CASE REPORT/KAZUISTIKA

Revision Arthroplasty for Periprosthetic Femoral Fracture Complicated by Multidrug-Resistant *Escherichia coli*: Case Report and Minireview

Reimplantace periprotetické zlomeniny femuru komplikovaná infekcí multirezistentní *Escherichia coli*: kazuistika a minireview

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SUMMARY

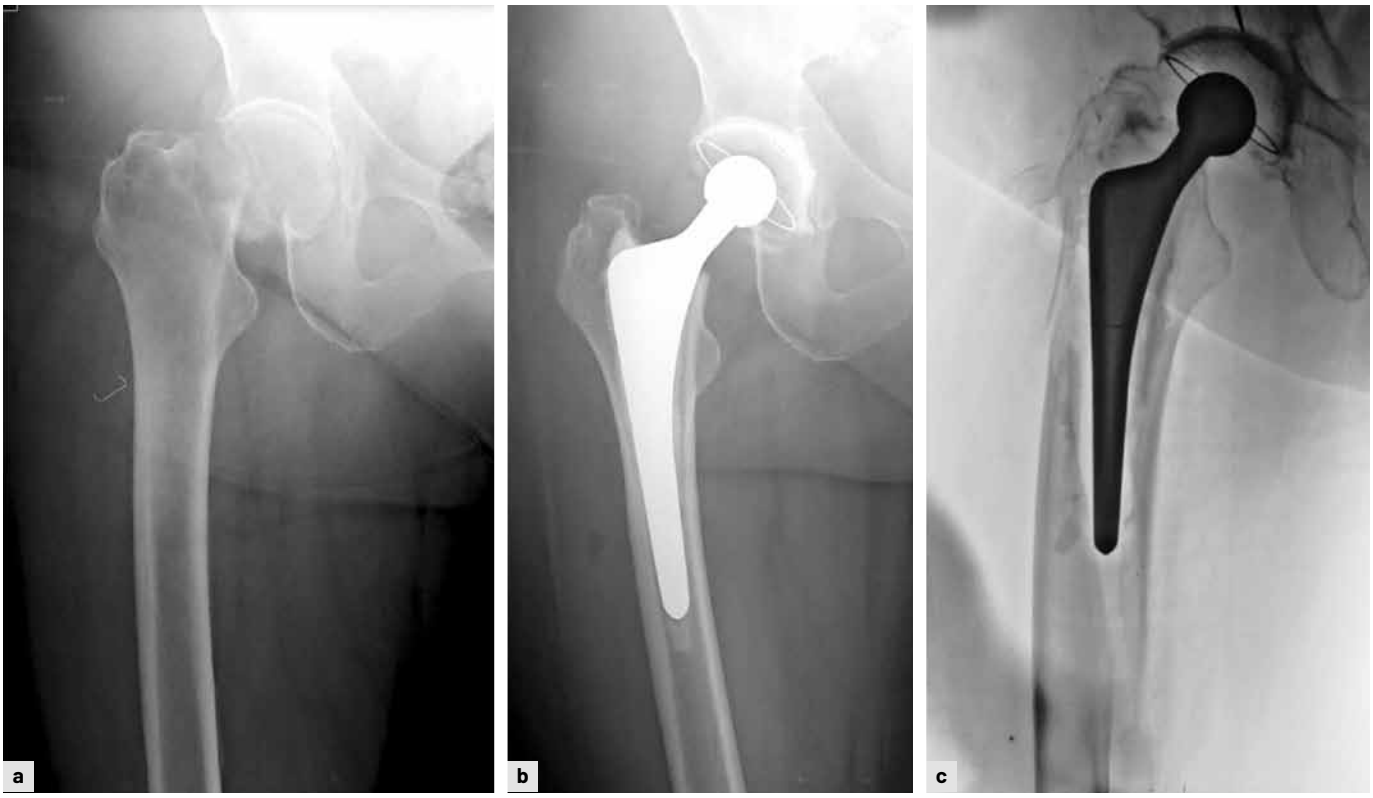
Periprosthetic infections caused by multi-resistant bacteria are one of the most fearsome complications in current orthopedics. Despite using aseptic modern practices, the number of infectious complications caused by multidrug-resistant strains is rising worldwide. We present a case of a woman with a non-healing wound after hip arthroplasty revision surgery performed in Egypt for periprosthetic femoral fracture. Upon admission, 11 days after surgery, she presented with a purulent secretion from surgical wound and signs of sepsis. Carbapenem-resistant *E. coli* was proven from a wound swab. Two-stage revision with a 6-week-long interval of targeted parenteral antibiotic therapy was indicated. During explantation, excessive femoral bone loss after inadequately performed trauma revision surgery was discovered. After antibiotic hip spacer period, the patient underwent implantation of a cemented tumorous revision hip implant followed by 6 weeks of antibiotic therapy. The patient was discharged in more than satisfactory condition, being self-sufficient using French crutches. In follow-up visits during next 2 years, no relapse of carbapenem-resistant infection occurred. In patients hospitalized or operated in high-risk areas, epidemiological anamnesis is of great importance and the possibility of importing multi-resistant bacteria should be considered. Infections caused by these bacteria prolong therapy and increase the cost of treatment significantly. The combination of arthroplasty extraction and targeted antibiotic therapy is recommended to treat periprosthetic infections.

