SHORT COMMUNICATION

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Antibiotic-loaded cement spacer for treatment of *Klebsiella* infected total hip and knee arthroplasty

Cementni spejser sa antibiotskim sadržajem za lečenje bolesnika sa totalnom artroplastikom kuka i kolena inficiranih bakterijom *Klebsiella*

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Abstract

Background/Aim. Infection following total hip arthroplasty (THA) or total knee arthoplasty (TKA) may have devastating consequences. Some bacterial strains are often encountered as agents of these infections, others occur less frequently but are sometimes burdened with more severe complications. *Klebsiella* spp. are uncommon causes of THA or TKA infection. The aim of this study was to identify an effective treatment algorithm for multidrug resistant *Klebsiella* spp. caused THA or TKA infections. **Methods.** During the 3-year period, from January 1 2009 to December 31 2011, we registered and treated 5 patients with THA or TKA multidrug resistant *Klebsiella* spp. caused infection. All the patients were primarily operated in other institutions, and were admitted in our clinic after the onset of infection symptoms. In three of the cases *Klebsiella* infection was complicated by additional infection (*Staphyloccocus aureus*, *Pseudomonas aeruginosa* and *Serratia marscescens*). In 3 of the cases we performed revision arthroplasty after double exchange of antibiotic-loaded articulating cement spacer, and in 2 of the cases the standard two-stage revision approach with one antibiotic cement spacer exchange was applied. **Results.** The mean length of follow-up after reimplantation surgery was 17.1 months (range 2–31 months). One patient died 2 months after the final reimplantation procedure. The initial *Klebsiella* infection was eradicated in all the patients. At the end follow-up after definitive reimplantation, the patients had no clinical, laboratory or microbiological parameters positive for active infection. **Conclusion.** According to our experience with multidrug-resistant *Klebsiella* TKA/THA infections, two-stage approach, in some cases with double articulating cement spacer exchange prior to definitive reimplantation, is the most effective treatment option.

Key words:
arthroplasty, replacement, hip; arthroplasty, replacement, knee; bacterial infections; klebsiella; orthopedic procedures; anti-bacterial agents; treatment outcome.

Apstrakt

Uvod/Cilj. Infekcije totalnih artroplastika kuka (THA) i totalnih artroplastika kolena (TKA) mogu imati teške posledice. Neke baterije su češći uzročnici, druge se javljaju ređe, ali su ponekad te infekcije opterećene težim tokom i komplikacijama. *Klebsiella* bakterije su retki uzročnici ovih infekcija. Cilj rada bio je identifikacija efikasnog algoritma za lečenje infekcija THA i TKA koje izaziva *Klebsiella*. **Metode.** U 3-godišnjem periodu, od 1. januara 2009. do 31. decembra 2011, registrovali smo i lečili pet bolesnika sa THA ili TKA infekcijom uzrokovanom multirezistentnim sojem bakterije *Klebsiella*. Svi bolesnici su primarno operisani u drugim ustanovama, a u našu kliniku su bili primljeni posle pojave znakova infekcije. Kod tri bolesnika infekcija bakterijom *Klebsiella* bila je komplikovana dodatnom infekcijom (*Staphyloccocus aureus, Pseudomonas aeruginosa* i *Serratia marscescens*). Kod tri bolesnika izvedena je reviziona artroplastika nakon dvostruke izmene antibiotskog cementnog spejsera, a kod dva bolesnika reviziona artroplastika sa jednom izmenom spejsera. **Rezultati.** Srednja vrednost perioda praćenja bila je 17,1 mesec (od 2 do 31). Jedan bolesnik preminuo je dva meseca nakon druge reimplantacione procedure. *Klebsiella* infekcije izlečene su kod svih bolesnika. Na kraju perioda praćenja nakon definitivne reimplantacija, bolesnici nisu imali kliničkih, laboratorijskih, niti mikrobioloških parametara pozitivnih na prisustvo aktivne infekcije. **Zaključak.** Nakon našeg iskustva sa TKA/THA infekcijama prouzrokovanim multirezistentnim sojevima bakterije *Klebsiella* ustanovili smo da je pristup sa dvostrukom izmenom artikularnih cementnih spejsera pre definitivne reimplantacije najefikasnija opcija lečenja.

