Musculoskeletal infections associated with *Citrobacter koseri*

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ABSTRACT

INTRODUCTION *Citrobacter koseri* is a well known cause of central nervous system infections in the paediatric setting. Musculoskeletal infections caused by *C koseri* are rare, with only 14 previously reported cases. We present the first recorded case of *C koseri* induced septic arthritis of the knee along with a review of the literature.

METHODS A search of the PubMed, Embase® and Google Scholar™ databases was undertaken. Only complete or near complete cases were reviewed.

FINDINGS Fourteen musculoskeletal infections were identified. Of these, five were associated with an operative procedure and five involved a septic joint. Surgical treatment was required in the majority of cases and cure was achieved in all cases following prolonged antibiotic use.

CONCLUSIONS *C koseri* associated musculoskeletal infections may complicate primary orthopaedic procedures. The organism can present aggressively and can be difficult to identify microbiologically. It is sensitive to newer generation beta-lactams, cephalosporin-based antibiotics and timely surgery.

KEYWORDS

Citrobacter koseri – Septic arthritis – Arthroscopy – Periprosthetic infection

Accepted 20 May 2016

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Infection is the most common complication following knee arthroscopy, occurring in approximately 0.85% of all procedures.¹ *Staphylococcus* spp are the predominant cause, especially methicillin resistant *Staphylococcus aureus* (MRSA).² Gram-negative organisms are cultured in up to 20% of patients with bacterial septic arthritis, and are seen primarily in children, the elderly, immunosuppressed individuals and intravenous drug users.² Gonococcal organisms are now a less common cause of septic arthritis in Europe and North America.³ Rarer organisms have been known to cause septic arthritis but only five previous cases have involved *Citrobacter koseri*.

Citrobacter spp are commonly found in the environment and the intestinal tracts of mammals.⁵ *Citrobacter freundii* and *C koseri* are the leading cause of human disease, and occur typically in the hospital setting.⁴ *C koseri* is a known cause of neonatal meningitis and brain abscess.⁵ However, infections of the musculoskeletal system are exceedingly rare. In addition to a review of musculoskeletal infections caused by *C koseri*, we present the first case of *C koseri* induced septic arthritis of the knee.

Case history

A 72-year-old avid golfer presented to the emergency department complaining of right knee pain. He was referred

by his general practitioner with a progressively worsening three-week history of knee inflammation following arthroscopy. On examination, his knee was grossly swollen with a marked effusion, warm and painful on palpation. The knee was held at 30° of flexion with under 10° of movement in either direction. He had been unable to bear weight for the preceding 7–10 days and a pitting oedema of the leg had begun to develop.

The patient's medical history was relatively unremarkable, with a 30-year history of well controlled gout and a recent diagnosis of hypercholesterolaemia, for which he took allopurinol and simvastatin. He had undergone an arthroscopic meniscectomy three weeks prior to his presentation, which was completed successfully. His recovery had been unremarkable up until one week following the procedure, when his knee gradually showed signs of infection, for which his general practitioner prescribed oral flucloxacillin 500mg four times daily and co-codamol (8 days before his presentation to the emergency department) with minimal effect. Blood tests taken on admission revealed elevated C-reactive protein of 218mg/l but no other significant abnormalities on either haematology or biochemistry. Knee radiography on admission demonstrated only mild osteoarthritic changes. Knee aspiration was performed and the sample sent for Gram staining, which yielded negative results.

Less than 24 hours following his emergency admission, the patient underwent an arthroscopic washout of his right knee with immediate relief of symptoms. Intraoperative samples were sent for culture, and he was started on non-steroidal anti-inflammatory drugs and intravenous antibiotics (flucloxacillin 4g daily). Passive motion exercises to the right knee were continued. Two weeks following surgery, the knee was again inflamed and the patient was unable to bear weight. As a consequence, the flucloxacillin dose was increased to 8g daily and a second arthroscopic knee washout was performed. It was during this period that extended culture results from the initial knee aspiration and arthroscopy indicated septic arthritis due to *C. koseri*. The patient was subsequently started on four weeks of intravenous ertapenem with a subsequent rapid improvement and full recovery.

Methods

A search of the PubMed, Embase® and Google Scholar™ databases was undertaken (from the year of their establishment to October 2015) using combinations of the following search terms: 'Citrobacter', 'diversus', 'koseri', 'septic arthritis', 'osteomyelitis', 'bone', 'joint' and 'infection'. Relevant results included both singular cases presented alone and sufficiently described cases reported as part of a larger cohort. The full text and reference lists of articles were reviewed for any additional publications that could have been missed during the database search.