Key words: hip arthroplasty, arthroplasty revision, periprosthetic fracture, periprosthetic infection, multidrug-resistant *E. coli*.

INTRODUCTION

Orthopedic implant-associated infections caused by multidrug-resistant *Enterobacteriaceae* are a growing challenge for healthcare providers due to their increasing incidence and the difficulties of medical and surgical treatment (12). Periprosthetic joint infection is one of the major complications and causes of implant failure after total joint arthroplasty (5). Local signs, such as serous or purulent secretion from the surgical wound, sinus tract communicating with the prosthesis, redness and higher temperature around the wound, and pain in the area of arthroplasty during physical

Acta Chir Orthop Traumatol Cech., 92, 2025, No. 5, p. 293–297



activity, or even at rest; as well as signs of sepsis can all be manifestations of periprosthetic infections (2). A prosthesis is a foreign body, and its mere presence is a risk factor for infection. The microbial load needed to produce an infection in a prosthetic joint is much less than that for a native joint (3). The incidence of infections by multidrug resistant infectious agent such as *Enterobacteriaceae* has increased in recent years (12). The rising incidence of these bacteria greatly complicates medical care, prolongs hospital stays and increases treatment costs (1). Risk factors include geographic location, older age, previous antibiotic therapy and long-term institutional care (19). The most common sites of infections with multi-resistant *Enterobacteriaceae* are the urinary tract, respiratory system and surgical wounds (21). Epidemiologically, the most serious are strains that produce carbapenemases, enzymes capable of hydrolyzing most β-lactams including carbapenems, these bacteria mainly include *Enterobacteriaceae* (especially *Escherichia coli* and *Klebsiella pneumoniae*), *Pseudomonas spp.* and *Acinobacter spp.* (4). According to Ambler, we can divide carbapenemases into three groups, group A and group D are serine beta-lactamases, group B are metallobetalactamases (8). The treatment options for infections caused by these bacteria are highly limited, with only colistin susceptibility remaining, along with new antibiotics that are very expensive and unavailable in some countries (15). We present a case of a woman with a non-healing wound after hip arthroplasty three stage revision surgery with culture-proven multidrug-resistant strain of gram-negative bacteria.

