Complex prosthetic joint infections due to carbapenemase-producing *Klebsiella pneumoniae*: a unique challenge in the era of untreatable infections

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SUMMARY

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Objectives—Limited clinical experience exists regarding the management of prosthetic joint infection (PJI) due to multidrug-resistant (MDR) Gram-negative organisms. We review three cases of carbapenem-resistant Klebsiella pneumoniae (CRKP) complicating PJI.

Methods—This was a retrospective study of all patients at a tertiary care institution with CRKP complicating PJI between January 2007 and December 2010. Demographic data, procedures, organisms involved, length of stay, antibiotic treatments, and outcomes were collected. Antimicrobial susceptibility testing was performed on CRKP isolates, and the mechanism of resistance was ascertained by PCR.

Results—This analysis demonstrated that: (1) the CRKP possessed blaKPC and were difficult to eradicate (persistent) in PJI; (2) multiple surgeries and antibiotic courses were undertaken and patients required a prolonged length of stay; (3) resistance to colistin and amikacin emerged on therapy; (4) the same strain of CRKP may be responsible for relapse of infection; (5) significant morbidity and mortality resulted.

Conclusions—These cases highlight the opportunistic and chronic nature of CRKP in PJIs and the need for aggressive medical and surgical treatment. Further investigations of the management of CRKP PJI and new drug therapies for infections due to MDR Gram-negative organisms are urgently needed.

Keywords
Carbapenem-resistant Klebsiella; pneumoniae; K. pneumoniae carbapenemase (KPC); Multidrug-resistant organisms; Carbapenem-resistant Enterobacteriaceae; Prosthetic joint infection; Colistin

1. Introduction
Primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) are among the most common operations in orthopedic surgery, with nearly 800 000 THAs/TKAs performed annually in the USA.1 Demand for THA and TKA is projected to significantly increase in the next two decades.2–4 One of the most devastating complications of THA and TKA is infection of the prosthesis. Patients with prosthetic joint infection (PJI) demonstrate a greater morbidity, prolonged hospital stay, and incur additional costs of care when compared to their non-infected counterparts.5 An increase in the rates of THA and TKA revision, with infection playing a role in up to 15% of cases, is occurring.6,7 While the overall infection rates among primary arthroplasty are less than 2%, rates have increased significantly for revision arthroplasty surgery.7

Factors that are associated with PJI include rheumatoid arthritis (RA), underlying malignancy, use of corticosteroids, and increased body mass index (BMI); the highest rates of infection occur in patients with these risk factors undergoing THA.4 Staphylococcus aureus and coagulase-negative staphylococci (CoNS) are the most common causes of PJI. Currently, Gram-negative bacteria are responsible for a substantial proportion of PJI, ranging from 5% to 23% of cases, especially among the elderly. Both Gram-negative and Gram-positive bacteria have been associated with device-related biofilms, which protect the organisms from many antimicrobial agents and the host immune system.8 However, the clinical outcomes of PJI caused by Gram-negative bacteria are reportedly less favorable than
those of infection caused by Gram-positive bacteria.\textsuperscript{9–11} The emergence of resistance to antibiotics among Gram-negative bacteria that cause PJIs is also a major concern. The emergence of resistance to fluoroquinolones is linked to failure of open debridement and loss of the prosthesis.\textsuperscript{12}

