The Infected Total Knee Arthroplasty

11

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11.1 Introduction

The goal of a total knee arthroplasty (TKA) is to relieve joint pain by replacing the degenerated cartilage with two metal components separated by a polyethylene component. This surgical procedure is not without risks and complications, the most concerning of which is infection. In fact, infection can become a real nightmare for both the surgeon and the patient. The exponential increase in the number of TKAs and secondarily in the number of revision total knee arthroplasties (RTKAs) have led us to predict the enormous economic impact that this issue will have on health systems in the future. The diagnosis of periprosthetic joint infection (PJI) is sometimes challenging, but when faced with a painful TKA we must always consider infection as the main potential cause of the problem. Once the diagnosis of infection has been reached by means of various clinical, analytical, microbiological, and radiological tools, we must try to identify the microorganism responsible for the septic loosening. After the removal of the implant and the administration of antibiotics, the objective will be to cure the infection and restore the functionality of the knee. RTKA for septic loosening constitutes a technical challenge, not only because of

the difficulty in eradicating the infection but also because of the lesser bone stock available. In RTKA, it might be necessary to use constrained implants, pure or rotational hinges, and augmentation (cones or sleeves). This chapter reviews some important classical concepts and also the latest developments on infected TKA, as well as their diagnosis and treatment.

11.2 Epidemiology: Incidence and Economic Impact of Infected Total Knee Arthroplasty

TKA is an effective procedure for relieving pain and restoring functionality in the later stages of osteoarthritis. However, one of the most devastating complications associated with the procedure is infection, which is present in 0.5–2% of all TKAs. The rate of PJI is higher in TKA than in total hip arthroplasty (THA) as a result of less soft tissue coverage and greater stress in terms of knee mobility. A study with over 11,000 TKAs showed a cumulative incidence of RTKA of 6.1% at 15 years, with 2% due to infection and 1.2% due to aseptic loosening [1]. With exponential growth in the demand for TKA worldwide due to the aging population and increased life expectancy, the number of RTKAs is expected to multiply in the coming years and result in up to $13 billion in U.S. healthcare spending by 2030 [2].

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Classically, infection, osteolysis associated with polyethylene wear, loosening, stiffness, and instability are the main causes of prosthetic failure. Delanois et al. [3] have reported that, in some series, infection is the main cause of revision (20.4%), followed closely by purely mechanical loosening, with an associated average cost of approximately $75,000. This study updated other classic studies by Thiele [4] and Bozic [5] that reported similar rates (26.8% and 25.2%, respectively), but with lower costs ($49,360). Another study noted an increase in hospital costs of about $40,121 when TKA leads to some type of septic problem [6]. The associated cost depends, among other things, on the therapeutic strategy used: debridement, antibiotics, and implant retention (DAIR) versus RTKA in 1 or 2 stages, which logically entails a higher cost. Alp et al. [7] had observed a hospital length of stay of up to 7 times longer in infected TKA (49 days versus 7) than in noninfected TKA. In addition, in septic cases, the associated cost of hospital measures increased by 2–24 times.

Therefore, to optimize quality while maintaining economic sustainability, it is imperative that orthopedic surgeons find ways to mitigate the costs associated with infection-based RTKA.

11.3 Risk Factors Associated with Periprosthetic Joint Infection

Considering the economic burden of septic loosening of a TKA, it is important to identify the risk factors associated with the problem, as well to introduce control measures when possible. Two types of risk factors can be described: those dependent on the patient and those secondary to the surgical intervention.

If we take into account the patient's own dependent factors, age and sex are not modifiable. The vast majority of meta-analyses find male and young patients to be at independent risk for PJI in both THA and TKA [8, 9]. Related factors that increase the risk of PJI [10] are summarized in Table 11.1.

Toxic habits such as smoking, alcohol, and the use of drugs that can interfere with wound healing, and which are widely used for the control of inflammatory arthropathies, such as corticosteroids, methotrexate, and TNF inhibitors, are associated with an increased risk of PJI. The American Rheumatological Association recommends that the administration of biological drugs be stopped one cycle before elective arthroplasty [11].

Infections in another location (urinary tract, oral, or skin) and the close administration of intra-articular corticosteroids are likely to be risk factors, sowing the seeds of transient bacteremia. Up to 24–35% of staphylococcal bacteremias can lead to infection in the context of TKA surgery [12].

The location of the arthroplasty, whether it is primary or revision surgery, the potential ability of the tissues to heal, or subclinical infections not detected during implantation are all factors dependent on the surgical procedure itself [13]. There is controversy as to whether the choice of implant (cemented or uncemented) increases the risk of infection. Houdek et al. argue that polyethylene tibial components are associated with a lower infection rate compared with metal-tray components [14]. A recent study in the British National Register advocates the use of antibiotic-impregnated cement on a routine basis, with a consequent reduction in the rate of infection,

Table 11.1 Factors associated with a high risk of infection in orthopedic surgery

Male gender
Poorly controlled diabetes mellitus (glucemia >200 o HbA1c >7)
Poor nutritional status
Morbid obesity (BMI > 40)
Long length of stay
Immune deficiency
Anemia
Abuse of alcohol, tobacco, and intravenous drugs
Active liver disease
Chronic kidney insufficiency
Posttraumatic osteoarthritis
Previous surgical procedure in the knee
Inflammatory arthropathies

Hb hemoglobin, *BMI* body mass index

although this remains a matter of debate, given its systematic application in primary surgery is not recommended [15]. Continuous drainage, significant hematomas and surgical wound dehiscence carry a higher risk of infection. An excessive duration of the surgical procedure significantly increases the possibility of contamination [16]. The use of antiaggregants or anticoagulants and blood transfusions for postoperative anemia has classically been associated with an increased risk of infection. However, clinical guidelines for the prevention of surgical site infection recommend that blood transfusions not be given after surgery unless absolutely necessary [17]. Additional measures include monitoring blood glucose values <200 mg/dl, chlorhexidine baths, and preparation of the skin with alcoholic solutions during the surgery.

