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Trends in the treatment of infected knee arthroplasty

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- Essential treatment methods for infected knee arthroplasty involve DAIR (debridement, antibiotics, and implant retention), and one and two-stage exchange arthroplasty.
- Aggressive debridement with the removal of all avascular tissues and foreign materials that contain biofilm is mandatory for all surgical treatment modalities.
- DAIR is a viable option with an acceptable success rate and can be used as a first surgical procedure for patients who have a well-fixed, functioning prosthesis without a sinus tract for acute-early or late-hematogenous acute infections with no more than four weeks (most favourable being < seven days) of symptoms. Surgeons must focus on the isolation of the causative organism with sensitivities to bactericidal treatment as using one-stage exchange.
- One-stage exchange is indicated when the patients have:
  1. minimal bone loss/soft tissue defect allowing primary wound closure,
  2. easy to treat micro-organisms,
  3. absence of systemic sepsis and
  4. absence of extensive comorbidities.
- There are no validated serum or synovial biomarkers to determine optimal timing of re-implantation for two-stage exchange.
- Antibiotic-free waiting intervals and joint aspiration before the second stage are no longer recommended. The decision to perform aspiration should be made based on the index of suspicion for persistent infection.
- Re-implantation can be performed when the treating medical team feels that the clinical signs of infection are under control and serological tests are trending downwards.

Keywords: infected total knee arthroplasty; periprosthetic infection; trends

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One of the most challenging complications leading to significant morbidity after total knee arthroplasty (TKA) is periprosthetic joint infection (PJI), with an infection rate of up to 2% after primary TKA and almost 10% for revision TKA.[1–4] Depending on the time from implantation to infection, current guidelines have classified the infection as acute-early, delayed-chronic, late-haematogenous acute, and late-chronic PJI (Table 1).[5] The management of PJI includes different surgical strategies and targeted antimicrobial therapies based on this PJI classification (Fig. 1).[6–8] Early PJI occurs within three to 12 weeks after index surgery, or in the case of late-haematogenous infection, within 10 days to three weeks of the development of symptoms. Late PJI is defined as PJI that develops after 12 months following the index surgery. The primary time distinction between early and late PJI is based on the assumed time of biofilm formation on the surface of the components, generally thought to be three to four weeks postoperatively. However, biofilm formation can occur at any time from a few hours to a few days.[9,10] Future classifications or grading systems will address the more precise timing of formation of the biofilm for the early treatment of PJI. Current treatment methods should consider the timing of PJI, systemic and local factors, and the immune status of the patient.[11]

The International Consensus Meeting (ICM-2018) has proposed a new validated, evidence-based scoring system for the definition of PJI.[12] However, there is no clear validated distinction from the current surgical treatment methods for PJI, with several different surgical methods being applied (Fig. 2). These include debridement, antibiotics and implant retention (DAIR), one or two-stage exchange arthroplasty procedure or, when these treatments are inadequate, salvage procedures such as resection arthroplasty, arthrodesis, and above-knee amputation.[1]

Debridement, antibiotics and implant retention (DAIR)

Debridement, antibiotics and implant retention is a less disruptive surgical method in early postoperative infections of less than four weeks or acute haematogenous infections with a duration of symptoms of less than three

Table 1. Classification of periprosthetic joint infection according to time from implantation to infection, possible clinical presentation with likely mechanism of infection.[5]

Time to infection	Time of presentation	Mechanism of infection	Organism	Clinical presentation
Early	< 3 months	Intraoperative contamination	Virulent bacteria (i.e. *S. aureus*)	Acute Sudden onset erythema, oedema, warmth, and tenderness
Delayed	3–12 months	Intraoperative contamination	Low-virulence bacteria (coagulase-negative staphylococci)	Chronic Joint pain and stiffness
Late	> 12 months	Haematogenous seeding	Virulent bacteria (i.e. *S. aureus*)	Acute Sudden onset erythema, oedema, warmth, and tenderness
		Intraoperative contamination	Low-virulent bacteria (i.e. *Cutibacterium acnes*)	Chronic Joint pain, sinus tract

