at the same time five further non-blind samples are taken for histological diagnosis. Once all samples are obtained, a single dose of antibiotic may be given [6].

13.5 Microbiological Sensitivity and Specificity of Joint Aspiration and Biopsy Sampling

In terms of culture growth, sensitivity of these tests varies from 12% to 100% [6, 21–23]. Specificity ranges from 50% to 100% [7, 24–28].

In dedicated comparative studies, there were two reports that demonstrated superiority of arthroscopic biopsy over aspiration [6, 23]. These were from a single German unit using a dry arthroscopic technique. Sensitivity and specificity arthroscopic biopsy was 100% and 95–98%, respectively, versus 69–73% and 73–95% for aspiration.

Two studies reported superiority of aspiration over open biopsy. Sensitivity and specificity for aspiration was 80–83% and 94–100%, respectively, compared to 79–83% and 90–100% for biopsy [7, 8]. Meermans and Haddad showed that combining aspiration and biopsy increased sensitivity and specificity in their study to 90% and 100%, respectively [7].

13.6 Joint Fluid Analysis

13.6.1 Microbiology

Conventional methods of culturing synovial fluid may include the inoculation of various media such as blood, chocolate blood as well as MacConkey and laked blood agar plates. Thioglycollate or cooked meat broth can also be used [17, 29].

Blood culture bottles have been shown to be superior in isolating organisms in synovial fluid when compared to conventional methods [29]. In a study of 805 synovial fluid specimens in patients with suspected septic arthritis, 77 isolates were grown across blood culture bottles (BCBs) and agar plates. Eighty percent were identified by bottle and 66% by plating. One percentage of BCBs yielded contaminants whereas 14% of agar plates did so [17].

Synovial fluid culture in BCBs has also been shown to be superior to culturing periprosthetic tissue processed using conventional methods. Sensitivity and specificity is 86–92% and 100%, respectively, versus 46–69% and 81–100% [16, 30].

Gram staining does not add to the diagnostic accuracy as sensitivity is very low and cannot safely rule out infection (please see below) [2, 21, 31–33].

13.6.2 Leukocyte Count and Differential

Joint fluid should be analysed for white cell count. Synovial fluid white cell counts in PJI of 1100–1700 μl have been shown to be sensitive and specific for infection in hip and knee arthroplasty [10, 34–36]. Sensitivities range from 90% to 94% and specificities from 88% to 91%. In terms of neutrophil differential, a cut-off of 64–65% has the optimal accuracy in the diagnosis of infection.

It should be noted that the white cell count in PJI is substantially lower than the level for septic arthritis of the native joint, which is typically in the range of 50,000–100,000 μl [37, 38].

13.7 Swab Technique and Efficacy

A swab uses a specialised bud of woven rayon that is applied to a target area to retrieve any bacterial inoculum. It is usually performed either instead of or shortly after synovial fluid aspiration and prior to any therapeutic joint irrigation. The swab is then inserted into its sheath, which usually contains culture medium with or without charcoal. Charcoal preserves certain fastidious bacterium such as *N. gonorrhoea*. The culture medium will preserve multiple bacteria for up to 24 h, after which time certain fastidious bacterial species may perish. If swabs are not delivered to the laboratory within 2 h, they must be refrigerated [12, 13].

Swab culture has been shown to be inferior to both synovial fluid culture and soft tissue culture and has even been shown to inhibit growth of some organisms [16, 39–41]. Sensitivity and specificity ranges from 61% to 70% and 89% to 99% for swabs, respectively, compared to 69–93% and 81–98% for periprosthetic tissue in two studies infected joint arthroplasties [16, 40]. Synovial fluid analysis has a sensitivity of 86% and specificity of 100% when compared to swab culture [16].

13.8 Soft Tissue Sampling Technique

Following arthrotomy and synovial fluid sampling, soft tissue sampling may take place prior to implant removal, debridement and washout.

Soft tissue sampling is important as bacteria form colonies within protective biofilms (sessile bacteria) that grow both on implants and organic material. This is in contrast to planktonic bacteria, which are less numerous and are found free floating in synovial fluid [10, 42]. The Oxford criteria in 1998 recommended five or six perioperative samples be taken with a positive culture of a single organism in three or more isolates in order to diagnose PJI [2]. Recently however Peel et al. have shown that three or four soft tissue samples should be taken for optimal diagnostic accuracy depending on whether BCBs or convention culturing techniques, respectively, are employed [19]. They found that if BCBs are used, specificity dropped from 93% to 10% (sensitivity increased from 92% to 98%) if the number of samples increased from three to five. Similarly if conventional culturing techniques are employed, specificity dropped from 78% to 22% (sensitivity increased from 97% to 98%). This is supported by Bemer et al., who assessed the agreement rate between microbiological diagnosis and modified Infectious Diseases Society of America (IDSA) criteria. They found that four specimens cultured on conventional and BCB media had the highest agreement of 98.1% [43]. Samples may include the capsule, membranous tissue from the femoral implant interface and tibial implant interface, granulation tissue and any other abnormal or purulent-looking tissue [2, 44–46]. Membrane covering the implant is superior to synovial capsule/pseudo-capsule in the histological diagnosis of infection. Its sensitivity is 83% vs 42% and specificity is 98% vs 98% [45]. However there is no difference between sample types for detecting microorganisms [46]. Each sample should be taken with a separate set of sharp sterile instruments including forceps and scalpel and placed directly into separate specimen containers, without contact with other surfaces such as gloves, gauze or drapes. These precautions are taken to reduce the risk of cross-contamination [2, 8, 44–46]. Diathermy may cause thermal damage to tissues and microorganisms, but sensitivities and specificities have not been ascertained for this method of dissection. Specimens at this point can be taken for permanent and frozen section if available. Implant removal follows this [2, 8, 47].

13.9 Histology Technique and Efficacy

Permanent and frozen section histology is a valuable tool in the diagnosis of periprosthetic infections, due in part to the variable microbiological culture yield and the strong correlation between infection and neutrophil aggregation [2, 48]. Histological findings of greater than five neutrophils per high-power field (HPF: X400 magnification) in five HPFs are incorporated into the Musculoskeletal Infection Society (MSIS) criteria for PJI [3].

Tissues taken for permanent section should be taken from the area of the bone implant interface as this yields greatest sensitivity [45]. At least two specimens should be taken using sharp dissection. The tissue should be pink tan as opposed to white to avoid analysis of fibrous tissue or fibrin. Specimens should be immediately fixed in formalin and transported to the laboratory for paraffin embedding. Five micrometre sections can be cut and stained with haematoxylin and eosin [2, 49]. A pathologist knowledgeable in periprosthetic infection should perform the anal-

ysis. Sections are first scanned to find areas with maximal inflammatory change and cellularity. Any polymorphonuclear (PMN) leukocytes should have intact cytoplasmic borders to be eligible for analysis [44, 50]. False positives can occur with rheumatoid patients who may have inflammatory infiltration resembling infection; however infiltrates are usually of a lymphoplasmacytic nature [49, 51, 52]. False negatives can occur with low virulence organisms, such as *P. acnes*, as it has been shown that 40% of these infections failed to fulfil histological criteria for infection [53].

There are multiple histological criteria for PJI based on the observation that there is strong correlation between infection and polymorphonuclear infiltration of affected tissues [2, 48]. The Feldman system, incorporated into the MSIS criteria, uses more than five polymorphonuclear cells per high-powered field (×400) in five separate microscopic fields. It has been found to be excellent at predicting a diagnosis of infection but moderate at ruling it out [45, 50]. A meta-analysis found no difference between the diagnostic accuracy of utilising either five or ten PMNs per HPFs [54]. Alternative systems include those described by Athanasou and also Morawietz. The Athanasou criteria are defined as an average of one neutrophil per high-power field after examination of ten fields [44]. The Morawietz classification specifies that at least 2 PMNs per high-power field over 10 HPFs must be found to diagnose infection [55]. Sensitivities and specificities have been described for their utilisation in frozen section below.

Permanent section correlated with 97.8% of 526 clinically suspected aseptic prosthetic loosenings and 99% (vs 89% confirmed by microbiology) of 91 cases of suspected septic loosening [56, 57].

13.10 Frozen Section Technique and Efficacy

Intraoperative frozen section analysis has been shown to have 78.1–100% correlation with permanent section [50, 57, 58]. In centres with dedicated pathologists available at the time of surgery, frozen section analysis intraoperatively can be used to determine if there is current infection and therefore whether to proceed to definitive revision or insertion of therapeutic cement spacer. It is important that a specially trained musculoskeletal pathologist, who is knowledgeable of the diagnostic criteria for infection, performs the microscopy [3].

Tissues sent for intraoperative frozen section are retrieved from the knee in the same manner as for permanent section. Specimens are snap frozen in carbon dioxide. Five micrometre sections are cut with a cryostat and stained with haematoxylin and eosin.

In terms of diagnostic criteria for frozen section, the Feldman system has been shown to have a sensitivity of 28% and specificity of 100% [59]. The Athanasou criterion has a sensitivity of 71.4% and specificity of 64.2% [59]. The Morawietz classification has shown a sensitivity of 86.6% and a specificity of 100%. However 19% of fresh-frozen specimens were not included in their analysis due to "unclear results" [58].

13.11 Soft Tissue Culture Techniques and Efficacy

Periprosthetic tissue that has been retrieved and transported to the laboratory should be processed in a class 2 microbiology safety cabinet, which provides a high-efficiency particulate arrestance (HEPA) filtered flow of air into the work area to prevent airborne microorganism contamination of the PPT samples as well as a degree of protection to the operator (class 1 cabinets do not prevent contamination on the work area, whilst class 3 cabinets provide absolute barrier protection to the operator involving work with extreme biohazards) [2, 60, 61]. The tissue should either be homogenised in 3 ml of brain-heart infusion broth or disrupted through vigorous agitation of the specimen in a pot with 5 ml sterile saline with the aid of sterile 1 mm glass Ballotini beads or other local equivalent process [60, 62]. The resulting suspensions can then be aliquoted onto blood and chocolate agar plates and thioglycollate (which

can support fastidious anaerobes) or Robertson's cooked meat broths (for aerobic organisms). Plates are incubated at 37 °C in 7% carbon dioxide aerobically and anaerobically for 2–5 days though local policies may be shorter than this [2, 10, 17, 18, 62]. Cloudy broths should be sub-cultured at 5 days or sooner if turbid on agar plates. Organisms should be identified using standard methods and antibiotic sensitivities determined by a comparative disc diffusion method, such as that described by Stokes et al. [63, 64]. The zone of inhibition of the test organism around an antibiotic disc is compared to the zone of inhibition of a standard, antibiotic-sensitive control strain. If the zone of inhibition of the test organism is no bigger than 3 mm, it is deemed to be susceptible to the antibiotic. An alternative would be to use the National Committee for Clinical Laboratory Standards method [2].

13.12 Conventional Techniques Versus Automated Blood Culture Bottle Culturing

Conventional methods of culturing with agar plates and broths have been compared to culturing with blood culture bottles (BCBs) used in combination with a continuous monitoring automated detection system. Hughes et al. cultured periprosthetic tissue (PPT) fluid suspension over 5 days and showed that BACTEC aerobic and anaerobic BCBs had a combined sensitivity and specificity of 87% and 98%, respectively, which was comparable to cooked meat broth. BCBs were significantly more sensitive than fastidious anaerobic (thioglycollate) broth and direct culture plates, which had sensitivities of 57% and 39% and specificities of 100%, respectively [62].

Peel et al. studied 369 patients of whom 117 had PJI. They cultured homogenised PPT in BACTEC aerobic and anaerobic BCBs and compared this to conventional agar and broth culturing techniques. They found BCBs had a sensitivity and specificity of 92.1% and 99.7% compared to 62.6% and 98.1% for traditional media. Applying IDSA criteria for infection, sensitivities were reduced to 60.7% vs 44.4% in favour of BCBs. This study also found that BCBs, particularly aerobic, yielded a positive culture more rapidly than any other medium, often within the 1 day compared to day 2 or 3 using conventional media. Aerobic BCB yielded no further organisms after day 7, whereas anaerobic BCBs after day 7 yielded further positive cultures, as well as contaminants, all of which were *P. acnes.* No further growth was achieved after day 14 [18]. Minassian et al.'s study was in concurrence and found that, using BCBs, 95% of organisms are detected within 3 days and 100% at 8 days using the aerobic type. With anaerobic bottles, 96% are cultured at 5 days and 99% at 10 days. The optimal diagnostic accuracy was at 4 days, which had a sensitivity of 84.3% and specificity of 97.9%. The use of both bottles was crucial as 14% of organisms were identified using the aerobic BCB alone whilst 27% were identified from the anaerobic BCB solely. Without the aerobic BCB analysis, *Pseudomonas*, *Corynebacterium* and *Candida* spp. would be missed. Similarly, without anaerobic culture the majority of *P. acnes* would not be identified [4].

For conventional culturing media, it has been shown that the use of Robertson's cooked meat broth and thioglycollate broth prior to agar plate inoculation is significantly more sensitive than the use of agar plates alone – 83% and 62.6%, respectively, vs 39–48.9% [18, 62].

In terms of culture duration, Neut et al. found that extending it, from 3 to 7 days when using aerobic thioglycollate broth and to 5 days of anaerobic culture on Brucella agar, increased sensitivity from 41% to 64% [65]. Schafer et al. in 110 hip and knee PJI patients found that extended culture of 7 days had a sensitivity of 73.6%. Furthermore a substantial number (n = 25) of infecting organisms, mainly *P. acnes*, would not have been detected if culture was not extended to 14 days. They found that "week-1" infecting organisms mainly consisted of staphylococci, enterococci, streptococci and *Enterobacteriaceae*. "Week-2" organisms consisted of *Propionibacterium* spp., Gram-positive bacilli and *Peptostreptococcus* spp. Fifty-two

percent of contaminants were grown within the first week of culture [66].

Butler-Wu et al.'s findings further supported extended duration culture in that a 13-day culture of both aerobic and anaerobic media was necessary to detect *P. acnes*. *P. acnes* is aerotolerant, and as such 29.4% of infections would have been missed if this extended period of culture was only applied to anaerobic media [53].

Given that culture-negative PJI is prevalent in 7–13.8% of cases using conventional culturing techniques and times of up to 5 days, it seems reasonable to extend culture times to up to 14 days for both aerobic and anaerobic media in cases where no organism has been identified. The use of enrichment broth, such as Robertson's cooked meat broth, should be used in all cases [2, 18, 53, 62]. Analysis of BCBs shows that it is reasonable to culture up to 7 days with an aerobic BCB and 14 days with an anaerobic BCB if no prior organism has been identified. Both types of BCB should be cultured.

13.13 Small Colony Variants

Small colony variants (SCVs) of bacteria are naturally occurring sub-groups that typically grow more slowly and in separate minute colonies within the parent bacterial population. SCVs occur in response to a selection pressure and can readily revert to the parent subtype of the pressure is removed. SCVs can be isolated from sites of infection particularly recurring or chronic ones and may also arise from exposure to certain antibiotics. These SCVs can be responsible for antibiotic resistance and unsuccessful treatment of infection. *S. aureus* and *S. epidermidis* commonly undergo formation of SCVs, but due to their very slow growth and identical morphology to their parent population, they are often missed. Prolonged sub-culture of up to 6 days or more on specific media, for example, avoidance of horse blood agar for thymidine-dependent SCV or using agar supplemented with thiamine or menadione, may help growth of certain SCVs [67, 68].

13.14 Tissue Gram Stain

Gram staining exploits differences in bacteria, namely, it detects the peptidoglycan layer in the cell wall, which is present in Gram-positive bacteria and retains a crystal violet dye. Gram-negative bacteria will only then be seen after adding a counter stain of safranin or fuchsine and will appear pink.

Gram stain has been shown to have little value in the PJI setting, and multiple studies have recommended against its use. Sensitivity has been shown to range from 0% to 27%. A negative Gram stain does not rule out infection [31–33]. Oethinger also found specificity to be 92%. This was possibly due to laboratory contaminates found in dyes and diluents causing false positives [69]. A complete preoperative workup, including serological testing, synovial fluid and soft tissue analysis and radiological studies, will more than negate any need for Gram staining. A limited role for the Gram stain may be as a diagnostic test in the suspected acutely infected knee; a positive result may indicate immediate surgical treatment and influence antibiotic selection.

13.15 Culture of Fungal and Unusual Bacteria

Fungal and atypical culture from suspected PJI is rare, and therefore microbiological processing is not routine [3, 5, 70]. Wadey et al. retrospectively reviewed a series of 253 infected orthopaedic cases, and from these, 446 acid-fast bacilli (AFB) cultures and 486 fungal cultures were processed as requested by the surgeons. No AFB cultures were positive, and 0.6% of fungal cultures were positive of which only one was clinically important [71]. In another series of 2116 cases of PJI, only 7 (0.3%) were due to *M. tuberculosis* [72].

Fungi may either be moulds that grow in multicellular filaments (hyphae), yeasts (unicellular) or dimorphic fungi, which can exist in either form. Candida (a yeast) makes up 80% of fungal PJI. Data for fungal PJIs are from multiple case reports and small case series. A working

group of orthopaedic surgeons looking at the management of fungal or atypical PJI studied 59 articles on the topic and recommended the following [73]:

1. Repeat aspiration to confirm fungal diagnosis.
2. Most routine manual and automated blood culture systems can support candida growth, but they are not so effective for moulds and dimorphic fungi.
3. If initial cultures are negative but suspicion is high, fungal selective growth media and/or alternative culture techniques such as the lysis centrifugation method should be included. Prolonged culture may be needed.
4. Isolation to species level is mandatory because antifungal therapy selection is often based on this information.
5. Candida resistance to fluconazole has been reported, and susceptibility testing should be requested if resistance is suspected.

Multiple atypical bacteria have been described as the cause of PJI. History of exposure and host susceptibility may help in the identification of unusual organisms. Risk factors for atypical bacteria include immunocompromised and autoimmune disease including rheumatoid arthritis (*Salmonella*, *Moraxella catarrhalis*, *Haemophilus influenza*, *Mycoplasma hominis*, *P. multocida*, *Echinococcus*, *Francisella tularensis*), diabetes mellitus (*Pseudomonas* spp.), steroids (*Aspergillus* spp.), previous antibiotic use (*Clostridium difficile*), HIV/AIDS (*Mycobacterium avium complex*), dog or cat bite (*P. multocida*), drinking unpasteurised products (*Brucella*, *Listeria monocytogenes*), farming occupational exposure (*Yersinia enterocolitica*, *Echinococcus*), after dental work or insertion of intrauterine device (*Actinomyces* spp.) and intravenous drug use [5]. Routine bacterial cultures will often fail to yield these organisms. Special precautions need to be taken to ensure safety for laboratory staff, for example, in cases of *Brucella*. Specialised media and prolonged incubation may need to be employed (over 30 days); however, BCBs have been able to isolate Brucella within 1 week. Serological testing, implant sonication, polymerase chain reaction techniques of culture specimens and other newer techniques may also help. Close communication with microbiologist is essential in the identification and management of these pathogens [5, 70].

13.16 Transport and Handling of Specimens

Manipulation and opening of containers should be kept to a minimum to decrease the risk of contamination.

Specimens should be placed in CE-marked, or internationally equivalent, leak-proof containers. Fluid should be inoculated in aerobic and anaerobic BCBs [18]. If possible, PPT should be placed directly into containers containing 20 ml of demineralised sterile water and 5 ml of 1 mm sterile glass beads at the time of surgery. When placed on an automated orbital shaker at, for example, 250 rpm for 10 min, the beads help to disrupt the PPT and release any bacteria into the fluid. This process leads to a sensitivity of 83.7% and specificity 91.3% when using conventional laboratory technique and is reportedly better than other series that do not use Ballotini beads. No comparative study has formalised this finding however [60]. Specimens should be transported to the laboratory and processed as soon as possible, ideally within 2 h [12, 47]. Microbiological analysis should then be performed in a class 2 safety cabinet.

Conclusions

Periprosthetic joint infection can be difficult to accurately diagnose with multiple factors potentially affecting the result. Adherence to guidelines, such as those from the Musculoskeletal Infection Society, and taking various steps (Table 13.1) to improve sampling and analysis can improve diagnostic accuracy. However, given that there is a degree of diagnostic uncertainty, results should always be interpreted in light of the clinical findings to enable appropriate management.

Table 13.1 Factors affecting diagnostic sensitivity and specificity

	With implementation		Without implementation or against rival procedure		
Technique/action	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Comments
Withholding antibiotic prior to sampling >2 weeks [10]	76.9	N/a	41.2	N/a	
Joint aspiration [7, 8]	80–83	94–100	79–83 (open biopsy)	90–100 (open biopsy)	
Aspiration and open biopsy [7, 8]	90	100	80–83 (aspiration alone)	94–100 (aspiration alone)	
Swab culture [16, 40]	61–70	89–99	69–93 (PPT culture), 86 (synovial fluid)	81–98 (PPT culture), 100 (synovial fluid)	No longer recommended
BCB culturing of synovial fluid [16, 30]	86–92	100	46–69	81–100	80% detection rate of organisms and 1% contamination rate vs 66% and 14%, respectively, in conventional media culture
BCB culturing of PPT [18, 62]	87–92.1	98–99.7	57 (fastidious anaerobic broth) 39 (agar plates)	100 (fastidious anaerobic broth) 100 (agar plates)	
Broth usage prior to agar plate inoculation [18, 62]	62.6–83	97–98.1	39–48.9	99.7–100	
Gram stain [31–33, 69]	0–27	92–100			No longer recommended
Feldman histological criteria [58, 59]	28	100	71.4 (Athanasou) 86.6 (Morawietz)	64.2 (Athanasou) 100 (Morawietz)	In the Morawietz analysis, 19% of fresh-frozen specimens were not included due to "unclear results" thus biasing the results
Membrane sample for histology [45]	83	98	42 (synovial capsule/ pseudo-capsule)	98 (synovial capsule/ pseudo-capsule)	
Synovial white cell count (SWCC)—1100–1700 μl [10, 34–36]	90–94	88–91	84 (SWCC >4200)	93 (SWCC >4200)	

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14 Sonication of Removed Implants in the Infected Total Knee Arthroplasty

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Abstract

Accurate diagnosis of total knee arthroplasty (TKA) infection is still a challenge. Although indirect diagnosis including serum biomarkers can help to make the diagnosis of infection, well-established international criteria require a microbiological diagnosis. In this context, sonication of retrieved implants at revision surgery stands as the best available option to harvest microorganisms colonizing the implant, those that maintain infection out of the reach of systemic antibiotic treatments. In this chapter, the rationale, evolution and current use and also the future perspective of implant sonication in the diagnosis of TKA infection will be reviewed.

14.1 Introduction

Diagnosis of total knee arthroplasty (TKA) infection relies on the combination of clinical findings, imaging and laboratory studies (from blood and synovial fluid). This latter group includes serum biomarkers, molecular testing, histology and especially microbiological techniques. Not all diagnostic tests are equally important for the diagnosis. In such a complex field where false positives and false negatives are frequent, a hierarchy is needed to understand the available evidence of infection in a specific case that would then inform the specific treatment.

A major accomplishment of the community in charge of patients suffering from TKA-related infection (in the orthopaedic field as well as in the infectious disease field) has been the international agreement on the definition of prosthetic joint infection (PJI), as reviewed by Tande and Patel [1].

Major criteria to provide definitive evidence of periprosthetic joint infection (PJI) include sinus tract communicating with the prosthesis and identical microorganisms isolated from two or more cultures. Purulence about the prosthesis may be definitive or supportive. Consensus also exists about the supportive (although not definitive) evidence provided by acute inflammation upon histological examination of periprosthetic tissue, single culture with any microorganism,

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single culture with a virulent microorganism, elevated synovial fluid leukocyte count, elevated synovial fluid neutrophil percentage and elevated serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values. However, these diagnostic criteria on a painful TKA only permit to diagnose the case as potentially infected. Some of these cases are considered infected even if no microorganism is identified. Without the etiologic diagnosis, the treatment may not be specific enough to eradicate the infection. To establish the etiological diagnosis of a TKA infection, identifying the causative microorganism together with its antibiotic susceptibility is a key diagnostic issue to provide the correct treatment [2].

Samples used to investigate this causative microorganism are usually from the synovial fluid and/or the periprosthetic tissues. In a recent European survey about surgical diagnosis of infected TKA [3], 93.6% surgeons treating infected TKA and answering the survey routinely obtained tissue samples at surgery. Those were sent for culture (98.8%) and histology (72.5%). In this survey, synovial fluid exams included microbiology in 97.7% of cases.