11.4 Preoperative Optimization in the Prevention of Infected Total Knee Arthroplasty: Risk Factors, Skin Preparation, Antibiotic Prophylaxis, and Decontamination Protocols

One study has suggested staphylococcal decolonization with nasal mupirocin in staphylococcal carriers, noting a decrease in the frequency of PJI (0.8%–0.2%) after its implementation, estimating a saving of approximately $700,000 in more than 2000 patients [18]. However, these measures are not yet included in clinical guidelines in some countries. Further supporting these protocols, another interesting multicenter study has shown that the implementation of a postdischarge methicillin-resistant *S. aureus* (MRSA) decolonization protocol with chlorhexidine and mupirocin was associated with a 30% lower risk of MRSA infection than nondecolonization [19]. Perioperative intravenous antimicrobial prophylaxis is optimized by the choice of antimicrobials, which should be administered in such a way as to achieve the optimal level of antibiotic at the tissue level at the time of incision (30–60 min before the start of the surgery). In our usual prac-

tice, we use a 2-g dose of cefazolin, although in cases of allergy or intolerance to B-lactams, we use vancomycin 1 g. Additional doses of prophylactic antimicrobials after surgery are not routinely recommended, even in the presence of drains [17].

Numerous studies have shown a link between obesity and a higher rate of superficial and deep infection after TKA [20]. A meta-analysis designed to determine the influence of bariatric surgery prior to TKA found a reduction in short-term medical complications, shorter hospital length of stay, shorter surgical time, and a lower rate of PJI in the short term, but not in the long term [21]. Another recent systematic review raises questions about the role of pre-TKA bariatric surgery and short-term outcomes, and more studies appear to be necessary to assess its ultimate influence [22].

In terms of nutritional status, several studies have been reported suggesting that albumin levels below 3.5 g/dl behave as an independent risk factor for long-term PJI; therefore, protein supplementation prior to TKA might be of interest [23].

Two interesting studies on risk factors in TKA have shown that the presence of inflammatory arthropathies, such as rheumatoid arthritis, and at least two comorbidities, such as diabetes mellitus and anemia, clearly increases the risk of PJI [24, 25]. In our practice, we recommend that the candidate selection process includes patients with hemoglobin levels above 1 g/dL.

Intra-articular administration of corticosteroids in the knee has been associated with an increased risk of PJI, although various studies are contradictory, with some suggesting a minimum of 3 months between infiltration and surgery [26]. O'Connell et al. had observed an association between dexamethasone administration and a significant increase in blood glucose levels in the immediate postoperative period in patients with diabetes mellitus following TKA, and they advised that dexamethasone should be used with caution in this population [27].

Within intraoperative measures, the routine use of antibiotic-impregnated cement remains a matter of debate. King et al. found that its use did

not reduce the risk of PJI compared with standard cement, although it was associated with a significant increase in healthcare costs [28]. However, the British National Register contradicts this statement [15].

With regard to the application of topical measures to reduce the risk of infection, a recent study has found that hydrogen peroxide and povidone-iodine constitute the most effective tool for the neutralization of *S. aureus* colonies [29]. In terms of skin preparation, the usual practice is to use chlorhexidine, shaving the day before the operation if necessary, always using a machine or electric shaver.

The application of topical vancomycin proposed in recent years as one of the alternatives and adjuvant measures has not yet reported a clear benefit in TKA, although it has been validated in spinal surgery [30]. It is widely accepted that increased surgical time correlates with an increased risk of postoperative infection [31].

The usual dose of cefazolin 2 g has already been discussed for intraoperative antibiotic therapy. It covers Gram-positive, Gram-negative, aerobic, and anaerobic bacilli; however, it is not effective against MRSA. In case of allergies or if cefazolin cannot be administered, clindamycin 90 mg (3–6 h) or vancomycin 15 mg/kg (6–12 h) are widely accepted alternatives [32].

Postoperative risk factors including transient bacteremias related to dental interventions or other infections and surgical wound (hematoma) management should be considered with special caution. Patients should be advised of the need for prophylaxis if they undergo such procedures prior to any invasive manipulation [33].

11.5 Microbiological Aspects of Infected Total Knee Arthroplasty

The bacteria involved in the pathogenesis of PJI have a special capacity to adhere to materials such as chrome-cobalt, polyethylene, titanium, and polymethylmethacrylate (PMMA), generating a real ecosystem with its own laws called "biofilm." The microorganisms in biofilms are up to 1000 times more resistant to antimicrobial agents than their planktonic forms, and the in vivo adjustment of the minimum inhibitory concentration for these agents is ineffective even at doses that are applied by the intravenous systemic route [34]. Our efforts should focus on preventing the formation of biofilms by reducing the bacterial load present in the surgical field.