CASE REPORT

During vacation in Hurghada, Egypt, an 80-year-old woman with previously implanted cemented total hip arthroplasty (THA) after femoral neck fracture (Fig. 1a, b) fell down the stairs, causing periprosthetic fracture Vancouver B3 type of her right femur (Fig. 1c). She was tended in a regional hospital, where one stage revision surgery with a 300 mm cemented stem combined with a Dynamic Compression Plates with Limited Bone Contact (LCDCP), multiple cerclages and massive cement augmentation of femoral cortical bone under the plate was applied (Fig. 1d). Metronidazole, meropenem and ceftriaxone in subtherapeutic doses were administered empirically as antibiotic prophylaxis. On the 11th postoperative day, the patient was repatriated to the Czech Republic to a regional hospital, antibiotic prophylaxis was terminated before the transfer. Upon admission, serosanguinolent secretions and dehiscence of the wound were described, with sutures still in situ. She had leukocytosis 13.6 $*10^9$/L and C-reactive protein (CRP) 89.43 mg/L. Procalcitonin was not tested. Therefore, swabs from the wound were performed for microbiological examination immediately. Monotherapy with clindamycin was initiated empirically according to common

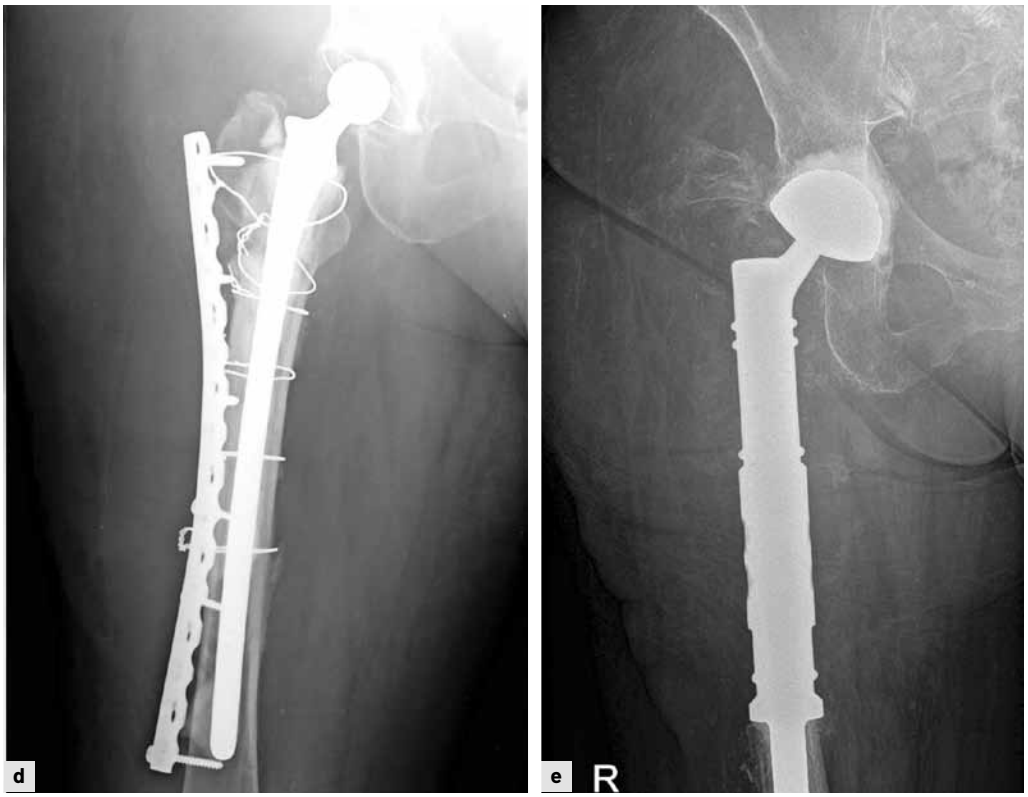


Fig. 1. **Antero-posterior X-rays illustrating the sequence of hip procedures over time: a – the initial femoral neck fracture that occurred three years before the periprosthetic fracture; b – treatment of the initial fracture with a cemented total hip arthroplasty; c – periprosthetic fracture of Vancouver type B3 (note: the image quality is low due to the original film technology and subsequent digitalization after repatriation); d – management of the periprosthetic fracture using a combination of osteosynthesis materials and bone cement; e – implementation of a modular tumor revision total hip arthroplasty to address significant bone loss in the proximal femur, following complications from both osteosynthesis and infection.**

