

Clostridioides difficile Bacteraemia and Septic Arthritis in a Sickle Cell Disease Patient

Moayad Alqurashi¹, Badr Madani², Mohamed Mursi¹, Nazik Eltayeb¹

¹Division of Adult Infectious Diseases, Department of Medicine, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

²Department of Family and Community Medicine, College of Medicine, University of Jeddah, Jeddah, Saudi Arabia

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ABSTRACT

Extra-colonic *Clostridioides difficile* infection is rare. Here we describe a sickle cell disease patient with avascular necrosis who presented with persistent bacteraemia due to *C. difficile* and septic arthritis in a native knee joint, which responded very well to medical and surgical treatment but recurred multiple times within weeks of the cessation of antibiotics.

LEARNING POINTS

- *Clostridioides difficile* can rarely have a wide variety of extra-colonic manifestations.
- Patients with sickle cell disease may have a higher predisposition to extra-colonic *C. difficile* infection (CDI) with high mortality and recurrence rates.
- Intravenous metronidazole or vancomycin are the most widely used treatments for extra-colonic CDI.

KEYWORDS

Clostridioides difficile, anaerobic bacteraemia, septic arthritis, pyogenic arthritis, sickle cell disease

INTRODUCTION

Anaerobic bacteraemia is identified in less than 13% of all positive blood cultures^[1]. *Clostridioides difficile* (formerly *Clostridium difficile*) is a spore-forming Gram-positive bacillus that is strictly anaerobic^[2]. The usual presentation of toxigenic strains includes antibiotic-associated diarrhoea and pseudomembranous colitis^[2]. Unusually, *C. difficile* can have extra-colonic manifestations that include appendicitis, spleen and liver abscesses, visceral abscess, scrotal abscess, cranial abscess, bone infection, prosthetic and periprosthetic joint infections, mycotic aneurysm, pericarditis and infective endocarditis, empyema and a spectrum of skin and soft tissue infections like cellulitis, vaginal abscess, perineal abscess and necrotizing fasciitis^[3-6].

Here we describe a case of extra-colonic *C. difficile* infection (CDI) presenting as bacteraemia with septic arthritis in a sickle cell disease (SCD) patient.

CASE DESCRIPTION

A 21-year-old woman known to have SCD presented to the emergency room (ER) in January 2020 with a 4-day history of constant right knee pain and progressive swelling. She denied any history of fever, nausea or vomiting, diarrhoea or dysuria. Physical examination showed normal vital signs initially with a swollen, tender right knee all over the joint along with limitation of movement on passive and active motion.

She also had weakness along her left side due to residual hemiparesis from a stroke 10 years previously. She had received a short course of ciprofloxacin 5 months before this presentation for a presumed urinary tract infection. However, she had not developed diarrhoea or abdominal pain since and had never been diagnosed with CDI or pseudomembranous colitis.

Initial investigation results are presented in *Table 1*. A right knee x-ray showed narrowing of the joint space (*Fig. 1*), while knee ultrasound showed a large effusion, synovial hypertrophy with debris and hyperaemia suggestive of septic arthritis (*Fig. 2*). Magnetic resonance imaging revealed a large amount of effusion on the right knee joint in addition to osteonecrosis and avascular necrosis (AVN) (*Fig. 3*).

