



# Two-stage approach to total knee arthroplasty using colistin-loaded articulating cement spacer for vancomycin-resistant *Pseudomonas aeruginosa* infection in an arthritic knee

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## Abstract

**Background** A two-stage approach to total knee arthroplasty (TKA) using an antibiotic-impregnated articulating cement spacer is an option for an infected arthritic knee. Vancomycin combined with broad-spectrum antibiotics can be used to make an antibiotic-impregnated articulating cement spacer. Causative organisms are sometimes not confirmed before surgery. Joint infections of multidrug-resistant organisms are increasing. Therefore, routine combinations of antibiotics may not be effective.

**Methods and results** We present a case of a patient who developed vancomycin-resistant *Pseudomonas aeruginosa* infection in an arthritic knee. A 71-year-old man was initially diagnosed with pyogenic arthritis caused by *Staphylococcus aureus*. He underwent arthroscopic debridement elsewhere. However, the infection persisted. He was referred to our hospital, and we performed a two-stage TKA using a vancomycin-based antibiotic-impregnated articulating cement spacer. Vancomycin-resistant *P. aeruginosa* was identified after surgery. Intravenous colistin was added. However, this failed, either because vancomycin was not effective against *P. aeruginosa*, or because insufficient systemic colistin due to colistin-induced acute kidney injury. Therefore, debridement was repeated, and colistin-loaded cement spacer was inserted. The spacer delivered high concentrations of colistin to the infected joint with decreased systemic effects. Thus, less systemic colistin was used. The infection was controlled without recurrent acute kidney injury. One year after surgery, conversion to TKA was successfully performed.

**Conclusion** A two-stage approach to TKA using a colistin-loaded articulating cement spacer can be used for an arthritic knee infected by vancomycin-resistant *P. aeruginosa*. Furthermore, local administration of colistin using a cement spacer can reduce the systemic side effects of colistin.

**Keywords** Colistin · Infected arthritic knee · Vancomycin-resistant *Pseudomonas aeruginosa* · Antibiotic-impregnated cement spacer · Two-stage approach

## Introduction

Treatment of an infected arthritic knee is challenging. Similar to two-stage revision total knee arthroplasty (TKA) in periprosthetic joint infection, the two-stage approach to

primary TKA using antibiotic-impregnated cement spacer can be used [1]. Although it is important to identify the causative organism and to use corresponding antibiotics, a vancomycin-loaded cement spacer is commonly used. However, a previous study revealed that routine use of vancomycin-based antibiotic-impregnated articulating cement spacer to treat infection caused by Gram-negative organisms showed poor clinical outcomes [2].

*Pseudomonas aeruginosa* is ubiquitous and is a prominent cause of nosocomial infections [3]. However, indiscriminate antibiotic use has increased its prevalence. *P. aeruginosa* characteristically presents with multidrug resistance. A previous study showed that 74.41% of *P. aeruginosa* isolates were resistant to vancomycin [4]. Colistin is not commonly used because of potential nephrotoxicity and neurotoxicity.

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However, the emergence of multidrug-resistant organisms has led to reconsideration of this option [5].