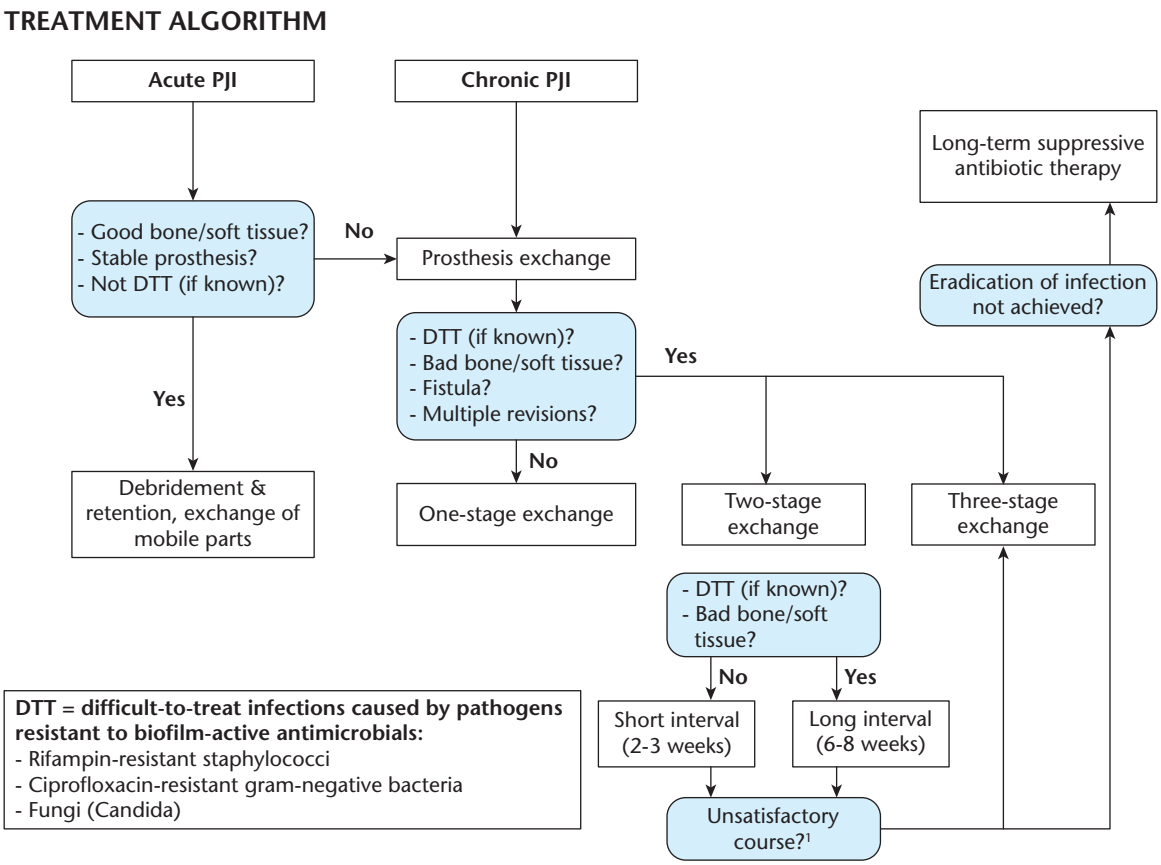

Fig. 1 Treatment algorithm for PJI.

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weeks. Some authors suggest that an acute haematogenous infection should be treated within one week to 10 days from the first clinical presentation for DAIR treatment.[13] DAIR seeks to preserve a stable implant in a functional patient.[13] The success rates vary among different studies, ranging from 16% to 82%.[14–16]

The concern that a failed DAIR undermines the future success of staged procedures is still controversial. There are few reports as to whether a failed DAIR leads to a higher risk of treatment failure with staged revision.[17–20] However, in a recent multicentre retrospective study that contained a subgroup analysis based on the type of infection,

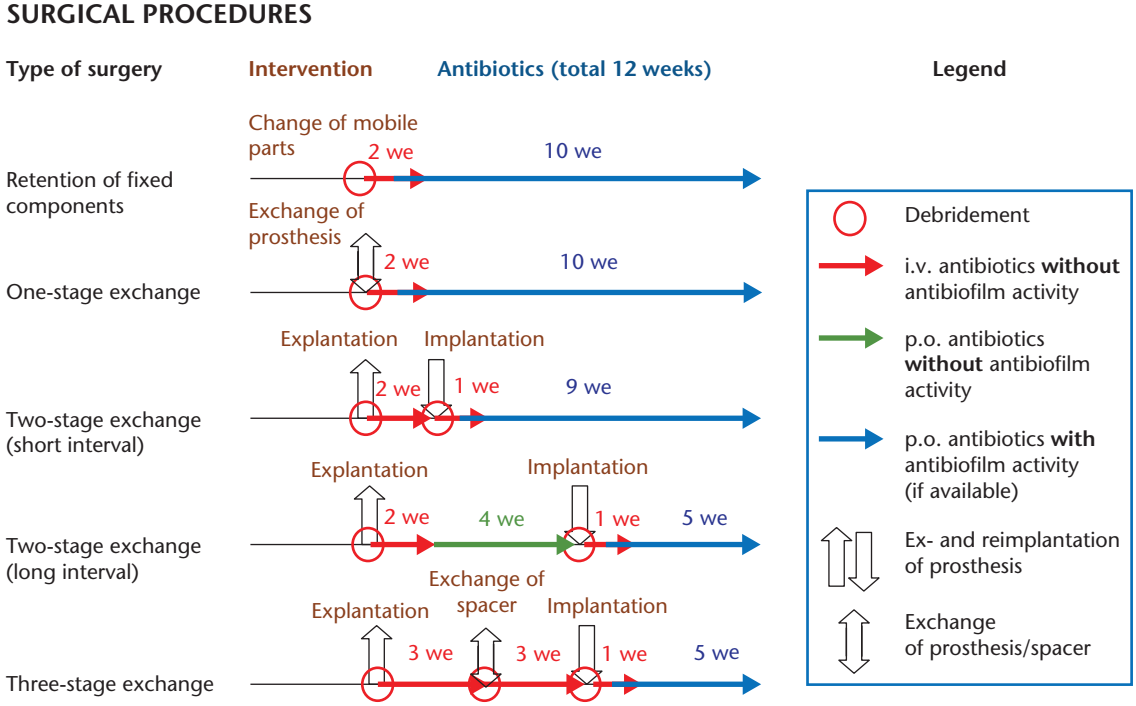

Fig. 2 Overview of the surgical strategies with possible scenarios.