Patients with culture-negative PJI have a diagnosis of infection without microbiological evidence. Periprosthetic purulence, acute inflammation determined by histopathology or a sinus tract communicating with the joint, without identifying causative microorganisms, can also be indicative of an infection, and the problem posed to the clinician in charge of the patient is significant [4]. This lack of microbiological confirmation may be due to prior antimicrobial therapy [5], or due to inadequate microbiological sample collection and processing at surgery, or also due to the inability of current methods to detect the pathogen (rare microorganisms or low-grade infections). The frequency of culture-negative PJI varies from 5% to 12% [4], and large centres with 7% culture-negative PJI tend to consider it a low incidence [6].

To increase the chances of culturing the causative microorganisms of prosthetic infection, its presence on the infected implant could offer the appropriate sample source to identify it.

14.2 Rationale

During the joint colonization process that gives rise to a PJI, inert biomaterials are more prone than living tissues to suffer from bacteria adherence, according to the "race for the surface" theory of Gristina [7]. Adhered bacteria on the biomaterials, without suffering from the immunological response found in living tissues, may develop an extracellular matrix with specific characteristics called biofilm that protects the microorganisms from the activity of antimicrobials and from the surrounding host defence mechanisms [8]. Biofilm not only affects treatment, frequently requiring the explantation of the prosthesis to eradicate infection, but also limits microbiological diagnosis. Bacteria firmly attached to the implant and protected by the biofilm cannot be easily sampled and cultured. Swabs may just collect sessile bacteria in the surrounding fluids, while scraping with blades frequently fails to dislodge biofilm from metals [9]. Although it became evident that causative microorganisms attached to the prosthetic components offered the best opportunity to be detected when the components are explanted at revision surgery, the processing of the retrieved implant in the microbiology laboratory was cumbersome. To culture the whole implant was not practicable due to its size and potential contamination, and other techniques to dislodge microorganisms from implants had to be considered.

The use of ultrasound to release bacteria attached to prostheses was included in the ISO (International Standardization Organization) standards. This technique consists of low-frequency ultrasound waves passing through the liquid around the prosthesis and creating areas of high and low pressure. Bacteria are liberated from the surface of the implant when microscopic bubbles that are formed during the low-pressure stage collapse during the high-pressure stage. The fluid surrounding the implant with the dislodged bacteria can be submitted for culture or analysis.

14.3 Evolution and Current Use

Different sonication protocols have been developed in an effort to obtain the highest possible numbers of viable bacteria from the implant sur-

face. In this context, the effects of the temperature, duration, composition of the sonication buffer and material in the sonication tube during bacteria sonication were evaluated [10], using sonication for 7 min at room temperature (22 °C). Further concentration of the sonicate solution by centrifugation allows a final volume of 400 μl to be obtained, and the suspended pellet can be divided into four portions of 100 μl for culture in different agar media. The duration of the sonication could be important to isolate Gram-negative bacilli, which can be eradicated with exposure longer than 15 min. While some protocols initially suggested culturing the sample for longer time periods [11], extending incubation of the samples to 14 days did not prove to add more positive results compared with a conventional 7-day incubation period [12].

At the end of the 1990s, Tunney et al. developed a sonication protocol for infected hip prostheses, followed by immunofluorescence and PCR (polymerase chain reaction) amplification [13]. Due to a high number of positive results in patients without clinical symptoms or signs of infection (potentially false positives), this method was not incorporated into clinical practice. Later, Trampuz et al. observed that the increased false-positive results associated with sonication could be due to the contamination of cultures by waterborne microorganisms in case of bag leakage and recommended the use of solid containers [14]. Using a protocol designed to avoid this problem, the same authors evaluated sonication in a classic study including a high number of patients with knee and hip prosthetic infections, with extremely good results that improved the sensitivity of periprosthetic tissue culture [15]. In this study, samples were processed in rigid plastic containers and vortexed prior to sonication in a high volume of buffer. Several months later, other studies [16] were published that confirmed the usefulness of sonication, even with different protocols [16, 17]. In the study performed by Esteban et al. [16], the risk of bag contamination was overcome by performing changes of the water in the sonicator before each procedure and by a careful inspection of the bags for leakages [16]. In this study, a concentration step using centrifugation of the sonicate and the use of a broad spectrum of culture media (designed to isolate uncommon organisms) was suggested to improve the sensitivity of the technique. The benefit of centrifugation was confirmed in a recent study, comparing the sensitivity of cultures after membrane filtration (30.3%) versus centrifugation (78.8%) [18]. Other studies using a combined approach with rigid plastic containers and centrifugation confirmed the good results [19].

Quantification of the number of microorganisms isolated from a sonicate fluid may help to distinguish infected from contaminated prostheses, and the breakpoint for infection is still a challenge. Importantly, centrifugation must be taken into account when a threshold is defined, without forgetting that the severity of infection is not only related to the amount of microorganisms but also to its taxonomy and antibiotic susceptibility.

Separate sonication of the implant components has also been suggested as an aid to determine if the isolate is a true pathogen or a contaminant (if the same microorganism was cultured after separate sonication of the different components). Most interestingly, a sonication study on separated components could not confirm a higher adherence to a particular component or to a particular biomaterial. Although the polymers were thought to more easily adhere microorganisms, this may not be true. Instead, the bacterial adherence primarily depends on the infective microorganism and the response of each individual patient and not specific materials (polymers) or components (polyethylene liners) [20].

The role of sonication of the polymethyl methacrylate (PMMA) spacer in a two-stage revision surgery of TKA is another matter of debate. Particularly, when PMMA spacers retrieved at the second stage of TKA revision surgery have shown attached microorganisms after sonication associated to poor outcome [21]. Therefore, PMMA spacers may be colonized in the long term if infection is not controlled, and spacer change may be required.

Previously cited sonication protocols have similarities that should be considered when incorporating the technique. After the implant retrieval, it must be placed in a sterile container

and sent to the laboratory with a maximum delay of 24 h (samples can be stored at 4 °C). In the laboratory, samples should be transferred to sterile containers, containing a specific volume of buffer. Samples should be then vortexed and sonicated during 5–7 min (not 15 min), and the sonicate should then be concentrated by centrifugation. The sediment will then be resuspended and inoculated in different media using a quantitative approach. Fungal cultures, mycobacterial cultures or both may be considered because samples are not easy to obtain and a maximum effort must be done to reach the most specific diagnosis.

In the above-mentioned European survey [3], implant sonication was only applied by one-third of survey respondents (36.4%), despite the available evidence of diagnostic effectiveness. This limitation may highlight the issues of cost and accessibility, but the current role of sonication to improve the diagnosis of TKA infection is still under development in many institutions.

14.4 Future Perspectives

Other centres have confirmed that the routine use of implant sonicate cultures in arthroplasty revisions improves the diagnostic sensitivity for detecting the presence of bacteria in both clinical and occult infections while maintaining the specificity [22]. The sensitivity of sonication was not affected by the timing of antibiotic interruption before surgery in a recent study [23], and it was concluded that sonication is an important tool to improve microbiological PJI diagnosis, especially in patients who received previous antimicrobial treatment.

When compared to culture alone, molecular detection of PJI based on sonication fluid can increase by one-tenth the number of patients diagnosed as having an infection [24]. Multiplex PCR-based systems, designed for the diagnosis of bone and joint infections using prosthetic-joint sonication, may play a role in rapid diagnosis of PJI, due to its high specificity and positive predictive value [25]. Sonication fluid may be a more appropriate sample than periprosthetic tissue for broad-range (BR) PCR analysis in patients with PJI [26]. Therefore, it is expected that sonication will spread and be incorporated into new diagnostic protocols of TKA infection for clinical standard management. Also, sonication may help to further spread research on early and accurate TKA infection detection, combining new molecular methods with precise sample isolation by implant sonication.

Conclusions

Sonication of retrieved implants at revision surgery is the best available option to harvest microorganisms colonizing the implant, those that maintain infection out of the reach of systemic antibiotic treatments. It is expected that sonication will spread and be incorporated into new diagnostic protocols of TKA infection for clinical standard management. Also, sonication may help to further spread research on early and accurate TKA infection detection, combining new molecular methods with precise sample isolation by implant sonication.

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15 Antibiotic Suppression in the Infected Total Knee Arthroplasty

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Abstract

Given its inefficiency to eradicate the infection and its potential costs, antibiotic suppression as definitive treatment of an infected total knee arthroplasty must only be used in patients who will not be able to undergo surgery due to the potential risks of the procedure. Antibiotic suppression commits the clinician to close observation of the patient and regular clinical follow-up. Repetitive knee aspirations must be avoided because of their potential complications and lack of therapeutic evidence. If it is possible, knee irrigation and debridement must be employed as this is superior to antibiotic suppression alone.

15.1 Introduction

Chronic antibiotic suppression is an alternative treatment strategy for patients who are not able to undergo surgery or patients in whom infection has not been eradicated despite surgery. This treatment consists of the administration of antibiotics indefinitely but with no curative intention, but with the objective of avoiding or reducing the symptoms related to the infection, and also avoiding its progression.

This treatment is reserved for patients who are not able to undergo surgery due to their clinical circumstances such as concomitant illness, fragility, or advanced age [1]. Obviously, the refusal of the patient to undergo another surgery is a clear indication for the suppressive antimicrobial therapy.

Factors other than the general clinical aspects of the patient are important. These include low bone stock, poor status of tissues around the prosthesis and multiple previous knee revision surgeries, and such circumstances may be indications for antibiotic suppression therapy.

The patient must be diligent with the dosage and timing, and also be fully aware of the consequences of this treatment. If the patient does not

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meet all these requirements, the treatment will probably fail.

There is another factor that is also essential: the status of the implant. If the prosthesis is loose [2], surgery is mandatory [3]. Antibiotic suppression can work against the infection in these cases, but the function of the patient will be far from optimal [4, 5]. Patients with more than one prosthetic implant will not be candidates for this kind of treatment.

Nevertheless, attempting to cure the infection with suppressive therapy is not really a realistic option. Eradicating the infection in every patient with only oral therapy is usually not achievable. The goal is to maintain knee function, to lighten symptoms, and to avoid the spreading of the infection that can cause severe damage to the patient's health.

And last but not least, the patient must be informed of the cost of treatment, economically, socially, and in terms of side effects of the long-term therapy with antibiotics. Cases of severe allergic reactions, toxicity, and other problems have been described, as well as development of resistant microorganism [6].

The most frequent type of infection is chronic infections. The most frequent bacteria are *Staphylococcus* coagulase negative, *Corynebacterium* spp., *P. acnes*, *Streptococcus*, and *Enterococcus* spp.

The second source of infection is acute hematogenous infection and early postoperative infection. Here the bacteria involved are usually more virulent and therefore more aggressive. *Staphylococcus aureus*, both methicillin sensitive and methicillin resistant, are the most frequent agents found here.

The detection of the bacteria causing the chronic infection is mandatory, because only with this certainty can personalized treatment for each patient be established, taking into consideration not only the agent but also the possible interactions, toxicity, and side effects.

15.2 Antibiotic Selection

The antibiotics prescribed must be individualized for every patient. It is necessary to use antibiotics with high oral bioavailability, good bone penetration, and few side effects and interactions. It is not necessary to undergo a prolonged initial intravenous phase, because the objective is not curative.

Combinations of antibiotics are also not recommended because they increase the risk of interactions and toxicity in prolonged treatments. It is recommended to use beta-lactams (amoxicillin, amoxicillin-clavulanic) followed by co-trimoxazole. Other options are clindamycin or doxycycline. Linezolid should be avoided given its dangerous side effects with prolonged use (neuropathy, myelotoxicity).

Rifampicin should not be employed as a sole agent but always in combination with other antibiotics and in the treatment of infections with implant preservation and curative intention (due to its anti-biofilm role and its good diffusion on it). Once the biofilm is well established, this kind of treatment is pointless.

Intermittent cessation of antibiotic suppression is not recommended, because doing this we will increase the risk of reinfection with a fatal prognosis in most of the cases. If toxicity appears, it is better to change the antibiotic than lay off the treatment.

Table 15.1 shows brief guidance with the main pathogen agents and their treatment options: antibiotic and dosing. The choice will be made under the criteria mentioned above.

Table 15.1 shows some practical examples of adequate chronic antibiotic suppression for some specific microorganisms. Of course, the possibilities of potential infectious agents and treatments are very much wider.

Another controversial aspect of antibiotic suppression is the length of treatment. Some authors did not include patients treated with less than 6 months of antibiotic suppression [1, 4–6]. Therefore, we must ensure that antibiotic suppression for patients that are not able to undergo surgery will last as long as the life of patients [1–7].

15.3 Major Side Effects

Antibiotic treatment can cause severe secondary effects that will make this therapeutic option problematic. The type of antibiotic

Table 15.1 Guidelines for antibiotic suppression in infected total knee arthroplasty (*TMP-SMX* trimethoprim sulfamethoxazole, *MS* methicillin sensitive, *MR* methicillin resistant)

Microorganism	Antibiotic	Three times daily	Two times daily	Once time daily
MS *S. aureus* MS coagulase-negative *Staphylococcus* *Streptococcus* spp. *Propionibacterium acnes*	Amoxicillin/clavulanic acid 500–800/125 mg	X		
	Clindamycin 300 mg	X		
	TMP-SMX 800/160 mg		X	
	Doxycycline 100 mg		X	
	Levofloxacin 500 mg			X
MR *S. aureus* MR coagulase-negative *Staphylococcus* *Corynebacterium* spp.	Clindamycin 300 mg	X		
	TMP-SMX 800/160 mg		X	
	Doxycycline 100 mg		X	
Enterobacteriaceae	Amoxicillin/clavulanic acid 500–800/125 mg			
	TMP-SMX 800/160 mg			
	Doxycycline 100 mg			
	Ciprofloxacin 500 mg			
			X	
Pseudomonas spp.	Ciprofloxacin 500 mg		X	
Anaerobics	Clindamycin 300 mg	X		
	Metronidazol 500 mg		X	

necessary to treat the infections will also be directly related to their side effects. Antibiotic suppression will require mandatory clinical evaluation of the patient, with the addition of the necessary blood analysis searching for other comorbidities like anemia, immunological alterations, hepatitis, and biochemical abnormalities that could indicate liver or kidneys problems.

Early side effects are usually digestive and cutaneous. The rest appear after the second or third weeks of treatment. Table 15.2 shows the most frequently found undesirable effects of antibiotics usually used for suppression of an infected total knee arthroplasty (TKA), both acute and chronic. In an elderly patient, many of the side effects shown in Table 15.2 can be potentially dangerous, especially pseudomembranous colitis related to clindamycin and the cutaneous Stevens-Johnson syndrome.

Other side effects like hepatotoxicity, cholestatic jaundice, and neutropenia can be treated by stopping antibiotic treatment at once but with the risk of TKA infection worsening which can also be fatal for the patient. A thorough assessment of the patient, noting and analyzing every new symptom that can indicate a severe side effect or inefficiency of the treatment, is paramount.

15.4 Antibiotics/Aspiration

This is another form of chronic suppression of an infection of TKA that combines the antibiotic treatment with the aspiration of the knee in order to decrease the bacterial load inside the joint [8].

Nevertheless, some authors have recognized the inefficiency of this kind of treatment, which is not really superior than antibiotic suppression alone [1–7, 9]. In addition, the consecutive puncture of the knee for evacuation is a clear point of entry for microorganism. For these reasons, the treatment with antibiotics/aspirations should be avoided as much as possible.

The aspiration of the knee is therefore only recommended for diagnostic reasons prior to TKA in patients that are able to tolerate surgery.

Table 15.2 Side effects of antibiotic suppression in the infected total knee arthroplasty (*TMP-SMX* trimethoprim sulfamethoxazole)

Antibiotic	Acute side effects	Chronic side effects
Amoxicillin amoxicillin/clavulanic acid	Nausea, diarrhea, rash, urticaria	Cholestatic jaundice, hepatitis, rash
Clindamycin	Diarrhea, nausea, vomiting, abdominal pain, rash	Pseudomembranous colitis
TMP-SMX	Rash, Stevens-Johnson	Neutropenia
Doxycycline	Nausea, joints pain, diarrhea, photosensitivity	Black cutaneous pigmentation
Linezolid (avoid)	Nausea, diarrhea	Anemia, thrombopenia, neurotoxicity, lactic acidosis

Conclusions

Antibiotic suppression for the treatment of an infection of a TKA, given its inefficiency to really control the infection and the potential costs, must only be taken into consideration for patients who will not be able to undergo surgery because of the potential risks of the procedure. If we choose this kind of treatment, we must accept the commitment to careful evaluation of the patient and regular clinical review. We must avoid frequent knee aspirations because of the potential complications and lack of therapeutic evidence.

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Arthroscopic Debridement of Infected Total Knee Arthroplasty

16

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Abstract

Arthroscopic debridement of infected knee arthroplasty is rarely used. Currently, it has a limited role as complete biofilm clearance is theoretically impossible. It is most effective in the very early phase of acute presentations of infected knee arthroplasty. It can be of use in cases where the organism is not associated with strong biofilm, in patients of extreme frailty, as an adjunct to suppressive antimicrobial medical therapy or as part of a diagnostic workup. If performed, high volumes of fluid and accessory portals should be used.

16.1 Introduction

Arthroscopic knee surgery has become one of the most commonly performed musculoskeletal procedures and has expanded to treat most knee pathologies. It traditionally enjoys the advantage of rapid recovery, reduced pain, less scarring and greater patient satisfaction when compared to arthrotomy. Arthroscopy is not, however, generally considered a frontline treatment for prosthetic knee joint infection, despite these advantages. Repetitive arthrotomies have a correlation with eventual poorer outcomes in terms of morbidity, soft tissue dysfunction and recurrent infection [1–4]; problems, theoretically at least, are not encountered with arthroscopy. It is certainly an order of magnitude less invasive than two-stage revision exchange arthroplasty, with which it must be compared as the established standard of care.

Arthroscopic debridement is probably better compared with open DAIR (debridement, antibiotics and implant retention) procedures as its indications and shortfalls are more similar. When evaluating the two against one another, it has limitations: it does not permit a radical debridement, exchange of polyethylene bearings (in itself possibly an independent risk factor for failure [5]) or unhindered access to the posterior aspect of the joint. Complete biofilm eradication is not a realistic aim, and its efficacy as a treatment of periprosthetic infection is constantly questioned [6–8]. The proposed mechanism of

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success in those cases where cure is achieved is through a reduction in the "bioburden" allowing for host immunity and subsequent antibiotics to overcome the infective process.

16.2 Suitability Criteria for Arthroscopic DAIR (Debridement, Antibiotics and Implant Retention)

Infection is confirmed on clinical symptoms (pain, effusion, swelling, fever) and biochemical markers [elevated plasma CRP (C-reactive protein level)]. It can be confirmed on aspiration and microbiological assessment though formal culture may follow arthroscopy to avoid delay. Rapid diagnostic microbiological techniques to determine species without formal sensitivities are useful guides to potential efficacy of arthroscopic treatment.

The patient must be fit for anaesthesia, and acute medical comorbidities should be managed rapidly prior to surgery. Biochemical imbalance, anticoagulation or diabetic adjustments are the common issues faced. The timescale may require reversal of anticoagulants if possible. Immunosuppressant treatments are not usually stopped as the timescale is too short. In the presence of systemic sepsis, surgery is urgent and should not be delayed for minor comorbidity corrections.

The knee should have healed surgical wounds with no presence of a sinus or abscess. Radiographs should be performed to rule out loosening, osteolysis and signs of osteomyelitis. These are all contraindications to arthroscopic treatment. If the knee is mechanically dysfunctional, revision exchange surgery is preferred.

Timing is critical, and most authors recommend it should be performed within 7 days of symptom onset, with several suggesting shorter timescales. Therefore, those patients presenting with acute symptoms from late haematogenous spread or those with early postoperative presentations are likely to be the most realistic surgical targets.

If microbiological information is available, it is invaluable in predicting chances of success; however, a protracted time to surgery should be avoided. Streptococcal species have a lower capacity to form biofilm (when compared to *Staphylococci* [9]) and are associated with higher success rates [10, 11]. Methicillin-sensitive *Staphylococcus aureus* (MSSA) and coagulase-negative *Staphylococci* are intermediately susceptible to implant retention [10]. Methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacteria are most resistant, with *E. coli* in particular highly unlikely to respond to arthroscopic DAIR [12] (or indeed any implant retention techniques).

Failure of arthroscopic DAIR is a contraindication to repeat surgery—one attempt may be deemed appropriate, but, in contrast to arthroscopic lavage of a native knee joint [13], repeat arthroscopic debridement is not indicated.

16.3 Technique

A high thigh tourniquet is applied and inflated. Standard anterolateral and anteromedial portals are used in the first instance with fluid sampling before irrigation for microbiological assessment. Fluid should be sent or cultured and for white cell counts, if available. At least four further samples should be taken with an arthroscopic punch, ideally aiming for bone-prosthesis interface points. Assessment should include microscopy, culture and sensitivity as a minimum. Histological analysis may be useful in doubtful cases or patients with inflammatory arthropathy. A superolateral portal is used for secondary irrigation as high volumes are used. An additional superomedial portal can be used to allow for further access. Posteromedial and posterolateral portals allow access to the posterior aspect of the joint as well as to the bone-cement-implant interface [12, 14, 15].

Debridement is performed with a soft tissue shaver in a systematic fashion. The surgeon should aim for complete synovial clearance of the suprapatellar pouch, medial gutter, intercondylar notch and lateral gutter. Attention is then turned to the bone-prosthesis interfaces and finally the posterior capsule. Thermal coagulation is minimized to reduce necrotic tissue for-

mation. Care must be taken throughout to avoid damage to bearing surfaces from cannulae and instruments; the femoral condyles are particularly at risk of scratching [16].

Irrigation should be via a pump through the superolateral portal, and combined suction and irrigation can be helpful [12, 15]. At the very minimum, 12 l of normal saline should be used for irrigation alone. The high volumes proposed are to maximise the removal of necrotic material. It should be noted that this takes time, and it is usual to take 45–60 min. Vancomycin can be added to the irrigant fluid at levels up to 250 mg per litre of saline. Closed, continuous irrigation suction with vancomycin is reported with 12 l of vancomycin solution per day used for up to 3 days [12]. Povidone-iodine or chlorhexidine lavage has been performed in the context of open DAIR procedure but has not been described for arthroscopic debridement [6, 17, 18]. A drain may be used for 24–48 h post-operatively or until drainage has ceased [14].

Close liaison with microbiology colleagues is mandatory. The patient should be started on broad spectrum antibiotics at induction of anaesthesia. Antibiofilm activity is mandatory in the antibiotics selected. If the bacterium has not been identified, assumption of *Staph aureus* and *Streptococcus* species is recommended as they are most frequently implicated in acute periprosthetic joint infection (PJI). Once the antibiogram is available, this should be narrowed down to an appropriate regime of intravenous or oral antibiotics depending upon the sensitivities. These are continued for a minimum of 12 weeks in most cases, with clinical and biochemical markers used to monitor recovery. Sometimes, arthroscopic DAIR is used as an adjunct to long-term suppressive antibiotics, and, in these cases, antibiotic therapy should be tailored accordingly.

16.4 Outcomes of Arthroscopic Debridement for Knee Infection

There is paucity of literature on the use of arthroscopy in PJI, particularly when used as a treatment modality (Table 16.1). Success rates range from complete failure [7] up to complete success [19]. However, the series are small, retrospective and heterogeneous, many reports being a subset of larger studies [6, 7]. There are some studies that have looked specifically at the procedure itself and have tried to analyse efficacy in terms of presentation, microbiology and procedural technique [12, 14, 15, 19–21] (Table 16.1).

Table 16.1 Literature specifically describing arthroscopic debridement and implant retention

Paper/reference	No. of knees	Duration of symptoms	Success rate	Comments
Flood et al. [19]	2	<12 h	100%	Gram +ve organisms with sensitivity
Waldman et al. [21]	16	<7 days	38%	
Dixon et al. [15]	15	not recorded	60%	Mixture of organisms, mostly *Staph* sp.
				Better results in cementless prostheses
Ilahi et al. [20]	5	<7 days	100%	12 l of irrigant
				Drain left in situ
Liu et al. [12]	17	<7 days	88%	Use of closed, continuous irrigation system
				Vancomycin added to irrigant
Chung et al. [14]	16	<72 h	62.5%	Remaining 37.5% underwent subsequent open procedure achieving 100% eradication

Arthroscopic debridement was first reported in two successful cases by Flood in 1988 [19]. However, larger series were less promising. Waldman et al. [21] reported 16 cases in 2000 with only 38% success. This contrasted with 83% success rate in a series of open debridements, performed by the same group. The group recommended it only in frail or anticoagulated patients.

Penicillin-sensitive streptococcal infection is reported to have the highest success rates. In a series of 19 patients from the Mayo Clinic, three were treated with arthroscopic DAIR with 100% success [22]. When looking at open DAIR, Zurcher-Pfund et al. demonstrated a much higher eradication rate with streptococcal infections over MSSA (up to 89%) [10]. This is likely due to a poorer rate and quality of biofilm production when compared to MSSA [9]. This is an area where arthroscopic debridement could be considered.