The most common primary foci of PJI are skin and soft tissue infections (*Staphylococcus aureus*), respiratory tract infections (*Streptococcus pneumoniae*), gastrointestinal infections (*Salmonella*, *Bacteroides*, *Streptococcus gallolyticus*), and urinary tract infections (*Escherichia coli*, *Klebsiella*, *Enterobacter spp.*). Hematogenous spread can also occur during dental procedures (*S. viridans*). In the case of infected intravascular devices, even mild bacteria such as *Staphylococcus epidermidis* can cause hematogenous infections [35]. As regards the time course of the infectious process, there is a correlation between the most frequent bacteria according to their greater or lesser virulence and the time of appearance of the clinical picture [36] (Table 11.2).

Thus, the most virulent microorganisms usually cause more symptomatic cases, with high analytical parameters and clinical flowering in the acute course of the disease, whereas the less aggressive ones appear in the context of insidious course pictures with symptoms of low representativeness. In terms of fungal infections, *Candida spp.* represents the greatest threat and is often associated with patients with immunosuppression and poorly controlled diabetes mellitus [37].

The prevalence of "culture-negative" PJIs is 0–42% in various series [38]. They are sometimes due to antimicrobial treatments that negatively affect cultures, to slow-growing or difficult microorganisms, or to species that are not as common as *Listeria monocytogenes*, *Cutibacterium acnes*, *Coxiella burnetii*, *Brucella*, *Bartonella*, and *Mycoplasma*. Improved culture media, better microbiological techniques, and the use of polymerase chain reaction (PCR) and genomic sequencing might allow the identification of new causes of infected TKA in the future [39]. However, despite the fact that PCR is

Table 11.2 Relationship between the microorganism and the time of infection after surgery

ACUTE (<3 months)	Subacute (3–12 months)	Chronic (>12 months)
S. aureus Gram-negative organisms Polymicrobial infection Anaerobic organisms	S. coagulase-negative Enterococcus Cultibacterium	S. aureus Strep-B hemolytic Gram-negative organisms

extremely sensitive, its specificity is low and therefore it is not appropriate to use it as a diagnostic tool in isolation, but rather as part of a combination of clinical, radiological, and analytical parameters that reveal that we are facing an authentic infection and treat it as such [40].

11.6 Diagnosis of Infected Total Knee Arthroplasty

The diagnosis of PJI is sometimes relatively simple when the course of symptoms is rapid after surgery, with a typical clinical presentation of the infectious process: heat, pain, erythema, and effusion (Fig. 11.1).

In the vast majority of situations, however, this is not the case, and the course is insidious, with signs and symptoms that must be supported by analytical, radiological, microbiological, and histological criteria to confirm the suspicion. The presence of fever can appear in the context of transient bacteremias; the existence of fistulae constitutes in itself a major criterion for considering a TKA infected (Fig. 11.2).

Many of the current diagnostic and supportive criteria depend on the accuracy of cultures, as well as on the inflammatory and immune response to infection and surgery.

Microbiological identification is not necessary to select the type of surgical examination, which is primarily based on clinical and radiological signs [41].

In an attempt to unify criteria, various aspects have been postulated by the societies specializing in infected TKA. The criteria agreed upon by the Infectious Diseases Society of America, the

Fig. 11.1 Total knee arthroplasty (TKA) with surgical wound dehiscence and purulent drainage: acute infection of less than 3 weeks evolution

MusculoSkeletal Infection Society (MSIS), and the International Consensus Group on Periprosthetic Joint Infection are shown in Table 11.3 [42]. New criteria have been defined at the European Bone and Joint Infection Society meeting in 2018 in Helsinki, Finland (Table 11.4) [43].

From a clinical point of view, the physical examination can reveal anything from clear signs of the temporality and virulence of the microorganism (heat, functional impotence, fistulae, purulent drainage) to a less striking picture with pain, clinical worsening, and reduced mobility. In any case, when faced with a painful TKA, a possible septic condition must always be ruled out. We must assess the possible associated inflammatory arthropathies that are part of the differential diagnosis (e.g., hyperuricemia, chondrocalcinosis, rheumatoid arthritis).

In the event of initial suspicion of a possible septic condition, we will initially request an ana-

Fig. 11.2 The existence of a fistula is one of the major criteria for infected total knee arthroplasty (TKA)

Table 11.3 MSIS (MusculoSkeletal Infection Society) criteria on periprosthetic joint infection (PJI) [42]

Major criteria (at least one of the following)	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
Minor criteria ≥6 → Infected 2–5 → Possible infected 0–1 → Not infected	1. Elevated serum C-reactive protein (CRP) concentration or D-Dimer → 2 2. Elevated serum erythrocyte sedimentation rate (ESR) → 1
	3. Elevated synovial leukocyte count or LER → 3
	4. Positive alpha defensin → 3
	5. Elevated synovial neutrophil percentage (PMN%) → 2
	6. Elevated synovial CRP → 1
Intraoperative diagnosis ≥6 → Infected 2–5 → Possible infected 0–1 → Not infected	1. Positive histology → 3
	2. Positive purulence → 3
	3. Single positive culture → 2

LER leukocyte esterase, *PMN* polymorphonuclear

lytical study with various parameters (polymorphonuclear leukocyte count [PMN], C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], and procalcitonin). None by themselves have sufficient sensitivity and specificity to confirm or exclude PJI, although they can serve as a guide or initial step for further testing. In low-virulence infectious processes (*Cutibacterium*, *Candida*, *Mycobacterium*, *Actinomyces*, *Corynebacterium*), these parameters are often within the normal range [44]. The sensitivity of combined CRP and ESR reaches 98% and should be considered as initial evidence for initiating further studies on suspected TKA infection [45].