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previously failed DAIR (F-DAIR) did not compromise the success rate of a subsequent staged revision, and overall success rate showed no statistically significant difference with a staged-only group (72% F-DAIR vs. 81% staged-only group).[21]

There are no specific contra-indications to using DAIR intervention, except that chronic PJIs should be considered an absolute contraindication. The success rate of DAIR is only 50% in chronic infections, and methicillin-resistant staphylococcal infection leads to a higher risk of failure when the duration of symptoms is up to four weeks.[22–24] Contra-indications to performing a DAIR procedure in acute PJI are also controversial. Several factors have been associated with the success or failure of DAIR in acute PJI. The results of DAIR are highly dependent on the preoperative isolation of bacterial micro-organisms and antibiotic-sensitive cultures. Most of the factors that affect the results of DAIR, such as host and implant factors, intraoperative variables, and antibiotic sensitivity of the causative organism have been evaluated in retrospective studies.[16,25,26] A preoperative risk scoring system has been developed to predict failure following DAIR, using early-acute kidney failure, liver cirrhosis, index surgery, cemented prosthesis, and C-reactive protein values (KLIC score) and acute haematogenous PJIs (CRIME80 score) (Fig. 3). This clinical score should be considered before planning the DAIR intervention.[27,28]

Aggressive debridement and exchange of the mobile parts should be performed in this method. Unchanged mobile parts during DAIR have been associated with high failure rates.[16,29,30] The International Consensus Group suggested that the irrigation and debridement protocol[31] should include aggressive intraarticular methylene blue-guided debridement, followed by the removal of the infected and non-bleeding bones and soft tissues. Increased vascular circulation improves the immune system and increases antibiotic penetration into periarticular tissues.[32,33] The literature shows that about nine litres of irrigation solution should be used during debridement.[34] This volume may be increased depending on the size of the surgical site and the severity of the infection. The washing pressure, however, is a controversial issue. Some authors support the low-pressure (< 15 pounds per square inch) lavage technique, while others advocate the high-pressure method (> 45 pounds per square inch).[1,34,35] High-pressure lavage may remove the infected and necrotic tissues, but deep tissues can be contaminated, too.

Following irrigation and debridement, combined intravenous antibiotic treatment should be ordered for the patient at the first step. The antibiotic treatment should last four to six weeks after the surgical procedure, and oral rifampicin treatment is recommended for up to six months.[1,6,36] Some authors have suggested antibiotic treatment for one year after DAIR. However, the long-term

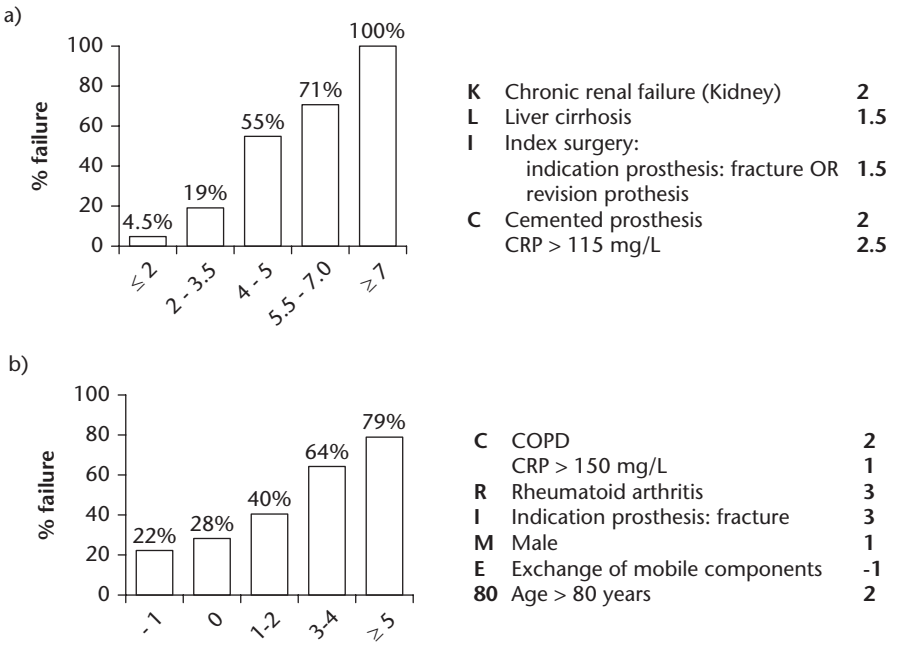

Fig. 3 (A) KLIC and (B) CRIME80 preoperative risk scores should be used to predict failure following DAIR.[27,28]

