**CASE**

A 22-year-old female with sickle cell disease presented with fevers, bilateral knee pain, and lethargy. Laboratory data revealed a leukocytosis and lactic acidosis. Blood and synovial fluid cultures grew a non-toxin-producing strain of *Clostridium difficile*. This case highlights the fact that nontoxigenic *Clostridium difficile* can cause significant disease.

**Keywords.** bacteremia; *Clostridium difficile*; hemoglobin SS disease; septic arthritis; sickle cell disease.
nontoxicigenic strains. As a result, this isolate had no amplification for the tcdC-encoding gene. PCR ribotyping confirmed that the isolate was Ribotype 039. The isolate was sent to ARUP laboratories for a cytotoxin cell assay, which provided confirmation that, phenotypically, no toxin was being produced.

DISCUSSION

The genus *Clostridium* comprises obligately anaerobic (or occasionally aerotolerant), Gram-positive rods. *C. difficile* causes symptoms ranging from mild self-limiting diarrhea to the development of full-scale pseudomembranous colitis [1]. Extra-intestinal *C. difficile* infections account for less than 0.2% of all *C. difficile* infections [2]. *C. difficile* bacteremia is even more uncommon and is generally part of a polymicrobial bacteremia involving other intestinal flora [2]. A recent literature review identified only 44 cases of *C. difficile* bacteremia between 1962 and 2015 [2]. Moreover, while review of the literature describes postinfectious sterile inflammatory arthritis as a complication of gastrointestinal *C. difficile* infection [3–5], cases of septic arthritis due to the organism itself are rare (Table 1). When it does occur, the majority of published septic arthritis cases [3, 6] involve prosthetic joints [7–12]. Review of the literature yielded only 1 case report of native large joint septic arthritis in an 11-year-old boy, also with Hemoglobin SS disease, who experienced right-sided shoulder discomfort and was found to be bacteremic with *C. difficile* despite having no gastrointestinal symptoms [13]. This publication did not describe ribotyping on the bacterial isolate in that case to assess for toxin production.

*C. difficile* diagnostic assays are designed to detect the absence or presence of organisms or toxins in patient fecal samples. However, these tests are unable to differentiate asymptomatic carriers from those patients with veritable disease. The majority of clinical laboratories utilize Food and Drug Administration–approved molecular tests that detect genes encoding *C. difficile* toxins. These nucleic acid amplification tests are rapid and highly sensitive, yet the positive predictive value can be low if the test is not ordered in the appropriate clinical context. The ProGastro Cd test (Prodesse, Waukesha, WI) and the GeneOhm Cdiff assay (BD Diagnostics, San Diego, CA) target toxin B (tcdB), while the Xpert *C. difficile* test (Cepheid) is a multiplex assay that amplifies 2 genes, tcdB and a gene that regulates toxin production (tcdC). In addition, multiplex gastrointestinal panels such as BioFire FilmArray (Biomerieux, Inc., Durham, NC) include a *C. difficile* toxin gene as one of its targets. Less expensive, less sensitive membrane enzyme immunoassays like the C. DIFF QUIK CHEK COMPLETE (Alere North America, LLC, Orlando, FL) have been used in some laboratories as screening tests before performing the molecular tests. In addition to assaying for toxins A and B in fecal samples, the test detects *C. difficile* antigen, glutamate dehydrogenase, as a screen for the presence of *C. difficile* in the stool. Clinicians may attempt to recover *C. difficile* from clinical samples, also called toxigenic culture, but the process is laborious and time consuming, requiring multiple days for isolation and identification. If isolates are recovered, whole-genome sequencing and ribotyping may be performed using research-only assays.

Only strains that carry the pathogenicity locus (PaLoc) possess the genetic information for the *C. difficile* enterotoxin, TcdA, and the cytotoxin, TcdB. Historically, only strains producing TcdA and/or TcdB were thought to cause *C. difficile* infection [1]. Outbreaks with more virulent strains such as B1/NAP1/027 and ribotype78 are associated with significant mortality [14, 15]. This case highlights that a non-toxin-producing isolate can be responsible for severe extra-intestinal disease due to *C. difficile*.

### Table 1. Review of Cases of Septic Arthritis due to *C. difficile*

| Case No. | Ref | Year | Sex | Age | Joint | Prosthetic | Comorbid Conditions | Diarrhea | C. difficile Bacteremia | C. difficile Therapy | Surgical Intervention | Outcome |
|----------|-----|------|-----|-----|-------|------------|---------------------|----------|------------------------|---------------------|---------------------|---------|
| 1        | 13  | 1994 | F   | 31  | Hip    | Yes        | Sickle cell disease | No       | No                     | Metronidazole       | Incision and drainage | Died    |
| 2        | 8   | 1995 | M   | 16  | Knee   | Yes        | Osteosarcoma of femur on chemotherapy | No       | No                     | Ornidazole          | Above knee amputation | Survived |
| 3        | 12  | 1999 | F   | 83  | Hip    | Yes        | Unknown            | Yes (toxin negative) | No       | Metronidazole          | Prosthesis removal  | Survived |
| 4        | 15  | 2009 | M   | 11  | Shoulder | No        | Sickle cell disease | No       | No                     | Metronidazole       | Incision and drainage | Survived |
| 5        | 14  | 2010 | F   | 66  | Hip    | Yes        | Chronic kidney disease | Unknown | Yes                    | Metronidazole       | Incision and drainage | Survived |
| 6        | 11  | 2013 | F   | 61  | Knee   | Yes        | Hypothyroidism     | No       | No                     | Metronidazole       | Above knee amputation | Survived |
| 7        | 10  | 2013 | F   | 47  | Shoulder | Yes        | Alcoholic hepatitis | No       | No                     | Metronidazole       | Prosthesis removal  | Unknown |
| 8        | 9   | 2013 | M   | 61  | Hip    | Yes        | AIDS, type 2 diabetes | No       | Yes                    | Metronidazole       | Incision and drainage | Survived |
CONCLUSION

To our knowledge, this is the first reported case indicating that non-toxin-producing strains of *C. difficile* can cause severe extraintestinal disease, including septic arthritis of a native large joint. In order to provide timely and appropriate therapy, it is important for clinicians and microbiologists to be aware of the various potential manifestations of infection with *C. difficile*.

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