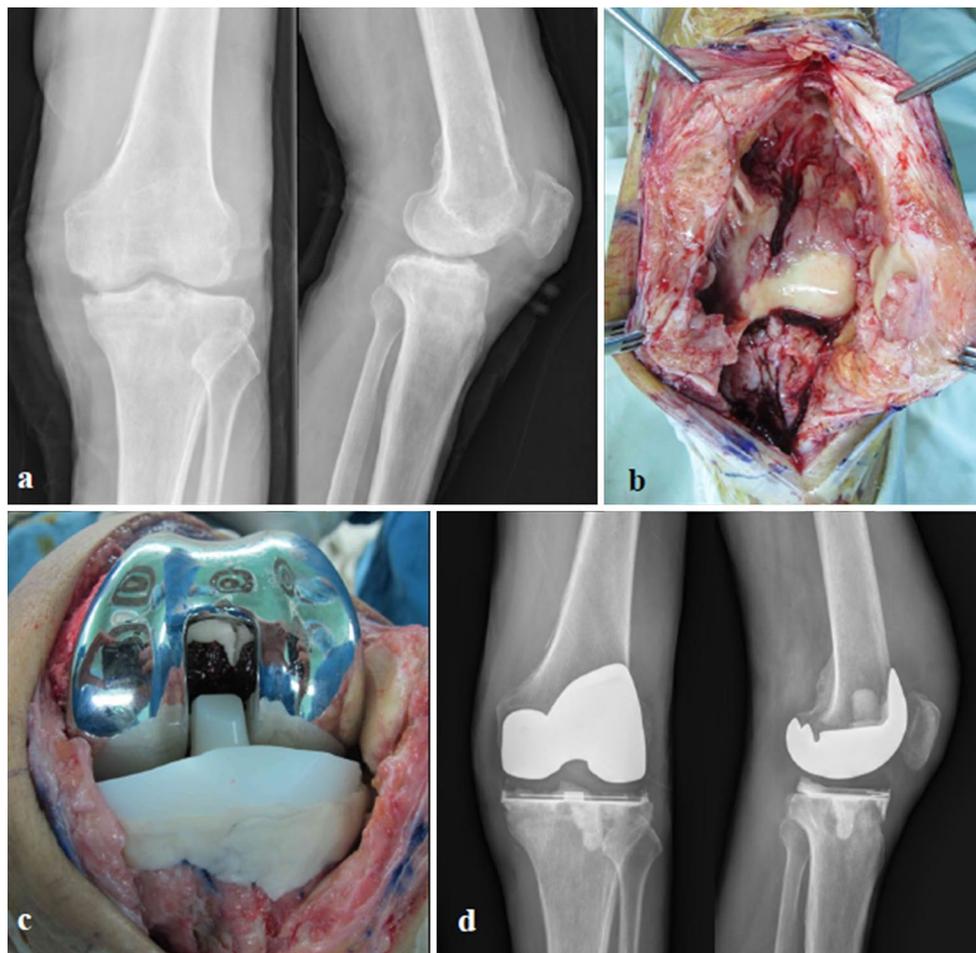
We describe a case of an arthritic knee infected by vancomycin-resistant *P. aeruginosa*. The patient was successfully treated using a two-stage approach to primary TKA with colistin-loaded articulating cement spacer and reduced systemic colistin.

## Patient and methods

A 71-year-old man was admitted to our hospital due to pain and increased warmth with moderate swelling of his left knee. He had been treated with acupuncture after a diagnosis of osteoarthritis at an Oriental Medicine Center. Six months prior to admission, he visited an orthopedic clinic because of aggravated left knee pain 3 days after acupuncture treatment. He was diagnosed with pyogenic arthritis and underwent arthroscopic debridement. Oxacillin-susceptible

*Staphylococcus aureus* was confirmed in a joint fluid sample. He received intravenous (IV) ciprofloxacin and cefotaxime for 6 weeks. Because of persistent wound discharge, he visited our hospital for further management.

He was in good health, except for type 2 diabetes mellitus. Discharge through a fistula in his left knee was observed. The C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were elevated (4.07 mg/dL and 120 mm/h, respectively). He was diagnosed with uncontrolled septic arthritis (Fig. 1a). Although no causative organism was detected in his joint fluid even after 4 weeks without antibiotics, empirical vancomycin was started on the assumption that methicillin-resistant *S. aureus* was still present. As he had a septic knee with end-stage osteoarthritis, we planned radical debridement and insertion of antibiotic-impregnated articulating cement spacer. After standard exposure, all infected tissues were removed (Fig. 1b). The prosthesis-on-polyethylene Hofmann technique [6] was used. Gentafix 1<sup>®</sup> bone cement containing 1 g of gentamycin per 40 g batch



**Fig. 1** Antibiotic-impregnated articulating cement spacer used as a first-stage procedure. **a** Preoperative radiographs (anteroposterior and lateral view). **b** Intraoperative photograph of infected knee. **c** Intraop-

erative photograph showing articulating spacer in situ. **d** Postoperative radiographs of antibiotic-impregnated articulating cement spacer (anteroposterior and lateral view)

plus 8 g of vancomycin was used to make the cement spacer (Fig. 1c, d). After surgery, multidrug-resistant *P. aeruginosa* was newly identified in the intraoperative tissue culture and was only susceptible to colistin. Intravenous colistin (150 mg every 12 h) was started. However, nephrotoxicity appeared 3 days after initial colistin use. Immediate hemodialysis was needed, and we reduced the colistin to 50 mg every 12 h.