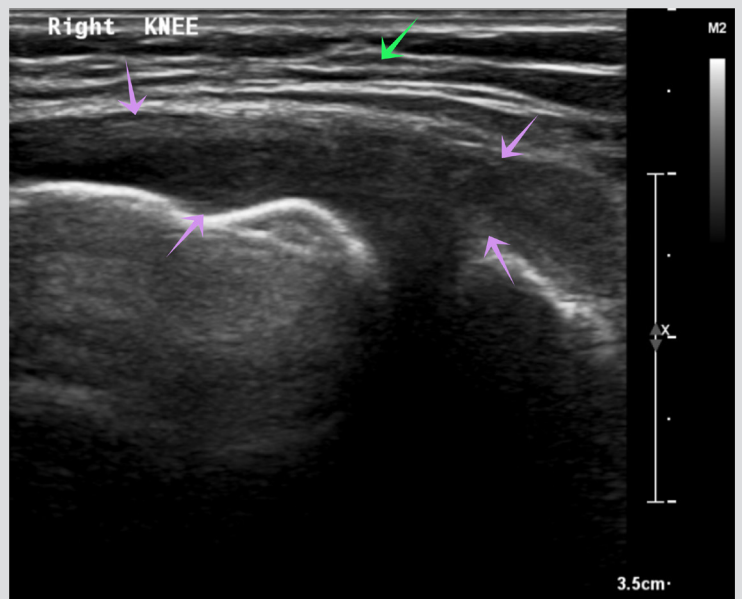


Figure 1. Right knee x-ray. Anterior-posterior view of the right knee showing narrowing of the knee joint space

Figure 2. Right knee ultrasound. Right knee ultrasound showing large joint effusion (purple arrows) and hyperaemia with debris (green arrow) suggestive of septic arthritis

Figure 3. Right knee magnetic resonance imaging. Right knee MRI with evidence of large joint effusion (yellow arrows), subcutaneous oedema (red arrow), and evidence of osteonecrosis and avascular necrosis of the femur (blue arrow)



Initial investigations			
Test	Result	Test	Result
WBC	9.7 K/ μ l	ALT	7 U/l
Hgb	4.8 g/dl	Creatinine	61 μ mol/l
Reticulocytes	10.6%	CRP	163 mg/l
PLT	731 K/ μ l	PCT	0.32 ng/ml
Total bilirubin	23 μ mol/l	<i>Clostridioides difficile</i> stool screening (GDH)	Negative (normal stool consistency)
Blood culture: <i>C. difficile</i>			
Antibiotic	Interpretation* (MIC**)	Antibiotic	Interpretation* (MIC**)
Ceftriaxone	Susceptible (12 μ g/ml)	Penicillin	Susceptible (0.50 μ g/ml)
Meropenem	Susceptible (1.50 μ g/ml)	Metronidazole	Susceptible (0.04 μ g/ml)

Table 1. Initial investigations and antibiotic susceptibilities

* As per the CLSI breakpoints.

** Calculated using the Epsilometer test (E-test; bioMérieux, Marcy l'Étoile, France)

ALT: alanine transaminase, CRP: C-reactive protein, GDH: glutamate dehydrogenase, Hgb: haemoglobin, PCT: procalcitonin, PLT: platelets, WBC: white blood cells.

With a presumed diagnosis of septic arthritis and vaso-occlusive painful crisis, the patient was admitted and given intravenous fluids and pain killers. She was also started on empirical antimicrobials, including piperacillin/tazobactam and vancomycin (VA) intravenously (IV). Three days after admission, she developed a high-grade fever reaching up to 39°C that was associated with chills. Joint aspiration fluid was purulent and bloody (confirming the diagnosis of septic arthritis), but the amount was insufficient for a cell count and analysis. Synovial cultures (aerobic and anaerobic) were negative for bacteria even after enrichment (probably because it was done a few days after antimicrobials were started) (Fig. 4).

Gram staining was not done. Blood cultures grew a Gram-positive bacillus from anaerobic vials in less than 24 hours for 3 consecutive days (four vials), which was identified as *C. difficile*. This result was confirmed using MALDI-TOF (Bruker MALDI Biotyper, Bruker Daltonik, Germany). Antimicrobial susceptibility testing was done using the Epsilometer test (E-test, bioMérieux, Marcy l'Étoile, France) (Table 1). VA was replaced with metronidazole (MZ) and ceftriaxone IV. Bacteraemia resolved on the third day, so ceftriaxone was stopped and the patient continued on IV MZ alone for a total of 18 days from the first negative blood culture followed by 3 weeks of oral MZ.

Unfortunately, the patient's symptoms recurred 6 weeks after discharge (2 weeks after she stopped her antimicrobial course); she was not compliant with the prescribed treatment. She was treated with another course of antimicrobials and three consecutive joint irrigations and debridement, but no organisms could be cultured from blood, purulent synovial fluid or intraoperative tissue from the knee. Intra-operative tissue samples were not sent for histopathological examination. The patient responded positively to the combined surgical and antimicrobial treatment and was discharged home in a stable condition. However, approximately 1 month after completing antimicrobial treatment, she experienced a third episode of possible septic arthritis. She visited our ER, where she, unfortunately, refused any further investigations or surgical interventions and left the hospital against medical advice and has been lost to follow-up since.

