Update article

Infection after total knee replacement: diagnosis and treatment

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ABSTRACT

Infection after total knee replacement (IATJ) is a rare complication. It is associated with increased morbidity and mortality increasing the final costs. Gram positive cocci and Staphylococcus coagulase-negative and Staphylococcus aureus are the most common isolated germs (>50% of the cases). Conditions related to the patient, to the surgical procedure and even to the post op have been identified as risk factors to IATJ. Many complementary methods together with clinical symptoms are useful to a proper diagnosis. Treatment for IATJ must be individualized but generally is a combination of systemic antibiotic therapy and surgical treatment. Prosthesis exchange in one or two stages is the first choice procedure. Debridement with prosthesis retention is an option in acute cases with stable implants and antibiotic sensible germs.

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Infeção em artroplastia total de joelho: diagnóstico e tratamento

RESUMO

Infeção após artroplastia total do joelho (IATJ) é complicaçãocomum. Está associada ao aumento da morbimortalidade e dos custos de internação. Cocos gram-positivos, sobretudo Staphylococcus coagulase-negative e Staphylococcus aureus, são os germes mais comumente isolados (> 50% de todos os casos). Condições ligadas ao paciente, ao procedimento cirúrgico e mesmo ao pós-operatório têm sido identificadas como fatores de risco para IATJ. Vários são os métodos complementares que se somam à investigação clínica para o diagnóstico infectioso e melhor caracterização do quadro. O tratamento para a IATJ deve ser individualizado,

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Introduction

Infection after total knee arthroplasty (TKA) is a topic of great interest for orthopedists and infectologists. Alternatives for diminishing the TKA infection rate have long been sought, given that these rates continue to be between 0.4% and 2% after primary arthroplasty and between 3.2% and 5.6% after revision arthroplasty.1-5 Long-term follow-up has shown a periprosthetic infection rate of 1.55% over the first two years after TKA and 0.46% per year after this period, until the tenth year.6,7 TKA is a procedure performed worldwide, with 600,000 surgical procedures per year in the USA and a mean survival rate of 95% over 15 years.8-10 Kurtz et al.10 predicted that there would be an increase in the demand for TKA of 673% by 2030. Although the TKA infection rate may seem low, the number of such injuries tends to increase with increasing numbers of procedures.

Clinical complications and increased costs associated with TKA injuries have been of growing concern. The mortality rate among patients over the age of 65 years who were awaiting a surgical procedure for treating TKA infection has ranged from 0.4% to 1.2%, and between 2% and 7% among patients aged over 80 years.11 The mean cost of treating TKA infections has been estimated as 50,000 dollars per patient and 250 million dollars per year, in the United States.12,13

The microorganisms most commonly encountered in TKA infection cultures are coagulase-negative Staphylococcus (30–43%) and Staphylococcus aureus (12–23%), followed by contamination due to mixed flora (10%), Streptococcus (9–10%), Gram-negative bacilli (3–6%) and anaerobic bacilli (2–4%). No germ is isolated in around 11% of the cases.14,15

This review had the aim of discussing the diagnosis and treatment of patients with a condition of TKA infection.

Risk and prevention factors

TKA infection has been correlated with a number of risk factors: diabetes, malnutrition, smoking, use of steroids, poor control over anticoagulation, obesity, cancer, alcoholism, urinary tract infections, multiple blood transfusions and revision surgery. The current guidance is that such factors should be identified and multidisciplinary intervention should be implemented before performing any procedure, with the aim of getting the patient into a better condition.16

Use of antimicrobial prophylaxis, care in preparing the patient’s skin before the operation and use of laminar flow in surgical theaters have reduced the intraoperative contamination rates. Forty years ago, for every 10 patients who underwent TKA, one would develop infection.17,18

Malinzak et al.19 reported that the infection rate was 0.51% among 8494 hip and knee arthroplasty procedures. They found that the risk factors for infection were obesity, early age and diabetes mellitus. Patients with body mass index greater than 40 and those with diabetes presented a 3.3 and 3.1 times greater chance of TKA infection, respectively. Glycemic control has been a topic greatly discussed. The benefits of rigorous control, both before and after the operation, were reported by Marchant et al.20 and Van den Berghe et al.21

Obesity is a risk factor and is also correlated with wound complications, as demonstrated by Winiarzky et al.,22 in a study in which 22% of the obese group of patients presented infection of the surgical wound and higher prevalence of deep infection. Obesity is not necessarily synonymous with nutrition, and evaluating transferrin, albumin and leukocytes has been important in these cases.