Despite IV colistin treatment for 6 weeks, signs of infection persisted, with elevated CRP and ESR. Vancomycin-resistant *P. aeruginosa* was cultured from knee joint fluid. Therefore, we performed extensive debridement and inserted a colistin-loaded articulating cement spacer. The spacer was made using GentaFix 1<sup>®</sup> bone cement with 1.2 g of colistin. An additional 6 weeks of dose-adjusted IV colistin was administered without complications. He was discharged without signs of infection 6 weeks after repeat surgery. One year after initial surgery, TKA with Vanguard<sup>®</sup> 360 revision knee system (Biomet, Indiana, USA) using cement mixed with colistin was successfully performed (Fig. 2). One year after TKA, there were no signs of infection, and the CRP and ESR were normal.

## Discussion

The two-stage approach to TKA using colistin-loaded articulating cement spacer successfully treated an arthritic knee infection caused by vancomycin-resistant *P. aeruginosa*, enabling reduced colistin side effects. Case reports described successful treatment of multidrug-resistant *P.*

*aeruginosa* with colistin-loaded cement spacer for infected TKA and osteomyelitis [7, 8].

In response to the emergence of multidrug resistance in *Pseudomonas*, *Acinetobacter* and *Stenotrophomas*, the use of colistin has recently increased [9]. However, nephrotoxicity is a concern. The prevalence of nephrotoxicity caused by systemic colistin use reportedly ranged from 14 to 58% [5, 10]. Given current knowledge, dosing should be reduced to 2.5–4 mg/kg in patients with a creatinine clearance < 30 ml/min, even though microbial eradication requires doses of 6–12 mg/kg/day [11]. Our patient developed acute renal failure only 3 days after IV colistin was started at 150 mg every 12 h. The dose was reduced to 50 mg every 12 h, possibly contributing to initial treatment failure.

Use of an antibiotic-impregnated cement spacer is an established treatment for periprosthetic joint infections [12]. For local administration of colistin using a cement spacer, several conditions should be considered. First, the antibiotic should be thermostable, as the polymerization of cement is an exothermic reaction that generates substantial heat [13]. Colistin is a thermostable and water-soluble antibiotic suitable for cement spacer use [14]. Local administration of colistin could be used to reduce the risk of side effects caused by systemic use. The concentration of colistin should be sufficient to eradicate the causative organism. One study reported the use of high-dose tobramycin and colistin-loaded cement spacer for treatment of osteomyelitis [7]. The authors measured the colistin level in both drainage from the operated site and plasma. They reported that local colistin level at the joint exceeded five times the minimal inhibitory concentration against the *P. aeruginosa* isolated 4 days after surgery [7]. Another study also found that the level of plasma colistin remained low despite the use of high-dose colistin-loaded spacer [15]. Therefore, a colistin-loaded cement spacer can be as effective as systemic use, while reducing the side effects of systemic use.

There are still concerns about use of an antibiotic-impregnated cement spacer for treatment of an infected arthritic knee. Bone resection is not necessarily required for a septic knee without osteomyelitis. Furthermore, infection can spread through the hole for the intramedullary alignment guide used to determine the bone resection plane. However, several reports showed that this technique was effective for simultaneously eradicating infection and treating osteoarthritis [1, 16, 17]. Compared with a static cement spacer for infected knee joint treatment, the articulating spacer eradicates infection while allowing range of motion prior to staged primary TKA [18]. Moreover, joint replacement surgery after use of an articulating spacer may be easier than with a static cement spacer [19]. In this case, we had to use an implant with a stem extension because of considerable bone defect due to repeated surgeries.



**Fig. 2** Postoperative radiographs after total knee arthroplasty with a stem extension (anteroposterior and lateral view)

This report has several limitations. First, we reviewed only one successfully treated case using a colistin-loaded cement spacer. However, our findings suggest that a colistin-loaded cement spacer can be a treatment option, especially when systemic colistin use is contraindicated. Second, we did not measure local colistin concentrations in drainage or synovial fluid [7]. Therefore, we could not compare the therapeutic range of local colistin use with plasma levels.

## Conclusion

A two-stage approach to TKA using a colistin-loaded articulating cement spacer can be used for an arthritic knee infected by vancomycin-resistant *P. aeruginosa*. Furthermore, local administration of colistin using a cement spacer can reduce the systemic side effects of colistin.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Human and animal rights disclosure** Every institution involved in this work has approved the human protocol for this investigation.

**Informed consent** Informed consent was obtained from the participants, and all investigations were conducted in conformity with ethical principles.

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