Timeline of Events - First Episode

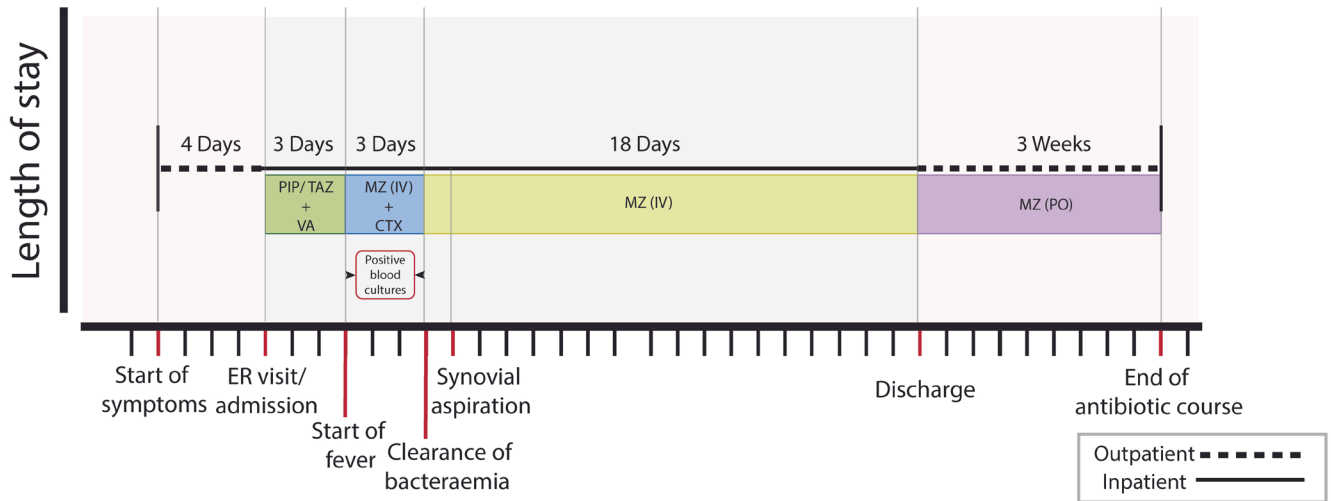


Figure 4. Timeline of events: first episode. Timeline of events showing the events of the first episode that started with symptoms at home followed by hospital admission through ER and empirical start of antibiotics, timing of the start of fever, the period of positive blood cultures, timing of blood culture clearance, timing of synovial aspiration, start of targeted therapy until discharge and the period at home after discharge until stopping antibiotics.

CTX: ceftriaxone, ER: emergency room, IV: intravenous, MZ: metronidazole, PIP/TAZ: piperacillin/tazobactam, PO: per os, VA: vancomycin

DISCUSSION

Antimicrobial use and advanced age combined with multiple comorbid conditions including liver cirrhosis, heart disease, pulmonary disease, chronic dialysis and immunocompromised status, are among the most common risk factors for CDI in general [2], while malignancy has been observed to be a possible risk factor for extra-colonic CDI specifically [7]. On the other hand, risk factors for septic arthritis, in general, include joint factors that act as a nidus for the infection to develop such as pre-existing joint disease, joint surgery or the presence of a prosthetic joint, while host factors include old age, skin infection and immunocompromised status [8]. Multiple cases of reactive and septic arthritis associated with CDI from prosthetic and native large joints have been reported in the literature [2,8]. Interestingly, native joint septic arthritis due to CDI has been almost exclusively reported in SCD patient who also had confirmed *C. difficile* bacteraemia or evidence of possible bacteraemia with sterile cultures primarily due to prior use of antimicrobials [8].