Other serological markers have been postulated as alternatives to the classics (IL-4, IL-6, sICAM1, and TNF-alpha). Procalcitonin has shown inconsistent results in recent publications, although it might play a role in differentiating between inflammatory arthropathy and septic shock, although always in combination with other elevated parameters [46]. In recent years, D-dimer has become a potentially useful new tool in the diagnosis of PJI and in monitoring the outcome of antimicrobial treatment. Recent studies give it a sensitivity and specificity of 80% [47]. However, more studies are needed to support its application and validity at the same level as other classical parameters [48].

Table 11.4 Criteria of the European Bone and Joint Infection Society

Test	Criteria
Clinical features	Sinus tract (fistula) or purulence around prosthesis
Leukocyte count in synovial fluid	>2000/µl leukocytes or >70% granulocytes (PMN)
Periprosthetic tissue histology	Inflammation (>23 granulocytes per 10 high-power fields)
Microbiology Microbial growth in	Microbial growth in
	Synovial fluid or
	>2 positive tissue samples (of at least 3 collected) or
	Sonication fluid (>50 CFU/ml)

Periprosthetic joint infection (PJI) is diagnosed, if >1 criterion is fulfilled

PMN polymorphonuclear, *CFU* colony-forming units

Synovial fluid analysis and culture should be performed when clinical suspicion and laboratory parameters suggest a septic process. Culture, cell count, and PMN are simple and inexpensive procedures that are useful in the diagnosis of infection. Culture is influenced by antibiotic treatments within 2 weeks prior to arthrocentesis. Controversy remains over the cut-off points for PMN count and percentage, which has been centered on 2000 leukocytes/ul and 70% PMN for subacute cases [49]. The sensitivity of the culture is 45–75% and the specificity is 95% [50].

It is recommended that aspiration be inoculated into pediatric blood culture media and maintained for up to 14 days to rule out the growth of low-virulence microorganisms. The use of swabs is not recommended, and the use of vials for definitive culture is recommended to prevent possible secondary contamination during sample transport [51].

Alpha defensin has been a revolutionary addition in recent years, as a test with high sensitivity and specificity. It is an antimicrobial peptide released when in contact with activated neutrophils in the context of a bacterial infection. We can differentiate two types of tests for this tool: qualitative alpha defensin (alpha defensin lateral flow, ADLF) and quantitative (identified through enzyme-linked immunosorbent assay). To assess its reproducibility, one study had reported that the ADLF had a lower sensitivity (85%) than the quantitative test, with a combined sensitivity of 95% [52]. In a recent study, ADLF showed a lower sensitivity than in previous publications (54.4%), but with a specificity of 99%, and is therefore considered not to be a screening tool but a confirmation tool for certain cases [53]. In a comparison with various serological and synovial markers, Lee et al. had observed a higher odds ratio in the diagnosis of PJI in favor of alpha defensin [54].

Leukocyte esterase (LER) has recently been included in the minor criteria for MSIS and is an enzyme present in activated PMN that is often found in infected body fluids. LER reagent strips are commonly used for the diagnosis of infections in other locations (urinary tract infections, peritonitis, and chorioamnionitis). McNabb [55] reported a specificity of 99.3% for LER as a tool to rule out a septic process.

PCR and other molecular techniques increase the sensitivity and specificity of cultures as additional tools for diagnosis. PCR is a molecular biology technique that amplifies a piece of DNA, creating millions of copies for easy identification. Jun et al. [56] reported a reduction in PCR sensitivity to 76% in a recent meta-analysis, with similar specificity (94%) as those reported in classical studies. However, PCR has identified low-virulence microorganisms such as *Cutibacterium* in cases initially considered as aseptic loosening, with greater sensitivity than other conventional techniques [57]. Another recent meta-analysis has reported a sensitivity of 81% and a specificity of 94% [58].

Sonication is a method that uses low-frequency ultrasound waves that pass through a liquid that surrounds the implant to separate biofilm microorganisms from the prosthetic surface [59]. It appears that this technique could better identify the microorganisms in the resulting liquid grown on plates for aerobic and anaerobic microorganisms. The cut-off point of 50 colony-forming units/ml has been estimated to have a sensitivity of 79% and a specificity of 99%, which is more accurate than conventional culture [60]. In patients with suspected PJI, sonication fluid might be a more appropriate sample than periprosthetic tissue for wide-range PCR analysis, even under systemic administration of antimicrobial therapy [61]. It is therefore expected that sonication will be incorporated into new diagnostic protocols for PJI in the coming years.