practice of the department. A carbapenemase-producing strain of *Escherichia coli* (OXA-48 type) with preserved sensitivity to gentamicin and colistin, and intermediate sensitivity to cefepime, imipenem, and meropenem, as well as *Acinetobacter baumannii*, which was sensitive only to colistin with intermediate sensitivity to imipenem and meropenem, were identified as the cause of the inflammation and as a first described case in the Czech Republic. Next samples were sent for confirmation. In the meantime, antibiotic therapy was changed to gentamicin after consultation with regional antibiotic center. Trimethoprim-sulfamethaxazole, that *E. coli* from urine sample was sensitive to, was also administered due to concomitant urinary tract infection. After obtaining confirming results, the patient was isolated in intensive care unit of the Department of Infectious diseases of Masaryk Hospital in Usti nad Labem. Minimal inhibitory concetrations (MIC) are shown in Table 1 and 2. Colistin 3MU i.v. every 8 hours and

Table 1. **Minimal inhibitory concentrations (MIC) for *E. Coli***

ANTIBIOTIC AGENT	MIC (BREAKPOINT)	SUSCEPTIBILITY
Amoxicillin/clavulanate	64 (8)	resistant
Ampicillin	64 (8)	resistant
Cefepime	4 (1)	intermediate
Cefotaxime	8 (1)	resistant
Ceftazidime	16 (1)	resistant
Cefuroxime	128 (8)	resistant
Ciprofloxacin	8 (0,25)	resistant
Colistin	0.5 (2)	sensitive
Gentamicin	0.5 (2)	sensitive
Imipenem	8 (2)	intermediate
Meropenem	8 (2)	Intermediate
Piperacillin + tazobactam	256 (8)	resistant
Trimethoprim + sulfonamid	640 (2)	resistant

Table 2. **Minimal inhibitory concentrations (MIC) for Acinetobacter baumanii**

ANTIBIOTIC AGENT	MIC (BREAKPOINT)	SUSCEPTIBILITY
Amikacin	16 (8)	resistant
Cefepime	8 (1)	resistant
Ceftazidime	8 (1)	resistant
Ciprofloxacin	2 (1)	resistant
Colistin	0,25 (2)	sensitive
Gentamicin	32 (4)	sensitive
Imipenem	4 (2)	intermediate
Meropenem	4 (2)	intermediate
Piperacillin + tazobactam	16 (16)	intermediate

Acta Chir Orthop Traumatol Cech., 92, 2025, No. 5, p. 293–297

imipenem/cilastatin 1g i.v. every 6 hours therapy was initiated. Due to a large wound dehiscence and purulent secretion and clinical signs of imminent sepsis with ongoing leukocytosis 11.8 *10^9/L, CRP 43.1 mg/L and already negative prokalcitonine 0.08 mg/L upon admission after transfer, a procedure of two-stage reimplantation of the THA was selected to gain control over periprosthetic infection. During THA explantation femoral bone loss of almost all proximal half of the femur, after inadequately performed trauma revision surgery with a huge bone cement augmentation and its thermal effect on the remaining bony structures was discovered. Debridement of fibrous and necrotic tissues was performed, and tissue samples were obtained for microbiological examination. An antibiotic hip spacer (Copal® G+C with 1 g gentamicin and 1 g clindamycin) was implanted. Postoperatively, rifampicin 300 mg p.o. every 12 hours was added to antibiotic therapy, but it was discontinued after 5 days due to nausea. The total duration of colistin administration was 33 days and of imipenem 6 weeks. The antibiotic therapy was guided by the local antibiotic center. At the end of the antibiotic hip spacer period, we performed revision of spacer with implantation of a cemented tumorous revision hip implant (Implantcast, Mutars-Filia)(Fig. 1e). Megaprostheses following infection cases relate to higher risk of further septic loosening of the implant, but we had no another option due to proximal femoral bone loss. The surgery was followed by 6 weeks of antibiotic therapy by meropenem and hyperbaric oxygen therapy. The patient was discharged after intensive rehabilitation, in more than satisfactory condition, being self-sufficient using French crutches. In follow-up visits during next 2 years, no relapse of carbapenem-resistant enterobacteria infection occurred.