Although specific ribotypes and the secretion of certain toxins have been associated with *C. difficile*-associated diarrhoea and *C. difficile* colitis, this association has not been found in extra-colonic CDI [2,7]; in fact, non-toxigenic strains of *C. difficile* tend to be detected more frequently in extra-colonic CDIs [4,8]. It has been noticed that extra-colonic CDI is mostly polymicrobial where *C. difficile* is thought to enhance other bacteria but can also be the only detected pathogen [4].

Unlike *C. difficile* colitis, there are no guidelines for the treatment or duration of treatment for extra-colonic CDI [7]. There are also significant gaps in the knowledge required for developing such guidelines, like pharmacokinetic/pharmacodynamic studies for anti-*C. difficile* antimicrobial parameters in different extra-colonic tissues and precise interpretation of breakpoints for antimicrobials by the CLSI and or EUCAST committees for the most frequently used antimicrobials in CDI [7]. The most frequently used antimicrobials for extra-colonic CDI in the literature include MZ and VA or both with variable response rates, high recurrence rates and mortality [7]. Surgical intervention has been necessary to treat some of the reported cases [7]. Faecal microbiota transplantation has been observed to improve arthritis due to psoriasis and probably other types of immune-mediated arthritis [9].

In our patient, the clinical presentation together with the risk factors strongly suggest septic arthritis type B according to the modified Newman's criteria [10]. The link between *C. difficile* bacteraemia and septic arthritis in this patient could be confirmed if it were possible to perform advanced molecular sequencing from the purulent fluid aspirated from the joint, but unfortunately this technique is not yet available for clinical use outside of advanced research laboratories.

The association between SCD and extra-colonic CDI (septic arthritis with or without bacteraemia specifically) should be considered when treating similar patients, especially if they have been exposed to multiple antimicrobials which decrease the yield of the cultures leading to diagnostic dilemmas.

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APPENDIX

DISCUSSION

Although the adjusted estimated total burden and the healthcare-associated burden of *Clostridioides difficile* infection (CDI) in the USA decreased by 24% and 36%, respectively, from 2011 to 2017, prevention of CDI is still a national priority^[1], as it is now the most common nosocomial infection in the USA after surpassing methicillin-resistant *Staphylococcus aureus*^[2]. Retrospectively, the incidence of extra-colonic CDI has been estimated at 0.58% in one study^[3], but there have been no nationwide incidence studies to assess the burden of CDI in general in Saudi Arabia^[4, 5]. An effort was made to calculate the prevalence that was estimated to be between 13.6% and 21.7% in two of the country's western cities^[6], while a multicentre study from the eastern region of Saudi Arabia estimated the prevalence at 23.5%^[4]. On the other hand, the incidence was estimated at 5.2%, 8.4% and 10% in the eastern, western area and central areas, respectively^[5]. These studies had different protocols for detection, which might have contributed to the discrepancy in incidence and prevalence^[4-6]. It is worth mentioning that the most hypervirulent strain of *C. difficile*, the North American pulsed-field gel electrophoresis type 1, restriction endonuclease analysis type B1, polymerase chain reaction ribotype 027 (NAP1/B1/027), or ribotype 027 for short, has been detected in Saudi Arabia many times^[5].

Extra-colonic CDIs have been mostly observed after gastrointestinal (GI) disease (CDI colitis or surgical/anatomical damage to the colon mucosa)^[7], but can present without any GI disease^[3, 8, 9]. A wide variety of possible presentations has been hypothesized to occur due to contiguous transmission after gastrointestinal surgery, transient bacteraemia, translocation from the colon, or possibly through environmental contamination with *C. difficile* spores^[10]. It has been observed that *C. difficile* testing from stool is negative in more than 50% of extra-colonic CDIs, which has been thought to be due to the inability of the standardized clinical method of detection to detect a very low bacterial load that is mostly colonizing the colon; the possible detection of *C. difficile* from samples taken from the skin and environment around patients with extra-colonic CDI supports this hypothesis^[10]. Other extra-colonic presentations related to CDI but not due to the bacterium itself include reactive arthritis or haemolytic-uraemic syndrome, which has been attributed to interruption of immunological tolerance during antigen presentation, especially in patients with underlying HLA-B27 status^[11].

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