Ključne reči:
artroplastika kuka; artroplastika kolena; infekcija, bakterijska; klebsiella; ortopedske procedure; antibiotici; lečenje, ishod.

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Introduction

Infection following total hip arthroplasty (THA) or total knee arthroplasty (TKA) may have devastating consequences for the patient. The incidence of infection associated with THA or TKA in many studies has been reported to range from less than 1% in general population to almost 4% in patient groups with comorbidities such as rheumatoid arthritis, that increase risk of infection [1–3].

Some bacterial strains are often encountered as agents of these infections, others occur less frequently but are sometimes burdened with more severe complications.

Bacteria belonging to the genus *Klebsiella* frequently cause human nosocomial infections. *Klebsiella* spp. are gram-negative, nonmotile, usually encapsulated rod-shaped bacteria, belonging to the family *Enterobacteriaceae* [4, 5]. These bacteria produce lysine decarboxylase but not ornithine decarboxylase and are generally positive in the Voges-Proskauer test. Members of the *Enterobacteriaceae* family are generally facultatively anaerobic, and range from 0.3 to 1.0 mm in width and 0.6 to 6.0 mm in length [5]. *Klebsiella* spp. often occur in mucoid colonies [4, 5]. The principal pathogenic reservoirs for transmission of *Klebsiella* are the gastrointestinal tract and the hands of hospital personnel. In particular, *Klebsiella pneumonia*, the medically most important *Klebsiella* species, accounts for a notable proportion of hospital-acquired urinary tract infections, pneumonia, septicemias, and soft tissue infections. It is estimated that *Klebsiella* spp. cause 8% of all nosocomial bacterial infections in the United States and in Europe [6]. Fortunately *Klebsiella* spp. are not common infective agents in TKA or THA infections, with a relatively small number of reports on the subject of *Klebsiella* periprosthetic infection in the literature [7, 8].

Two-stage reimplantation with antibiotic loaded cement spacers and 4–6 weeks of antibiotic treatment remains the most successful procedure for infection resolution. In most of the series success rates are up to 95 % [9, 10]. In cases of persistent multidrug-resistant (MDR) *Klebsiella* spp. infection there is a limited role for one-stage exchange and even two-stage reimplantation may not warrant eradication [11]. In some cases additional unconventional steps may be required for successful treatment.

The aim of this study was to identify an effective treatment algorithm for multidrug resistant *Klebsiella*-caused THA or TKA infections.

Methods

All investigations were conducted in conformity with ethical principles of research, and informed consent for participation in the study was obtained.

Since January 2009 to January 2012 we registered and treated 5 patients with THA or TKA multidrug-resistant *Klebsiella*-caused infection. All the patients were primarily operated in other institutions, and were admitted in our clinic after the onset of infection symptoms. The hospital records, operative notes, medications, laboratory reports, microbiological analysis data with antibiograms, and follow-up reports were reviewed. Collected data included patient age, gender, comorbidities, dates, initial arthroplasty procedure and subsequent reimplantation procedures, culture results with antibiograms, type of spacer, antibiotic combination mixed in the cement, *iv* and oral antibiotic therapy with the duration of antibiotic therapy.

There is the established protocol for the diagnosis and management of infected THA and TKA in our institution. It starts with preoperative clinical and laboratory evaluation. Aspiration is routinely performed if a patient was without antibiotics for at least 14 days prior to aspiration. If the results a positive for infection a patient is admitted and scheduled for surgery. All the patients in this series were initially planned for two-stage rearthroplasty. Preoperative and postoperative laboratory evaluation consisted of complete blood count, urine, biochemical analyzes, C-reactive protein, erythrocyte sedimentation rate, fibrinogen, and in some cases interleukin-6 was obtained. Intravenous (*iv*) antibiotic therapy was started after intraoperative cultures and tissue samples were obtained. In the first stage extraction of THA or TKA implants and debridement were performed followed by implantation of antibiotic loaded cement spacer (Figure 1).