Time from onset of symptoms seems to be a crucial variable in the ultimate success of arthroscopic debridement, irrigation and implant retention. If the symptoms are less than 12 h old and the arthroscopy is performed within 12 h of admission, the success rate may be 100% [19]. In previously well-functioning TKRs, arthroscopic debridement up to 72 h from the onset of symptoms can result in a 62.5% success rate [14]. Most literature on the subject involves patients with late-onset infections due to acute haematogenous spread. Ilahi et al. demonstrated 100% survivorship of implants in five patients treated within 7 days of clinical onset [20]. Liu et al. included 17 patients in their study with, again, less than 7 days of acute symptoms, reporting an 88% prosthesis survival rate [12].

Implant type may have a bearing on the outcome. Dixon et al. noted a trend suggesting a more favourable outcome following arthroscopic debridement of cementless TKRs over cemented ones [15]. Some authors have theorised that infection eradication may be more effective in cementless TKR due to the absence of an "avascular" zone, i.e. bone-cement-prosthesis interface [23]. It is harder to perform arthroscopy on more constrained prostheses, and there does not appear to be a place for arthroscopic treatment of revision implants. Arthroscopic DAIR of compartmental knee replacements is not, as yet, reported.

There are papers reporting particularly poor results. Byren et al. evaluated the use of debridement and implant retention in 112 cases (13% arthroscopic debridement), finding success rates of 47% for arthroscopic washout and 88% for open washout. Arthroscopic surgery was also a significant predictor of failure of subsequent revision surgery [6]. Dixon et al. reported implant retention in 9 of 15 patients [15]. The 2013 International Consensus on Periprosthetic Infection had 90% agreement that there is no role for arthroscopic debridement of infected knee replacement [24].

Failure of DAIR is associated with failure to exchange meniscal bearings and failure to perform extensive debridement of the whole soft tissue envelope. As neither is possible in arthroscopic debridement, many authors dismiss the technique as inadequate and do not routinely practise it.

There has not been a prospective trial comparing arthroscopic with open debridement, and it seems unlikely that there ever will. Similarly, there are no studies alluding to arthroscopy followed by lifelong suppression treatments.

Conclusions

The aim of treatment is elimination of all microorganisms with maintenance of a stable, pain-free joint. The patient will benefit most from the least invasive technique which eradicates infection. Avoiding revision surgery reduces the risks of bone loss or aseptic failure mechanisms. Avoiding an arthrotomy means less damage to the extensor mechanism and lower wound failure rates. The choice of treatment of acute PJI is multifactorial, and the doubts as to the efficacy of arthroscopic debridement mean that it is often overlooked. It is, undoubtedly, the least invasive surgical option and can be considered in a small number of patients who meet several criteria. It is only suited to acute infective presentations of well-fixed implants. Success is far from guaranteed and is only likely in streptococcal infection. The arthroscopic surgery is only the

beginning of treatment, and prolonged antibiotic therapy is mandated. It should never be used in chronic infected cases.

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17 Open Debridement and Polyethylene Exchange (ODPE) in the Infected Total Knee Arthroplasty

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Abstract

Of the methods used for the treatment of periprosthetic joint infections (PJIs), open debridement and polyethylene exchange (ODPE) is technically the least demanding, the most economical, and with lower morbidity in comparison with one- or two-stage revision arthroplasty. However, the failure rate of ODPE can be high and can compromise outcomes of the two-stage revision. ODPE has been recommended as a treatment for PJI in patients with an early (<4 weeks) postoperative infection or an acute hematogenous infection if the duration of clinical signs and symptoms is less than 3 weeks. ODPE should not be recommended in chronic infection (>4 weeks postoperatively, insidious onset of symptoms). ODPE is indicated in patients who have a well-fixed prosthesis and local soft tissues in good condition (no abscess or sinus tract). ODPE has shown to be particularly effective in PJIs caused by low-virulence organisms. ODPE can be a good option in elderly patients with less bone stock and multiple comorbidities, for whom anesthesia and more invasive/complex surgery could be dangerous. ODPE has been shown to be effective in non-immunocompromised patients. Arthroscopic irrigation and debridement have inferior results as compared with open debridement.

17.1 Introduction

Open debridement and polyethylene (PE) exchange (ODPE) is also known in the literature as DAIR (debridement, antibiotics, implant, retention) or IDCR (irrigation and debridement with component retention) [1, 2].

Of the methods used for the treatment of periprosthetic joint infections (PJIs), ODPE is technically the least demanding, with reduced cost and lower morbidity in comparison to one- or two-stage revision. However, the failure rate of this procedure

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can be high and can compromise outcomes of the two-stage revision. Sherrell et al. [3] reviewed 83 PJIs that underwent a two-stage revision total knee arthroplasty (TKA) after a failed ODPE with a failure rate of 34%, higher than previously reported failure rates of two-stage revision (mean 11%).

On the other hand, a recent study by Brimmo et al. [4] has demonstrated that the failure rate of two-stage revision TKA is not increased by prior failed ODPE. They showed an estimated overall success rate of 91% at 4 years in patient who underwent preliminary ODPE, in comparison with the group without prior ODPE whose success rate was estimated as 84.8% at 4 years.

In this chapter, we discuss the role of ODPE in the infected TKA.

17.2 Indications

ODPE is recommended for a small subset of patients [5, 6]:

1. Early (<4 weeks) postoperative infection (Tsukayama [7] type II) or an acute hematogenous infection (Tsukayama [7] type III) if the duration of clinical signs and symptoms is less than 3 weeks. ODPE should not be recommended in chronic infection (>4 weeks postoperatively, insidious onset of symptoms).
2. Patient who have a well-fixed prosthesis and local soft tissues is in good condition (no abscess or sinus tract).
3. The identified pathogen (not merely its methicillin resistance) should influence the decision for prosthesis retention in knee PJIs [8]. ODPE has shown to be particularly effective in PJIs caused by a low-virulence organism. ODPE is a reasonable option if an agent with activity against biofilm microorganisms is available. Intravenous treatment should be administered for 2–4 weeks, followed by oral therapy [9].
4. Finally we should assess the patient's health status. ODPE can be a good option in elderly patients with less bone stock and multiple comorbidities, for whom anesthesia and more invasive/complex surgery could be dangerous. ODPE has been shown to be effective in non-immunocompromised patients.

Arthroscopic irrigation and debridement have inferior results as compared with open debridement.

Exchange arthroplasty in one or two stages has disadvantages such as pain, financial implications, and the potential need for a constrained prosthesis. The best results for quality of life and functional outcome, according to the 36-Item Short-Form Survey (SF-36) and Western Ontario and McMaster Universities Arthritis Index (WOMAC), occur in patients undergoing ODPE as compared to one-stage and two-stage revision [10].

Furthermore, the patients treated with ODPE whose infections were successfully eradicated had equivalent functional outcomes compared to a control group of patients with non-infected TKAs. Dzaja et al. no found difference in scores: WOMAC, Knee Society Score (KSS), and the 12-Item Short-Form Health Survey (SF12) or range of motion (ROM) [11].

17.3 Surgical Technique

Joint aspiration should be carried out to identify the organism prior to surgery. If the patient is otherwise stable, tissue cultures (×5) are obtained before starting antibiotics.

The surgical procedure includes:

- The tourniquet is inflated by elevation or remains uninflated according to surgeon preference.
- Under aseptic conditions, the joint is accessed via the previous surgical approach, and the scar is excised. If more than one previous skin incision exists, the most lateral incision should be used.
- Excision of any sinus tract.
- Medial parapatellar arthrotomy (Fig. 17.1).
- Total and meticulous synovectomy. Remove all synovial tissue in the suprapatellar pouch, followed by the medial and lateral gutters. If exposure is inadequate, a quadriceps snip can be necessary (Figs. 17.2 and 17.3).
- Circumferential exposure and debridement of prosthesis–bone interfaces. Removal of cement, wires, cables, and nonabsorbable sutures should be included. The stability of the prosthesis must be confirmed intraopera-

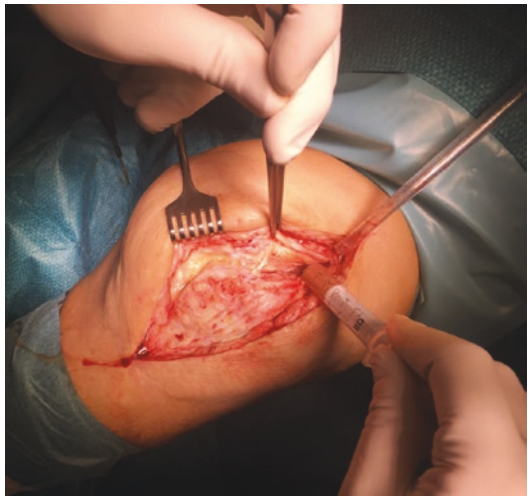

Fig. 17.1 Medial parapatellar arthrotomy and aspiration of the articular fluid to analyze with the aim of identifying the causing microorganism

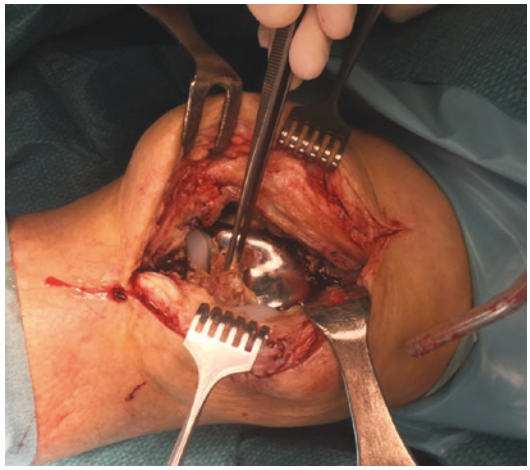

Fig. 17.2 Intraoperative photograph of a patient with an acute infection after total knee arthroplasty (TKA). Note the thickened synovial tissue

tively (integrity of the cement–bone or prosthesis–bone interfaces and implant firmly fixed and mechanically sound) [12].

- Exchange of the PE insert. This allows access to the posterior aspect of the joint and between the metal tibial tray and the PE.
- The joint is filled with a 0.35% betadine solution or 0.05% chlorhexidine gluconate [13] and allowed to soak for 3–5 min. All retained components must be scrubbed.

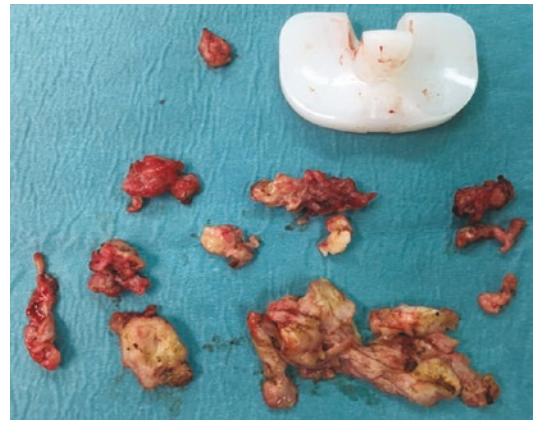

Fig. 17.3 Synovial tissue and polyethylene (PE) insert removed

- The joint is irrigated with 6–10 L of irrigation solution. The use of pulse lavage is acceptable.
- The operating team must change gowns, gloves, and instruments: the redraping is done, and new PE insertion is performed.
- Finally, wounds are closed primarily; drains are used, which are removed at 48 h or when drainage ceases.

17.4 Risk Factors for Failure

17.4.1 Acute Hematogenous Infection

The treatment of acute hematogenous PJIs with ODPE has been shown to be successful in the majority of patients (76% survivorship at 2 years). Survivorship of the prosthesis was 45% for patients with a staphylococcal infection and 96% for patients infected with organisms other than *Staphylococcus* species. In patients who developed recurrent infection, the rate of success was less than 50%. Twenty-five percent of patients died within 2 years of the treatment of their infection, indicating that an acute hematogenous infection may be a marker of poor general health predisposing to this complication [14].

Vilchez et al. [15] reported that ODPE in patients with hematogenous PJI due to *S. aureus* had a worse outcome than early postsurgical

infections (failure rate 58.7% vs 24.5%, respectively).

17.4.2 Virulence of the Microorganism

Many studies have reported that virulence of the microorganism was one of the risk factors for the failure. Silva et al. [16] reported in a systematic review that if the infecting bacteria are resistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE), it would be better to consider a two-stage revision rather than ODPE.

In a multicenter retrospective study, Bradbury et al. [17] reviewed 19 cases of acute periprosthetic MRSA infection managed by ODPE and suggested that the total failure rate of ODPE in acute periprosthetic infection (<4 weeks) was 16 cases (84%). They recommended a two-stage exchange arthroplasty for periprosthetic MRSA infection.

Streptococcal PJI is associated with high recurrence rates, which are even higher than observed in staphylococcal PJIs. Zürcher-Pfund et al. [8] reviewed 599 published cases of PJIs treated with ODPE and found an overall recurrence rate of 47% with a significantly higher rate for streptococcal than staphylococcal infection 43/54 (79.6%) and 144/324 (44.4%), respectively ($p < 00.01$).

In a multicenter study of PJI managed by ODPE using rifampin for MRSA infections, Lora-Tamayo et al. [18] stated that it may have contributed to homogenizing methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA prognoses.

The relatively poor results of staphylococcal infections are likely due to biofilm production and associated antibiotic resistance. Biofilm formation is enhanced in staphylococcal foreign body infections compared to streptococcal PJIs [19].

17.4.3 Sinus Tract

The presence of a sinus tract has been associated with treatment failure and is a contraindication to ODPE [9]. Marculescu et al. [20] revised 99 PJI treated with ODPE. The PJIs that involved a sinus tract at presentation were associated with treatment failure of 39%, compared with 64% among those without sinus tract at presentation.

17.4.4 Polyethylene (PE) Exchange

PE exchange is usually recommended as a part of thorough debridement. Choi et al. [21] showed that not exchanging the PE insert was an independent risk factor for failure. They report 59% failures in cases without PE exchange resulting in a poor infection control rate. Infection control rates were higher when PE was exchanged than when it wasn't ($p < 0.001$). Regardless of the causative organisms, lack of PE exchange resulted in poor outcome.

Kim et al. [22] reported that PE exchange was one of the factors affecting the success of ODPE. They performed PE exchange in cases of open debridement and did not perform PE exchange in cases of arthroscopic debridement. They report 58.8% failures treatment in cases without PE exchange resulting. They concluded that PE exchange can prevent the recurrence of infections.

17.4.5 Arthroscopic Versus Open Debridement

Arthroscopic debridement is a less invasive procedure than open debridement. Some authors have employed arthroscopic debridement in acute infections. Ilahi et al. [23] reported 100% success in seven patients, and Liu et al. [24] reported 88% success rate in 15 patients they treated, but others report a lower success rate when compared to open debridement. Waldman et al. [25] suggested that only 38% of infected knees were successfully treated using arthroscopic debridement and recommended the use of open debridement for infected TKA.

An ODPE procedure is difficult to carry out arthroscopically because this does not allow access to all compartments and some parts of the joint, especially the posterior compartment; it is impossible to exchange the PE insert and remove

microorganisms present between the metal tibial tray and the PE liner [22]. For this reason, it is not currently recommended in the treatment of PJI.

17.4.6 Single Versus Multiple ODPE

Most studies would regard the need for a further procedure as failure of the index procedure. Vilchez et al. [26] showed that the need for a second debridement ($p = 0.002$) was an independent predictor of failure. Therefore, repeated ODPE procedures are not recommended and indicate failure and the need for an alternative procedure. However, Mont et al. [27] performed one to three irrigation and debridement procedures based on systemic signs, knee symptoms, or the results of knee aspirations.

17.4.7 Preoperative Erythrocyte Sedimentation Rate (ESR)

Kim et al. [22] reported that the preoperative ESR was one of the factors affecting the success of ODPE. The mean preoperative ESR in the success group (69.1 ± 35.5 mm/h) was lower than that in the failure group (103.5 ± 43.7 mm/h; $p = 0.021$). Kuiper et al. [1] demonstrated that ESR at presentation above 60 mm/L was one of the factors associated with failure of ODPE. More studies including a greater number of cases are needed.

Table 17.1 summarizes the success rates of OPDE in the infected TKA.

Table 17.1 Success rates of open debridement and polyethylene exchange (OPDE) in the infected total knee arthroplasty (TKA)

Study	Number of cases	Success rate
Marculescu et al. [20]	99	60%
Byren et al. [12]	112	72%
Sherrell et al. [3]	83	66%
Lora-Tamayo et al. [18]	345	55%
Kim et al. [22]	28	60, 7%
Lindberg-Larsen et al. [28]	105	57%

Conclusions

The literature has not identified randomized controlled or prospective trials of the ODPE procedure as a treatment option for PJIs. The literature consists of various retrospective series both in orthopedic and microbiology journals with variable opinions over each aspect of ODPE. It may well be appropriate in selected cases, although the potential risk of a worse outcome from the salvage staged revision procedure should be considered.

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18 One-Stage Revision Arthroplasty in the Infected Total Knee Arthroplasty

Jurek R.T. Pietrzak, David A. George, and Fares S. Haddad

Abstract

A single-stage exchange arthroplasty is becoming an increasingly viable option in patients with chronic periprosthetic knee infections. In this chapter, we discuss the history of a single-stage exchange, its advantages, patient inclusion criteria, the surgical technique, role of antibiotics, and outcomes in terms of infection eradication, functional outcome, and economic impact.

18.1 Introduction

There is an increased demand for primary total knee arthroplasty (TKA) worldwide. In the UK, the number of TKAs performed in the NHS has increased from 74,000 in 2007 to 86,000 in 2013. A substantial increase in the need for revision TKA exists simultaneously, with a 92% increase in the number of revision TKAs performed in the UK [1] over the last 5 years. Similar escalating trends have also been seen in the Australasian and Nordic joint registries [1–3].

Multiple indications for revision surgery exist, including periprosthetic fractures, aseptic loosening, malaligned symptomatic prostheses, and implant wear or infection. The principles of managing an infected prosthesis include the eradication of infection, prevention of recurrence, and functional restoration, within the constraints of an ever-increasing financial strain [4].

The current gold standard for the treatment of chronic periprosthetic joint infection (PJI) of the knee is a two-stage arthroplasty revision and is discussed in depth in subsequent chapters [5, 6]. Here, we discuss the merits of a single-stage (one-stage) revision arthroplasty for the infected knee prosthesis.

18.2 Background

In the 1970s, Buchholz introduced the concept of adding antibiotics to bone cement [7]. This was met initially with much skepticism, but he demonstrated that this novel approach of manipulating the antibiotic content of cement reduced the infection rate from 3% to less than 1%. This principle has been designated as the cornerstone for

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the implementation of a one-stage exchange arthroplasty at the Endo-Klinik, Hamburg (Germany). One-stage exchange arthroplasty was subsequently first described by Buchholz [8] in 1981 and then by Freeman [9] in 1985.

Although a one-stage exchange remains a relatively unorthodox, unconventional, and unfamiliar approach to PJI in many parts of the world, it is being performed increasingly routinely throughout Europe, yielding encouraging results [10, 11]. A one-stage exchange revision strategy has been reported to eradicate infection in 67–100% of patients [5, 10–15]. As a result, interest in one-stage revision for PJI in TKA is intensifying worldwide.

18.3 Perceived Advantages

One-stage revision involves only one operation. It entails the removal of the infected prostheses, surgical debridement of all necrotic and infected tissue, and subsequent reimplantation of definitive revision prostheses at a single sitting. In comparison, a two-stage revision involves a further separate operation to repeat the debridement and exchange the temporary spacer (implanted during the first stage) for the definitive revision prostheses, after a defined, often protracted, period.

Therefore, the potential exists for improving the patient experience through a single operation. A shorter inpatient hospital stay is expected with subsequent reduced economic burden for the patient, hospital, and the insurance provider, the functional outcome may be improved as the knee may immediately be mobilized, and the emotional status of the patient may be enhanced with less time off work and away from their home and hobbies [16–18].

18.4 Inclusion Criteria

In order to optimize the outcomes of a one-stage exchange, strict inclusion criteria are employed to identify those patients most likely to benefit from one-stage exchange:

1. Have insignificant bone loss and a soft tissue defect that may be closed primarily.
2. Are not immunocompromised.
3. Have a low virulent organism which is sensitive to available bactericidal antibiotic therapy identified preoperatively.
4. Patients should be able to tolerate an esthetic.

An international consensus group of arthroplasty surgeons and researchers reached a strong consensus (78%) on which patient groups should not have one-stage exchange [19, 20]. The criteria included:

1. The presence of generalized sepsis
2. Infections in which the bacteria is not identified
3. Infection caused by drug-resistant bacteria
4. The presence of a sinus tract
5. The presence of severe soft tissue deficiency over the joint

A chronic discharging sinus is mostly regarded as a poor prognostic sign [11], as this may prevent the accurate isolation and subsequent identification of the organism by potentiating the contamination of preoperative cultures. Despite a two-stage exchange arthroplasty being recommended, some centers report a 86% infection eradication rate in patients with a chronically discharging sinus treated with one-stage exchange at an average of 7-year follow-up [21].

Patients should have a two-stage revision procedure in the event that the preoperative work-up has identified a multidrug-resistant organism like methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-resistant *Staphylococcus epidermidis* (MRSE), unusual commensals or pathogens with atypical resistance profiles. The inability to precisely identify the infective pathogen, and therefore not have the sensitivity profile for antibiotic regime planning, should also exclude patients from undergoing one-stage exchange.

Patients who are immunosuppressed and have concurrent sepsis, or acute or chronic focal sites of infection, should be excluded from undergoing a one-stage exchange. The presence of a systemic disease, such as diabetes, rheumatoid arthritis, or HIV may not be a definitive contraindication for one-stage exchange [22–25]. Patients should however not be on any long-term medication or

immunosuppressant drugs for the management of these chronic diseases.

A systematic review revealed higher unsuccessful outcomes in those patients undergoing a single-stage exchange in the presence of an underlying rheumatologic condition, poor physiological status, or infection with an atypical organism [26].

The quality of the local skin and bone stock may also preclude a one-stage exchange. Bone loss should be no more than an Anderson type I or II defect [27, 28]. In Anderson type 1 defects, the tibial and femoral metaphyseal bone is intact with minor defects that do not affect the stability of the implant, and subsequently the use of primary implants is preferable. In type 2 defects, the femoral and/or tibial metaphyseal region is damaged with loss of cancellous bone that can affect a condyle or tibial halfplate or both, which may require augmentation to restore the joint line and the stability of the knee. In the event of considerable bone loss, the use of allograft may be necessary to ensure structural integrity and implant stability. The use of allograft, however, is not a favorable surgical adjunct in one-stage exchange with its heightened potential for becoming infected.

Infection that has spread to and involves the neurovascular bundle excludes the potential to embark on this course of treatment too [29]. Furthermore, the inability to achieve soft tissue coverage precludes a one-stage procedure, and a two-stage revision should be advised [22, 23].

Failure of two or more previous attempts at a one-stage exchange, including isolated joint washouts and debridement and implant retention (DAIR), should also preclude the patient from undergoing another effort [30]. However, no randomized clinical trial exists today delineating definitive indications and contraindications for the selection of one-stage rather than a two-stage approach.

18.5 Surgical Technique

The outcome of the one-stage exchange is technique dependent. Efficient, extensive debridement and meticulous surgical technique are imperative [72]. The reduction of the bioburden is a fundamental component of the procedure. Here we describe the technique undertaken by the senior author (Figs. 18.1, 18.2, 18.3, 18.4, and 18.5).

One-stage exchange surgery should be viewed as two entirely separate surgical procedures making up a single operation. Prophylactic antibiotics should not be given preoperatively as per routine and only once sufficient samples have been taken and sent to the microbiologist. A laminar flow theater is preferred, however, not a necessity.

A tourniquet should be applied but not inflated during the initial surgical debridement, making it easier to distinguish between healthy, bleeding tissue and necrotic, infected tissue. This also decreases the potential for complications related to tourniquet use.