With regard to the culture, as previously mentioned, the use of swabs for samples is not recommended, and the number of five tissue fragments for subsequent microbiological analysis has been established as a reference. The sensitivity of the conventional culture is approximately 60–65%. Growth maintenance time in cultures is normally 14 days, although 42.4% are positive on day 3 and 95% on day 8, depending on the microorganism [62]. The current consensus on the true incidence of PJI with negative culture is between 7% and 15% [63]. An interesting algorithm has been presented by Palan et al. [64] for negative cul-

tures: suspend antibiotics 14 days before sampling; extend the culture for 14–21 days; and consider sonication/Micro DTT, atypical microorganisms/fungi, and 16s RNA analysis.

Histological examination of periprosthetic samples obtained during surgery is one of the basic tools in the diagnosis of infected TKA. Neutrophil detection is performed by field magnification of 400, and the presence of 1–10 neutrophils [50] presents a very high sensitivity and specificity (91% and 92%, respectively). The optimal limit is a count of 39 CD15+ neutrophils, although the percentages vary according to the virulence of the microorganism [65].

With regard to complementary radiological studies to support the suspected diagnosis of infected TKA, various imaging tests can be useful: conventional radiography, fistulography, ultrasonography, bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).

In septic or mechanical loosening, weight-bearing anteroposterior and lateral radiographs allow areas of osteolysis (Fig. 11.3) and rapidly progressive radiolucent lines to be visualized, although only in advanced cases of the disease, with a sensitivity below 15%.

Fistulography is currently a technique in disuse, although it identifies the fistulous path from the skin to the surrounding tissues of the prosthesis. The ultrasound scan can confirm effusion, serves as a support for arthrocentesis if necessary, and with the help of Doppler, assesses the vascular status and possible neurological complications.

Three-phase bone scintigraphy has a high sensitivity (90%) and a specificity of 18–35%. It should be remembered that it can be positive throughout the first year after implantation, so it is not useful in acute/subacute infections. The combined colloidal scintigraphy of 111In-oxine-labeled leukocytes and 99mTc-sulfide is considered the gold standard in nuclear medicine to differentiate septic versus aseptic prosthetic joints. Fluorodeoxyglucose PET/CT does not appear to play a significant role in the evaluation of infected TKA [66].

In recent years, single-photon emission computed tomography has been considered a useful tool for identifying areas of osteolysis in the femoral and tibial prosthetic components, as well as for assessing the progression of patellofemoral osteoarthritis in cases of prosthetic loosening [67]. On the other hand, CT scans identify collections or abscesses around the prosthesis and measurement of bone defects and are useful in the preoperative planning of a RTKA to assess the need for supplements, cones, or sheaths. The MRI images show artifacts due to debris and the metal components of the implants. These images allow various patterns of hypertrophic synovitis and the joint fluid to be identified [68].

An interesting diagnostic algorithm has recently been proposed by the Pocket Guide to Diagnosis & Treatment of PJI, PROIMPLANT Foundation (version 9, October 2019) and has recently been included in a publication [69].

11.7   Treatment of Infected Total Knee Arthroplasty

The strategy used for the management of the infected TKA depends on the characteristics and the temporality of the implementation of the septic process. It includes, in most cases, surgical intervention, followed by empirical antimicrobial treatment at first and then specific treatment once the microorganism responsible for the condition has been identified.

Similarly, the Pocket Guide to Diagnosis & Treatment of PJI, PRO IMPLANT Foundation (version 9, October 2019) offers an excellent algorithm to summarize the therapeutic strategies available for infected TKA.

In cases of acute infection or with hematogenous spread from another septic site, DAIR has proven to be a useful tool [70]. Rodriguez-Merchan has published a success rate of 65%, finding differences according to the microorganism causing septic failure (*Streptococcus* and *S. epidermidis* have a better response than *S. aureus*) [71]. One study found a cure rate of 80%, indicating that DAIR can be a successful treatment, depending on individual patient factors, the

Fig. 11.3 Areas of osteolysis (arrows) in infected total knee arthroplasty (TKA) in a conventional radiological study
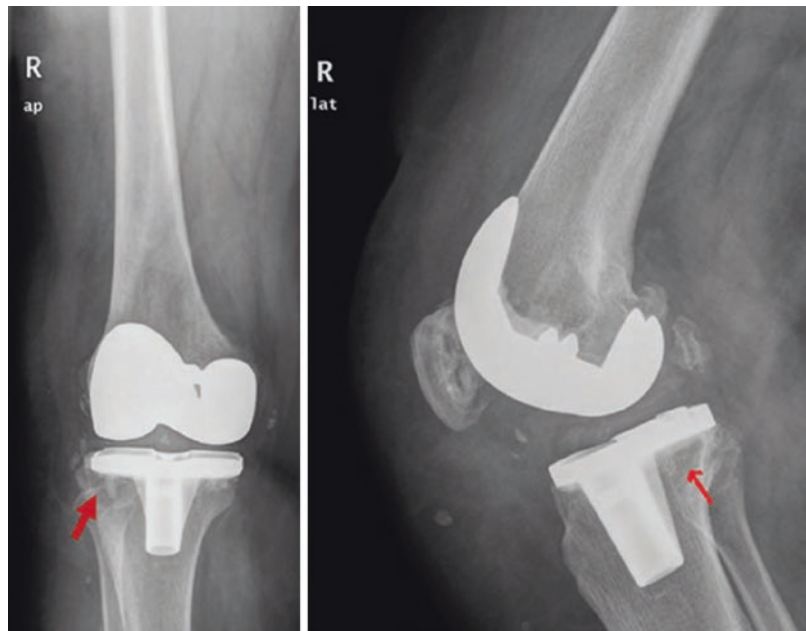
microorganisms involved, the duration of antibiotic therapy, and the optimal timing of surgery [72]. A recent systematic review shows data similar to previous reviews, with success rates between 57% and 81%, depending on the subgroup analysis and the presence of certain factors associated with a poorer response [73]. One multicenter study has shown a high failure rate of 57% after DAIR [74]. Differences in results have been demonstrated if the technique is performed in the first 2 weeks, with success rates of 82%, versus 50% if performed later [75]. Therefore, if there is any suspicion, be aggressive. At the same time, more research is needed on the use of intraoperative adjuvant therapy and the role of postsurgical antibiotic suppression. A systematic review shows that there is currently no evidence to support the use of debridement and long-term (more than 1 year) antimicrobial suppression therapies [76].