In the past two decades, \textit{Klebsiella pneumoniae} has emerged as a multi- and extremely-drug resistant Gram-negative pathogen.\textsuperscript{13} Strains of \textit{K. pneumoniae} have acquired plasmids with myriad mechanisms of antibiotic resistance, such as \textit{qnr} against fluoroquinolones, 16S rRNA methylases against aminoglycosides, and, against cephalosporins and carbapenems, extended-spectrum beta-lactamases (ESBLs), New Delhi metallo-beta-lactamase (NDM), and \textit{K. pneumoniae} carbapenemase (KPC).\textsuperscript{14–17} Because of the paucity of antibiotic options to treat them, infections caused by carbapenem-resistant \textit{K. pneumoniae} (CRKP) pose a significant threat to our health care system. Vulnerable patients in acute and long-term care facilities experience bloodstream, respiratory, and urinary tract infections that often lead to unwanted outcomes.\textsuperscript{18–20} CRKP-related PJIs may be particularly complicated by the development of biofilms. Although CRKP biofilms have not been documented in PJIs, they have been associated with endoscopes.\textsuperscript{21} Thus, the combination of plasmid-acquired and biofilm-associated microbial resistance may explain the severe outcomes described here.

In this report, we recount our experience with three cases of CRKP-related PJI. This single institution case series illustrates the unique management challenges faced by clinicians and the adverse clinical outcomes experienced by patients in an era of potentially ‘untreatable infections’.\textsuperscript{22}

\section*{2. Materials and methods}

We conducted a retrospective study of all patients at a tertiary care institution (Cleveland Clinic Foundation, Cleveland, Ohio, USA) with CRKP isolated from cultures of clinical samples between January 2007 and December 2010. CRKP was defined as \textit{K. pneumoniae} isolates having a minimum inhibitory concentration (MIC) \(\geq\) 2 \(\mu\)g/ml against ertapenem, meropenem, or imipenem and a positive modified Hodge test (Clinical and Laboratory Standards Institute (CLSI) 2009). CRKP-related PJI were diagnosed if CRKP was recovered from intraoperative prosthetic joint and tissue specimens, synovial fluid culture, and/or from a sinus tract communicating with the prosthesis. Demographic data, type and number of procedures, involved organisms, hospitalization cost and length of stay, antibiotic treatments, and outcomes were ascertained for cases of CRKP-related PJI. Antimicrobial susceptibility testing was performed on CRKP isolates, including the following antibiotics: ciprofloxacin, amikacin, gentamicin, ceftazidime, piperacillin–tazobactam, doxycycline, tigecycline, and colistin.

The mechanism of carbapenem resistance was ascertained by PCR amplification of \textit{bla}_{KPC}, \textit{bla}_{NDM}, \textit{bla}_{VIM}, and \textit{bla}_{IMP}.\textsuperscript{14–17,19} Genetic similarity among CRKP strains was investigated by repetitive sequence-based PCR (rep-PCR) using the DiversiLab strain typing system (Bacterial BarCodes; bioMérieux) (as validated in Rice et al.\textsuperscript{14}). Isolates with >95\% similarity were considered of the same clonal type.\textsuperscript{16} Multilocus sequence typing (MLST) was performed on all CRKP strains as described by Diancourt et al.\textsuperscript{23} DNA sequences of...
seven housekeeping genes (rpoB, gapA, mdh, pgi, phoE, infB, and tonB) were compared with the MLST database (http://www.pasteur.fr/recherche/genopole/PF8/mlst/).

3. Results

Between the years 2007 and 2010, 221 patients were identified as having cultures of clinical samples with CRKP. Twenty-three (10.4%) patients with CRKP possessed a bone and joint-related infection. Three (1.3%) of these cases involved an infected orthopedic joint prosthesis. All cases occurred in patients with TKA, and in all cases CRKP were recovered as part of a polymicrobial or ‘complex’ infection. The initial pathogen was methicillin-susceptible S. aureus (MSSA) in two cases, whereas the other case was a polymicrobial infection with vancomycin-resistant enterococci (VRE), vancomycin-susceptible enterococci (VSE), and Proteus mirabilis. Demographic data, comorbidities, number of procedures, organisms involved, hospitalization cost (on one patient only) and length of stay, antibiotic treatments, and outcomes are summarized in Table 1.