The skin is prepared twice with 3M DuraPrep solution which contains iodine povacrylex and

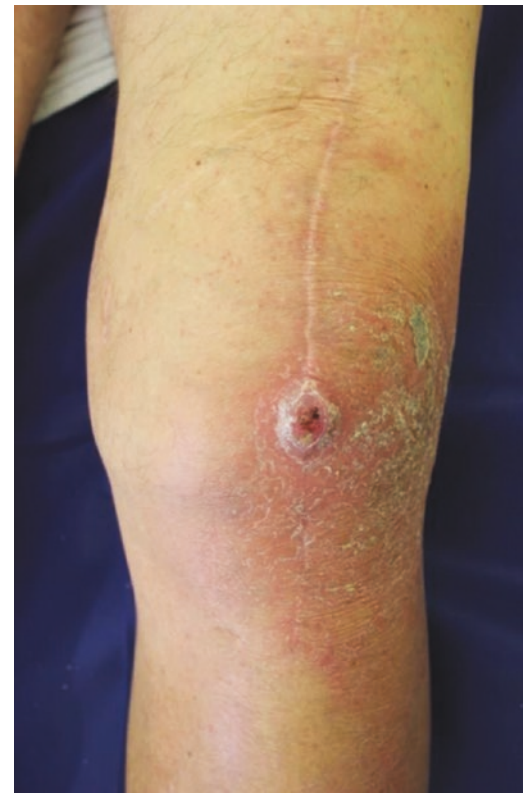

Fig. 18.1 Left PJI knee infection, with a sinus

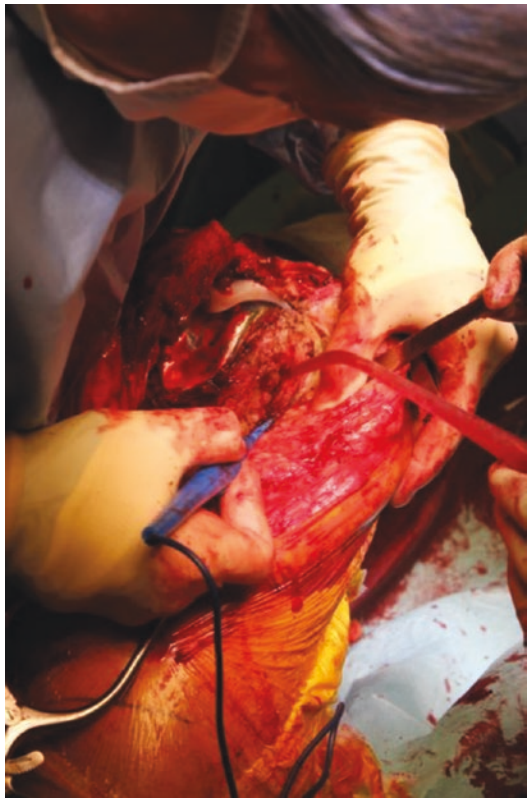

Fig. 18.2 Complete excision of all necrotic tissue

Fig. 18.3 Minimal bone loss seen after removal of the tibial component

isopropyl alcohol [11]. The skin is covered by a 3M Ioban antimicrobial incision drape.

During the initial phase, the surgeon must take great care when planning the skin incision. Previous skin incisions must be clearly marked to ensure they are distinctly visible after skin preparation and draping [31–33]. Skin necrosis may be avoided by ensuring that surgical incisions are generally at an angle of >60° to old incisions and skin bridges of >7 cm are preserved [32–34].

In the presence of multiple scars, the incision most recently made should be used, and the most lateral longitudinal surgical incision through which adequate exposure is possible should be selected. The blood supply to the anterior part of the knee is mostly derived from the medial aspect, and therefore the safest skin incision is the most lateral [32, 33, 35]. Cutaneous blood supply arises from deep to superficial, and therefore thick skin flaps are essential. Preexisting transverse skin incisions should be transected at a perpendicular angle [33, 36].

Fistulae must be incorporated into the skin excision and radically excised down to the joint capsule [29]. A plastic surgeon may need to be on hand if any musculocutaneous flaps are anticipated, but this will often necessitate a two-staged exchange arthroplasty.

Once incised, the first part of the operation involves a knee joint arthrotomy and the aggressive open surgical debridement of the periarticular soft tissue envelope. Careful attention must be paid to the posterior capsular soft tissue which is often neglected. It is essential to remove all prosthetic components without any unnecessary bone loss and inadvertent periprosthetic fractures. It may be easier to remove the cemented prostheses than well-fixed, uncemented implants. It is important to remove all cement within the distal femoral and proximal tibial canals to remove biofilm and necrotic tissue [11].

Cortical windows may be utilized to gain access to the interface in uncemented implants with good bony ingrowth. High-speed burrs and curved sharp osteotomes may facilitate expeditious extraction. Universal or special extraction instruments may be employed to remove the implants. However, general punches may be used to good effect. The amount of resected material in the debridement of a one-stage exchange must be extensive and may even exceed that removed in a two-stage procedure [29].

Multiple specimens should be collected for microbiological and histopathological evaluation representing the whole surgical field [37, 38] and

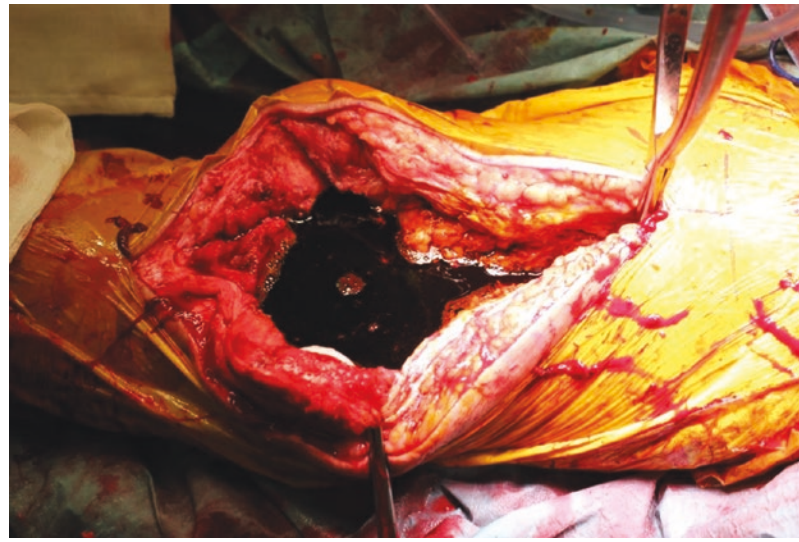

Fig. 18.4 Betadine placed in the wound at the end of the debridement

Fig. 18.5 Hydrogen peroxide acting as a mechanical debridement

labeled appropriately to reflect the anatomical area from which the specimens are taken (minimum of five specimens). This step is imperative to guide appropriate postoperative antibiotic therapy.

The administration of parenteral antibiotics selected empirically preoperatively or based on culture sensitivities should be administered after all specimens have been obtained. The omission of preoperative, prophylactic antibiotics until intraoperative microbiological specimens have been obtained is controversial [11]. Some studies have shown that they have no impact on subsequent isolation of organisms from these specimens. Regardless of preoperative antibiotics, bacterial cultures from intraoperative specimens and preoperative aspirates have been shown to be the same in 97% of cases [39].

Irrigation of the surgical field with copious amounts of fluid is essential. After debridement, 12 L of warm 0.9% saline via low pressure pulsatile lavage is used. Thereafter, 100 mL of a 50:50 mix of 3% hydrogen peroxide and 100 mL of sterile water solution are added. The excess hydrogen peroxide is subsequently removed from the surgical field by 100 mL of sterile water

solution. Next, 200 mL of sterile 10% aqueous povidone-iodine is used as an irrigant.

Antibiotics can be added to irrigation fluids [40, 41]; however, this has not been shown to result in any significant clinical improvements [42, 43]. Care should be taken as systemic absorption and toxicity, bacterial resistance, and additional costs may result from complications of this practice [40, 41].

Once satisfied that the surgical field is macroscopically clear of infected tissue, the wound is packed with povidone-iodine-soaked gauze, and the wound edges are approximated with a continuous one Vicryl.

A sterile antimicrobial drape is used to cover the wound, thus maintaining sterility while in use. Soiled drapes are exchanged for clean sterile ones, and the surgical team don new gowns. Additionally all the equipment, reusable or disposable, are removed from the operating room, and new instruments are brought into the theater.

The wound is then opened, sutures discarded, and the entire surgical field undergoes a further lavage. Similarly to a two-stage exchange, at this point intravenous antibiotics should be given as per recommendations of the microbiologist and infectious disease specialist [44]. Antibiotics may also be added at the time of inserting the definitive implant by adding it to the cement [45] and mixing it to bone graft (if uncemented) [46] along the femoral stem or via adjuncts such as calcium sulfate pellets [47, 48].

The tourniquet is inflated before cementing to improve the cement-bone interface [49]. Before closure, the wound is again irrigated with 1 L of 0.9% sodium chloride. Drains may be inserted to prevent postoperative hematoma formation. Expeditious drain removal ideally within the first 24 h will allow high concentrations of antibiotics postoperatively in the surgical field.

18.6 Antibiotic Role

As already discussed, the use of antibiotics and cooperation between the surgeon and their infectious disease and microbiology colleagues are essential in a single-stage exchange.

In uncemented single-stage revisions, Winkler et al. utilizes vancomycin-impregnated allograft and has demonstrated high local levels of vancomycin over 2–8 weeks [46]. This sustained elution prevents local bacterial contamination and biofilm formation, preventing reinfection in 92% of 37 infected hip replacements seen at a minimum of 4 years of follow-up [46].

Postoperatively, the optimal timing to switch from intravenous antibiotics therapy to oral remains controversial. The decision is influenced by the host, duration of symptoms, bacteria type, and the antimicrobial sensitivity [50] and typically given for 10–14 days [44]. Streptococci infection may demand longer periods of antibiotic therapy. Oral antibiotics may be commenced after 2 weeks.

The choice of antimicrobial agent may need to be modified, if the resistance profile of the bacteria isolated during the one-stage exchange differs from the previous cultures [51]. Advice should be sought from the microbiologist or infectious disease specialist, an integral member of the multidisciplinary team.

18.7 Outcome Measures

18.7.1 Infection Eradication

The results of the literature comparing one-stage and two-stage exchange arthroplasty are based mainly on individual single center, small retrospective series with short- to medium-term follow-up [52]. In these papers, a standardized definition of the endpoint or treatment failure is often lacking.

Von Foerster et al. [53] reported the first series of one-stage exchanges in 1991 from the Endo-Klinik in Hamburg [18]. This series involved 104 TKAs that were revised for PJI. A constrained, stemmed, rotating-hinge prosthesis was used in all cases. A favorable outcome was reported in 76 cases (73%), a follow-up of between 5 and 15 years, but persistent infection was seen in 20 knees.

Buechel [54] reported on a series of 22 TKA PJI managed with a one-stage exchange. The

infection was eradicated in 20 knees (90.9%) at a follow-up of 10.2 years. He reported good or excellent knee scores in 18 knees (85.7%). Parkinson [52] proposed a 6-week postoperative course of sensitive oral antibiotics after eradicating infection in 100% of the 12 patients at a mean follow-up of 2 years.

In a comparison of outcomes between one- and two-stage revisions for infected TKAs, Bauer et al. [55] conducted a retrospective multicenter study involving 107 patients with no differences in the ability to eliminate infection between either technique. However, Silva [14] reviewed data from 30 papers, and a one-stage exchange showed a favorable outcome.

Chew et al. [26] conducted a systematic review of 12 studies describing one-stage exchange arthroplasty in 433 revision surgeries. This meta-analysis highlighted the heterogeneity in reviewing this condition as there were marked differences in these papers with regard to surgical techniques, implant usage, and philosophies in fixation and antibiotic regimens, and often surgical techniques were not described within the original papers.

18.7.2 Function

Early ambulation and a prompt initiation of functional exercises is a significant benefit of one-stage exchange, compared to the two-stage exchange where an articulating or non-articulating spacer may be used. Postoperative rehabilitation focuses on improving range of movement to prevent joint stiffness and fibrosis and recovery of normal gait. Immediate full weight bearing with crutches should be commenced within the first postoperative day.

Buechel [54] and Singer [10] reported good to excellent functional outcomes in most patients who underwent one-stage exchange arthroplasty. They published Knee Society Scores (KSS) of 79.5 and 72, respectively, which is better than they had seen in two-stage revisions.

Haddad [5] used strict selection criteria to determine suitable patients for a one-stage exchange and subsequently compared the outcomes directly with those patients who underwent two-stage revision surgery for chronic PJI of the knee. Infection control was achieved in all of the patients who underwent one-stage exchange surgery, while the infection was eradicated in 93% of the two-stage group. The functional outcomes were also significantly superior in the one-stage group (KSS score, 88 vs. 76; $p < 0.001$).

Zahar et al. [56] reported on the Endo-Klinik's 10-year survival rate for one-stage exchange of infected TKA was 93% ($p = 0.007$). Correspondingly, the 10-year survival rate for knees revised for a reason other than infection with a one-stage exchange arthroplasty during this period was 91% (mean, 5.2; 95% CI, 86–95%; $p < 0.002$).

Baker et al. [57] compared the functional outcomes using Patient Reported Outcome Measures (PROMs) and satisfaction rates in 33 one- and 89 two-stage revision TKA for PJIs. Assessment of outcomes using PROMs was unable to demonstrate any difference between the two approaches. The ultimate satisfaction rates were equivalent, and no difference in general health perception was noted. The conclusion was that eventual functional results could not be used as a determinant in the selection of either one- or two-stage revision.

A meta-analysis undertaken by Kunutsor et al. [58] comparing both treatment options, demonstrated comparable postoperative knee range of movement and equivalent knee scores, although the numbers in the one-stage exchange cohort are comparably small.

One must also consider the significant psychosocial implications of the infection and the impact of subsequent investigations and medical and surgical treatments. It affects all aspects of the patients' lives as demonstrated by Moore et al. [59]. They highlighted the emotional distress and psychosocial imposition were greater in those treated with a two-stage revision than a one-stage exchange, as a result of the longer periods of immobility and time in-between surgical procedures. An increased need for psychosocial and rehabilitative support during the duration of treatment and rehabilitation may be necessary.

18.8 Economic Impact

Revision TKA represents a significant economic burden. Individual surgical procedures are expensive as a consequence of the combined costs of preoperative investigations, prostheses and instrumentation, an extended hospital stay, and weighty pharmacological costs [60]. The expense attributed to the revision implants and preoperative investigations has been implicated as a major cost driver to improving patient care [60]. The forecasted cost of revision TKA in the USA is predicted to surpass $2 billion by 2030 [61].

Direct comparisons of the differences in costs involved between the one- and two-stage philosophies are challenging. The type of hospital facilities, individual patient factors, surgeons, and the infecting organism itself influence these costs.

It may, however, be inferred that in the event of only one major surgical procedure, less patient morbidity, operative time, operating room utilization, hospital and surgeon costs, and duration of antibiotic therapy exist. No overwhelming evidence exists that this is indeed the current situation [30, 62–66].

There may also be added unforeseen costs involved in the treatment of one-stage exchange arthroplasty as a consequence of increased reinfection rates. This amounts to extra costs to supplement additional diagnostic tests and clinical work-up as well as the likelihood of the ancillary expense of reoperation. Contention, therefore, exists whether two-stage revision is perhaps more advisable in PJIs caused by highly virulent organisms. MRSA has been recognized as a source of particular expense as it is onerous and costly to successfully eradicate it [63, 67].

Wolf et al. [68] endorsed one-stage exchange arthroplasty over two-stage exchange using a Markov expected-utility analysis considering quality-adjusted life years as health endpoints. In doing so, the reported rates of successful infection eradication form the basis when comparing the expense involved in one- and two-stage revision surgeries. A benchmark rate for infection clearance of 93% was deemed appropriate for two-stage revision and 85% for a one-stage exchange.

Therefore, when managing 100 cases of septic TKA with this technique, 200 operations are performed. During a two-stage exchange, 214 operations will ultimately be undertaken (additional 14 surgical procedures as a result of the 7% failure rate). In contrast, the one-stage exchange translates into 15 cases that fail as a result of reinfection, and if revised later to two-stage revisions, this will equate to an additional 30 surgical procedures (total 130 surgical procedures). Subsequently, based upon this hypothetical group of patients, the implementation of a one-stage exchange would ultimately decrease the number of surgical procedures by 84 cases.

The financial cost attributed to each revision procedure is difficult to estimate but quoted as approximately £26,000 [69] but may be as high as £75,000 [70]. Therefore based upon Wolf et al. [68] theoretical cohort, a potential saving of £2,184,000 may be achieved if these extra 84 operations are not undertaken.

Realistically, the total cost saved may indeed be greater, as the expense of hospital admissions and drug charges and other consumables have not been taken into account. Although most patients are elderly, in younger patients there are hidden costs involved including time away from work, missed income, and even loss of employment [71].

Conclusions

PJI remains a significant clinical challenge to physicians, a devastating functional and emotional complication for patients and a dramatic financial drain on health economics throughout the world. The one-stage exchange has the potential to address many of these factors, and its advantages have been well documented with comparable functional outcomes and eradication rates to a two-staged exchange.

It is difficult to directly compare these treatment modalities across many hospitals and studies due to a lack of universal agreement on the definition of infection, as well as diagnostic thresholds, and various surgical techniques adopted that sufficient evidence is not available. It is therefore imperative that

future research focuses on large multicentered randomized control trials concentrating on vital therapeutic outcomes such as the prevention of reinfection and knee functioning to shape and guide the blueprint for subsequent management of this devastating complication.

Every treatment strategy is unique and is best served by a multidisciplinary team as highlighted in previous chapters. A multidisciplinary approach with microbiologists, infectious disease physicians, critical care anesthetists, plastic surgeons, and orthopedic surgeons with a particular interest in infection is essential.

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Two-Stage Revision of Infected Total Knee Arthroplasty

19

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Abstract

Two-stage revision is still considered the gold standard for the treatment of deep periprosthetic infections of the knee. Multidisciplinary collaboration between the departments of orthopedic surgery, infectious diseases, microbiology, and pathology is crucial for obtaining high infection resolution rates, which means that such surgical procedures must only be performed in hospitals that offer such specialties. The purpose of a two-stage revision is to eradicate infection and restore joint integrity so that the knee is pain-free, stable, and well aligned with the new prosthesis. The use of articulating spacers is advisable in the first stage of the revision, while a highly constrained implant is recommended for the second stage to ensure adequate knee stability.

19.1 Introduction

Two-stage revision total knee arthroplasty (TKA), described for the first time by Insall in the 1980s, remains the gold standard in the treatment of infected total knee arthroplasty. The final goal of two-stage revision is to eradicate infection so that the knee is functional, stable, and pain-free.

Revision TKA (rTKA) involves a difficult and demanding surgical technique, which requires a thorough knowledge of the knee's anatomy and biomechanics if an optimal result is to be achieved. The purpose of this chapter is to review the role of two-stage revision in managing the infected total knee replacement.

19.2 First Stage of Revision TKA

19.2.1 Surgical Approaches

As far as the skin is concerned, the surgeon should identify previous incisions, fistulas, or any skin or soft tissue alterations that could make it more challenging to approach the joint.

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The incision should be long enough to allow an adequate exposure of the tibia and the femur and sufficient mobility of the extensor mechanism (Fig. 19.1). The incision should go through the skin and the subcutaneous tissue and reach the deep fascia. Excessive dissection of the subcutaneous tissue should be avoided.

The presence of previous incisions may influence the approach. Whenever possible, the previous incision should be incorporated to the new incision. In the presence of several prior incisions, the most lateral one should be used as most of the blood supply to the skin comes from the medial side [1, 2]. Parallel longitudinal incisions should be avoided as they could result in skin necrosis if the distance between them is less than 7 cm. If only part of the previous incision can be used, the angle between the two incisions must be of at least 60° so as to prevent skin damage in the area of the posterolateral corner. Previous transverse incisions do not entail a risk for skin devascularization, which means that they can be crossed by the new incision or they may be ignored during revision surgery.

Exposure of the knee joint and of the primary prosthetic components during rTKA is often complicated by a stiff, thickened, and fibrotic capsule and by the synovitis observed in the majority of cases. Painless flexion contractures and the infection itself, as well as wear particles and repeated trauma in cases of unstable prostheses, tend to result in stiffness and loss of elasticity of the periarticular structures and often make knee exposure more difficult. For this reason, the surgeon must conduct a thorough and systematic resection of the structures that constrain the joint, which include the fibrosis, the synovial tissue, the suprapatel-

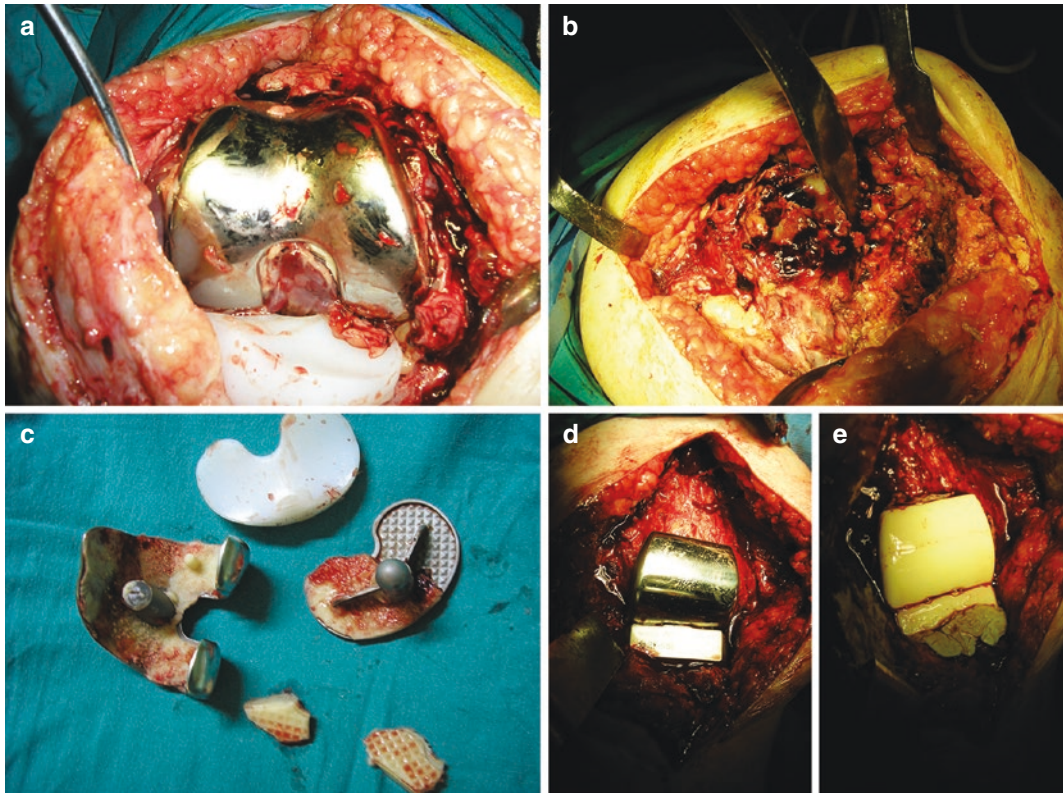

Fig. 19.1 (**a–e**) Intraoperative views obtained during the first surgical stage in the patient before removing the implant (**a**) and after implant removal (**b**). (**c**) Extracted components. (**d**) Trial articulating spacer. (**e**) Final articulating spacer implanted with gentamicin-loaded cement

lar bursa, and both the lateral and medial recesses. The surgeon must possess an in-depth knowledge of the knee's anatomy in order not to damage key structures for knee stability (collateral ligaments and stabilizers of the extensor mechanism).

Several extended approaches have been described for revision of TKA in the setting of a stiff knee. Although in most cases a thorough resection of fibrotic tissue is enough to afford appropriate exposure of the prosthetic components, the surgeon should be familiar with such approaches as they facilitate extraction of prosthetic components, soft tissue balancing, bone defect reconstruction, and long stem implantation in complex cases involving stiff knees, reducing surgical time and associated complications [3].

19.2.1.1 Anteromedial Approach

This is the surgical approach used in over 90% of revision TKA procedures. The incision is performed en bloc, without dissecting the subcutaneous tissues to minimize the risk of necrosis, and must be continued proximally to allow adequate exposure of the prosthesis. Distally, the incision should extend to about 7 cm below the inferior pole of the patella. All intra-articular tissues (synovial membrane, fibrotic tissue, and joint capsule) are thoroughly resected until healthy tissue is encountered. The knee must be progressively flexed until 100° of flexion are obtained, which in most cases requires meticulous soft tissue release. Knee flexion accompanied by external rotation of the tibia relaxes tension from the extensor mechanism and reduces the risk of patellar tendon avulsion, which is one of the most dreaded complications at this stage of the procedure. Medial release should continue posteriorly to the posteromedial corner of the tibia. In the event of persistent stiffness, the lateral retinaculum must be released to allow lateral eversion or displacement of the patella. Removal of the polyethylene insert facilitates exposure of the components and should be performed routinely at this point prior to deciding whether additional soft tissue releases are necessary.

19.2.1.2 Anterolateral Approach

This approach must be selected when there is a previous lateral incision and in cases with valgus deformities, flexion contracture, or external tibial torsion. The approach is performed from the vastus lateralis, lateral to the quadriceps tendon, and continues along the lateral border of the patella down to the tibial tuberosity.

19.2.1.3 Extended Approaches

In cases where, in spite of a careful soft tissue release, 100° of knee flexion or an eversion or lateral displacement of the patella cannot be obtained without excessive tension, the surgeon may extend the approach proximally to the quadriceps tendon or perform a tibial tuberosity osteotomy. Proximal techniques appear to be the preferred option for the majority of authors [4].