One-stage RTKA of an infected TKA is not the technique of choice for the vast majority of surgeons. The main benefits are a single surgical procedure, a shorter period of antibiotic treatment, and lower costs. In general, 1-stage RTKA is reserved for cases of known availability of endovenous and oral antibiotic therapy, provided that the microorganism responsible for the septic process has been identified before the surgical intervention. This technique is increasingly performed routinely in Europe, where it has been reported to eradicate infection in 67–100% of patients [77]. Two-stage RTKA could be considered overtreatment in a number of patients with PJI, and it is associated with increased morbidity, a longer hospital stay, poorer functional outcomes, and higher costs. For patients with good soft tissue conditions, low bone loss, and the possibility of treatment with "biofilm-active" antibiotics, 2-stage RTKA might be the treatment of choice. Innovative solutions such as implants coated with an antibacterial hydrogel have been incorporated into the market. In a recent study, Capuano et al. [78] have shown a recurrence rate of infection of 9.3% compared with 13.6% for the group in which RTKA was performed in two steps. The differences in the virulence of certain microorganisms are challenged by another recent article that sought to identify bacteria-independent risk factors that lead to poor outcomes [79]. The study did not find a different recurrence rate between groups of microorganisms depending on whether they were simple or difficult to treat.

George and Haddad [80] published an update on the surgical technique for 1-stage RTKA, emphasizing that it should be aggressive. They propose the use of a chemical debridement with 12 l of 0.9% sodium chloride, povidone-iodine, and hydrogen peroxide.

Massin et al. [81] have described the presence of fistula and Gram-negative bacteria as unfavorable risk factors. Ford [82] has reported that 68.75% of staphylococci have a higher risk of recurrence, especially if they are coagulase-negative or methicillin-resistant. Gherke [83] had established contraindications for the performance of 1-stage RTKA: failure of >2 previous 1-stage procedures; infection spread to the neurovascular axis; unclear preoperative bacterial identification; unavailability of appropriate antibiotics; high antibiotic resistance; and fistulous tract with unclear bacterial specification.

Therefore, 1-stage RTKA appears to be a viable alternative to 2-stage RTKA, provided there are no contraindications, reducing morbidity and costs. The decision should be based on the risk factors related to the patient and the microorganism involved and on the contraindications mentioned earlier [84].

Two-stage RTKA continues to be the gold standard in the handling of infected TKA. The first stage consists of the extraction of the prosthetic components to preserve the largest bone stock, extensive debridement, thorough washing, taking at least five samples for microbiological analysis, and implanting a cement spacer impregnated with a broad-spectrum or specific antibiotic, depending on whether the microorganism is known before the intervention (Fig. 11.4).

With respect to the type of spacer, there is currently unanimity of opinion. Articulated spacers improve eradication and functional outcomes compared with static spacers. For example, Lichstein et al. [85] had reported that 94% of their patients were infection free at 3.7 years of follow-up, and Siddiqi et al. [86] had reported an 80% success rate. When a difficult-to-treat pathogen is isolated the first time, a prolonged interval of 4–6 weeks allows antimicrobial treatment to be applied in the prosthetic-free interval. Longer intervals (>8 weeks) should be avoided, espe-

cially if spacers are in place, given they decrease the concentration of antibiotics in the bone cement. On the other hand, high-dose antibiotics can cause adverse effects such as nephrotoxicity and acute renal failure [87, 88]. This possibility implies that after implantation of spacers, patients should be monitored for possible complications related to systemic antibiotic absorption. The most commonly used combination at present is composed of articulated spacers impregnated with 1 g of gentamicin and 1 g of tobramycin (+2 g of vancomycin) for 40 g of PMMA cement.

In fungal infections, additional debridement with change of the spacer after 2–4 weeks is recommended, given this reduces the microbial load. If necessary, it is imperative that this type of intervention is performed in centers with a multidisciplinary team, including orthopedic surgeons, plastic surgeons, microbiologists, pathologists, and infectious disease specialists. If primary skin closure is impossible due to soft tissue compromise, early cooperation with plastic surgeons will allow skin coverage by free or pedicle grafts or flaps.