Findings

Septic arthritis is an infection of a joint caused most commonly by bacteria, especially *Neisseria gonorrhoeae*, *S. aureus* and the *Streptococcus* genus.⁶ *N. gonorrhoeae* is responsible for the majority of cases in young, sexually active patients while the majority of the remaining cases occur in the immunocompromised and those with an artificial joint.⁶⁻⁹

Diagnosis is clinical but aided by routine laboratory tests and joint aspiration for Gram staining and culture. Radiology for assessment of joint and bony integrity may occasionally be required but is of limited value.⁶⁻⁹ Confirming the diagnosis of periprosthetic infections is more challenging given the clinical implications and chronicity of the disease but recent advances with the use of synovial fluid biomarkers may improve the process.¹⁰ Treatment consists of urgent intravenous antibiotics, and rapid joint drainage and washout.^{7,8} In cases where septic arthritis develops following joint arthroplasty, the entire prosthesis should be removed and time allowed for the infection to settle prior to revision surgery.⁷⁻⁹

C. koseri is a non-sporulating, aerobic, Gram-negative bacilli of the Enterobacteriaceae family. Belonging to this genus are *C. freundii* and *C. koseri*, which account for the majority of human illness.^{4,11} They are frequently found in soil, water and as part of the normal gastrointestinal and

genitourinary flora of many animal species (including our own).^{4,5,11,12} Over 70% of *Citrobacter* infections are nosocomial and they are frequently associated with invasive procedures.⁴ As a group, they most commonly infect the urinary and digestive tracts in immunocompromised individuals but are rarely involved in infections of the musculoskeletal (MSK) system.^{3-5,11,15,14} *C. koseri* is a well known cause of severe central nervous system infections in neonates, where it is fatal in 30% and permanently debilitating in as many as 80% of those afflicted.¹⁵⁻¹⁸

MSK infections secondary to *C. koseri* are exceedingly rare, with only 14 previously reported cases identified since the 1980s (Table 1).^{12,15,16,19-28} Only five of these involved septic arthritis,^{16,19,20,26,27} with two of these pertaining to artificial joints.^{26,27} The first two reported cases with septic arthritis occurred in middle aged men with a history of alcoholism.^{19,20} In both cases, treatment required drainage and prolonged antibiotics for 6-8 weeks.

In the third case, a three-week-old neonate developed a septic glenohumeral joint with associated osteomyelitis two weeks after sustaining a growth plate fracture of the ipsilateral humerus.¹⁶ The infant was managed with urgent surgical debridement and targeted antibiotics following *C. koseri* positive culture results. Despite over 20 days of antibiotics and major surgery, the child recovered well with few sequelae at 14 months of age.

The remaining two septic arthritis cases occurred following arthroplasty and both required replacement of prostheses.^{26,27} The first of these involved a shoulder prosthesis that was inserted secondary to trauma and was reported as part of a larger series looking at removal of infected prostheses.²⁶ The infection was chronic in nature, requiring three months of antibiotic therapy. The more recent case occurred following primary hip arthroplasty.²⁷ The patient presented approximately three weeks following surgery with elevated inflammatory markers and clinical manifestations of sepsis. As in our case, he was treated successfully with ertapenem, along with an exchange of the prosthetic head and liner.

The remaining nine MSK cases consisted of osteomyelitis, predominantly in the foot^{12,21,22,28} and vertebral column.²⁵⁻²⁵ Perhaps not surprisingly, the organism favours the extremes of age and 'at risk' or immunocompromised groups,^{16,21-25} with diabetes mellitus and peripheral vascular disease posing a significant risk for the development of pedal osteomyelitis.

In total, five of the previously reported cases of *C. koseri* MSK infections were associated with an operative procedure and three involved an implanted device (Table 1). Other MSK infections involving the organism have been reported as part of larger cohorts with little individual case detail.^{4,29} The organism can be difficult to detect, which means that samples taken for microbiological analysis frequently take prolonged periods of time to be reported positive and it may appear in combination with a variety of other organisms.^{12,21,22,27} *C. koseri* bacteraemia may itself predispose to other, polymicrobial infections,⁴ adding to its overall risk profile. Antibiotics alone are unlikely to be effective; resistance to penicillins is

Table 1 Summary of *Citrobacter koseri* musculoskeletal infections. All cases were cured.