DISCUSSION

OXA-48 carbapenemase, which was identified in this case report, was first described in 2001 in Turkey, when it was isolated from a *Klebsiella pneumoniae* strain (13). Since then, carbapenem-resistant *Klebsiella pneumoniae* has gradually spread around the world, in Europe mostly in Greece, Italy, Romania, Hungary and Croatia. Other highly prevalent carbapenem-resistant enterobacteria include *E. coli*, that shows a marked increase in incidence in Europe, especially in Spain, and around the Mediterranean, mostly in Egypt and Turkey (6). Two-stage revision is considered the gold standard for treatment of chronically infected and complex infections as the successful eradication of a periprosthetic joint infection exceeds 90% (17), however, evidence-based knowledge on approaching periprosthetic joint infection caused by carbapenem-resistant *Enterobacteriaceae* is sparse (12). In a case report by Adams et al., the periprosthetic joint infection was treated also with a two-step reimplantation revision with 1-stage static spacer and i.v. meropenem (1). In our case the bacteria were intermediate sensitive to meropenem, imipenem together with colistin administration brought desirable clinical answer. Pfang et al. published a series of 25 different cases with orthopedic infections caused by multidrug resistant *Enterobacteriaceae*, they highly recommend implant removal in cases where age and comorbidities allow extraction to gain control over infections (12). The presence of the implant favors the formation of biofilms, conditioning difficulty for bacterial eradication (12). The bacteria in biofilms have decreased sensitivities to antibiotics and other antimicrobial agents (9). Rifampicin has been shown to be the most common partner drug of effective combinations against especially staphylococcal biofilms (10). The rise of nosocomial infections due to multidrug-resistant Gram-negative bacteria led to the higher usage of colistin, that has been proved to be an effective antimicrobial agent and should be administered as part of a combination therapy (11). Both custom-made and prefabricated articular hip spacers is an important step in the one or multiple-stage revision technique (18). Its purpose is to stabilize the tension of soft tissues and thus maintain limb length, guarantee the sufficient local release of antibiotics, and reduce hematoma formation (14). In direct contact with the infected bone and soft tissues, spacers release locally high amounts of antibiotics to eradicate biofilm-protected microbes. The major complications are dislocation and spacer's rupture (16). The average retention time of a spacer was approximately 5 months in a review conducted by Rava et al. (14). The decision on reimplantation requires a supporting clinical examination, normal laboratory studies, and negative cultures 2 weeks after completion of i.v. antibiotics. Prolonged spacer retention is feared to lead to sub-inhibitory concentrations of the antibiotic and thus promote superinfection with resistant bacteria, however, this risk does not seem to be a problem in the clinical practice (18). The indications for megaprosthesis for nontumorous cases have been expanded to include even some non-neoplastic conditions of the hip and knee, such as excessive bone loss in failed arthroplasty, either due to periprosthetic fracture or deep infection (20). Megaprostheses have a relatively high complication rate, approximately 10-times the one observed in regular arthroplasty, however by allowing limb preserving surgery, they offer valuable solutions to maintain patient's quality of life (7). Cemented stems in revision hip arthroplasty seem to have favorable long-term survival rates in cases of revision total hip arthroplasty (5).

CONCLUSIONS

Therapy for arthroplasty infection caused by multidrug-resistant bacteria is a long and demanding process for the patient and a wide team of physicians consisting of an orthopedist, an infectious diseases specialist, a microbiologist, a clinical pharmacist and other specialists. The combination of surgical

removal of the arthroplasty and long-term appropriate antibiotic therapy appears to be the most advantageous therapy for arthroplasty infection caused by multi-resistant bacteria. Removing the joint replacement significantly increases the chances of gaining control of the infection and the possibility of successful cure of the patient. Reimplantation of the arthroplasty in the second period after the infection has healed may be considered. In our case, we chose a combination of long-term administration of antibiotics (colistin and imipenem/cilastatin) and surgical solution, arthroplasty extraction and spacer implantation with subsequent reimplantation in the second period with a good effect. ■

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