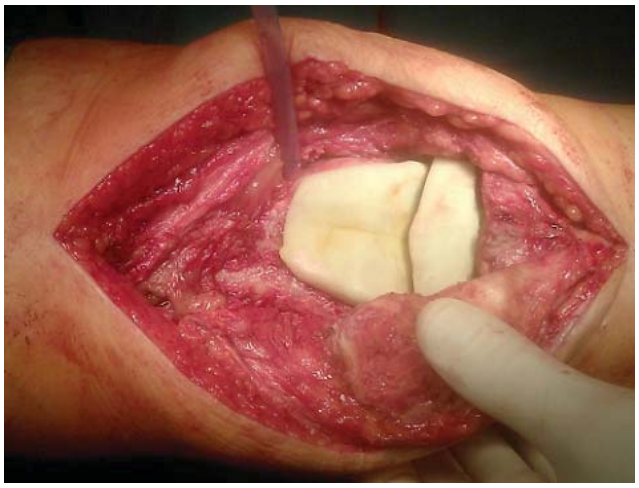

Fig. 1 – Articulating knee spacer.

In all the cases we used Refobacin® Revision (Biomet) bone cement containing a combination of two antibiotics: 1.0 g gentamicin and 1.0 g clindamycin *per* 40 g of bone cement. In one case where cultures, in addition to *Klebsiela* spp. were positive for *Staphyloccocus aureus* we intraoperatively added 2 g of vancomycin *per* 40 g of bone cement. In all the cases StageOne (Biomet) knee or hip spacer molds were used to make articulating spacer molds. After spacer placement no drains were used. Postoperatively, all the patients were regularly monitored by the infectious disease specialist, *iv* and afterwards oral antibiotic regimen was based upon pathogen sensitivity profile obtained from intraoperative cultures. Postoperatively, it consisted of combination of *iv* antibiotics in two cases, in other two cases *iv* meropenem 1 g every 8 h for two weeks, and in one case imipenem/cilastatin 0.5 g every 6 h for two weeks was applied. All patients underwent regular controls of renal, hepatic and hematologic

parameters during *iv* antibiotic therapy. *Iv* antibiotic therapy, was modified during treatment according to suggestions of infectious diseases specialist, but in all cases after spacer implantation duration of *iv* antibiotics lasted less than four weeks, and oral administration of antibiotics was continued afterwards. According to preoperative clinical, laboratory and intraoperative findings, second stage procedure with removal of articulating spaces had two possible outcomes, either final reimplantation of definitive prosthesis or three stage procedure with extraction of previous spacer, additional debridement and reimplantation of new knee or hip articulating spacer, and conditionally the 3-stage procedure with definitive reimplantation.

Klebsiella infections of THA and TKA in this study were found to be eradicated when at the end of a 12-month follow-up period after definitive reimplantation, the patients had no clinical, laboratory nor microbiological parameters positive for active infection.

Results

During a 3-year period, from January 1, 2009 to December 31, 2011, we registered and treated 5 patients with THA or TKA multidrug-resistant *Klebsiella*-caused infection. All the patients in the series had microbiologically confirmed *Klebsiella* prosthetic joint infection. During the treatment in 3 cases there were other pathogens isolated. All the patients were female, the mean age at the time of diagnosis of infection was 67.4 years (Table 1).