A total of 10 CRKP isolates were saved from the three patients. Results of antimicrobial susceptibility testing of CRKP isolates from case 3 are presented in Table 2. Using validated PCR primers and controls, all CRKP isolates were determined to harbor blaKPC. Genetic typing with rep-PCR demonstrated a high percentage of similarity between isolates belonging to two of the patients (cases 1 and 2). Case 3 was infected with CRKP with a different rep-PCR pattern. However, the six CRKP isolates obtained from this patient were similar to each other (Figure 1). MLST revealed that all strains belonged to sequence type (ST) 258. Of note, ST258 and the rep-PCR strain types identified in these three cases were similar to the predominant CRKP strains in our institution (data not shown).

4. Case studies

4.1. Case 1

A 58-year-old male suffering from osteoarthritis and diabetes mellitus presented to the Cleveland Clinic with left knee pain and swelling, fever, and hypotension. Clinical evaluation indicated that the infection originated from an infected left TKA implanted 5 years earlier. Blood and synovial fluid cultures obtained upon admission grew methicillin-susceptible S. aureus (MSSA) (Table 1). Antibiotic treatment with intravenous (IV) oxacillin was started and a two-stage left knee revision arthroplasty was planned, with initial explanation of the prosthesis and placement of an antibiotic spacer. Two weeks after explantation and spacer placement, the patient had a wound infection due to Alcaligenes faecalis. The wound was debrided and antibiotics were changed to piperacillin–tazobactam resulting in a good initial response.

Two months later, the patient presented with wound dehiscence and cement exposure. Tissue cultures from the knee capsule grew CRKP (see Figure 1, case 1, isolate 1) and VRE. After left medial and lateral gastrocnemius muscle flaps, split thickness skin grafting, and exchange of the antibiotic spacer, he was started on IV daptomycin and oral doxycycline. Within 2 months of this last procedure he underwent another spacer exchange and radical knee debridement: he required patellectomy and quadriceps plasty with rotation of the
muscle into the open wound area. Purulence was present in the femoral and the tibial canals and in the posterior recesses of the joint. Intraoperative cultures were positive for CRKP, *Acinetobacter baumannii*, and *Candida parapsilosis*. He was discharged from the hospital on IV tigecycline and oral fluconazole only to be readmitted a week later with wound drainage, fever, and hypotension. Synovial fluid and blood cultures were still positive for CRKP. Despite left above-the-knee amputation, maximum medical support, and combined antibiotic therapy with IV colistin, amikacin, and tigecycline, the patient died on postoperative day 3.

His C-reactive protein (CRP) levels did not change significantly (26.7 mg/dl at the time of diagnosis, 24.6 mg/dl 24 h prior to death); his white blood cell count (WBC) decreased abnormally from $16.2 \times 10^9/l$ to $1.9 \times 10^9/l$ at the time of death.

### 4.2. Case 2

A 72-year-old male underwent left TKA for osteoarthritis, complicated 3 years later by a late PJI with development of a fistulous tract. The patient was treated with a two-stage revision with interval placement of an antibiotic spacer. Peri-articular soft tissue cultures obtained intraoperatively were positive for *Proteus mirabilis*, VRE, and VSE. Treatment with oral ciprofloxacin, linezolid, and rifampin were initiated. He was discharged to a skilled nursing facility. Eight weeks after the placement of the antibiotic spacer, he developed wound dehiscence and required re-revision and spacer exchange; intraoperative cultures were sterile. He was started on IV daptomycin and ciprofloxacin. Seven days later, the patient developed bacteremia with methicillin-resistant *S. aureus* (MRSA) and underwent evacuation of a hematoma and removal of the tissue expander. At this time, intraoperative cultures grew carbapenem-resistant *A. baumannii* and CRKP (see Figure 1, case 2, isolate 1). He was treated with IV vancomycin and tigecycline for 3 months, followed by oral doxycycline for 2 months.