Quadriceps Snip

The arthrotomy is extended proximally and distally at an angle of 45° up to the border of the vastus lateralis [3]. This technique does not require any changes to the rehabilitation protocol following the revision procedure and allows immediate active mobilization.

V-Y Quadriceps Turndown

This extended approach may be considered when a quadriceps snip is not sufficient. It consists in continuing the quadriceps snip arthrotomy through the vastus lateralis tendon and the lateral retinaculum up to the superior portion of the iliotibial band, thus preserving the vascularization of the lateral geniculate artery. This approach entails a postoperative restriction of knee flexion for 4–6 weeks and may induce a knee extension lag. For that reason, it is only used in very specific cases where lengthening of the extensor mechanism is required.

Tibial Tuberosity Osteotomy

An 8–10 cm-long osteotomy is performed on the medial side, leaving a bone bridge on the lateral cortex and fixing the osteotomy posteriorly with K-wires and a screw. To carry out this osteotomy, the anteromedial incision must be lengthened exposing 10–15 cm of the proximal tibia. A saw

must be used from medial to lateral, creating a 10-cm-long, 2-cm-wide, and 1-cm-thick bone fragment. The lateral part of the osteotomy is completed with a chisel. The fragment is elevated subperiostically, taking care to spare the periosteum and leaving the muscle attached to the fragment. Flexion, extension, and weight bearing are allowed from the second week post-op. This technique has been associated with a large number of complications, including fractures of the bone fragment, delayed healing, and loosening of the fixation devices. In contrast to the V-Y quadriceps turndown, tibial tuberosity osteotomy results in low postoperative patient satisfaction and a lower postoperative range of motion. However, the V-Y quadriceps turndown tends to give rise to a significant knee extension lag [4].

19.2.2 Prosthetic Component Removal

Removal of the prosthetic components may be challenging. Care must be taken to preserve as much bone as possible and avoid a fracture, which could compromise reconstruction of the knee during the revision procedure. Multiple instruments can be used to successfully remove a prosthetic component such as osteotomes, a Gigli saw, chisels, powered instruments (saws, reamers, etc.), and ultrasound devices, which are particularly useful for cement removal [5].

The majority of present-day prostheses come with specific removal instruments that contribute to minimizing bone destruction when the prosthesis is extracted. Prosthetic components must be removed in a predetermined sequence: the first component to be extracted is the polyethylene insert, followed by the femoral component. The last component to be removed is the tibial component. There is no consensus on the advisability of revising the patellar component if the latter is not loose or if there are no clear signs of abnormal wear. In these cases, the short- and medium-term results of patellar component retention are similar to those of patellar component retention [6].

In prosthetic systems with an all-poly tibial component (with no metal tray), the all-poly tibia must be the first component to be removed. The prosthesis-cement interface should be approached with an oscillating saw and chisels.

In cemented components, the cement-prosthesis interface should be approached first, thereby preserving as much bone stock as possible for the subsequent reconstruction.

With stemmed components, ease of removal usually depends on the type of stem used and the firmness of the fixation achieved. At times, it is possible to remove the main body or the tibial or the femoral component first and leave the removal of the stem for later. In general, extraction of well-fixed cemented stems and some rough and porous-surfaced cementless stems may prove extremely challenging for the surgeon, making it necessary to resort to instruments specifically designed to remove hip prosthetic stems and to techniques such as a Wagner-type osteotomy.

19.2.3 Articulating Spacers and Antibiotic-Loaded Cement

Once the components and the cement have been removed, and the joint has been prepared by meticulous debridement of nonviable soft tissues, aggressive synovectomy, and careful reaming of the canal, an articulating spacer with antibiotic-loaded cement is placed in the surgical site, and the skin is closed until the infection has resolved and the second surgical stage can be performed (Figs. 19.2 and 19.3).

The cement used to fix the spacer must be loaded with antibiotics. The antibiotics may be added either during the manufacturing process or by the surgeon in the operating room. Although antibiotic-loaded cement is useful in preventing infection, the amount of antibiotic it contains is usually insufficient to treat an established infection. The antibiotic should ideally be water soluble and thermally stable to withstand the exothermic reaction generated during cement polymerization, be active against bacterial pathogens, possess an extended release profile, and show little local toxicity. Additionally, it should be selected on the basis of the results of preoperative cultures and should cover the most common nosocomial pathogens (empirical treatment).

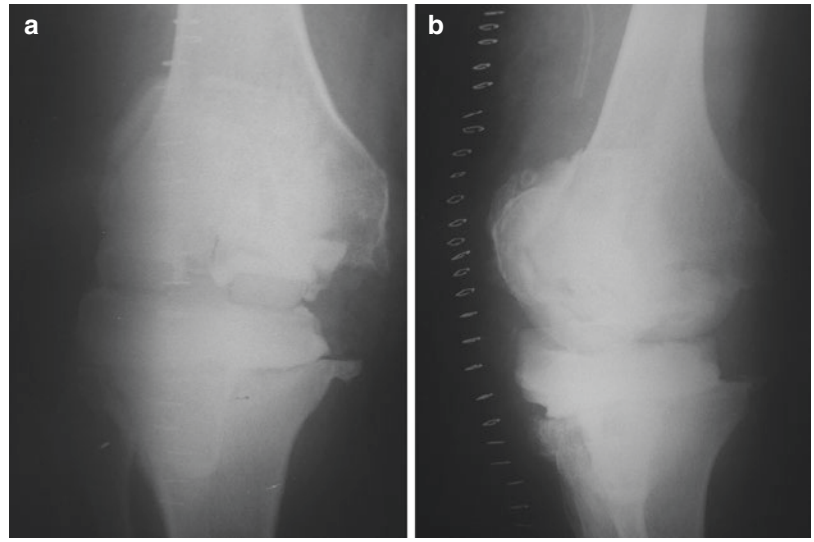

Fig. 19.2 (**a–b**) Anteroposterior (**a**) and lateral (**b**) knee radiographs of the patient of Fig. 19.1 following the first surgical stage. The image shows the articulating spacer implanted during the first surgical stage

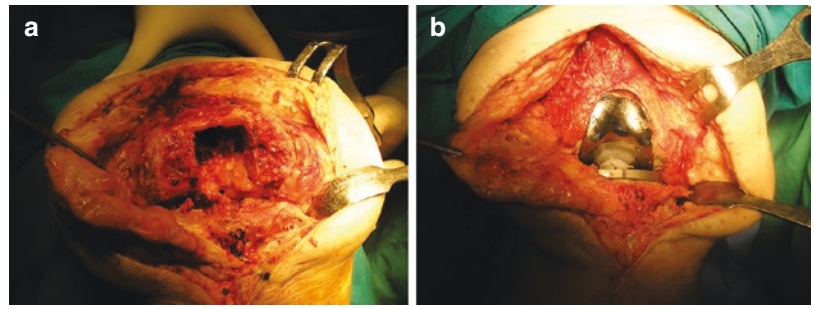

Fig. 19.3 (**a–b**) Intraoperative view of the same patient of Fig. 19.1 obtained during the second surgical stage and before (**a**) and after implantation of the new prosthesis (**b**). A rotational hinge prosthesis was implanted

The most frequently used antibiotics are aminoglycoside antibiotics (gentamicin and tobramycin) although the use of vancomycin is becoming increasingly widespread as it covers gram-positive bacteria as well as methicillin-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE). Although there is no consensus on the amount of antibiotic needed for a 40 g bag of cement, some series suggest that the required dose ranges between 2 and 5 g of gentamicin, 2.5–9.5 g of tobramycin, and 3–9 g of vancomycin [7]. Ceftazidime is also a useful antibiotic as it covers both gram-positive and gram-negative bacteria, as well as *Pseudomona.*

Spacers can be classified into static or dynamic, depending on whether they allow joint motion between the first and second surgical stages. Both contribute to preventing instability, pain, and soft tissue contractures and maintaining the joint space until implantation of the new prosthesis. Static spacers are only indicated in cases of soft tissue involvement or severe bone defects. In these cases mobility is restricted as a result of severe joint instability, which means that the use of articulating spacers is contraindicated [8].

Dynamic (articulating) spacers allow greater knee range of motion during the first and second surgical stages, are associated with the same infection control rate as static spacers [9], and, according to some studies [10], allow a greater arc of knee motion following the second surgical stage. Three types of dynamic spacers have been described.

19.2.3.1 Cement-on-Cement Spacer

These spacers may be produced by a manufacturer or be custom-made by the surgeon intraoperatively using molds of variable sizes or shaping them using the explanted components as a model. These spacers have demonstrated infection resolution rates of 80–100% in different series. Complications such as spacer subluxation or

breakage are uncommon. Although placement of these spacers tends to be straightforward, care must be exercised to ensure correct orientation of the femoral component so as to minimize the incidence of spacer breakage.

19.2.3.2 Cement-on-Polyethylene Spacer

This kind of spacer consists of a handmade cement femoral component and a stemmed all-poly tibial component. The infection control rate for this type of spacer has been reported to be in excess of 90% [11].

19.2.3.3 Metal-on-Polyethylene Spacer

This category includes a wide range of options that go from using the re-sterilized retrieved femoral component with a new polyethylene insert [12], both fixed with antibiotic-loaded cement, to using the PROSTALAC system [13], which consists of a femoral component with a stainless steel articulating surface and a posterior-stabilized all-poly tibial component. The PROSTALAC system exhibits infection control rates, ranging between 88% and 95% in the different series. Disadvantages of this kind of spacer include its relatively poorer infection control potential and its higher cost.

Few studies exist that compare the different kinds of dynamic spacers. In a comparison of cement-on-cement vs. metal-on-polyethylene spacers, Jämsen et al. [14] obtained a higher Knee Society Score (KSS) and a shorter first-stage operative time in patients with a metal-on-polyethylene spacer. Nonetheless, no significant differences were observed following the second surgical stage between the groups as regards knee range of motion.

19.3 Patient Management Until the Second Surgical Stage

19.3.1 Intravenous Antibiotic Treatment

Insall [3] reported that a period of approximately 6 weeks of intravenous (IV) antibiotic treatment must precede the second surgical stage. However, the length of this treatment period has been called into question as it may increase the cost of hospitalization, exacerbate the toxic effect of antibiotics, and aggravate bacterial resistance to commonly used antibiotics. As periarticular tissue receives little vascular supply in the presence of periprosthetic infection, delivery of systemic IV antibiotics to the joint may prove challenging. The use of spacers fixed with antibiotic-loaded cement tends to be effective as the antibiotic is released at the infection site and bactericidal activity lasts several months. Several studies on the effect of short-course (2–3 weeks) intravenous antibiotic therapy [15, 16] have shown infection resolution rates similar (>90%) to protocols based on long-term IV antibiotic therapy. Few studies compare both regimens (short vs. long) of systemic antibiotic treatment in revision TKA. Hsieh et al. [17] compared a 1-week vs. a 6-week regimen IV treatment in hip revision surgery and found no significant differences regarding infection control in both groups. However, length of hospital stay, cost, and nephrotoxicity were higher in the longer regimen.

A short (usually 2-week) course of broad-spectrum IV antibiotics can be used. Once the causative pathogen has been identified through intraoperative cultures, oral therapy is instituted on the basis of an antibiogram following consultation with the multidisciplinary team, including microbiologists and infectious disease physicians. Antibiotic treatment is completed after hospital discharge until C-reactive protein (CRP) and ESR (erythrocyte sedimentation rate) levels have decreased and clinical signs of infection have disappeared, which normally occurs after 4–6 weeks. When that happens, antibiotic treatment must be discontinued, and a 2-week clearance period must be observed before the second surgical stage. These indications may vary according to the patient's immune status, the condition of the soft tissues, and the type of causative organism. For example, in immunocompromised patients, or those with large fistulas or virulent microorganisms such as methicillin-resistant *Staph aureus*, the duration of systemic antibiotic treatment must be extended, and the second sur-

gical stage deferred until resolution of the infection can be ascertained or a first stage repeated.

19.3.2 Serological Tests and Joint Fluid Analysis

Decrease in CRP and ESR values, together with the absence of signs of infection in the knee, is the most commonly used parameter indicating that the second surgical stage can be carried out safely.

There is no clinical evidence regarding the values of these parameters that unequivocally indicate resolution of infection. Furthermore, several studies go as far as to question the validity of CRP and ESR [18, 19] as methods to monitor the body's response to IV antibiotic treatment. These studies, which record CRP and ESR values prior to the second stage, show no statistically significant differences in the mean values of these parameters between patients with reinfection and those where infection resolved in a definitive manner. Nevertheless, a statistically significant reduction in CRP and ESR values was identified between the first and the second surgical stages both in patients where infection was eradicated and in those where it was not. For that reason, fewer and fewer authors recommend delaying the second stage until full normalization of CRP/ESR values, although most of them emphasize that a significant decrease in those values must be ascertained.

Other potential early infection markers following TKA, such as cytokines and—more specifically—IL-6, may play an important role in the future. However, no studies have as yet been published on the usefulness of monitoring interleukin-6 (IL-6) values for determining the efficacy of IV antibiotic treatment between the two surgical stages of revision TKA [20].

Controversy exists regarding the need of an aspiration prior to the second surgical stage to analyze the synovial fluid and determine the white blood cell count. Some authors have observed low sensitivity of cultures prior to the second surgical stage in spite of a clearance period with no antibiotic administration. Mont et al. [21] prospectively analyzed a series of joint fluid cultures prior to the second surgical stage and found a sensitivity of 75%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 97%. Other authors have called these good results into question [22] reporting practically negligible sensitivity and positive predictive values in their studies. Although these authors advise against routine use of aspiration on the basis of the low sensitivity values they observed, we believe that, given its high specificity, the technique may be useful to analyze the joint fluid prior to the second surgical stage in cases of recurrent or persistent infection.

19.4 Second Surgical Stage

Once the decision to embark on the second surgical stage has been adopted, the macroscopic appearance of the tissues should be considered as it plays an important role in deciding whether to proceed with the implantation of a revision prosthesis. Intraoperative histologic frozen section analyses [Musculoskeletal Infection Society (MIS)], criteria of the periprosthetic tissue, and the new diagnostic tests based on alpha-defensin detection (Synovasure^{R}, Zimmer) contribute to ruling out the presence of active infection. Nevertheless, they cannot completely exclude this possibility. In a comparison of the sensitivity and specificity and the positive and negative predictive values of both tests, Kasparek [23] showed that intraoperative histologic frozen sections were less sensitive (58% vs. 67%) but more specific than the alpha-defensin test (96% vs. 93%) and concluded that both tests (if positive) were more useful to detect infection than to rule it out. Figure 19.4 shows the algorithm used by the authors in cases of deep periprosthetic infection of the knee.

19.4.1 Femoral and Tibial Reconstruction

The key to achieving correct kinematics in rTKA surgery lies in reestablishing appropriate joint line height and restoring accurate ligament balancing through proper management and correction of existing bone defects. The most common

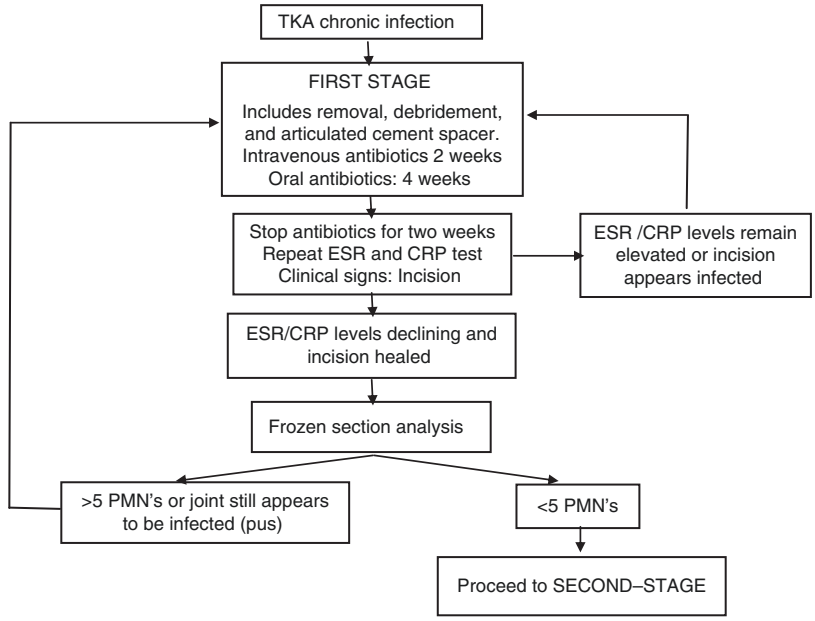

Fig. 19.4 Algorithm used in our hospital for management of infected total knee prostheses (*ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PMN´s* polymorphonuclear neutrophils)

Table 19.1 AORI (Anderson Orthopedic Research Institute) classification of bone defects in revision knee arthroplasty

Type of defect	Description
Type 1	Cystic lesions in the cancellous bone with an intact cortex below the joint line
Type 2A	Metaphyseal bone defect involving a femoral condyle or tibial plateau
Type 2B	Metaphyseal cancellous bone defect in both condyles and/or both tibial plateaus
Type 3	Femoral or tibial metaphyseal defect with damage to the collateral ligaments and/or the patellar tendon footprint

classification of bone defects in rTKA [24] is the Anderson Orthopedic Research Institute (AORI) scale (Table 19.1).

These defects can be managed with surgical techniques and prosthetic implants, including:

- Modular stems and supplements
- Porous tantalum cones
- Titanium wedges

19.4.1.1 Use of Modular Stems and Supplements

The use of revision stems makes it possible to obtain fixation distal to bone defects, achieving primary stability of the prosthetic component. Stems may be cemented, cementless, or hybrid (a cementless press-fit stem combined with a cemented femoral or tibial baseplate).

The majority of authors recommend the use of stems in revision knee arthroplasty, regardless of the size of the defect in the bone. Nelson et al. [25] analyzed 130 rTKAs and compared 67 stemmed to 63 stemless revisions. Although the bone defects in the stemmed revision group were more severe, the failure rate was significantly higher (44% vs. 9%) in the stemless revision group.

+ AORI Type 1 Defects

These defects, which do not affect the metaphyseal bone, are rare in rTKA. They are <5 mm in size and may be treated with cement filling or a cancellous bone allograft. The use of a stem is recommended to offload the defective area, although this is not strictly necessary as the bone's weight-bearing structure is not usually involved.

+ AORI Type 2 Defects

These larger defects (>5 mm) can be treated with cement and 5 mm or 6.5 mm screws inserted into the defective condyle. This technique may be used in elderly and/or low-demand patients. In other patients these defects are often managed with metal supplements, which increase the con-

tact area between the bone and the implant and improve stability.

In femoral reconstruction, defects in the distal femur and in the posterior condyle are often caused while extracting the primary component. The use of supplements of up to 10 mm in thickness may contribute to reconstructing these common defects, thereby staving off complications such as malrotation of the new femoral component, choice of a smaller component than necessary, and elevation of the joint line.

Some authors [26] report a 50–80% incidence of joint line elevation following rTKA. An elevated joint line is associated with a poorer clinical and functional outcome, resulting in pain, patella baja, and flexion instability. Patella baja limits flexion and increases wear. Flexion instability causes pain and promotes the release of wear particles, which causes the instability to progress over time. Although there is currently no consensus on the amount of joint line elevation that can be tolerated without clinical symptoms, some studies [27] indicate that an elevation above 4 mm could prevent correct functioning of the revision prosthesis. The causes of joint line elevation include:

- Bone loss in the distal femur, which requires the femoral component to be placed in an elevated position.
- Undersized femoral component: in the presence of a non-corrected posterior condylar defect, an undersized femoral component is usually implanted that sits directly on the bone. The flexion gap created is larger than the extension gap, which calls for the use of a thicker-than-normal polyethylene insert to ensure proper stability. This permits flexion and extension stability, albeit at the expense of elevating the joint line.

The most common anatomic landmarks [28] used in revision knee arthroplasty to determine the height of the joint line include the lateral and medial epicondyles, the fibular head, and the inferior pole of the patella. The ideal joint line should be located 25 mm distal to the lateral epicondyle, 30 mm distal to the medial epicondyle, 10–15 mm proximal to the fibular head, and 10 mm distal to the inferior pole of the patella.

Reestablishment of posterior femoral condylar offset is crucial to achieve adequate flexion stability and a larger prosthetic range of motion. As mentioned above, the presence of a posterior femoral condyle defect in rTKA may make it necessary for the surgeon to choose a smaller femoral component than originally planned, using a thicker polyethylene insert to fill the flexion gap. The impact of this loss of posterior femoral condylar offset on the long-term survivorship of the prosthesis has not as yet been ascertained [29]. This problem can be addressed in either of two ways: using a larger femoral component together with metal supplements to correct the distal and posterior defects or shifting the femoral component further posteriorly, employing a posteriorly,placed short cemented femoral stem or an offset femoral stem. This would allow a more accurate balancing of the flexion and extension gaps in the rTKA.

Wedge- or block-shaped metal supplements are often used for tibial reconstruction. These supplements, which may be placed in one or in both halves of the tibial plateau, are normally between 5 mm and 25 mm in size, depending on the different revision knee prosthetic models and designs. Some authors [30] suggest that blocks are more stable than wedges.

Most authors agree that the use of stems is advantageous for tibial reconstruction in the context of rTKA. Nevertheless, controversy remains regarding the fixation method that best suits each case. Cemented stems allow immediate primary fixation, are less dependent on the anatomy of the medullary canal, and can be shorter than cementless ones because distal fixation is not required. Nonetheless, cemented stems could be more difficult to revise and may lead to stress shielding in the surrounding bone. Multiple studies show good long-term results with cemented stems [31]. Cemented diaphyseal press-fit stems can also be used in the proximal metaphyseal area of the implant.

The use of cementless stems requires that the tibial and femoral canals be intact. Also, as these stems must be fixed distally, they are usually longer than cemented stems, which may influence their position in the tibia given that the canal is normally located medial to the tibial plateau. The fact that

the tibial anatomy influences the positioning and alignment of the stem means that the use of offset asymmetric stems is highly effective for correcting tibial deformities in rTKA.

The results obtained with stems and metal supplements for AORI type 2A defects are excellent with medium-/long-term survivorship rates in excess of 90% in some published series [32].

+ AORI Type 2B and Type 3 Defects

Three techniques are available to reconstruct the tibial/femoral metaphysis and create a stable platform that can support the implant:

**Impaction Grafting*

This involves the use of a packed cancellous bone graft to fill the defect and prepare the surface to permit effective cement interdigitation and ensure stable stem fixation. This technique can be used in contained defects that do not involve the cortex. More complex cases might require the use of metal meshes, which help contain the compacted graft. Good medium-term results have been reported for this technique with no incidence of stem loosening [33]. Impaction grafting may be used with young patients.

**Structural Allograft*

This is a technique used to replace tibial and/or femoral segments both in central and peripheral locations. No metal mesh is needed when defects are uncontained. The graft is modeled and prepared intraoperatively so that it fits snugly into the defect. Several complications such as implant loosening, infection, and non-unions have been reported with this technique, but some studies describe good long-term results with 10-year rTKA survivorship at 74% [34]. A recent study of 551 cases of rTKA with structural allografts, with a mean follow-up of 5.9 years, showed a high rate of poor results (6.5% graft failure, 3.5% aseptic loosening, and 5.5% infection) [35].

**Highly Porous Metal Metaphyseal Cones and Sleeves*

These special implants have been developed in response to the high failure rate associated with structural grafts.

Tantalum cones: Tantalum is a ductile metal with a high friction coefficient whose elasticity modulus is similar to the bone. Cones are press fitted into the defect and serve as a platform for the tibial or femoral components that are attached to the inner surface of the cone by means of cement. Cones are always used in conjunction with stems to provide enough stability for correct osteointegration. The cone/implant interface could be considered a weak link, but no failures at that interface have been observed clinically in medium-term follow-up series. In a study of 66 cases with tantalum cones in the tibia with minimum 5–9-year follow-up, Kamath et al. [36] reported a survivorship rate of 96% for these moderate to severe defects. Studies have also been published for the femoral side, albeit with shorter follow-ups (2–3 years) [37]. The survivorship rate reported in these studies was >90%.

Titanium sleeves: These implants are stepped in shape and coated with titanium beads to produce an interconnected porous surface for bone ingrowth. They are united to the femoral or tibial component with a Morse taper union. For the sleeve to be cementless, sufficient axial and rotational stability must be achieved intraoperatively in metaphyseal bone, which means that this type of implant should not be used for very severe defects. Short- and medium-term results of these implants are good, with revision rates below 2.5%. In a series with 104 rTKAs with metal sleeves and a mean follow-up of 43 months, Agarwal et al. [38] only had to revise 2 sleeves that had come loose. As this occurred in two cases where a stem had not been used, the authors recommend that a stem should always be used in combination with the sleeves.