There is controversy regarding the timing, duration, and protocol of antibiotic treatment in the prosthetic-free interval. In general, most antimicrobial regimens include a variable period of 2–6 weeks of intravenous therapy, followed by 2–4 week oral therapy if an alternative is available, then 4–6 weeks without antibiotics, assessing the patient's response until the second RTKA. There is variability in the literature depending on the preferences of the microbiology team and the infectious disease specialists.

Osmon et al. [89], in their Infectious Diseases Society of America guidelines, generally recommend 4–6 weeks of intravenous antibiotic therapy, followed by oral therapy for a total of 3 months. Perhaps these guidelines are too aggressive and their application in Europe is not as strict due to the unwanted effects of systemic antimicrobial therapy. However, a recent randomized controlled trial [90] had a control group that was not given antibiotics after RTKA and another group that received oral antibiotic therapy for 3 months. The reinfection rates were completely different: 19% reinfection in the con-
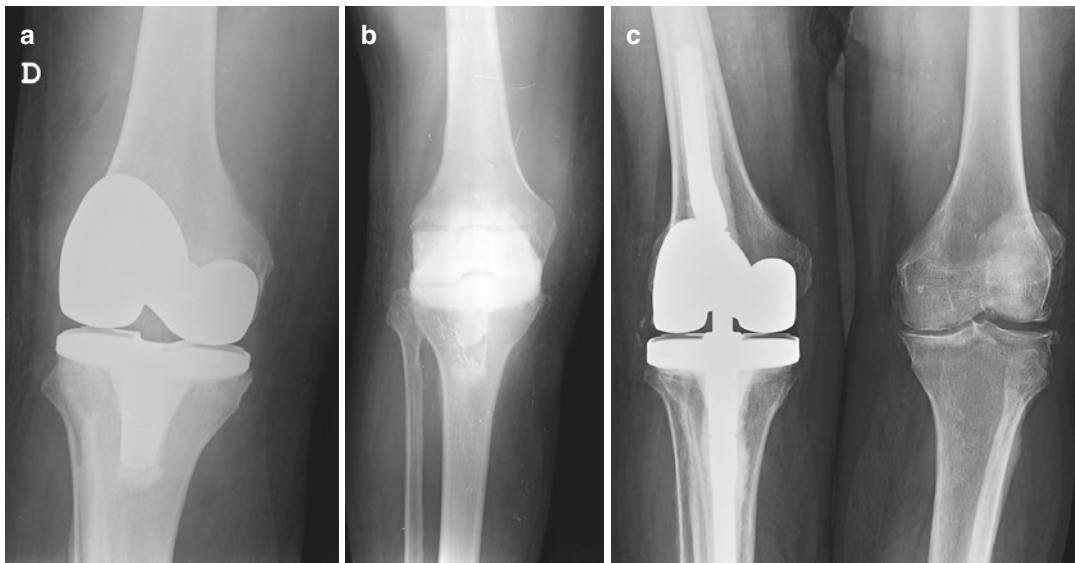
Fig. 11.4 (**a–c**) Infected total knee arthroplasty (TKA): (**a**) Three weeks after prosthesis implantation, acute infection by *S. pyogenes* was diagnosed; DAIR (debridement, antibiotics, and implant retention) was performed. (**b**) Given the poor response to DAIR, a 2-stage revision total knee arthroplasty (RTKA) was performed. Image of the articulated spacer. (**c**) Reconstruction with a constrained condylar knee (CCK) design

trol group and 5% in the oral antibiotic group, highlighting that its application significantly reduced RTKA failure rates. Other regimens advocate switching to oral treatment 14 days after surgery (for *Streptococcus*, 3–4 weeks of endovenous therapy are necessary), provided that an oral alternative with good bone penetration is available, wounds are dry, and local and systemic inflammatory conditions (CRP and ESR) have returned to normal. The role of arthrocentesis and preimplantation biopsies is controversial, with a high rate of false positives (absence of infection) and negatives (presence of infection), so they are not routinely recommended. According to various clinical guidelines, the time-off period for administration of antimicrobials also varies [91].

The administration of antimicrobial therapy after the second period can vary from 6–12 weeks, depending on whether microorganisms are growing in the samples obtained during surgery.

Ford et al. [82] have published a series of 80 patients who underwent 2-stage RTKA, noting that 17.5% were never reimplanted, 30% had at least 1 serious complication, 11% still underwent spacer replacement, and of the remaining patients with successful reimplantation, 73% remained free of infection. These data show that although 2-stage RTKA is the treatment of choice for the vast majority of orthopedic surgeons, it is not without its complications. RTKA is sometimes affected by poor soft tissue status, low bone stock, and patients with high comorbidity, which can condition the reconstruction of the joint even with modern designs available on the market (supplements, cones, sheaths, or mega prostheses).

In certain cases of infected TKA, after failure of all the previously described strategies, knee arthrodesis might be necessary (Fig. 11.5), or even amputation. In these circumstances, 4–6 weeks of targeted antibiotic therapy are required. Depending on the level of amputation, if persistent proximal intramedullary osteomyelitis is present, prolonged antibiotic treatment of osteomyelitis after surgery might be required.