Twelve months after the second revision surgery, the patient underwent re-implantation of the knee prosthesis. Intraoperative cultures were positive for MSSA, and he was treated with IV oxacillin. Three weeks postoperatively, he developed purulent wound drainage and wound cultures grew carbapenem-resistant *A. baumannii*, while synovial fluid from the knee grew CRKP (see Figure 1, case 2, isolate 2). He underwent synovectomy and polyethylene removal, and all prosthetic joint components were exchanged. After a second washout 1 week later, cultures remained positive for CRKP (see Figure 1, case 2, isolate 3). He completed an 8-week course of IV oxacillin and tigecycline and was placed on a long-term suppressive regimen with oral doxycycline. Unfortunately, the patient died 4 months later.

His CRP levels decreased from 2.4 mg/dl at the time of diagnosis to 0.4 at time of discharge. Likewise, his WBC decreased from $12.5 \times 10^9/l$ to $8.2 \times 10^9/l$ at the time of discharge.

### 4.3. Case 3

A 70-year-old female underwent right knee arthroplasty revision 1 month after a primary TKA, because of recurrent dislocation of the prosthesis. She had a history of rheumatoid arthritis treated with methotrexate and hydroxychloroquine. An area of purulence within the
subcutaneous tissue was noted during the surgical revision, although it did not track to the prosthesis. All hardware was removed, and an antibiotic-impregnated cement was placed. Intraoperative tissue cultures were positive for *Corynebacterium sp* and VSE. She received IV vancomycin for 6 weeks followed by TKA re-implantation. The postoperative period was complicated by multiple episodes of infection at the surgical site, which required wound debridement and wound therapy with negative-pressure. She was discharged to a skilled nursing facility.

Five months after the primary TKA, CRKP (see Figure 1, case 3, isolate 1) was isolated from the surgical wound and she underwent hardware explantation. Peri-articular tissue cultures also grew CRKP (see Figure 1, case 3, isolate 2). Initially, she was treated with IV tigecycline, but it was stopped due to nausea. Therapy with IV colistin was initiated, but was later discontinued due to circumoral paresthesias. The patient was again treated with IV tigecycline, but she developed drug-induced cholestasis and acute kidney injury. Therefore, antibiotics were held.

Two years after the primary TKA, she underwent a spacer exchange; intraoperative cultures remained positive for CRKP (see Figure 1, case 3, isolate 3), which was now resistant to amikacin. Despite treatment with IV tigecycline (which was tolerated well), a new lateral sinus tract developed requiring excision and spacer exchange. Tissue cultures, however, were negative.

Six months after the spacer was exchanged, a second revision was needed because the spacer fractured. She underwent a muscle flap from the left thigh to the right knee, which was complicated by wound failure requiring debridement and an infection in the wound from the donor area caused by *Streptococcus pneumoniae* and MRSA. She completed a course of IV tigecycline and vancomycin, followed by long-term oral ciprofloxacin and clindamycin.

Six months later, the spacer was removed and a distal femoral TKA was placed. Cultures were negative, although she had been empirically re-started on IV tigecycline before the surgery. On postoperative day 7, she developed partial dehiscence of the surgical wound and cultures grew CRKP, while cultures of the synovial fluid remained negative. Despite aggressive surgical debridement, the patient became septic requiring amputation above the right knee, followed by right hip disarticulation. Therapy with IV colistin was initiated, but changed to IV tigecycline and amikacin after development of acute kidney injury. Additionally, she required five subsequent wound debridements. Culture of tissue obtained from these procedures grew CRKP, eventually resistant to amikacin and colistin. Amikacin was replaced with ciprofloxacin, but CRKP (see Figure 1, case 3, isolate 6) persisted. As there were no signs of systemic infection, all antibiotics were discontinued. At 8-month follow-up, her surgical site appeared well-healed with no signs of infection.