In our hospital, the technique used to reconstruct bone defects depends on their size and location. We always recommend the use of stems in revision TKA. Different types of reconstruction are available depending on the type of defect to be treated (Table 19.2).

Table 19.2 Type of reconstruction recommended by the authors according to the different AORI (Anderson Orthopaedic Research Institute) defect types

AORI defect type	Reconstruction
Type 1(< 5 mm)	Filled with cement/morselized bone graft
Type 2 (5–10 mm)	Modular tibial/femoral augments
Type 2B and type 3	Tantalum cones/titanium sleeves

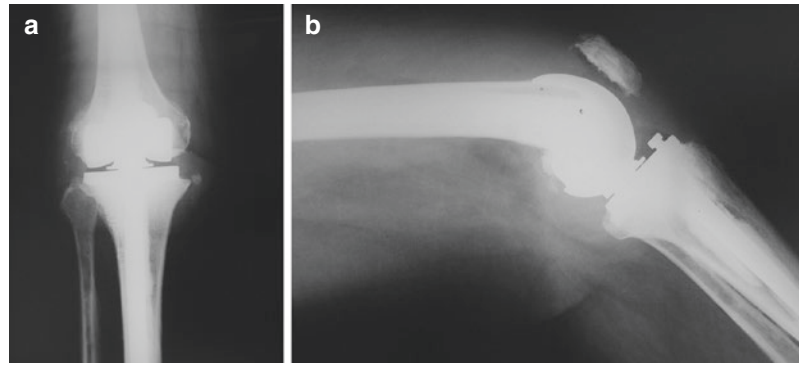

Fig. 19.5 Anteroposterior (**a**) and lateral (**b**) knee radiographs of the same patient of Fig. 19.1 following the second surgical stage. Images show the prosthesis already in place, with the infection resolved

19.4.1.2 Revision of the Patella

There is no consensus as to whether the patella should be revised in the course of the second surgical stage [39]. Bearing in mind that the purpose is to achieve a painless and well-aligned patella as well as a well-functioning extensor mechanism, causing as little damage as possible during surgery, the surgeon can choose between the following alternatives, depending on the condition of the patellar component and the amount of residual bone stock:

- Keep the primary patella in place.
- Perform a patelloplasty (patellar component resection with patellar bony shell retention).
- Perform a patellectomy.
- Reconstruct the patella with bone graft or a porous trabecular metal implant.

19.4.1.3 Degree of Implant Constraint

In the context of rTKA, most authors recommend using as little constraint as possible while ensuring proper joint stability. Most revision procedures can be successfully completed using a constrained yet unlinked prosthesis (constrained condylar knee, CCK), in the presence of damaged collateral ligaments and moderate bone defects. In cases with greater soft tissue damage where collateral ligaments have been destroyed or with very severe bone defects, a rotational hinge prosthesis may be required (Fig. 19.5) [28].

Conclusions

Two-stage revision remains the gold standard for the treatment of deep periprosthetic infections. Multidisciplinary collaboration between the orthopedic surgeon, infectious disease, microbiology, and pathology departments is crucial for obtaining high rates of infection eradication in a two-stage revision. For that reason, these procedures should only be performed in hospitals that offer such specialties. The purpose of two-stage revision is to resolve the infection and reconstruct the joint in order to achieve a knee that is pain-free, stable, and well aligned with the new revision prosthesis.

Surgery should begin with an appropriate approach and careful component removal, minimizing bone loss at this first surgical stage. The use of dynamic spacers with antibiotic-loaded cement has resulted in shorter systemic antibiotic treatment and an improvement in patient function in the period prior to implantation of the new prosthesis. The most commonly used parameters to determine the best time for implantation are still CRP and ESR values. Intraoperative histologic analyses are not conclusive enough to rule out the presence of infection during the second surgical stage.

It is important to reestablish the height of the joint line and accurately balance the flexion and extension gaps during the second surgical stage. We recommend the use of stems in the majority of cases. There are different options to address the reconstruction of bone defects, although these can more often than not be managed with modular metal supplements in the tibia or the femur. As unconstrained an implant as possible should be used provided that it guarantees knee joint stability.

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Knee Arthrodesis in the Infected Total Knee Arthroplasty

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Abstract

Knee arthrodesis is a limb salvage option for complex periprosthetic joint infections where revision total knee arthroplasty (TKA) is no longer reasonable. We will review the development of knee arthrodesis and examine its place alongside permanent resection arthroplasty and above-knee amputation (AKA) for treatment of the infected TKA. Indications and contraindications are discussed before the fundamental principles of perioperative management, with an emphasis on radical debridement as the most important step in achieving successful infection clearance. Knee fusion may be performed using external fixators in mono- or multiplanar configurations, internal compression plating, and long or short modular or non-modular intramedullary nails. Alternatively, bridging implants derived from endoprostheses may be used to overcome significant bone defects. There are certain advantages and disadvantages specific to each method of fixation, which should be considered prior to surgery. The evidence and outcomes reported in the literature with respect to these are reviewed, before we mention some post-operative considerations and strategies that may help to improve outcomes in the future.

20.1 Introduction

Knee arthrodesis is a limb salvage option for complex periprosthetic joint infections (PJI) and serves as an alternative to above-knee amputation (AKA) or permanent resection arthroplasty in cases where revision total knee arthroplasty (TKA) is no longer practical. However, the concept itself is nothing new, and knee arthrodesis has been performed for a variety of indications long before the advent of successful TKA in the 1970s.

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Perhaps the earliest example of an orthopaedic implant being used in the knee is that of the mummy of Usermontu, where a 23 cm iron pin with remarkably advanced biomechanical properties (including a tapered corkscrew design in the femoral part and three flanges in the tibial part to resist rotation) was identified on x-rays of the mummified remains of an ancient Egyptian priest. Further forensic analysis revealed that it had been cemented in place with resin around 2600 years ago [1].

The introduction of modern-day anaesthesia revolutionised the practice of surgery, and invasive procedures became possible to treat debilitating conditions. Nevertheless, early attempts at knee surgery at the turn of the last century were particularly unsatisfactory, especially when compared with some encouraging results of interpositional hip arthroplasty. In 1918, Allison and Brooks discussed these early methods and their limitations, stating that 'a rigid knee joint is preferable to one with good motion and poor stability' [2]. Indeed, the following decades saw a growing interest in techniques to facilitate knee arthrodesis.

Compression of the excised joint was first described by Key in 1932, who found that 'bony union was obtained in an unusually short time' for four patients with tuberculosis of the knee [3]. In 1948, Charnley reported satisfactory fusion in six patients with old tuberculous disease and nine cases of osteoarthritis, using a screw clamp that eventually became eponymous [4]. A decade later, he reported success in 169 out of 171 cases (98.8%) of knee arthrodesis using the same Charnley clamp [5]; the various indications included tuberculosis (40%), rheumatoid arthritis (22%), and osteoarthritis (34%). In 1959, Moore and Smillie reported the outcomes of 126 patients who underwent knee arthrodesis for rheumatoid arthritis (52%), tuberculosis (19%), and osteoarthritis (12%), but with different methods of stabilisation [6]. They found that the average time to fusion was faster with compression fixation (14 weeks) than either bone grafting with spica casting (21 weeks) or crossed pins (19 weeks).

Around the same time that Charnley popularised external fixation for knee arthrodesis, Chapchal introduced intramedullary (IM) nailing to 'shorten the period of treatment, give better fixation immediately after arthrodesis, and make the use of plaster cast unnecessary' [7]. The procedure was performed in two patients with complete limb paralysis following poliomyelitis and in five knees with painful ankylosis; six out of seven cases went on to successful union (86%). Although the indications for performing knee arthrodesis have since been considerably narrowed due to improvements in preventative medicine, antimicrobial therapies, antirheumatic drugs, and the development of TKA itself, external fixation and IM nailing remain the most popular methods of fusion to this day.

20.2 Indications

Knee arthrodesis was used as a salvage procedure following infections of the uncemented Walldius hinged knee endoprosthesis, prior to the development of polycentric and condylar implants. In 1960, Walldius himself reported successful fusion after the explantation of 5 infected prostheses, from his original series of 64 arthroplasties [8]. Nelson and Evarts described arthrodesis as a treatment option for failed TKA in 1971 [9], which has since become its predominant indication.

Although improvements in surgical techniques and implant design since the 1970s have meant that the modern TKA has a high rate of success, PJI remains a devastating complication. Its increasing burden reflects a rising number of arthroplasty procedures each year, especially in patients with risk factors such as obesity and diabetes [10, 11]. The incidence of PJI following primary TKA is around 1–2% and significantly higher following revision TKA [12].

The decision to undertake a limb salvage procedure is not always simple, as the outcomes of revision for infected TKA have benefitted from the development of international consensus and collaboration, a greater understanding of the principles of debridement, microbiological sampling techniques, and combinations of local and systemic antibiotic therapies [13]. Revision or re-

revision arthroplasty is therefore an attractive option for the surgeon and patient who wish to preserve range of motion and function; these are inevitably sacrificed with a knee fusion, although it provides the potential for a painless, sensate, and stable base of support.

The general indications for choosing knee arthrodesis in favour of joint reconstruction are uncontrollable recurrent infections, poor soft tissue coverage (Fig. 20.1), significant bone loss, an immunocompromised patient, gross instability, or failure of the extensor mechanism [14, 15]. It has also been suggested for post-traumatic degenerative joint diseases in young patients with high functional demands, neuropathic joints, or paralytic conditions with gross deformity, and is an alternative to hinged endoprosthetic reconstruction following tumour resection surgery around the knee [15–18]. It is important to note that the outcomes of knee arthrodesis following PJI are less successful than in aseptic cases, with delayed union or nonunion being more likely in the presence of infection [19].

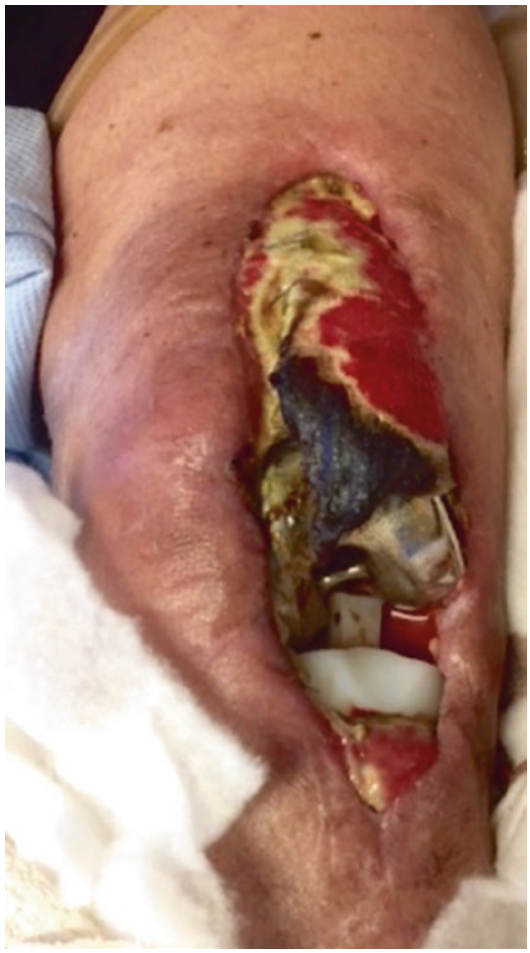

Fig. 20.1 Infected revision TKA with loss of soft tissue coverage, extensor mechanism failure, and exposure of the underlying implant. The patient subsequently underwent knee arthrodesis for limb salvage

20.3 Contraindications

The contraindications to knee arthrodesis include contralateral AKA, significant arthritis of the ipsilateral hip or ankle, or arthrodesis of the contralateral hip or knee. The latter may be considered a relative contraindication, as bilateral knee fusions have been reported in the literature [5, 20], but cause significant functional limitation. Knee arthrodesis may cause accelerated wear of the ipsilateral hip or ankle, due to increased hip abduction and ankle dorsiflexion as compensatory gait mechanisms. Degenerative changes of the spine may also lead to rehabilitation difficulties, as the compensatory pelvic tilt will generate more stress across the lumbar spine [14, 19]. In addition, any patient who would be medically unfit to undergo primary or revision TKA owing to medical comorbidities would not be considered a suitable candidate for knee arthrodesis.

20.4 Limb Salvage Alternatives

Permanent resection arthroplasty and AKA are the alternatives to knee arthrodesis for the infected TKA where revision or re-revision is not a viable option.

20.4.1 Permanent Resection Arthroplasty

Presented as an alternative to fusion for salvage of the infected TKA by Kaufer and Matthews in 1986 [21], permanent resection or excision

arthroplasty of the knee involves the removal of any prosthetic material and thorough debridement of the synovium, with no subsequent joint reconstruction (Fig. 20.2). The absence of any metalwork makes biofilm formation less likely. Patients are fitted with a cast or brace postoperatively, as a period of stability is required for the soft tissues to settle, prior to commencing flexion and extension as comfort allows. Whilst resection arthroplasty will generally allow a limited range of movement and is more likely to be comfortable when sitting, the development of a fibrous ankylosis is unsurprisingly less stable and has less load-carrying capacity than that of a solid fusion, making ambulation more difficult.

In 1987, Falahee et al. reported that infection was cleared in 25 out of 28 knees which underwent resection arthroplasty (89%) for infected TKA but that the subjective rate of dissatisfaction was 39% [22]. An important finding was that those with lower functional demands tolerated the procedure better. Lettin et al. reported better results in a smaller cohort of 15 patients: an eradication rate of 100% and subjective dissatisfaction at 20% [23]. More recently, Mine et al. found that there was no infection recurrence in nine patients following permanent resection arthroplasty combined with a pedicled muscle flap [24]. The subjective rate of dissatisfaction was 33%, and there was no apparent correlation between pain, limb length discrepancy, and patient satisfaction. Although it should be reserved in the first instance for patients whose functional demands are low, a resection arthroplasty may be converted to an arthrodesis at a later stage [21, 22].

20.4.2 Above-Knee Amputation

AKA is generally considered the last option for the infected TKA but may be necessary in the presence of certain comorbidities, such as peripheral vascular disease. Although AKA will be discussed separately in the following chapter, there are two contrasting perspectives on choosing between knee arthrodesis and AKA following PJI: the first is that arthrodesis is preferable for younger patients with high functional demands and AKA should be reserved for older patients who are less likely to tolerate multiple limb reconstruction or staged salvage procedures; and the second is that younger patients can adjust far more easily to using an above-knee prosthesis and limb preservation should be attempted in older candidates, who are less likely to achieve functional independence.

Although each case must be considered individually, there is some evidence that appears to

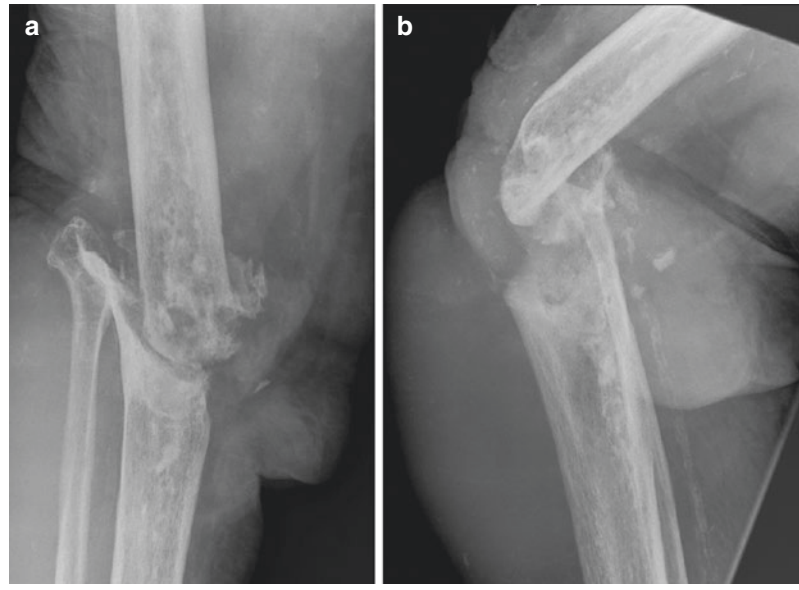

Fig. 20.2 Anteroposterior (**a**) and lateral (**b**) right knee radiographs of a permanent resection arthroplasty

support the second theory. The energy expenditure for walking is 25% greater for AKA compared with arthrodesis, measured at 0.20 mL/kg/min and 0.16 mL/kg/min of oxygen, respectively [19]. Comparative studies have concluded that knee arthrodesis is associated with better function and ambulatory status than AKA following recurrent PJI [25–27], whilst indicating that AKA represents a greater psychological burden for patients. However, a recent investigation into the outcomes of 2634 patients who were arthrodesed and 5001 patients who underwent AKA for infected TKA suggested that, conversely, the first philosophy is perhaps being adopted in clinical practice [28]. There was a significant increasing trend towards AKA rather than arthrodesis over the 7-year study period, and patients who underwent AKA tended to be older. Systemic complications, in-hospital mortality, and length of stay were significantly higher in the AKA cohort, but without case matching, this may simply reflect the increased age and comorbidities of those patients.

20.5 Pre-operative Planning

Careful pre-operative assessment and preparation are fundamental to achieving a successful outcome. Medical conditions and systemic issues, such as peripheral vascular disease, diabetes mellitus, cardiac disease, respiratory conditions, renal impairment, immunosuppression, obesity, and smoking, can significantly increase the risk of intraoperative and post-operative complications relating to anaesthesia, wound healing, clearance of infection, progress towards union, and functional rehabilitation.

Both knees must be examined for alignment, range of motion, extensor lag, fixed flexion deformity, and ligamentous stability, and it is also important to assess both hips and ankles, in addition to the spine. Peripheral vascular and neurological examinations should be performed, with a careful review of scars from previous operations, as a candidate for knee arthrodesis may have had multiple TKA revisions and previous wound issues. Whilst the ideal approach is through a previous longitudinal midline incision, which is extended proximally and distally as required, this may not be appropriate if there are lateral parapatellar scars. As the vascular supply to the skin is derived from medial perforating vessels, creating lateral skin flaps should be avoided where parallel scars exist [15, 29]. Pre-operative input should be sought from plastic surgeons where there is any uncertainty or if soft tissue reconstructive techniques, such as skin grafting or flap coverage, may be required.

Anteroposterior and lateral standing knee radiographs should be obtained, in addition to long-leg films which help to assess alignment, the position of existing implants, estimated bone loss, any limb length discrepancy, and for sizing IM devices. Shortening of the affected limb is inevitable following knee arthrodesis, and it is important for the surgeon to consider at this stage whether bony union and an acceptable post-operative limb length discrepancy (usually less than 5 cm) are achievable following explanation and debridement, as this will influence the method of fixation. For the patient, a pre-operative trial with the knee immobilised in an extension brace, splint, or cylinder cast to simulate post-operative function and adjust to some activities of daily living can be useful, especially since there is a 30% increase in energy expenditure for ambulation with a knee fusion [19].

Pre-operative microbiological sampling is performed according to the principles introduced in earlier chapters. It is important to remember that the causative organism is not always identified [30], which may influence the decision whether to perform a one- or two-stage procedure [13]. The appropriate inventory should be available in theatre for intraoperative sampling and the possibility of a difficult extraction of the previous implant.

It has also been shown that knee arthrodesis procedures are often lengthy and associated with considerable intraoperative blood loss. In a series of 15 patients who underwent fusion with a long IM nail, Crockarell Jr. and Mihalko found that the average operating time was 210 min and mean estimated blood loss was 1143 mL [31]. Bartlett et al. reported a mean operating time and estimated blood loss of 141 min and 753 mL, respectively, in ten patients who received a cemented, coupled

implant arthrodesis (Stanmore Implants Worldwide Ltd., Middlesex, UK) [32]. Letartre et al. had similar findings with 19 patients who received the coupled IM Endo-Model Knee Fusion Nail (Waldemar LINK GmbH and Co, Hamburg, Germany), with an average operating time of 143 min and mean blood loss of 710 mL [33]. It is therefore important to address pre-operative anaemia, thrombocytopenia, or coagulation disorders and have cross-matched blood available for transfusion.

20.6 Intraoperative Principles

Irrespective of the preferred method of fixation, there are a number of intraoperative techniques which can help to facilitate the best possible outcome.

20.6.1 Debridement

Radical debridement is the imperative determinant of successful infection clearance and should not be compromised in favour of subsequent reconstruction, regardless of whether a one- or two-stage procedure for arthrodesis is undertaken. We recommend that the knee joint and IM canals are debrided according to a cyclical protocol, using principles developed by Lautenbach, as it may be difficult to achieve sufficient clearance of infection in a single pass [34–36].

All surfaces are surgically debrided of membrane, biofilm, and avascular tissue with curettage and rongeurs, and the IM canals are reamed successively under power to remove all persistent necrotic and infected tissue. Multiple intraoperative tissue samples should be taken with non-contaminated instruments. Once the bone surfaces and canals appear visibly debrided, normal saline is used as powered pulse lavage to wash out residual debris and to make any remaining membrane and biofilm oedematous. A second pass of curettage and mechanical debridement is performed to remove the residual oedematous membrane and biofilm, with successive cycles being undertaken as required. Chemical debridement may also be performed using antimicrobial agents such as 3% acetic acid, chlorhexidine, or povidone-iodine solution [34, 37].

20.6.2 Bone Apposition

Bone contact is a fundamental aspect of knee arthrodesis, and although debridement takes precedence, the minimal necessary bone resection should be performed where possible to allow vascular cancellous apposition and prevent excessive limb shortening. Interdigitation of the bone ends may improve stability, but multiply revised knees will inevitably have less bone stock, and cortical apposition might only be achievable in such cases. Bone loss can be assessed according to the Anderson Orthopaedic Research Institute (AORI) classification system [38, 39], in which tibial and femoral defects are scored separately, based on radiographic evaluation of metaphyseal integrity:

Type	Description
1	Minor femoral or tibial bone defect with intact metaphyseal bone, not compromising revision component stability
2	Damaged metaphyseal bone. Loss of cancellous bone requiring reconstruction (cement fill, augments, or bone graft) to restore joint line level and provide revision component stability A: defects involving only one tibial or femoral condyle B: defects involving both medial and lateral tibial or femoral condyles
3	Deficient metaphysis. Bone loss involving a significant portion of the distal femur or proximal tibia, occasionally associated with patellar tendon or collateral ligament detachment

More recently, Klinger et al. have proposed an intraoperative classification system of bone loss, specifically for knee arthrodesis [40]:

1. Mild—full bony contact achievable
2. Moderate—incomplete bony contact
3. Severe—minimal or no bony contact

Charnley emphasised the importance of cancellous apposition and compared this principle ‘to that of a fracture without displacement under ideal conditions’ [4, 5]. However, his series comprised native joints that were arthrodesed before the development of TKA, and improvements in revision techniques have meant that metaphyseal bone is now commonly deficient in salvage procedures. Fusion rates are lower in

those who have undergone higher numbers of failed previous TKA revisions, as demonstrated by Hak et al. in a series of 36 patients who underwent arthrodesis with an external fixator [41] and Razii et al. with 12 patients who received a long IM nail [42].

20.6.3 Bone Grafting

Bone grafting can be performed for cases with extensive bone loss as an alternative to endoprosthetic implants. Autologous cancellous bone grafting is generally preferable to allograft, and it should also be placed around the periphery of the arthrodesis site to promote revascularization from the surrounding soft tissues. With multiple previous revisions, IM circulation of the bone is usually compromised following explanation of prior implants and the cement mantle.

Bone grafting techniques include vascularised fibular grafts – which can be free transfers or rotated on the vascular pedicle of the peroneal artery – and grafts from the iliac crest or patella [19, 43, 44]. Lee et al. reported using mixed autologous iliac graft and deep-frozen femoral head allograft in a series of eight infected arthroplasty patients who received an IM nail, and all went on to union [45]. More recently, the application of free vascularised fibular grafts has been discussed for revision limb salvage procedures following explantation of infected IM nails in failed knee arthrodesis [46], although the literature on these grafts has traditionally tended to focus on the management of bone loss following tumour resection.

20.6.4 Alignment

The ideal position for limb alignment is with the knee in approximately 5–15° of flexion and 5–7° of anatomical valgus [15, 19], to allow sufficient ground clearance during the swing phase, with the initial contact in stance phase in slight external rotation to match normal gait. Slight knee flexion improves gait efficiency, due to the push-off direction of gastrocnemius [47], but with considerable bone loss, a position closer to full extension maintains as much length as possible. The knee should not be fixed in more than 20° of flexion, as the patient will have a short-legged gait which causes significant pelvic tilt and strain on the lower back.