Persistence of drainage during the postoperative period and wound complications are also factors associated with infection. Galat et al.23 reported that the infection rate was higher in the group of patients in whom there was hematoma formation. This was also reported by Parviz et al.,24 who indicated that the infection rate was higher in cases with persistent drainage through the surgical wound and in patients who presented RNI > 1.5.

Clinical presentation and diagnosis

The evaluation and management of patients with TKA infection should follow a logical, clear and reproducible sequence. The American Academy of Orthopedic Surgeons (AAOS) has developed clinical practice guidelines for this process (Figs. 1–3).

TKA infections can be temporally divided into three types: acute (less than three months), subacute (three to 24 months) and chronic (>24 months).25,26 The time period analyzed relates to the start of the infectious condition and is important in determining the treatment. The first two forms of presentation are linked to the surgical procedure and the last to bacteremia, generally relating to the skin, teeth or genitourinary tract.27 Acute infections are characterized by pain, edema, heat, erythema and fever, commonly caused by virulent germs such as S. aureus and Gram-negative bacilli. Patients with subacute conditions (coagulase-negative Staphylococcus and P. acnes) usually have signs and symptoms that are non-evident and may present persistent pain, implant loosening or both, which makes aseptic loosening a differential diagnosis.14 The chronic condition has variable presentation, with signs and symptoms that are similar to those reported in the acute and subacute conditions. From the assessment and the clinical history, it can be defined whether the patient has
high or low likelihood of infection, which is important for the subsequent propaedeutics.

After clinical and temporal characterization, laboratory tests form part of the investigation of infections. C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) are evaluated in patients with suspected TKA infection. Carvalho Junior et al.²⁸ demonstrated that CRP and ESR return to levels lower than the preoperative levels in 30 and 80
Combining the clinical history, laboratory alterations and culture results guides and enables identification of the infectious condition. In around 5–10% of the cases, alterations may exist throughout the propaedeutics, but without confirmation from culturing. Berbari et al.\(^{44}\) reported that it was important that the treatment should be guided in accordance with the entire investigation, and not just the results from culturing. In evaluating 897 cases of periprosthetic infection, they found that 7% of the cases had false negative cultures. All of these cases underwent surgical or drug treatment with a five-year success rate of greater than 70%.

**Treatment**

The primary objective in treating TKA infection is to eradicate the infection. Pain relief and reestablishment of function are secondary objectives, but no less important. Through the influence of the American literature, debridement with retention (D+R) and replacement in a single procedure (1T) are used less frequently. In addition, temporary placement of a spacer containing antibiotics, followed by replacement with the definitive implant (2T)\(^{44-46}\) and suppression therapy (ST), has also been proposed. Segawa et al. defined four clinical phases of TKA infection that are useful for guiding the treatment: I – infection identified at the time of the procedure; II – acute postoperative infection; III – identification some years after the original procedure, coming from a distant focus; IV – chronic infection.

The surgical treatments that exist in cases of infectious conditions are D+R, 1T, 2T, resection arthroplasty, arthrodesis, amputation and ST.\(^{44}\) The choice of best treatment depends on the patient’s condition, the condition of the implant and the germ that was isolated.

D+R is a good alternative for patients with early postoperative infectious states and acute hematogenic conditions, provided that the duration of symptoms is no more than three weeks, the skin coverage conditions are adequate, the implant is stable and an antimicrobial agent with effective action is available. It has been recommended that initial venous antibiotic therapy should be used for two to four weeks, with conversion to oral medication after this period.\(^{46,47}\) Byern et al.\(^{58}\) demonstrated that the infection-free survival rate after D+R treatment was 82%, with a follow-up of 2.3 years. Failure was associated with arthroscopic treatment, infections in revision procedures and infection due to S. aureus. Trebse et al.\(^{59}\) applied a D+R protocol to a series of 24 patients with an 86% success rate over three years and defined that the factors for a good prognosis were the presence of a stable implant, absence of fistulas contiguous with the prosthetic component and duration of symptoms less than three weeks.

Replacement in a single procedure is a good option when there is good skin coverage, absence of comorbidities and infection not caused by multiresistant germs. Jämsen et al.\(^{50}\) reported that the infection eradication rates ranged from 73% to 100% over 122 months of follow-up using this strategy.