In 3 of the cases we performed 3-stage revision arthroplasty (double exchange of articulating cement spacer prior to reimplantation with definitive prosthesis), and in 2 cases 2-stage revision artheroplasty. The mean length of follow-up after the reimplantation surgery was 17.1 months (range 2 to 31 months); one patient died two months after the final reimplantation procedure. There were 3 infected THA and 2 TKA. The average time after primary arthroplasty and onset of infection symptoms was 28 days in the cases of THA and 39 days in the TKA cases. All the patients in the series had microbiologically confirmed *Klebsiella* prosthetic joint infection. In 2 of the cases of infected THA and in one case of infected TKA preoperative aspiration was positive for *Klebsiella*, and in other cases *Klebsiella* was isolated from intraoperatively obtained cultures and tissue samples.

During the treatment in 3 cases *Klebsiella* infection was additionally complicated by an infection with another bacteria. Two cases of *Klebsiella* infected total hips treated with double exchange of articulating spacer were complicated with additional pathogen, in one case during the first spacer exchange procedure *Pseudomonas aeruginosa* was obtained from intraoperative cultures, and in the other case *Staphyloccocus aureus* was found postoperatively in aspirations after first spacer implantation. One case of infected TKA was also treated with double spacer exchange, *Serratia marscescens* was isolated from knee aspirations after the first spacer exchange procedure. Adjustments in antibiotic therapy in these cases were made according to the resistance of *Klebsiella* and concomitant bacteria by an infectious diseases specialist.

Table 1

Patients characteristic and procedures

Patients characteristics (age, gender, Dg, Co)	Primary arthroplasty	Infecting bacteria	Secondary concomitant infecting organism	First spacer procedure and duration	Second spacer procedure type and duration	Second/third stage reimplantation
71 f; Dg: Osteoarthritis, Co: DM, urinary tract infection, hypertension	Cemented THA	*Klebsiella* spp.	*Pseudomonas aeruginosa* (isolated in cultures from first spacer implantation)	Articulating hip spacer for 12 weeks	Articulating hip spacer for 12 weeks	Eradicated, reimplantation-cemented THA
72 f, Dg: Rheumatoid arthritis; Co: DM, urinary tract infection	Cemented THA	*Klebsiella* spp.	*Staphylococcus aureus* (isolated from cultures obtained from aspirations after first spacer implantation)	Articulating hip spacer for 12 weeks	Articulating hip spacer (Refobacin cement with addition of vanco-mycin) for 12 months	Eradicated, reimplantation-hybrid THA
72 f; Dg: Femoral neck fracture; Co: hypertension	Cementless THA	*Klebsiella pneumoniae*		Articulating hip spacer for 8 weeks	None	Eradicated, reimplantation-cemented THA, patient died two months after final reimplantation
59 f; Dg: Osteoarthritis; Without Co	Bilateral simultaneous TKA (right knee got infected	*Klebsiella pneumoniae*	*Serratia marscescens* (isolated in cultures obtained during first spacer implantation)	Articulating knee spacer for 8 weeks	Articula-ting knee spacer (Refoba-cin cement) 3months	Eradicated reimplanted, cemented LCCK prosthesis
62 f; Dg; Rheumatoid arthritis; Co: DM, hypertension	Cemented TKA	*Klebsiella* spp.		Articulating knee spacer for 6 months	None	Eradicated, reimplanted cemented rotation hinge knee

Dg – primary diagnosis; Co – comorbidity; f – female; DM – diabetes mellitus; THA – total hip arthroplasty; TKA – total knee arthroplasty; LCCK – legacy constrained condylar knee.

One patient in the series with *Klebsiella* infected THA, 72 years old, was admitted to our hospital with evident signs of sepsis, severe anaemia and hepatorenal failure. This patient had cementless THA, at another institution, after femoral neck fracture, 5 weeks prior to admission in our hospital. Prior to sepsis development the patient was treated for two weeks with oral antibiotics at another outpatient clinic and was referred to our hospital when clinical and laboratory findings indicated sever deterioration. Besides obesity and high blood pressure before the primary arthroplasty the patient had no other comorbidities. This patient underwent 2-stage revision surgery, after first stage procedure and articulating spacer implantation there were significant positive improvements in the patient status. Hepatorenal failure persisted and required regular consults with nephrology and infectious diseases specialists. Eleven weeks after spacer implantation and subsidence of infection signs second stage procedure, cemented THA was perfomed. Initially early postoperatively patient was stable and recovering without complications. But one month after reimplantation cardiac and renal insufficiency developed, and the patient died 8 weeks after the reimplantation procedure. Considering reimplantation THA, at the time of death the patient was clinically, laboratory and microbiologically infection free.