20.7 External Fixation

20.7.1 Monoplanar Frames

Various configurations of external fixators have been developed since the Charnley clamp [4, 5]. Although the popularity of monoplanar external fixators has declined since the main indication for knee arthrodesis shifted towards the infected TKA, some recent papers have reported good results with this technique (Fig. 20.3). Roy et al. used the dynamic axial fixator (Orthofix SRL,

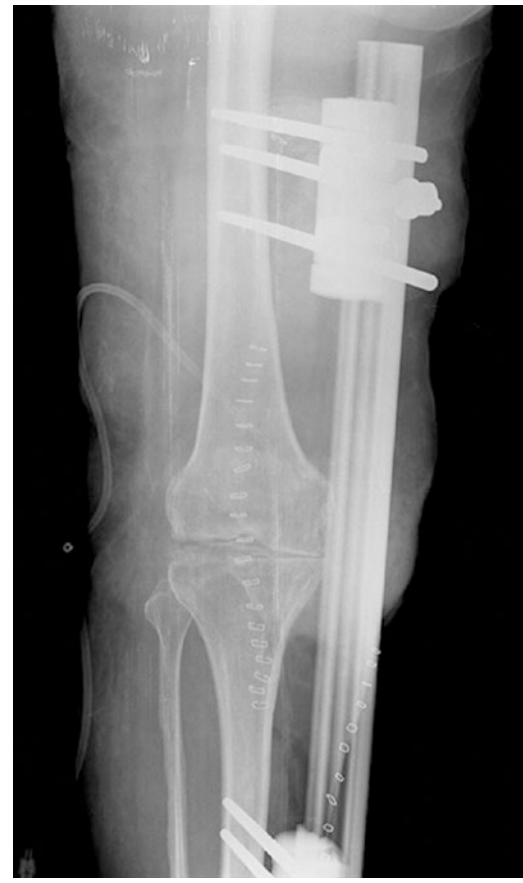

Fig. 20.3 Anteroposterior radiograph of right knee following arthrodesis with a monoplanar external fixator (Adapted from Roy et al. [48])

Verona, Italy) in 24 patients for a variety of causes, including infected TKA, previous tuberculosis, and complex trauma [48]. All went on to union, although there were wound complications in six patients (25%). Balci et al. achieved union in 16 out of 17 patients (94%) following infected TKA [49], with a different unilateral external fixator (LRS; Tasarim Med, Istanbul, Turkey). Complications in addition to the one nonunion included pin-tract infections in 11 patients (65%), three fractures (18%), and one infection recurrence (6%).

20.7.2 Biplanar Frames

Biplanar fixators provide greater stability than their monoplanar counterparts [14, 41] and gained popularity in the 1980s [50, 51], but they have largely been overlooked in the literature in recent years in favour of circular frames. Whilst a monoplanar fixator is less cumbersome for the patient and permits easier mobilisation, surgeons who would consider sacrificing this benefit to obtain greater stability might well prefer to use a circular frame rather than a biplanar fixator.

20.7.3 Circular Frames

The majority of series describing knee arthrodesis with external fixation in the last two decades have used circular frames. Different options exist, such as the Sheffield Ring Fixator [52] or the Ilizarov frame (Fig. 20.4), which allows both rigidity and alignment of fixation to be adjusted, whilst also enabling limb lengthening if required. Circular frames have been reported as an improvement over previous methods of external fixation, allowing for accurate alignment in both the coronal and sagittal planes, but the operation is technically challenging [14]. Compared with IM nails and compression plating, however, removal of the hardware is relatively easy.

Reddy et al. achieved union in 15 out of 16 cases (93.75%) of infected revision TKA treated with the Ilizarov method [53], although pin-tract infections occurred in five patients (31%) and pin loosening in three patients (19%). Spina et al. reported union in 13 out of 17 (76.5%) infected TKA patients (12 primary and 5 revision prostheses) treated with an Ilizarov frame [54]. Oostenbroek and Roermund have suggested that this method of arthrodesis can be per-

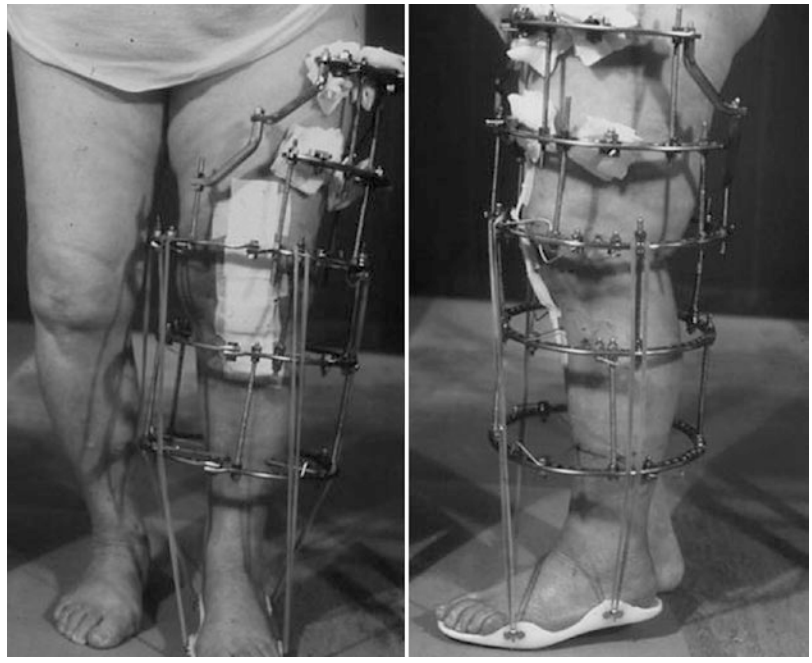

Fig. 20.4 Clinical photographs showing external fixation with an Ilizarov frame to achieve left knee fusion. A foot splint provides support and prevents an equinus contracture (Adapted from Spina et al. [54], with permission from Springer)

formed in the presence of active infection, having achieved primary fusion in 14 out of 15 cases (93%), but they did report an 80% incidence of complications, including pin-tract osteomyelitis in three patients [55].

20.8 Compression Plating

Fewer articles have discussed the use of internal compression plating than either external fixation or IM nails, although impressive results have been reported with this method. Early studies described a single compression plate applied either anteriorly or laterally [56, 57], but more recently, dual plating techniques have been adopted for greater stability (Fig. 20.5). Nichols et al. achieved a fusion rate of 100% in 11 patients using two compression plates applied medially and laterally, although there was a complication rate of 18%, where 1 patient suffered a femoral stress fracture and another had persistent infection. They concluded that 'staggering the plates may help to prevent late stress fractures' [58].

Kuo et al. reported success in a series of three patients who underwent knee arthrodesis with dual locking compression plates (LCP) following PJI [59]. They noted that locking screws provide angular stability without the need for exact plate contouring, and the LCP itself has been shown to perform well under prolonged cyclical loading. Although a benefit of compression plate osteosynthesis is that it can be performed through the same incision following explantation and debridement, it may be necessary to extend the incision for adequate exposure. Furthermore, sufficient bone stock is required, and post-operative rehabilitation involves a long-leg cast and delayed weight-bearing.

20.9 Intramedullary Nailing

IM nails are the most popular fixation devices for knee arthrodesis following infected TKA, allowing early post-operative mobilisation as a result of their stability and rigidity, whilst lacking the obtrusive design of external fixators or indeed the risk of pin-tract infections. Both long Küntscher nails and shorter modular or non-modular devices are available [14].

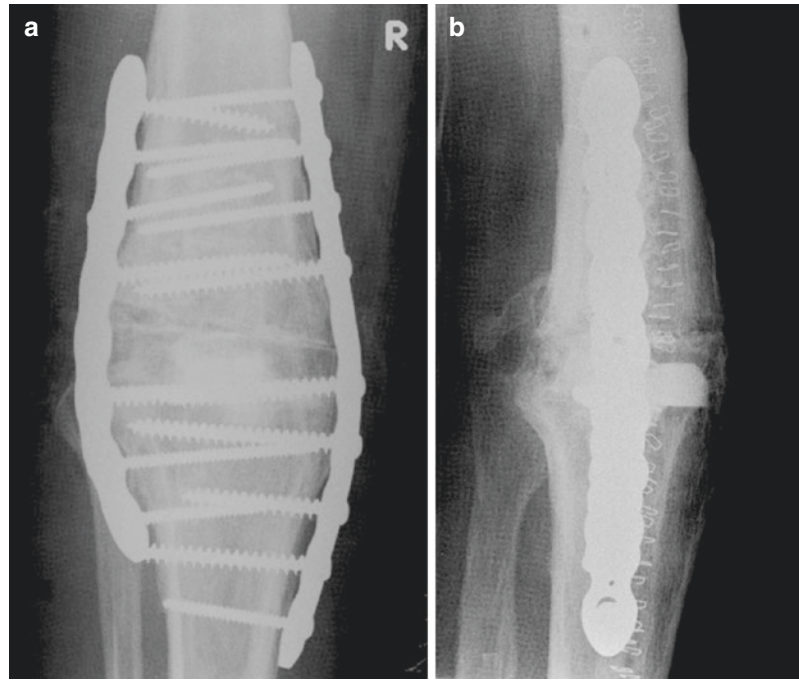

Fig. 20.5 Anteroposterior (**a**) and lateral (**b**) radiographs of right knee arthrodesis with dual locking compression plates

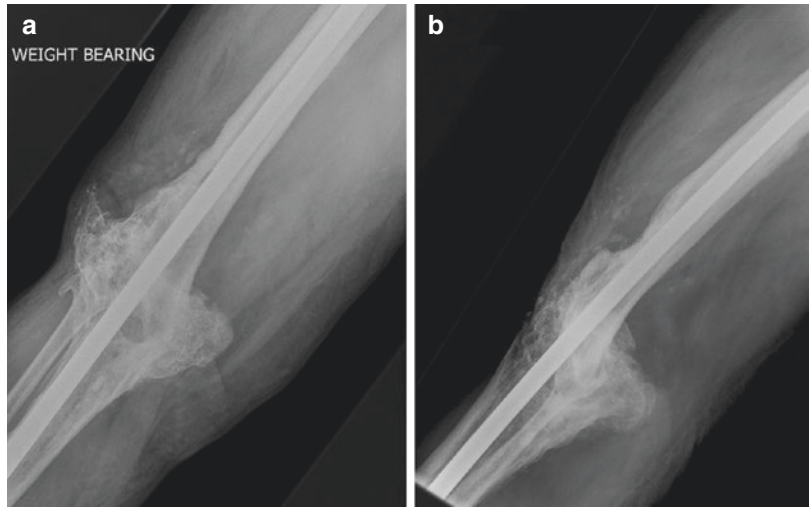

Fig. 20.6 Anteroposterior (**a**) and lateral (**b**) radiographs of right knee arthrodesis with a long IM nail (Biomet Arthrodesis Nail) (Adapted from Razii et al. [42], with permission from Springer)

20.9.1 Long Intramedullary Nails

Studies of knee arthrodesis with a long IM nail (Fig. 20.6) following PJI have reported high fusion rates and infection clearance of around 80–100%, even in the presence of severe bone loss [31, 42, 60–63]. The majority of these case series have described the results of a two-stage procedure, but it is possible to perform single-stage arthrodesis with an IM nail for selected patients [42, 64], if the recommendations of the International Consensus on Periprosthetic Joint Infection relating to revision TKA are met [13] and the principles of debridement are strictly adhered to [34]. The Biomet Arthrodesis Nail (Biomet Inc., Warsaw, Indiana, USA) has shown good results in the literature for more than two decades [42, 60, 62] but is no longer manufactured. Similar devices, however, such as the TRIGEN Knee Fusion Nail (Smith & Nephew plc, London, UK) and the T2 Knee Arthrodesis Nail (Stryker Corp, Kalamazoo, Michigan, USA), are currently available [31, 63].

The surgical technique for a long IM nail involves reaming of the tibia from within the knee wound, with the tibial canal diameter determining the IM nail diameter. The femur is reamed retrograde and then antegrade through a separate proximal incision over the piriformis fossa. Femoral and tibial canal lengths are measured separately, with the sum of the canal lengths used to assess the required nail length, although surgeons can also estimate this pre-operatively from long-leg radiographs. The nail should span from the level of the greater trochanter to 2 cm above the ankle and locked proximally to prevent migration, a recognised complication in unsecured nails [60]. Distal locking screws are generally unnecessary, as three-point fixation over the length of the nail avoids rotational instability whilst still allowing dynamic axial compression [42, 61].

Disadvantages of the long IM nail include a lengthy procedure with considerable intraoperative blood loss [31], even when compared with modular nails [32, 33], and there are risks of diaphyseal osteomyelitis in cases of recurrent infection and nail migration if locking screws fail. Although extraction of a long nail is relatively easy, antegrade nailing cannot be performed in the first instance if there is an ipsilateral hip replacement or femoral shaft deformity [15].

20.9.2 Short Intramedullary Nails

Short IM nails tend to be of a modular design (Fig. 20.7), with a coupling mechanism that allows the respective components to be inserted into the femur and tibia through the same incision that the infected TKA prosthesis has been explanted, before the device is secured in posi-

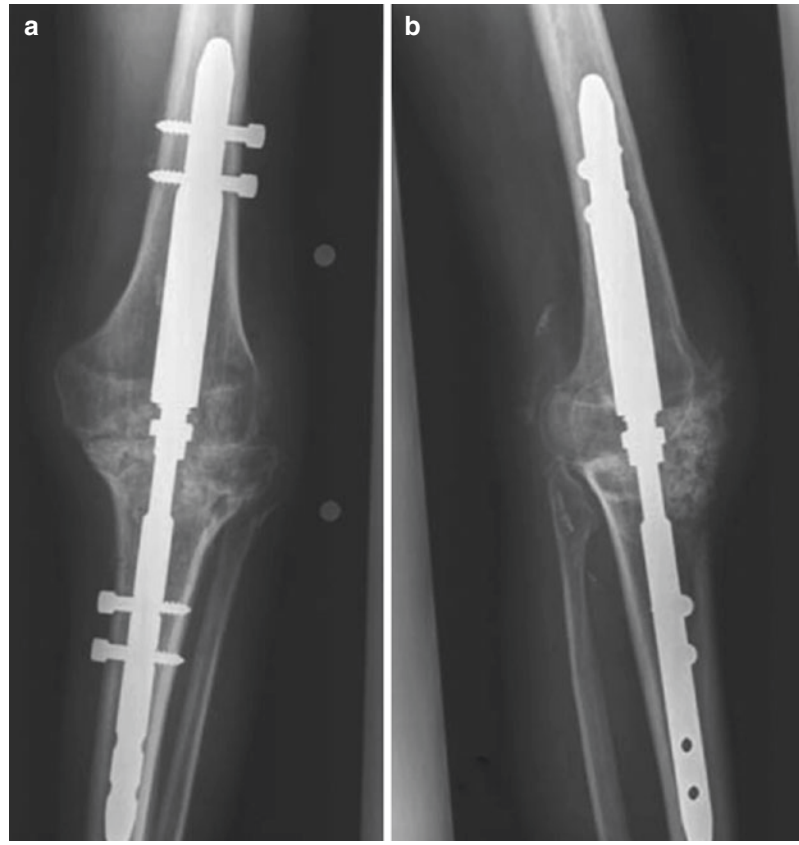

Fig. 20.7 Anteroposterior (**a**) and lateral (**b**) radiographs of left knee arthrodesis with a short, modular IM nail (Wichita Fusion Nail) (Adapted from Bono and Wardell [65], with permission from Springer)

tion with a central locking screw (or screws) [65]. Such implants can be accommodated when there is an ipsilateral hip replacement or proximal femoral metalwork in situ, and their modularity is useful when there are different-sized tibial and femoral canals [19]. Compared with long nails, however, short IM devices are more difficult to extract or revise, with a risk of extensive secondary bone loss [61].

Another complication associated with short IM devices is the risk of periprosthetic fracture, due to the potential stress risers at the extremities of the nail. Hinarejos et al. reported fractures above and below such an implant in a patient following a minor fall [66]. The existing nail was extracted through the femoral fracture site, as the arthrodesis was solid, and was revised to a long antegrade nail. The Wichita Fusion Nail (Stryker Corp, Kalamazoo, Michigan, USA) has demonstrated good fusion rates of 86–100% in the literature, although complication rates between 20 and 57% have also been reported [67–70]. Some other examples of coupled IM nails include the Neff Femorotibial Nail (Zimmer Inc., Warsaw, Indiana, USA) and the Mayday Arthrodesis Nail (Orthodynamics Ltd., Christchurch, UK), with reported fusion rates similar to those of the Wichita Fusion Nail [71–73]. The short Huckstep nail, which is a non-modular design, can either be inserted antegrade through the piriformis fossa similar to a Küntscher nail [74] or through an incision at the knee, retrograde into the femur and then antegrade into the tibia [75].

20.10 Comparison of Fixation Methods

Several studies have compared the outcomes of IM nailing with other techniques. In a series of 26 patients, van Rensch et al. found that IM nails gave the highest primary fusion rate (8 out of 10

patients) compared with external fixation (3 out of 10) or compression plating (3 out of 6) [76]. Six patients subsequently underwent revision arthrodesis, with both of those who received IM nails going on to union. Schwarzkopf et al. achieved similar fusion rates with both IM nailing (81.5%) and compression plating (78%) in a series of 43 cases [77]. Yeoh et al. studied 18 patients, where 10 out of 11 with an IM nail (91%) united, but only 2 out of 7 with a monoaxial external fixator (29%) did so [78]. Complication rates were considerably lower in the IM nail cohort, whose overall fusion rate increased to 100% following revision nailing in one patient. Similarly, Mabry et al. found 23 out of 24 patients went on to union (96%) following IM nailing, whilst 41 out of 61 (67%) did so with external fixation [79]. Interestingly, although the overall complication rate was lower in the IM nail group, deep infection recurrence was slightly higher at 8.3%, compared with 4.9% in the external fixation group.

20.11 Implant Arthrodesis

For cases where bone-on-bone fusion cannot be achieved, modular IM nails have been adapted to overcome massive defects (Fig. 20.8). These bridging implants act like an intercalary endoprosthesis, and their modularity allows for individualised segmental deficit reconstruction. The most popular device for this purpose appears to be Endo-Model Knee Fusion Nail, and stem designs for either cemented or cementless IM fixation are available.

Hawi et al. reported an overall success in 26 out of 27 patients (96.3%) who underwent a single-stage procedure with the nail, where the defect between the femur and tibia was filled with antibiotic-loaded cement, as well as the IM canals [80]. Three patients required revision arthrodesis (11.1%) to overcome persistent infection, and one underwent AKA. Rao et al. successfully performed a two-stage procedure in five out seven patients (71%) with cementing of the IM canals, but not the central defect, relying solely on the coupling mechanism [81]. One patient was revised due to infection and another with aseptic loosening.

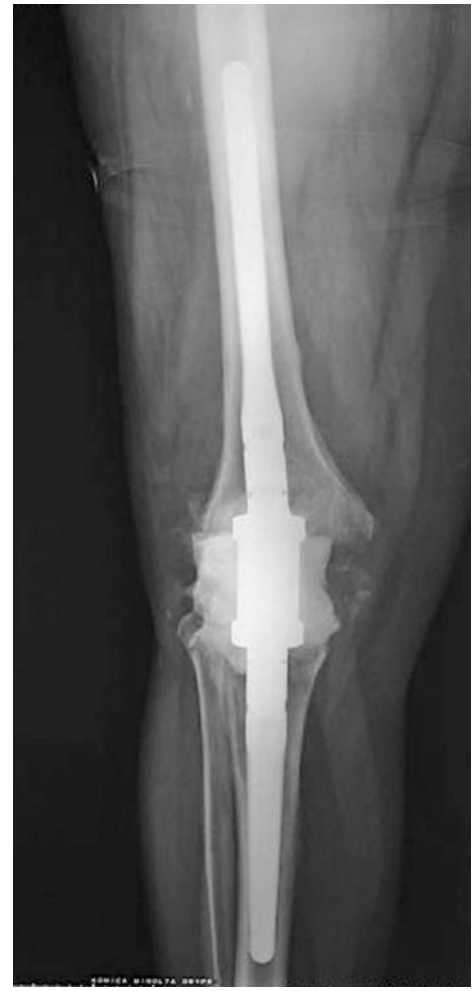

Fig. 20.8 Anteroposterior radiograph of right knee stabilised using a bridging modular implant (Endo-Model Knee Fusion Nail) without bone-on-bone fusion. The defect between the femur and tibia is filled with antibiotic-loaded cement, but the IM fixation is cementless (Adapted from Scarponi et al. [82], with permission from Springer)

Scarponi et al. used the cementless version of the same nail with a two-stage procedure in 38 patients [82]. With this technique, the defect between the femur and tibia is still filled with antibiotic-loaded cement, but each stem has a sanded titanium surface that is press-fit inserted into the diaphysis. They reported success in 34 patients (89.5%). One patient with infection recurrence underwent revision arthrodesis, another received suppressive antibiotic therapy following debridement and revision of the modular component, and two underwent

AKA. Bartlett et al. reported 90% infection clearance in ten patients who received the Stanmore knee arthrodesis prosthesis [32]. The risk of infection recurrence with implant arthrodesis and 'conventional' IM nails consequently appears to be similar.

20.12 Post-operative Principles

Most patients who undergo uncomplicated knee arthrodesis can expect to mobilise without pain as they progress towards union, although certain activities will inevitably be more uncomfortable, such as climbing stairs or sitting when legroom is restricted [19]. Ambulation may be supported with a walking stick or crutch and a shoe lift to reduce any limb length discrepancy.

Radiographic fusion is generally defined as trabecular bridging between the femur and tibia on anteroposterior and lateral projections, whilst the eradication of infection is indicated by clinical wound healing, stable observations, and normal blood markers. The choice of antibiotics for each individual is based upon pre- and intraoperative microbiological sampling, and each case should ideally be discussed with a microbiologist. Oral antibiotics are usually administered for a minimum of 6 weeks following a relatively short course of intravenous antibiotics after the definitive procedure, although this is dependent on the complexity of the case and host requirements. Prolonged systemic antibiotics have their own complications and are therefore generally reserved for multiresistant organisms [30, 80, 83].

In most circumstances, attempting conversion of a knee fusion to a TKA is not encouraged. Although successful examples have been described in the literature [84, 85], there is a high risk of complications such as infection recurrence, arthrofibrosis, or extensor dysfunction, so any decision to perform such a procedure must be taken with great caution [86–88].

Conclusions

Knee arthrodesis is a technically challenging but important salvage option for the infected TKA, especially in the presence of bone loss and extensor mechanism failure. Each candidate must be carefully assessed to determine the most appropriate method of fixation, although IM nailing is recommended where possible, in view of the reported fusion rates, and to allow early mobilisation. As our understanding of PJI develops, so will strategies to improve outcomes. Silver-coated implants have shown promise in both oncology and infected arthroplasty patients [89, 90], whilst customised local antibiotic carriers such as Stimulan (Biocomposites Ltd., Keele, UK) may provide better elution properties than antibiotic-impregnated cement and avoid the need for subsequent removal [91]. It should be emphasised, however, that a radical debridement remains paramount to infection clearance. As with any complex surgery, better outcomes are likely to be achieved when performed by experienced surgeons in specialist centres with multidisciplinary input.

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21 Above Knee Amputation in the Treatment of Failed Septic Total Knee Arthroplasty

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Abstract

This chapter will review current concepts on above knee amputation (AKA) in the treatment of failed septic total knee arthroplasty (TKA). Most patients are satisfied with their AKA, insomuch as they would have taken an amputation earlier. However, their functional level following AKA for infection is low, with only half of patients managing to walk. More than six previous procedures attempting limb salvage and failed *gastrocnemius* flap are possible poor prognostic factors. A substantial percentage of patients fail to have a prosthetic limb fitted, and those who do seldom obtain functional independence. Knee fusion (KF) in treatment of recurrent infection after TKA has a better functional and ambulatory result compared to patients receiving AKA. KF patients have significantly higher rates of postoperative infection (14.5% versus 8.3%) and transfusion (55.1% versus 46.8%), whereas AKA patients have a higher rate of systemic complications (31.5% versus 25.9%) and in-hospital mortality (3.7% versus 2.1%). AKA patients have lower hospital charges ($79,686 versus $84,747), longer length of stay (11 versus 7 days), and higher 90-day readmission rate (19.4% versus 16.9%). KF is therefore preferable to AKA for patients who have persistent infected TKA after a failed two-stage reimplantation procedure.

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21.1 Introduction

Infection is a serious complication of total knee arthroplasty (TKA). Control of infection after a failed two-stage TKA is not always feasible, and clearing infection may necessitate an above knee amputation (AKA) or knee fusion (KF) [1–4]. The purpose of this chapter is to review current concepts on AKA in the treatment of failed septic TKA.