Note. DAIR, debridement, antibiotics, and implant retention.

antibiotic treatment suppresses but does not eradicate the infection with a higher re-infection rate.[37] The efficiency of antibiotic-loaded polymethylmethacrylate (PMMA) beads and other non-biological or bio-absorbable antibiotic carriers (e.g. calcium sulphate beads or resorbable gentamicin-loaded sponges) have not yet been validated for use during DAIR. One recent article reported that the use of antibiotic-impregnated (DAPRI) calcium sulphate beads in addition to the DAIR procedure might lead to an increase in the overall success rate in implant-retention revision surgery.[13] Selecting the best surgical technique and antibiotic is mandatory for satisfactory results in DAIR.

Exchange arthroplasty

One-stage exchange arthroplasty

Since the early introduction of one-stage exchange arthroplasty for PJI, this intervention has increased in popularity among selected patients. The procedure has multiple advantages, such as less morbidity and better functional outcomes, reduced length of stay, and less overall cost as reported by several prognostic and observational studies.[38–41] There is no evidence-based superiority of the two-stage revision over one-stage revision arthroplasty for the eradication of acute PJI. The reported success rate of one-stage exchange arthroplasty has ranged between 75% and 95%.[39,40,42] The high success rate of the one-stage procedure is strongly associated with patient selection criteria and specific operative planning protocols.

Preoperative identification of the causative micro-organisms is mandatory in one-stage exchange since polymicrobial infections and atypical and gram-negative organisms have been associated with a higher failure rate. In their literature review in 2000, Jackson and Schmalzried concluded that the presence of an infection with resistant micro-organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) / methicillin-resistant *Staphylococcus epidermidis* (MRSE) were associated with a high failure rate.[43] On the other hand, a reported long-term experience from the HELIOS ENDO-Klinik (Hamburg, Germany) does not accept resistant micro-organisms as absolute contra-indications to the performance of one-stage surgery.[44] According to the ICM-2018, one-stage exchange arthroplasty may not be a good option for patients with signs of systemic sepsis, extensive comorbidities, infection with resistant organisms (difficult-to-treat micro-organisms [DTT]), culture-negative infection and poor soft tissue coverage.[45]

Indications for one-stage revision arthroplasty

a) Host/local
   - Non-immunocompromised host
   - Absence of systemic sepsis
   - Minimal bone loss/soft tissue defect allowing for primary wound closure

b) Microbiology
   - Isolation of the pathogen
   - Known sensitivities to bactericidal treatment

Relative contra-indications to one-stage revision arthroplasty

- Severe damage of soft tissues where direct closure of the joint and the wound is not possible, and/or a complicated sinus tract, which cannot be excised along with the old scar.
- Culture-negative PJI, where the causative organism and its susceptibility are unknown.
- Radical debridement of the infected soft tissue or bone is not possible (due to any reason).
- Local antimicrobial treatment is not possible (due to any reason).
- Lack of proper bone stock for the fixation of the new implant.

Surgical technique

In this technique, extensive debridement is mandatory as a first step and the surgeon should achieve free bleeding in the periarticular soft and bone tissues. All membranes and well-fixed cement particles must be removed, especially from the posterior capsule. Extensive debridement of the bone and posterior soft tissues must be as radical as possible, including all areas of osteolysis and the necrotic bone. During the removal of well-fixed cement and components, some specific surgical tools such as high-speed burrs, curved saw blades, curved chisels, long rongeurs, curetting instruments, long drills, cement taps and a Gigli saw might be needed to protect the bone and the ligaments. Numerous samples must be taken for microbiologic evaluation from all periarticular areas, especially from the tibial and femoral intramedullary canals and the posterior capsule. Pulsatile lavage throughout the procedure is recommended, but there is no description of its specific benefit in the literature.[35] After the irrigation, gauze pads with antiseptic solutions (povidone-iodine, chlorhexidine, etc.) are packed into the intramedullary area and all around the joint. The wound edges are approximated with a few sutures. During a 30-minute waiting period, the operating team changes their scrub suits and a new set of instruments is used for the second step of the one-stage procedure.[46,47] Using antibiotic-loaded cement for re-implantation as well as specific post-operative antibiotic regimes are essential for success.[41] In selected patients, improved results for one-stage revision were reported in a recent systemic review.[48]

Two recent meta-analyses, which compared the outcomes of one-stage versus two-stage exchange arthroplasty in patients who developed PJI after TKA, demonstrated statistically equivalent re-infection rates for both protocols.[49]

Two-stage arthroplasty

The two-stage technique has been the gold standard for PJI. As the name suggests, the technique has two stages; the first stage includes the removal of all components and cement, and extensive debridement of the bone and periarticular soft tissues. There is no standard data that can guide surgeons to determine the optimal time for re-implantation after explant. Surgeons prefer to follow up clinical evidence of the infection and normalization of the laboratory test results after an antibiotics period of appropriate length. There is no gold standard for the serum and synovial markers tests to define the optimal timing for re-implantation.

Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely used for diagnosis, monitoring the treatment and evaluating their role in identifying the optimal timing of reimplantation.[50–54] However, ESR and CRP levels can still be elevated in patients who have been treated or can be normal in cases of a persistent infection. In different studies, no cut-off values could be determined and there were no significant differences between infected and non-infected cases in terms of average ESR and/or CRP values at the time of re-implantation.[51–55] The serum D-dimer test has been recently studied amongst other biomarkers. According to one study, D-dimer outperforms ESR and CRP in determining the time of re-implantation; thus it may be more widely used to identify the optimal time for re-implantation.[56]

Synovial fluid aspiration and analyses for cell count, culture and biomarkers before re-implantation are widely used to determine the optimal time for re-implantation and to detect persistent infection.[57,58] Zmistowski et al reported elevated synovial fluid white blood cell (WBC) counts and that polymorphonuclear leukocyte (PML) percentage could be used to diagnose persistent infection, but did not give a cut-off value to determine re-implantation time.[59] The sensitivity of the microbiological culture of the joint aspirate is very low according to the literature and could also be misleading due to false-positive cultures.[60,61] Leukocyte esterase (LE) tests have demonstrated high specificity (100%), but low sensitivity (25%) in identifying persistent infection.[62] A positive LE result can show a high association with failure of re-implantation.[63] IL-6 and IL-1β showed the most significant decrease between stages, but due to the low sensitivity of these tests, they cannot be used widely in determining the optimal re-implantation time.

The efficacy of the Musculoskeletal Infection Society (MSIS) criteria in determining infection resolution in PJI has also been evaluated. Despite the clinical importance of these criteria, the lack of sensitivity of these tests does not make them useful in diagnosing persistent infection.[62–64] Intraoperative frozen sections can be used to diagnose persistent infection, but there is still controversy about the optimal diagnostic cut-off value (number of polymorphonuclear leukocytes (PMNs) per high-power field). Della Valle et al showed 25% sensitivity in their results, whereas George et al increased the performance of the frozen section up to 50% sensitivity.[64,65]

At the second stage, aggressive debridement is recommended, and many samples are mandatory for microbiological evaluation.[66] Following extensive debridement and removal of the spacer, the next step is the preparation of the tibia and the femur. There is no consensus about stem fixation. Some authors have employed antibiotic-loaded cemented stems in the medullary canals for both the tibia and the femur, thus facilitating an effective antibiotic level in the medullary canals.[66,67] Other authors have advocated that uncemented stems provide correct alignment, and easy removal of the component if re-infection is detected.[39] Hybrid techniques have also been described; stems are applied uncemented and cemented to the lower surface of the components at the metaphysis.[67,68] There are no significant differences in terms of re-infection rates among these fixation techniques in comparative studies.[39,67–71]

No validated metrics allow for the determination of the optimal timing of re-implantation. Thus, the timing of re-implantation should take into account the resolution of the clinical signs of the infection, the downtrend in serological markers, and, if aspiration is performed, the results of synovial analysis. There is no certain timing for the interval between the two stages, but generally, it takes from three to four weeks to 12 weeks between the first and the second stages.[66,72] According to local tissue conditions and to the time to recovery after the first stage, a short interval of two to four weeks can be set during the same hospitalization period, or if the culture identifies a DTT micro-organism in the first stage, a longer interval of four to six weeks is preferable (Fig. 2). Longer time intervals of over eight weeks should be avoided as the antibiotic bone cement spacer loses its antibiotic concentration.[73] Increased duration between resection and re-implantation was associated with a higher risk of re-infection after two-stage exchange treatment of infected TKA.[74,75] On the other hand, Aali Rezaie et al reported that the inter-stage interval was not a statistically significant predictor of failure in patients undergoing two-stage exchange arthroplasty (Fig. 4).[76]