One patient in the series, 59 years old, had bilateral simultaneous TKA, during primary arthroplasty procedure right knee was done first, and there was *Klebsiella pneumoniae* infection of the right TKA, the left knee was infection free. The onset of infection signs was 6 weeks after primary arthroplasty. This patient was treated with double spacer exchange. The first spacer was removed after 8 weeks, and the second one after 3 months. *Serratia marscescens* was isolated from knee aspirations after the first spacer exchange procedure. Antibiotic therapy was altered according to antibiograms by an infectious disease specialist.

In four of the cases end-stage procedures were performed as cemented total hip or knee arthroplasty, Refobacin® Revision (Biomet) bone cement was used in all the cases. In one case a hybrid total hip was definitive implant.

All the patients were allowed immediate full weight bearing. We did not note spacer fractures in any of the cases. In one case of *Klebsiella* THA infection after first stage exchange 4 weeks postoperatively hip spacer dislocation was noted (Figure 2).

The average time between removal of primary implants and definitive reimplantation was 6.8 months (range 2–15 months).

The initial *Klebsiella* infection was eradicated in all the patients, at the end follow-up after definitive reimplantation, patients had no clinical, laboratory or microbiological parameters positive for active infection. Clinically, at the last follow-up, except for the patient who died, in both cases of revision TKA knee, society functional score [12] improved from 30 to 90, and in cases of revision THA, Harris hip score [13] improved from 57.15 to 89.7.

We have noted the effects of articulating spacer cement abrasion phenomena (Figure 3.) and in each case thorough debridement and copious irrigation was perfomed during each step of the treatment.

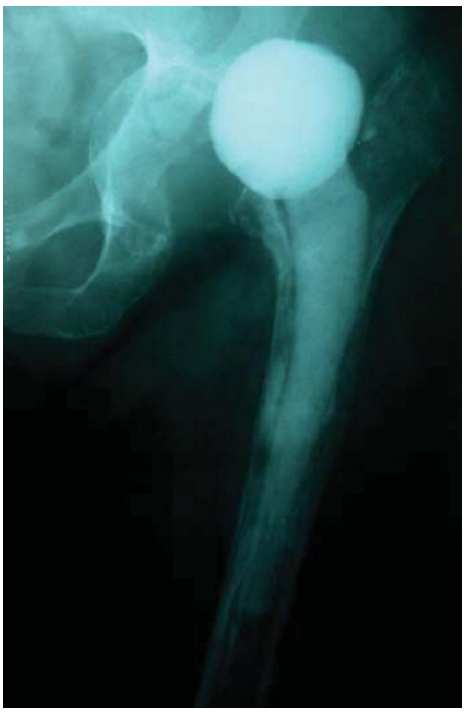

Fig. 2 – Dislocated hip spacer.

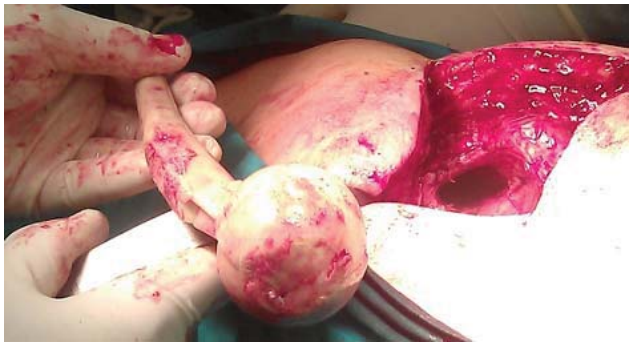

Fig. 3 – Removed articulating hip spacer – abrasions.