Her CRP levels decreased significantly from 27.1 mg/dl at the time of diagnosis to 0.6 mg/dl 24 h prior to discharge; her WBC improved from $27.4 \times 10^9/\text{l}$ to $8.1 \times 10^9/\text{l}$ at the time of discharge.
5. Discussion

This unique case series serves to highlight the opportunistic, deleterious, and chronic nature of CRKP as a cause of PJI. In our series, CRKP PJIs exacted a tremendous cost in terms of morbidity, disability, health care expenses, and lost lives. Poor clinical outcomes occurred with CRKP PJI despite the implementation of intensive medical and surgical treatment regimens. Patients with multiple comorbidities may be mostly affected, and the MDR profile of the causative organisms may dramatically impact effective antibiotic therapy. A notable aspect of these cases was the persistence of CRKP, which also influenced length of stay and the need for recovery in post-acute care facilities. The sums of these factors lead us to conclude that CRKP PJIs are potentially incurable infections. In addition we found that: (1) CRKP was very difficult to eradicate (persistent) in PJI; (2) multiple surgeries and antibiotic courses need to be undertaken and patients require a prolonged length of stay; (3) resistance to ‘last line agents’ (colistin and amikacin) emerges on therapy; (4) the same strain of CRKP may be responsible for relapse of infection.

When compared to 19 previously reported Gram-negative PJIs with non-resistant strains, it is clear that CRKP-related infections are more severe. Specifically, the median duration of hospital stay was longer (101 days vs. 31 days), median WBC was higher (14.92 × 10⁹/l vs. 8.1 × 10⁹/l), and mortality was higher (67% vs. 5%) for patients with CRKP PJIs. Another case series of 31 patients with Gram-negative PJIs, reported that irrigation and debridement alone was successful in eradicating 70% of infections. This was in stark contrast to our CRKP patients, who underwent 10 or more procedures. Interestingly, all of the previously reported Gram-negative PJIs were monomicrobial, while CRKP arose at least 2 months after prosthetic infection with a different primary organism. Thus, early and adequate treatment of primary PJIs may help prevent CRKP adverse outcomes.

The steady increase in the rates of CRKP infections in the USA is worrisome. In 2007, up to 8% of all K. pneumoniae isolates reported to the US Centers for Disease Control and Prevention (CDC) were carbapenem-resistant (compared to less than 1% in 2000) due to the widespread dissemination of the K. pneumoniae carbapenemase (KPC) gene, blaKPC. Isolates of blaKPC-harboring CRKP responsible for PJI in this report belonged to ST258, the predominant lineage of KPC-harboring organisms in the USA and in other parts of the world. The factors underlying the success of this particular lineage or clonal group remain unclear, although its MDR profile likely confers a selective advantage in the setting of broad-spectrum antibiotic therapy.

These cases of PJI illustrate the potential for ST258 KPC-producing CRKP to cause persistent infection, as documented with the use of molecular typing techniques (Figure 1). The long duration of CRKP infection and colonization may create additional opportunities for its dissemination in the health care system. This may be of particular importance in long-term care facilities, which have emerged as ‘silent reservoirs’ of MDR organisms, and where it is more difficult to implement antimicrobial stewardship and infection control programs aimed at controlling CRKP.
The successful management of PIs depends on the combination of surgical and antibiotic therapy, through different approaches, including one-stage irrigation and debridement (with possible polyethylene exchange), two-stage revision procedure, and a hybrid modality with partial component exchange and retention of the prosthesis.\textsuperscript{29,30} The risk of failure of these different approaches is considerable and depends on the type of surgery performed. A case series of 53 first-time PI, secondary to Gram-negative organisms, reported a 2-year survival rate of 27% (95% confidence interval (CI) 16–34%) for debridement and retention of the prosthesis, 69% (95% CI 59%–84%) for resection arthroplasty, and 87% (95% CI 80–99%) for two-stage exchange.\textsuperscript{10} Ineffective antibiotic therapy may affect these outcomes, as demonstrated by treatment failures when prostheses are retained and organisms become resistant to fluoroquinolones.\textsuperscript{12} Of note, CRKP are often resistant to fluoroquinolones (as well as beta-lactams), leaving aminoglycosides, tigecycline, and polymyxins (chiefly in the form of colistin) as the only active antibiotics against this type of organism. Use of these agents may be limited by side effects and toxicity (gastrointestinal in the case of tigecycline, renal with aminoglycosides and polymyxins).\textsuperscript{31} Unfortunately, the doses of polymyxins that are commonly used to treat CRKP may lead to a relatively high rate of nephrotoxicity.\textsuperscript{32} Our series demonstrated that resistance to amikacin and colistin can also occur during the course of therapy. We note that in the case of amikacin resistance, we suspect that either horizontal gene transfer has occurred (acquisition of an aminoglycoside modifying enzyme on a mobile plasmid) or there has been up-regulation of an efflux pump. The mechanism of colistin resistance in \textit{K. pneumoniae} is not fully known, but likely does not involve a plasmid-mediated process.