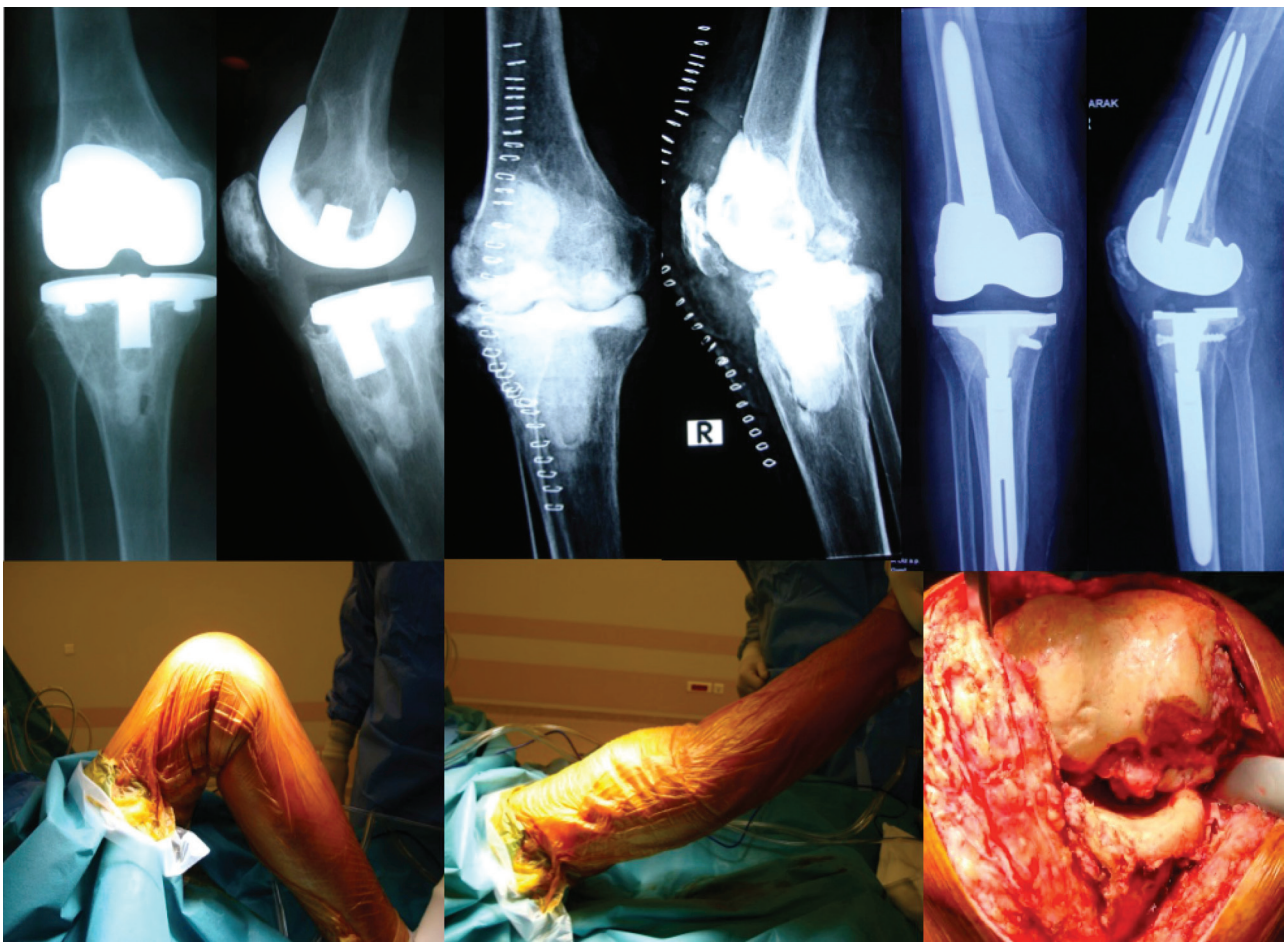

Fig. 4 A 74-year-old female infected with a multi-drug-resistant organism (E.Coli and E.faecalis) after 13 years from index TKA. Handmade articulating antibiotic load spacer (6-gr teoicoplanin) was prepared with two-package gentamycin bone cement. Re-implantation was performed after 15 months. AP-lateral radiological view at the last follow-up showed no loosening after seven years. We observed high range of motion with hand made articulating spacer at the beginning of second stage revision arthroplasty.

Note. TKA, total knee arthroplasty; AP, anterior-posterior

The choice of antibiotic will depend on various factors, such as the features of isolated pathogens, route of administration, and duration of treatment. Highly bio-available antibiotic regimes against pathogens are applied intravenously or in oral form.[77] Individual regimens should be planned in line with a discussion between orthopaedic surgeons, microbiologists and infectious disease specialists. Targeted antimicrobial therapy should be planned when the causative micro-organism has been identified. The most controversial issue is the duration of antibiotic treatment. Some authors have shown that using a shorter duration (three to six weeks) is adequate to prevent infection recurrence.[77–79] Also, the use of broad-spectrum antibiotics is recommended in early PJI.[80]

In the staged interval, the aim is the maximal reduction (instead of eradication) of the causative organism and the treatment of the soft tissue and bone infection. Antibiotic treatment should be continued until the second stage. Antibiotic-free waiting intervals and joint aspiration before the second stage are no longer recommended. According to ICM-2018, there is no conclusive evidence to support the need for an antibiotic holiday before re-implantation or to determine its ideal length. After re-implantation, antibiotic treatment is continued for six weeks (with a total time of up to 12 weeks after explantation) (Fig. 2).[73] In some cases, long-term chronic suppressive antibiotic therapy may be needed, especially in multimorbid elderly patients in whom further surgical options are not possible due to medical or surgical reasons.