21.2 General Concepts on Above Knee Amputation (AKA)

According to Remes et al. [5] in old people with peripheral arterial disease, major lower extremity amputation causes great loss of mobility, exposing them to the risk of losing their independent living status. In 2009, these authors analyzed predictors of institutionalization and considered prosthesis use by major lower leg amputees with peripheral arterial disease. They found that older age, living alone, and unilateral AKA or bilateral amputation predicted ongoing institutionalization. Of prosthesis users, 69% (27/39) were younger than 75, and 44% (17/39) were both domiciliary and community ambulators. Reasons for not using a prosthesis after amputation were short anticipated life expectancy: old age, combined with unilateral AKA or bilateral amputation, unilateral AKA or bilateral amputation, and a comorbid health problem such as hemiparesis, paraplegia, uremia, dementia, or alcohol abuse. After 1 year, 72% (36/50) of amputees who were able to return home and 9% (3/32) of institutionalized amputees used a prosthesis. Most patients were unable to return home after their first major lower extremity amputation. Comorbid health problems particularly affecting functional capacity also impeded ambulation with a prosthesis.

In 2010 D'Ayala et al. [6] reported the effect of blood transfusion on the prevalence of adverse postoperative consequences in patients undergoing major amputations. They reviewed 300 patients undergoing either AKA or below knee amputation over a 5-year period. Of the 300 patients undergoing major amputation, 191 (64%) had one or more blood transfusions. Patients undergoing blood transfusion were 2.5 more prone to experience a postoperative cardiac arrhythmia, 12.8 times more likely to develop acute renal failure, 5.7 times more likely to have pneumonia, and 2.2 times more likely to have a urinary tract infection. Each of these adverse postoperative complications was more likely in the transfused group. The postoperative mortality was 13% for the transfused group and 6% for the non-transfused group, although not statistically significant. The intensive care unit stay and overall hospital stay were significantly longer in patients who had blood transfusions (difference of 2.1 and 5.4 days, respectively). Blood transfusion in patients undergoing major lower extremity amputation was associated with an increased prevalence of adverse postoperative complications and prolonged intensive care unit and hospital stays. D'Ayala et al. [6] suggested a restricted approach to blood transfusion in patients needing major amputation. We think that the correct conclusion is that the need for a transfusion is associated with a great deal of morbidity.

Infection following major lower limb amputation is frequent, but surgical influences on the rates of infection are not defined. In 2012 Coulston et al. [7] reviewed a prospective database that included all patients who underwent a major lower limb amputation from March 2008 to July 2010. Infection was classified using Centre for Disease Control (CDC) criteria, and multivariate analysis was carried out to identify significant risk factors. They assessed the influence of perioperative surgical factors on their results. They analyzed 127 patients with a median age of 78 years. About 35% of patients had a wound infection following surgery. There was a higher infection rate in below knee amputation than AKA. No relationship was found between the grade of the operating surgeon, perioperative antibiotics, length of surgical procedure, and use of a nerve catheter with the postoperative presence of infection. There was a higher rate of infection with the use of suction drains. The use of skin clips rather than sutures was associated with a higher rate of infection. The main conclu-

sion of Coulston et al. [7] was that skin clips and surgical drains were associated with a greater risk of infection in major limb amputation and their use should be obviated.

In 2012 Nelson et al. [8] reported a preoperative mortality risk stratification tool for patients facing major amputation. Patients who underwent above knee (AKA) or below knee amputation (BKA) from 2005 to 2010 were identified from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database. They investigated the association of preoperative factors with 30-day mortality. Multivariable models were used to create a computerized prediction tool. Of 9368 patients, 4032 underwent AKA and 5336 BKA (below-the-knee amputation). The 30-day mortality rate after AKA and BKA was 12.8% and 6.5, respectively. The complication rate was statistically greater after AKA although numerically similar (28.5% versus 26.6%), whereas the rate of reoperation was much greater after BKA (22.7% versus 11.7%). Preoperative factors that predicted mortality after both surgical procedures included older age, dependent functional status, dialysis, steroid use, preoperative sepsis, delirium, thrombocytopenia, increased international normalized ratio, and azotemia. The prediction tools developed and validated by Nelson et al. had concordance indices of 0.75 for AKA and 0.81 for BKA (good predictive accuracy). Preoperative factors anticipated mortality after major amputation, and the risk calculator that Nelson et al. [8] reported may facilitate informed decision-making and provide pragmatic perspectives for surgeons and patients faced with limb-threatening disease.

In 2013 O'Brien et al. [9] analyzed predictors of early amputation failure (defined as need for reoperation within 30 days postoperatively) after adjustment for a number of preoperative and intraoperative variables. All patients from the 2005 to 2010 American College of Surgeons NSQIP database who underwent isolated lower extremity amputation were included for analysis (excluding patients with earlier operation within 30 days, patients undergoing an open amputation, and patients undergoing another procedure during amputation). The main conclusion of O'Brien et al. [9] was that an increased operative time and heightened supervision of participating surgical trainees can diminish the risk of early amputation failure. In addition, some clinical situations, such as sepsis or emergency procedures, should impel surgeons to contemplate either an open amputation procedure or a more proximal closed amputation.

In 2016 Wise et al. [10] reported preoperative risk factors predictive of both 30-day mortality and extended length of stay (LOS) in AKA patients. The 30-day mortality rate was 9%, and mean postoperative LOS of discharged patients was 9.3 days. Thrombocytopenia (platelet count $<250 \times 10^6$/mL) and preoperative septic shock were detected as independent risk factors for 30-day mortality. Burn etiology, leukocytosis (white blood cell count $>12 \times 10^6$/mL), and guillotine amputation were independently related to extended LOS. Excluding patients with AKAs due to trauma, burn, or malignancy, only thrombocytopenia (platelet count $<250 \times 10^6$/mL) and leukocytosis (white blood cell count $>12 \times 10^6$/mL) were independent risk factors for in-hospital mortality and extended LOS, respectively. Preoperative septic shock and thrombocytopenia were independent risk factors for 30-day mortality after AKA, while burn etiology, leukocytosis, and guillotine amputation made a contribution to extended LOS.

21.3 Above Knee Amputation for the Infected Total Knee Arthroplasty

In 2011 Fedorka et al. [1] investigated the etiology of AKA and the functional results of AKA after infected TKA. They analyzed 35 patients who underwent AKA after an infected TKA. The amputations were carried out an average of 6 years (range, 21 days to 24 years) after primary TKA. There were 19 females and 16 males with a mean age of 62 years (range, 26–88 years). Patient demographic information, comorbidities, surgical treatments, cultures, and culture sensitivities were collected. Complications and functional status, including SF-12 (short-form 12)

and activities of daily living questionnaires, after AKA were analyzed. The minimum follow-up was 7 months (mean, 39 months; range, 7–96 months). Two patients died due to cardiac arrest, and 13 more died during the follow-up period of unconnected causes. Nine patients needed irrigation and debridement for nonhealing wounds after AKA, and two patients had repeat AKA for osseous overgrowth. Of the 14 patients fitted for prostheses, eight were functionally independent outside of the home. Patients fitted with a prosthesis had higher mean activities of daily living scores (58 versus 38) and also tended to be younger with fewer comorbidities than those who were not fitted with a prosthesis. Fedorka et al. [1] found low functional status in living patients with an AKA after infection with only half of the patients walking after AKA.

In 2015 Khanna et al. [2] assessed patient satisfaction following AKA and tried to identify factors which may be indicative of successful outcome following AKA. A review was performed on seven patients who underwent an AKA for a recurrent periprosthetic knee infection. Patient satisfaction was calculated through a modified questionnaire. All patients were satisfied with their AKA, and six of seven stated that they would have taken an amputation earlier. Greater than six attempts at limb salvage and failed *gastrocnemius* flap were found to be possible poor prognostic factors. Despite poor function, patients with chronically infected TKAs were satisfied following an AKA.

In 2015 Rodriguez-Merchan [3] reviewed the evidence to determine which treatment method after failed two-stage reimplantation TKA, AKA, or KF yielded better function and ambulatory status for patients after a failed two-stage reimplantation. The main conclusion was that KF should be strongly considered as the treatment of choice for patients who have persistent infected TKA after a failed two-stage revision arthroplasty. Patients could walk at least inside the house, and activity of daily living independence was achieved by the patients with successful KF, although walking aids, including a shoe lift, were required. An intramedullary nail led to better functional results than an external fixator. The functional outcome after AKA performed after TKA was poor. A substantial percentage of the patients were never fitted with a prosthesis, and those who were seldom obtain functional independence. Only 50% of patients were able to walk after AKA.

In 2016 Carr et al. [4] compared KF and AKA in the treatment of failed septic TKA. A national database was interrogated, and the data of patients who underwent either KF or AKA for an infected TKA between 2005 and 2012 were examined. Procedure volumes, postoperative complications, hospital charges, length of stay, and 90-day readmission rates were evaluated. A total of 2634 patients underwent KF and 5001 patients underwent AKA for septic TKA. The percentage of total patients who underwent AKA increased significantly throughout the study period compared to KF. Patients who underwent AKA tended to be older and have more medical comorbidities. KF patients had a significantly higher rate of postoperative infection (14.5% versus 8.3%) and transfusion (55.1% versus 46.8%), whereas AKA patients had a higher rate of systemic complications (31.5% versus 25.9%) and in-hospital mortality (3.7% versus 2.1%). The AKA cohort had lower hospital charges ($79,686 versus $84,747), longer length of stay (11 versus 7 days), and higher 90-day readmission rate (19.4% versus 16.9%).

21.4 Basic Concepts on Prosthetics After Above Knee Amputation

Amputation of limbs is still carried out commonly [11]. In the USA in 2005, there were 1.6 million amputees, predicted to rise to 3.6 million by the year 2030 [11]. The most frequent cause of amputation remains a vascular problem, mainly as a complication of diabetes mellitus, with traumatic amputations the second most common cause [12] representing 12.5% of all amputations. Among traumatic amputations those of the upper limbs are the most prevalent 68.6% [13].

The cost of an amputation is high. The estimated cost of a limb amputation at 5 years is over

500,999 $, almost double than the mean health care of a single individual [14, 15]. To such an amount must be added the price of the prosthesis, which has been estimated to be 450,000 $ at 5 years [16].

Amputees usually suffer multiple complications. Moreover, the amputation itself is in many cases the consequence of a chronic condition. Amputees have a higher risk of cardiovascular disease [17], obesity [18], osteoarticular pain [19], and depression [20]. The estimated mortality of an amputee at 5 years is 74% [21].

A very common problem is the association of amputation and obesity. Lower limb amputees usually present a body mass index (BMI) higher than nonamputated people [22]. It is well known that the greater the level of amputation, the higher the incidence of obesity. Obesity usually increases during the first year after amputation [18]. However, that obesity which is associated with a worse prognosis has not been demonstrated [23].

Amputation is considered a means to save life, not a failure. It has been reported that patients whose limbs are saved frequently have a greater loss of quality of life than amputees. This is due to the multiple procedures of reconstruction that they require [24].

Amputees benefit from being managed by a multidisciplinary team [25]. In such a team, the most important member is the patient. The team must include a surgeon, a specialist in physical medicine and rehabilitation, a therapist, a psychologist, and a prosthetic technician.

The goals of amputation surgery must include the elimination of all nonviable tissues, creating a residual limb that can be fitted with a prosthesis. To achieve such a goal, it is very important that the residual limb has a cylindrical shape and is well cushioned with soft tissues (muscles, fascia), without bony protrusions or sharp edges, with an adequate length (without an excess of soft tissues), gentle handling of nerves, and good control of edema, hematoma, and postoperative pain (Fig. 21.1).

Newer techniques of osteointegration have been developed. In this technique a female coupling is inserted into the residual bone of the stump and fixed with cement. The exoskeletal prosthetic system is then united by means of a male coupling inserted into its female counterpart. The major complication is persistent infection requiring ongoing antibiotic suppression. The residual limb can also fracture above the female device inserted into the bone [26].

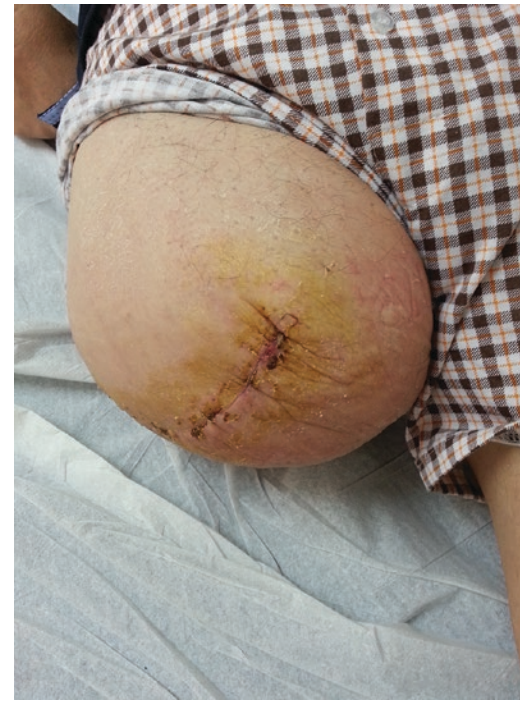

Fig. 21.1 Residual limb after amputation secondary to an infected TKA. Taking into account that surgery was performed 3 weeks before, the stump still shows edema but not hematomas. Note that the stump has an epithelized scar and cylindrical shape. It is well cushioned with soft tissues, without bony prominences, and with an adequate length

Stump revision may be required for several indications: bony painful sharp edges, symptomatic neuroma, deficit in soft tissue coverage, need of increasing the length of the residual limb, excessive soft tissues, heterotopic ossification, and adhered scars. All the aforementioned conditions may interfere with the prosthesis fitting process.

The goal of physical medicine and rehabilitation is to encompass the whole process, from surgery to the resumption of independent living. Preoperative evaluation is paramount. Its aims are to determine the best possible level of

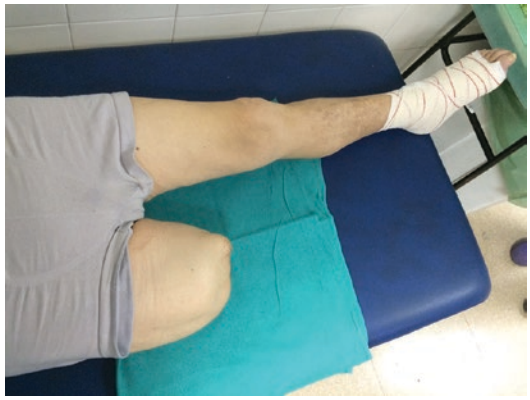

Fig. 21.2 Residual limb during the preprosthetic phase. It is painless, with reduced edema, adequate healing of the surgical wound, and well conformed and aligned and with a good articular and muscular status

Fig. 21.3 Shaper bandages of the stump during the preprosthetic phase. They are capelin and ear bandages with decreasing compression that must be put daily. Their objectives are to help cure the surgical wound, reduce the sensation of ghost limb, and provide a cylindrical shape to the stump

amputation, to inform the patient about the postoperative rehabilitation process, and to agree the mid- and long-term objectives. It will help diminish the patient's anxiety about their future and provide adequate patient education.

21.4.1 Prosthesis Fitting Phases

The primary goal of a transfemoral amputee after an infected TKA is to resume functional gait. To achieve this goal, it is paramount to consider three essential phases from the point of view of physical medicine and rehabilitation:

1. Preprosthetic Phase

   In this first phase, the main goals are to get a good control of phantom limb pain and stump edema, an adequate healing of the surgical wound, a well-aligned and well-conformed painless stump, and a good muscular and articular status both of the residual limb and the contralateral limb (Fig. 21.2). These are paramount in order to progress to the second phase. Tools employed to achieve them include the provision of adequate analgesia, daily conforming bandages of the stump (Fig. 21.3), postural recommendations, muscle-strengthening exercises (mainly pelvitrocantheric), and weight bearing on the healthy limb (Fig. 21.4).

   Most amputees do not have pain interfering with their quality of life or requiring regular analgesia beyond 6 months after the amputation surgery [27].

   It is important to differentiate phantom limb sensation (that does not require treat-

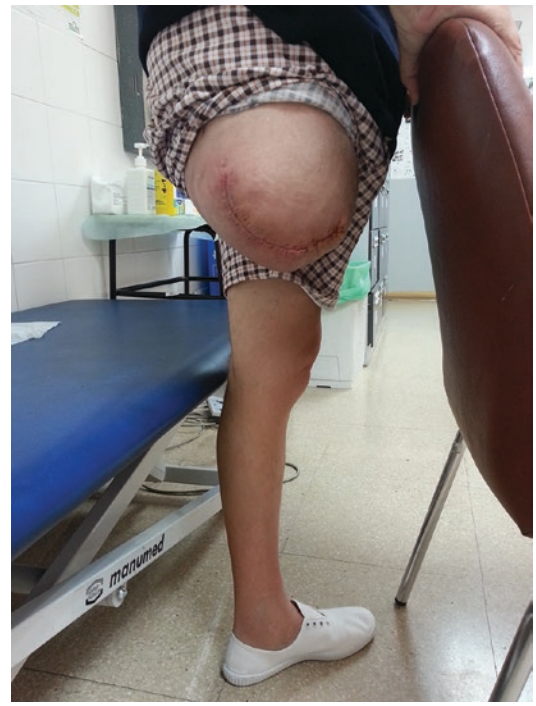

Fig. 21.4 Amputee performing monopedestation during the preprosthetic phase. The goals are to maintain patient's verticality, preserve the alignment of the residual limb, maintain the functional status of the contralateral limb, and reduce the sensation of ghost limb

ment) and phantom limb pain. It is common for the distal part of the phantom limb to approach the distal end of the residual limb and then to fully disappear, in a process called telescoping. We must also differentiate ghost limb pain and stump pain. Treatment of these painful conditions is different and has been reported [28]. With ghost limb pain, in addition to pharmacological measures (because it is a neuropathic pain), attention must be paid to potential signs of depression, anxiety, and sleep disturbances. Smoking cessation must also be encouraged [29].

2. Prosthesis Fitting Phase

This must be started as soon as possible, provided the patient fulfills the objectives of the aforementioned phase. In this stage the physician will decide, agreeing with the patient, what components must be part of the prosthesis according to the patient's expected level of activity. The length of the stump is important. A very short residual limb will provide poor stability and a lower lever arm to propel the prosthesis during swing phase. However, an overlong stump will not allow space for the components of the prosthetic knee. The recommended length to allow the use of prosthetic knees with a microprocessor is 10.2 cm from the articular line of the amputated knee to the bony end of the stump. In this phase it is important to obtain the cooperation of a prosthetic technician with experience in the manufacturing of this type of exoprosthesis. At the time of prescribing the prosthesis for a transfemoral amputee, the following components must be considered (Fig. 21.5):

(a) Inner liner: This is directly in contact with the stump; it can be made of different materials such as urethane, silicone, or gel. It covers the residual limb and facilitates suspension with the outer liner. It has to be carefully unwound over the residual limb. Moreover, it requires constant care and hygiene, may produce heat, and needs replacement every 6–12 months.

Fig. 21.5 Components of a transfemoral prosthesis: liner, outer lace, suspension system, knee, and prosthetic foot

(b) Outer liner: This is a rigid case, usually made of different thermoplastics or carbon fiber, that picks up the residual limb and serves as a structure of union with the exoskeleton. It is important to mention that in transfemoral amputations, weight bearing is via the ischial spine (in contact with the outer liner), never over the distal part of the stump. Even so, stump pain is usually caused by problems related to the liner. In transfemoral amputees, the usual point of pain is the lateral zone of the distal femoral end which is in contact with the wall of the liner [30]. Other causes of pain are the presence of a neuroma, edema, bony prominences, or vascular claudication.

(c) Suspension system: There are three types of suspension systems:
- Atmospheric: Based on the presence of an air chamber between the surfaces of the two aforementioned liners (inner and outer). Within this category can be included vacuum systems.
- Anatomical: Implies that the prosthesis is united to the pelvis by means of a belt system connected to the liner. These are usually employed when an atmospheric suspension system is impossible to use. On occasions these are used when the atmospheric suspension system is not enough to get a good union between the residual limb and the liner, reinforcing this suspension system.
- Osteointegration: Eliminates the need for a liner, because it couples the prosthetic components directly with an implant, which is integrated in the bone. Among the reported benefits of this system are facility of use, decrease of energy consumption, and improvement of the range of motion of the hip [31].

(d) Prosthetic knee: Prosthetic knees are currently divided into those with mechanical control and those with electronic control [32]. Mechanical knees can have one axis or multiple axes, and mechanisms can be of constant friction or hydraulic. Moreover, they have some characteristics that differentiate them such as a manual block, assistance with extension, and weight-activated stance control and stance flexion. The indication for the type of knee will depend on the patient's functional level and economic considerations. Electronic knees (controlled by a microprocessor) allow a gait with lower attention and lower energy consumption [33]. Some of the reported benefits of this type of knee are facilitation of rising from a seated position and the use of stairs [34]. Another benefit is the decreased load on the healthy knee during stair ascent [35]. Despite the evident advantages of knees with a microprocessor, they require maintenance work, an electric recharging, and imply an added weight and a high economic cost.

(e) Prosthetic foot and ankle: Prosthetic feet classically have been divided into a number of categories: SACH (solid ankle cushion heel) foot, flexible foot, dynamic response foot, single axis foot, and multiple axes foot. However, the aforesaid categories do not classify their mechanical properties [36]. Moreover, there is no scientific evidence to endorse the prescription of a particular type of foot [37]. It has even reported that feet belonging to the same category do not present the same mechanical properties [38]. At the time of prescribing a particular foot, we must take into consideration the weight it bears and the space needed to accommodate its mechanism. The keel of the foot is its most important component; it is the part of the prosthetic foot that simulates the anatomical structures responsible for providing stability and mobility during support and movement. Modern materials allow the accommodation of the prosthetic foot to the ground and absorb impacts and the return of mechanical energy, to facilitate the takeoff during the gait. The movement that the human ankle usually performs is commonly incorporated into the foot design itself. Hydraulic mechanisms that regulate ankle movement can be employed, controlled by a microprocessor. These sophisticated feet allow the patient to walk with a similar gait to nonamputees [39].

The choice of components will depend on the level of activity of the patient that is going to use it and also on their esthetic preferences [40]. In every case, the indication must be individualized and agreed by the physician in charge, the patient, and the prosthetic technician.

3. Post-prosthesis Fitting Phase

The patient must learn to use his/her prosthesis. That is to say, to put it and remove it by himself/herself, reeducate stability in bipedal gait, with or without technical aids (Fig. 21.6). Moreover, the patient must learn how to climb stairs and ramps, as well as get up after a fall. Such training will have to be made in the ther-

Fig. 21.6 Amputee during the post-prosthetic phase. The patient is reeducating gait and using a cane in the contralateral hand

apy room with the help of an experienced physiotherapist. In addition, during this phase the patient must be instructed on the need of adaptations at home to facilitate the activities of daily living in an autonomous way and reduce the risk of accidents.

The characteristics of these patients imply that they must be followed strictly, needing periodical reevaluations in the outward clinics of physical medicine and rehabilitation [41].

It must be remembered that an amputation implies some changes in the life of patients. There are changes in their body image, functional abilities, social and economic life, and problems in their own control [42]. Therefore, mental health must be taken into account; an evaluation of the physical status before amputation must be beneficial. In those patients not prepared for the loss of a limb, the psychological, social, vocational, and sexual impact of amputation may have greater impact in the quality of life than the loss of the limb itself [43]. Almost 30% of amputees develop symptoms of depression [44]. Posttraumatic stress syndrome is also very frequent. Programs of psychological support are beneficial in amputees. They lead to a reduction of depression symptoms in up to 50% of cases compared to other programs of support in groups of patients [45].

To sum up, amputation must not be considered a therapeutic failure after an infected TKA, because in many cases prosthetic and rehabilitation solutions after amputation can provide a better quality of life in the short and long terms. The amputee can benefit from an individualized and multidisciplinary approach made within the context of a specialized unit.

Conclusions

The majority of patients are satisfied with their above-the-knee amputation (AKA) (they would have taken an amputation earlier) in the treatment of failed septic total knee arthroplasty (TKA). However, functional status in patients with an AKA after infection is low, with only 50% of the patients walking after AKA. Greater than six attempts at limb salvage and failed *gastrocnemius* flap are poor prognostic factors. A high percentage of the patients never have a prosthesis fitted, and those who are seldom obtain functional independence. Patients receiving knee fusion (KF) for recurrent infection after TKA have better function and ambulatory status compared to patients receiving AKA. KF patients have a significantly higher rate of postoperative infection (14.5% versus 8.3%) and transfusion (55.1% versus 46.8%), whereas AKA patients have a higher rate of systemic complications (31.5% versus 25.9%) and in-hospital mortality (3.7% versus 2.1%). AKA patients have lower hospital charges ($79,686 versus $84747), longer length of stay (11 versus 7 days), and higher 90-day readmission rate (19.4% versus 16.9%). KF must be recommended as the treatment of choice for patients who have persistent infected TKA after a failed two-stage reimplantation procedure.

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