In device-associated infections, it is possible that bacteria are enclosed in slime-forming biofilms.\textsuperscript{33} This complicates both treatment strategies to eradicate biofilms and diagnostics, as bacteria tend to conglomerate, lowering the culture yield. Sonication of the prosthesis could aid in higher culture results.\textsuperscript{34} Whether CRKP biofilm formation plays a role in the resilient nature of these infections is unknown.

Further complicating the treatment options for CRKP-related PI, pharmacologic studies suggest that the synovial fluid and bone distribution of the remaining active antibiotics against CRKP is limited. Aminoglycosides appear to be less active in synovial fluid and bone, perhaps because of the acidic environment of the synovial fluid.\textsuperscript{35} Reports also indicate that colistin distribution to bone is only between 15% and 25%.\textsuperscript{36} However, when used in combination with rifampin and imipenem,\textsuperscript{37} or with tigecycline,\textsuperscript{38} colistin has been reported to successfully treat MDR \textit{Pseudomonas aeruginosa}-related osteomyelitis.

Evidence exists suggesting that the outcomes of serious infections (e.g., bacteremias) caused by KPC-producing CRKP are improved with the use of combination therapy, either carbapenems in conjunction with tigecycline or with colistin,\textsuperscript{39} or tigecycline combined with colistin.\textsuperscript{40} Interestingly, tigecycline alone also seems to have poor distribution into the synovial fluid and bone. As shown in a report by Ji et al., the synovial and/or bone concentrations of tigecycline ranged from 31% to 41% of those found in the serum,\textsuperscript{41} which is typically below the MIC of most Gram-negative bacteria. One of the few antibiotics with consistent evidence of high bone penetration is fosfomycin (not available for intravenous use in the USA). Although the bone concentrations of fosfomycin may reach up to 43% of
the serum concentration, these concentrations are above the MIC of most bacteria.\textsuperscript{42} Fosfomycin retains excellent activity against contemporary KPC-producing CRKP isolates, and synergistic bactericidal activity against CRKP has been demonstrated between fosfomycin and carbapenems.\textsuperscript{43,44} Therefore, fosfomycin, administered as part of combination therapy, has the potential to become a preferred antibiotic for CRKP bone-related infections. However, the use of fosfomycin in CRKP PJI has yet to be validated by clinical experience.

In conclusion, the devastating effects of CRKP PJI and their almost intractable nature underscore the crisis precipitated by the emergence of multidrug-resistant Gram-negative organisms. That such infections can complicate TKA, an increasingly common procedure aimed at improving function in older adults with disability, should serve as a warning to health care professionals and the public. Efforts to prevent and control CRKP applied throughout the continuum of health care are justified to avoid this type of infection. The future availability of new drugs containing beta-lactamase inhibitors such as avibactam (formerly designated as NXL-104) may offer a reprieve against KPC-producing organisms, but would not overcome other carbapenemase types now circulating worldwide (e.g., NDM, VIM, or IMP metallo-beta-lactamases).\textsuperscript{45,46} In the meantime, the combined use of currently available antibiotics as part of the management of these uniquely challenging infections needs to be investigated further.