Reference	Age in years	Site	Type of infection	Co-morbidities	Antibiotics (duration in weeks)*	Surgery	Cultures**
Lipsky, 1980 ¹²	59	Foot	Osteomyelitis	DM, PVD	Cefazolin (NA)	Amputation	<i>C koseri</i>
Lipsky, 1980 ¹²	54	Foot	Osteomyelitis	DM, BPD	Erythromycin + cefazolin + meticillin (NA)	Amputation	<i>S aureus</i> , <i>S agalactiae</i> , <i>C koseri</i>
Jansen, 1981 ¹⁵	Neonate	Proximal tibia	Osteomyelitis	Intrapartum asphyxia	Cefamandole + gentamicin (6)	Nil	<i>C koseri</i>
Holt, 1981 ¹⁹	47	Sternoclavicular joint	Septic arthritis, osteomyelitis	Hypoproteinaemia, alcoholism	Moxalactam (6), followed by cefradine (8)	Spontaneous drainage	<i>C koseri</i>
Fuxench-Chiesa, 1983 ²⁰	45	Sternoclavicular joint	Septic arthritis, osteomyelitis	Alcoholism	Moxalactam (6)	Open drainage	<i>C koseri</i>
Boberg, 1984 ²¹	45	Foot (surgical site infection)	Osteomyelitis	HTN, hypothyroidism	Cefotaxime (2), followed by cefalexin (2)	Resection of 4th metatarsal head	<i>C koseri</i>
Simons, 1985 ²²	70	Foot	Osteomyelitis	NA	Aztreonam (4)	Debridement	<i>C koseri</i> , <i>S aureus</i>
Müller, 1992 ²³	74	Lumbar vertebrae ^a	Osteomyelitis	Pneumonia, OA, AF, cholelithiasis, GORD, smoker	Ofloxacin (3), followed by ciprofloxacin (2)	Debridement	<i>C koseri</i> , <i>K pneumoniae</i> , <i>S epidermidis</i>
Sotto, 1994 ²⁴	72	Cervical vertebrae and disc	Discitis, osteomyelitis	Angina, HTN, recent prostatectomy	Amikacin (3) + imipenem (11)	Percutaneous drainage	<i>C koseri</i>
Hayani, 1997 ¹⁶	Neonate	Glenohumeral joint	Septic arthritis, osteomyelitis	Proximal humerus fracture	Gentamicin + ceftioxone (3)	Debridement	<i>C koseri</i>
Canario, 2004 ²⁵	42	Vertebrae, psoas muscle	Osteomyelitis, abscess	TB, infected metalwork	Levofloxacin (>4) ^b	Laminectomy, drainage and metal removal	<i>C koseri</i>
Maynou, 2006 ²⁶	54	Shoulder prosthesis ^c	Septic arthritis	NA	NA (12)	Prosthesis resection	<i>C koseri</i>
Kaufman, 2011 ²⁷	53	Hip prosthesis	Septic arthritis	DM, gout, obesity, HTN	Ertapenem (6)	Debridement, prosthesis exchange	<i>C koseri</i>
Yagci, 2011 ²⁸	68	Foot	Osteomyelitis	DM, PVD	Piperacillin/tazobactam (3), followed by moxifloxacin (3)	Debridement	<i>E coli</i> , <i>C koseri</i>
Present case	72	Knee	Septic arthritis	Gout, hypercholesterolaemia	Ertapenem (4)	Arthroscopic washout	<i>C koseri</i>

AF = atrial fibrillation; BPD = bronchopulmonary dysplasia; DM = diabetes mellitus; GORD = gastro-oesophageal reflux; HTN = hypertension; NA = not available; OA = osteoarthritis; PVD = peripheral vascular disease; TB = tuberculosis

*The duration of antibiotic treatment has been rounded to the nearest week.

**Cases reported as *C diversus* have been listed as *C koseri*.

^aCase consisted of two admissions; ^bPatient treated with 4 weeks of oral levofloxacin in addition to an undefined period of parenteral treatment; ^cLimited information available as case reported within a wider series

common^{4,29} and there are some reports of resistance to newer antibiotics.²⁴

Conclusions

C. koseri poses a significant risk following orthopaedic procedures, in particular arthroplasty surgery, with two of the most recently reported joint infections occurring following such procedures. There can be a delay in diagnosis and multiple samples may be required before the organism is identified microbiologically. Despite the aggressive nature of *C. koseri* MSK infections, with rapid diagnosis the organism responds well to newer beta-lactam and cephalosporin-based antibiotics as well as timely surgery. Health workers involved in the care of orthopaedic patients with suspected surgical site infections should be vigilant for *C. koseri* as a potential causative organism.

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