If these criteria are not all fulfilled, the best option is to replace the implant in two procedures (2T). In these cases, a mobile or rigid joint spacer made of polymethylmethacrylate (PMM) should be used. This has the objectives of keeping the soft tissues under tension, diminishing the “dead space” and enabling local release of antibiotic.\(^{51,52}\) In these cases, Zimmerli et al.\(^{46}\) recommended that the second procedure should be performed after as short a time as possible (two to four weeks), which diminishes the costs and the duration of hospital stay. Haleem et al.\(^{51}\) reported that the success rate over five years of follow-up was 93.5% and over 10 years, 85%. Macheras et al.\(^{55}\) reported that the infection-free survival rate was 91.1% over 12.1 years of follow-up.

Despite concerns among infectologists that spacers with low release of antibiotics (which occurs after a few weeks of

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**Fig. 4 – Algorithm for treating acute or subacute prosthetic infection.**
use) might function as sites for bacterial fixation (through formation of biofilm), there is no consensus regarding the ideal length of time for the spacer to be kept in use. Della Valle\textsuperscript{53} suggested that the minimum time should be eight weeks, provided that after the end of the initial antibiotic therapy (six weeks), the values from inflammatory tests continue to show progressive reductions over the subsequent two weeks.

Another point that is still under discussion is the mixture of antibiotics with the PMM and its concentration. There is no standardization of the quantity used. Empirically, 10\% of its weight has been used, which represents 4 g of antibiotic for each unit (40 g). It is known that high doses of antibiotic may alter the mechanical properties of the spacer and make it easily breakable.\textsuperscript{54} Despite this, Anagnostakos et al.\textsuperscript{55} reported that they used high doses of antibiotics in PMM, without major clinical repercussions or side effects. Although manufactured formulations of PMM in association with gentamicin and tobramycin exist, the dosage of these antibiotics in the mixture does not reach the 10\% mentioned above. When the antibiotic is mixed in on the surgical table, it is possible to add the antibiotic to the most external layer of the PMM and increase its area of contact with the bone surface (placement as a surface coating). The choice of antimicrobial agent depends on the germ to be treated and the thermoresistance of the agent, given that the polymerization reaction of the PMM when associated with barium is exothermic and may interfere with the properties of the antibiotic. Gentamicin, tobramycin and vancomycin are good alternatives as thermoresistant agents.\textsuperscript{56,57}

In addition to surgical treatment, systemic antibiotic therapy should be maintained. It has been recommended that there should be six months of treatment for patients with TKA infection who present unfavorable skin coverage conditions.\textsuperscript{55,56} The antimicrobial agent should have bactericidal action, even against slow-growth germs or biofilm producers. Before starting any treatment, the susceptibility of the germ should be tested and alternative regimens should be discussed, given the growing levels of resistance.\textsuperscript{57,58} A combination of rifampicin with quinolones has been used most often, with good results in vitro, in vivo and in clinical trials. Options such as linezolid, sulfamethoxazole-trimethoprim and minocycline are possible, although so far no clinical studies for validating their use have been published. The best option is to discuss the best antimicrobial therapy for each case with the hospital infection control committee.\textsuperscript{58,59}

If the patient is not in a suitable clinical condition for the new procedure, ST with long-duration antimicrobial medication becomes the best option. In these cases, the objective becomes one of controlling the acute manifestations, rather than eradication of the infection. Arthrodesis and amputation are options for immunocompromised patients and for those for whom new arthroplasty would not improve their function.\textsuperscript{59}

Using the AAOS and Zimmerli recommendations described in Figs. 4 and 5, Giulieri et al.\textsuperscript{60} reported that the cure rate was 83\%, while Trampuz et al.\textsuperscript{61} Tsukayama et al.\textsuperscript{62} Meehan et al.\textsuperscript{63} and Betsch et al.\textsuperscript{64} observed cure rates of 90\%, 91\%, 89\% and 57\%, respectively. Betsch et al.\textsuperscript{64} found values lower than

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**Fig. 5 – Algorithm for treating infection that is not qualified for debridement + retention.**
those of the others because they had a greater number of 2T procedures, with a greater number of cases of advances disease or microorganisms of greater virulence. The risk factors for therapeutic failure were described as polymicrobial infection and infection due to Gram-negative bacilli, mycobacteria and fungi.

With better comprehension of the pathogenesis of the disease and development of new diagnostic and investigative techniques, better treatment and management of TKA infection will be achieved, with fewer complications and morbidity–mortality.

Final remarks

After TKA infection has been diagnosed, its treatment should be individualized but generally involves a combination of systemic antibiotic therapy with surgical treatment. Replacement of the implant in one or two stages is the preferred procedure. Debridement with retention of the prosthesis is an option in acute cases that have stable implants and present germs that are sensitive to the antimicrobial agents.

Conflicts of interest

The authors declare that there were no conflicts of interest.