Discussion

The purpose of this study was to identify an algorithm of treatment of multidrug-resistant *Klebsiella*-caused THA/TKA infections. *Klebsiella* infections of TKA/THA are relatively rare [7–9], but can be very difficult to treat and sometimes can lead to sepsis, multiorgan failure and ultimately have fatal outcome.

There are few factors that additionally complicate treatment. *Klebsiella* infections of TKA/THAs can be complicated by an additional bacterial infection. Polymicrobial arthroplasty infections were seen in 6 of 10 knee arthroplasty patients; these infections involved a mixture of Gram-positive and Gram-negative species, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus species*, *Escherichia coli*, and *Enterobacter cloacae* [7, 14–20]. In our series in three cases *Klebsiella* arthroplasty infection was additionally complicated by an infection with another bacteria (*Staphyloccocus aureus, Pseudomonas aeruginosa* and *Serratia marscescens* were identified).

In addition to the multiresistant ability, *Klebsiella pneumoniae* has several adhesive factors, such as type 1 and type 3 pili, which help bacteria to adhere to abiotic or biological surfaces. The adherence of *Klebsiella pneumoniae* to cardiac valve prostheses, catheters of urinary tracts, intestinal cells, and bladder epithelial cells has been previously reported [21].

Two-stage treatment is currently the most common approach for management of an infected joint prosthesis, static antibiotic-impregnated cement spacers have traditionally been used, increasingly, however, mobile or articulating spacers are being utilized [22–24]. Although comparisons in the literature of static and articulating spacers have shown average eradication rates of approximately 90% and 92%, respectively [25], articulating spacers have some potential advantages, including more effective maintenance of the joint space and prevention of soft tissue contracture, facilitation of local antibiotic delivery, early mobilization, full or in some cases limited weight bearing, and possible reduction in bone loss.

In all cases we used antibiotic-loaded cement articulating hip and knee spacers. In our series of *Klebsiella* infected TKA/THA simplex two stage revision was not always sufficient option, and in some cases repetition of articulating antibiotic cement spacer prior to final reathroplasty was required for eradication of infection.

We used the term 3-stage reimplantation for the procedures of repetition of antibiotic cement spacer prior to reimplantation of definitive prosthesis. In the literature generally accepted understanding of 2-stage reimplantation concept, as it was firstly described by Insall et al. [26] and further promoted by other authors [14, 17, 27,] points to the procedures where the stage one is the operation with removal of infected implants and application of cement spacer, after a certain period of time followed by the stage two, spacer removal and definitive prosthesis implantation. Some authors consider as 2-stage reimplantation procedures even cases where two cement spacers exchanges occur before definitive rearthroplasty [7]. It could be that in situations where spacer elution time has subsided, but infection signs are still present and there are clear indications for one more spacer repetition, a more appropriate term is 3-stage reimplantation. This slight change in arthroplasty terminology could contribute to better recognition and follow-up of persistent periprosthetic joints infections caused by MDR bacteria treated by double cement spacer exchange.

Fink et al. [28] noted that articulating spacers used in 2-stage revision surgery of infected prostheses have the potential to abrade and subsequently induce third-body wear of the new prosthesis. Given the presence of abrasion debris, they recommend total synovectomy and extensive lavage during the second-stage reimplantation surgery to minimize the number of abraded particles and any retained bacteria.

Spacer fractures were reported [29, 30] but we had no fractured cemented spacer in the series.

Our study has some limitations. The major deficiencies are a small number of patients, and its retrospective design. Larger series and prospective research may be needed to provide adequate predictions for the appropriate treatment modality. The small number of patients, and heterogeneity of the series prevent us from making a definitive recommendation of which primary treatment is required for eradication of infection and restitution of function.

Conclusion

In our limited experience with multidrug-resistant *Klebsiella* total knee arthroplasty and total hip arthroplasty infections, we consider that 2-stage and 3-stage revisions (double articulating cement spacer exchange prior to definitive reimplantation) are the most effective treatment options.

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