In the current literature, the two-stage technique for PJI management has been accepted as the gold standard, but there is no high level of evidence for proving its higher success rate than the single-stage revision.[81]

Spacers

The ideal spacer should contain sufficient pharmacokinetic and mechanical properties over a prolonged period of time in order to eradicate the isolated organism. In vitro analysis of the release of antibiotics from cement spacers has been well reported. The cement type, the addition of one or a combination of two or more antibiotics, the amount or ratio of the antibiotics, the duration of spacer implantation and the spacer geometry can affect the pharmacokinetic properties of spacers and the amount of antibiotic release from spacer.[82–84]

In the majority of the studies that evaluated the antibiotic concentrations in the joint fluid, the local concentrations of aminoglycoside (either gentamicin or tobramycin) and vancomycin between the first 24 postoperative hours and seven postoperative days after spacer implantation were measured. The local antibiotic elution showed a biphasic profile, initially showing high concentrations, which decreased over time. An impregnation dose of 3 g of vancomycin and 4 g of aztreonam which were incorporated into 40 g of cement, had the highest elution values.[85] The same study reported large discrepancies for the measured concentration when a gentamicin–vancomycin combination was used.[85] Anagnostakos et al determined the maximum concentrations of gentamicin and vancomycin, respectively, when 1 g of gentamicin and 4 g of vancomycin (both powder) were impregnated into 80 g of cement for spacer production.[86] Hsieh et al reported that average local levels of gentamicin and of vancomycin showed differences when liquid gentamicin was combined with vancomycin powder.[87] Sufficient antibiotic elution can be achieved after spacer implantation and at spacer removal, but identification of the causative micro-organisms and antibiotic sensitivity are required to increase the efficiency of local antibiotic therapy.

Different designs of spacers have been described in the literature. Functionally, spacers are divided into two main groups: dynamic and static. Usually, the spacers are made of bone cement loaded with antibiotics. The aim of using a spacer is to preserve ligament balancing and limb length. Different designs of articulating spacers have been described in the literature as well as generic spacers. Some authors have used the removed and autoclaved femoral component of the infected prosthesis along with a new inlay.[88] Manually moulded or manufactured spacers can also be used (Fig. 5).[89,90]

Improved function and a higher range of motion (ROM) have been reported with the use of articulating spacers (Figure 4).[91,92] On the other hand, some authors have reported no improvement in ROM.[93] Successful rates of infection eradication were reported for both techniques, reaching up to 95%.[69,93] However, articulating spacers may have some disadvantages. The lack of collateral ligaments (unstable joint) increases the risk of spacer dislocation and subsequent bone loss. On the other hand, surgeons may prefer to stabilize the joint with a non-articulating spacer for better and quicker healing of the wound after the first stage.

Spacer exchange (three-stage exchange)

Spacer exchange is an additional procedure, and it is termed as 'three-stage exchange'.[94] This procedure is performed in cases of persistent infection, spacer fracture or dislocation. The technique provides the possibility for additional debridement and local antibiotic treatment via the new antibiotic-loaded spacer.[95–97] On the other hand, this procedure delays the re-implantation time and increases the morbidities related to additional surgery. More likely, these patients have comorbidities such as obesity, rheumatoid diseases, malnutrition, diabetes, peripheral vascular diseases, and infection with resistant or polymicrobial organisms.[98,99] Due to comorbidities, the success rate of spacer exchange is low, with a high failure rate of re-implantation.