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Figure 1.
Dendrogram illustrating the results of molecular typing with rep-PCR of carbapenem-resistant *Klebsiella pneumoniae* isolated from three cases of prosthetic joint infection. Isolates obtained from cases 1 and 2 share >97% similarity, indicating that they belong to the same strain type. Isolates from case 3 belong to a different rep-PCR strain type, but are similar to each other.
Table 1
Characteristics and clinical outcomes of cases of prosthetic joint infection caused by carbapenem-resistant *Klebsiella pneumoniae*

| Variable                                    | Case 1                                                                 | Case 2                                                                 | Case 3                                                                 |
|---------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|
| Age (years), sex                            | 58, male                                                               | 72, male                                                               | 70, female                                                            |
| Comorbidities                               | Osteoarthritis, diabetes                                               | Osteoarthritis, coronary artery disease, congestive heart failure      | RA on immunosuppression with methotrexate and hydroxychloroquine     |
| Onset of first PJI (months from index surgery) | 60                                                                    | 36                                                                    | 1                                                                     |
| Primary organism PJI                        | MSSA                                                                   | VSE, VRE, *Proteus mirabilis*                                          | *Corynebacterium* sp and VSE                                         |
| Onset of CRKP PJI (months from first PJI)   | 2                                                                     | 2                                                                     | 5                                                                     |
| Number of procedures (n)                    | 10                                                                    | 12                                                                    | 57                                                                    |
| Antibiotics                                 | Oxacillin; piperacillin–tazobactam; daptomycin and oral doxycycline; tigecycline and flucloxacil; colistin, amikacin, and tigecycline | Ciprofloxacin, linezolid, and rifampin; daptomycin and ciprofloxacin; vancomycin and tigecycline → doxycycline; oxacillin, oxacillin and tigecycline → doxycycline | Vancomycin; tigecycline; colistin; tigecycline; tigecycline; tigecycline and vancomycin → oral ciprofloxacin and clindamycin; tigecycline; colistin; tigecycline, and amikacin; ciprofloxacin |
| WBC ×10⁹/l (median (IQR))                  | 9.07 (0.63, 12.49)                                                    | 8.45 (7.73, 9.75)                                                     | 8.92 (7.40, 11.68)                                                   |
| Hospital LOS (days)                         | 51                                                                    | 101                                                                   | 225                                                                   |
| Hospitalization costs ($)                   | N/A                                                                   | N/A                                                                   | 850 000                                                              |
| Functional status                           | Above-the-knee amputation                                              | Full                                                                  | Disarticulated                                                       |
| Outcomes                                    | Died                                                                  | Died                                                                  | Alive with major disability                                          |

RA, rheumatoid arthritis; PJI, prosthetic joint infection; MSSA, methicillin-susceptible *Staphylococcus aureus*; VSE, vancomycin-susceptible *Enterococcus sp*; VRE, vancomycin-resistant *Enterococcus sp*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; WBC, white blood cell count; IQR, interquartile range; LOS, length of stay; N/A, not available.
Table 2

Antimicrobial susceptibility testing of carbapenem-resistant *Klebsiella pneumoniae* isolates from prosthetic joint infections

| Antibiotics | Case 3, isolate 1 MIC (in μg/ml) and interpretation | Case 3, isolate 6 MIC (in μg/ml) and interpretation |
|-------------|-----------------------------------------------------|-----------------------------------------------------|
| Amikacin    | 4 S                                                  | >64 R                                               |
| Colistin    | <2 S                                                 | >8 R                                                 |
| Gentamicin  | >16 R                                                | >16 R                                               |
| Tigecycline | 1 S                                                  | 1 S                                                  |
| Tobramycin  | >16 R                                                | >16 R                                               |
| Imipenem    | >16 R                                                | >16 R                                               |

MIC, minimum inhibitory concentration; S, susceptible; R, resistant.