In elderly patients with multimorbidity and contraindications for additional surgical treatment or in those with technical limitations for limb preservation, long-term antibiotic suppression with implant retention can be a therapeutic alternative. The causative microorganism must
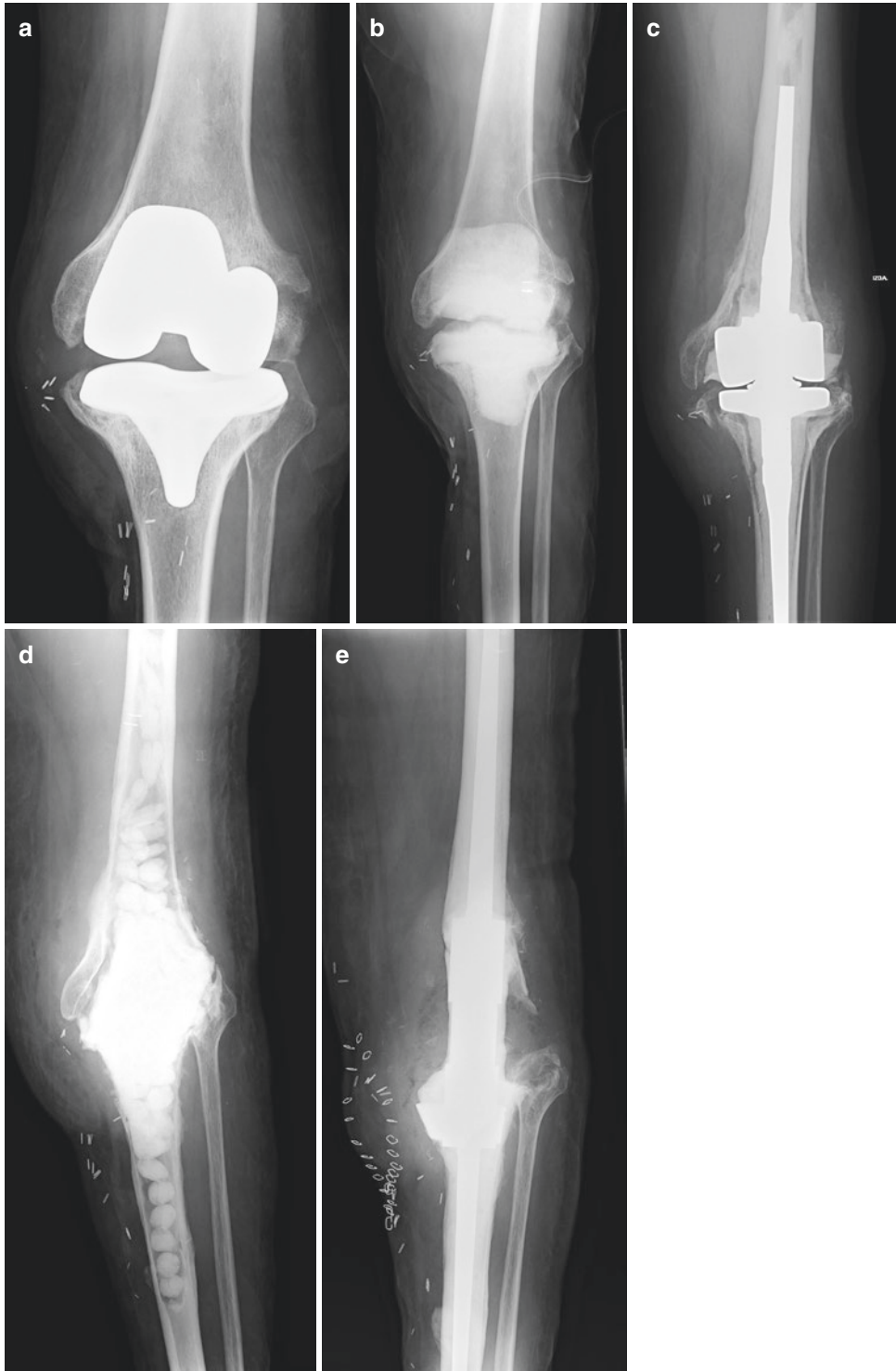
Fig. 11.5 (**a–e**) Resolution of infected total knee arthroplasty (TKA) (*S. epidermidis, S. lugdunensis*, and *Candida spp.*) by intramedullary nail arthrodesis after failure of a 2-stage revision total knee arthroplasty (RTKA): (**a**) septic loosening; (**b**) first time of revision and implantation of articulated spacer; (**c**) failure of the second revision at 4 years, showing areas of osteolysis around the femoral and tibial stems; (**d**) new spacer with gentamicin beads; (**e**) definitive arthrodesis with intramedullary nail

be known. Della Valle et al. showed in a classical review that when antimicrobials are resuspended, relapses occur in >80% [92].

11.8 Conclusions

Infected TKA is one of the most devastating complications in orthopedic surgery. Its cure rate ranges from 67% to 100% according to published series. Given the exponential increase in the number of primary TKA and RTKA procedures and the implied economic impact on health systems, risk factors related to PJI must be identified to implement measures to control them. The diagnosis of PJI is based on clinical suspicion, together with a series of radiological, laboratory, microbiological, and histological tests. Therapeutic strategies include DAIR, 1- or 2-stage RTKA, comprehensive antimicrobial treatment, and alternatives such as arthrodesis or amputation, and chronic antibiotic suppression. In the future, efforts should be directed toward implementing risk factor prevention measures, diagnostic alternatives based on molecular tests, and new specific antimicrobial therapy targets.

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