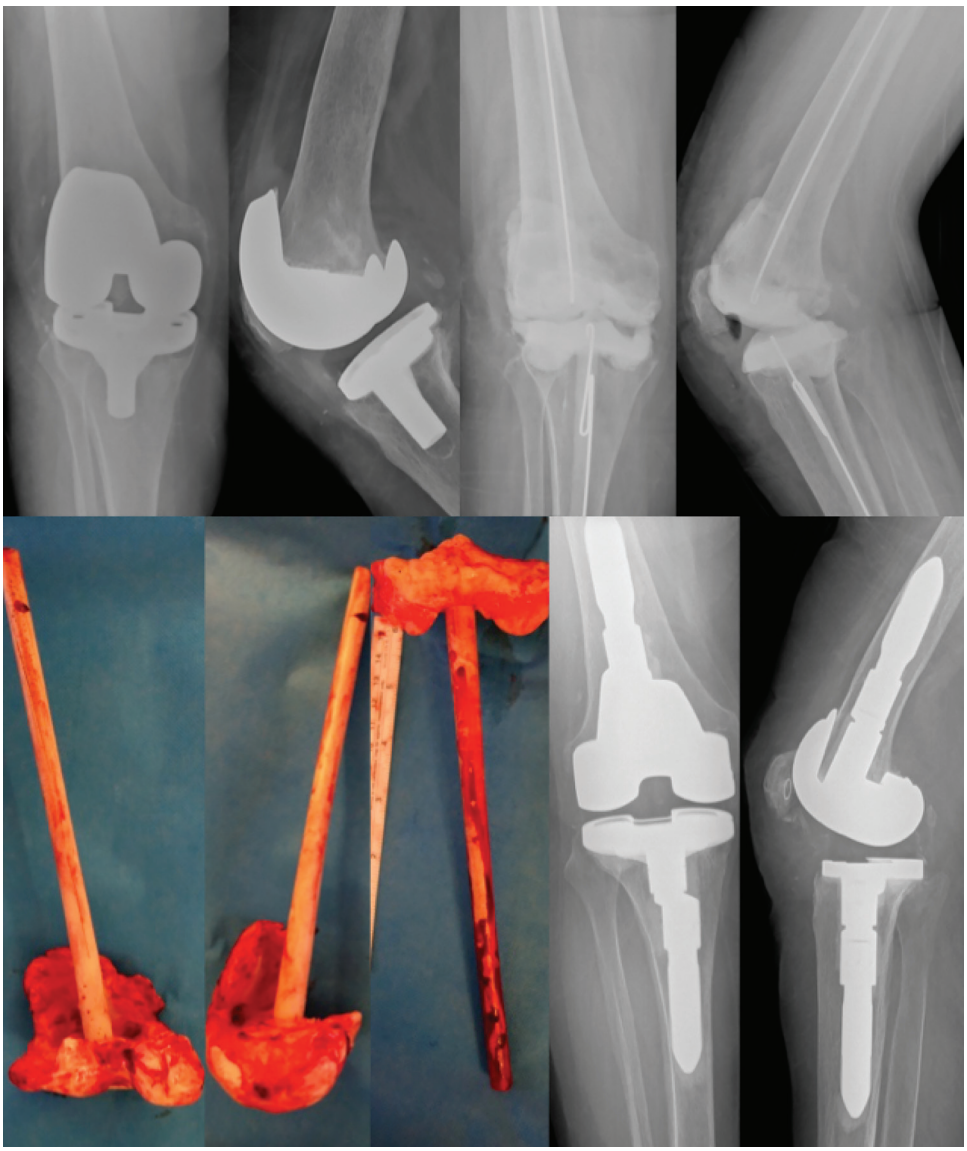

Fig. 5 A 77-year-old female with chronic PJI. Causative organism: E.faecalis. Two-stage revision with handmade articulating spacer with 8-gr teikoplanin. After nine weeks re-implantation was performed. AP-lateral radiological view at the last follow-up showed no loosening with infection-free three years.

Note. PJI, periprosthetic joint infection; AP, anterior posterior

Salvage procedures

Arthrodesis: The most common indications for knee arthrodesis are persistent infection after repeating staged knee revisions, massive bone or soft tissue loss, and irreparable damage of the extensor mechanism.[100,101] The main goal of knee arthrodesis in infected TKA is to provide pain relief and stability, especially in active young patients. Various knee arthrodesis techniques using intramedullary nails, monoplaner or circular external fixators, screwed plates, and cannulated screws, have been described in the literature.[102–105] Intramedullary nailing has achieved the best fusion rates of 88–100% amongst these techniques.[106] However, intramedullary nailing should only be used after the successful eradication of the infection.[107] Monoplaner fixators in combination with radical debridement and local or systemic antibiotherapy achieved a fusion and infection eradication rate of 94%.[102] Arthrodesis is an optimal treatment method with acceptable pain relief and functionality for failed PJI patients.

Resection arthroplasty: Resection arthroplasty is a salvage procedure that involves the removal of all components, debridement of the infected soft tissues and the bone without re-implantation of new components. The procedure has a very limited indication. It is more suitable

for low-demanded patients while providing well-sitting comfort than knee arthrodesis. Although successful results were reported in the eradication of infection, the resection arthroplasty had poor functional results due to pseudoarthrosis.[108,109]

Amputation: Knee arthrodesis or above-knee amputation (AKA) are the two main options to eradicate the infection when PJI becomes uncontrollable despite multiple attempts at revision procedures. A greater percentage of patients in the AKA group were above the age of 80 years compared with the arthrodesis group in the literature.[110] Besides, comorbidities such as diabetes mellitus, congestive heart failure, coronary heart disease, chronic kidney disease, and chronic obstructive pulmonary disease are observed much more often in the AKA group compared with the arthrodesis group. Currently, patients with more comorbidities are preferred for AKA instead of arthrodesis in septic failure of TKA. However, it should be noted that a decrease in functional status after AKA is inevitable. Only half of the patients have achieved independent ambulation.[110]

Conclusions

Appropriate debridement with the removal of all avascular tissues and foreign materials that contain biofilm (> four weeks after operation) is mandatory for optimal surgical treatment. DAIR is a standard procedure with an acceptable success rate in acute infection; surgeons should focus on the preoperative isolation of the causative organism like one-stage exchange. A complete exchange of the prosthesis in one-stage arthroplasty for chronic infections is indicated when the patients have minimal bone loss/soft tissue defect allowing primary wound closure and easy to treat micro-organisms. One-stage exchange is associated with lower morbidity and higher functional outcomes compared with multiple-stage revisions. Currently, no study has shown which biomarkers need to be checked to decide the optimal timing for re-implantation during the course of a two-stage exchange for PJIs. Re-implantation can be performed when the treating medical team feels that the infection is under control.

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