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Case Report

# Cefadroxil-Induced *Clostridium difficile* Infection Following Total Knee Arthroplasty

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ABSTRACT

Perioperative infection prophylaxis is a fundamental element of total knee arthroplasty (TKA). There has been a recent trend toward the use of extended postoperative oral antibiotics in high-risk patients. We describe a case report of a patient who underwent a primary TKA and subsequently developed *Clostridium difficile* colitis after an extended course of postoperative prophylactic oral cefadroxil. Following the *C. difficile* infection, the patient eventually developed bacteremia and a multidrug-resistant *Escherichia coli* prosthetic joint infection which required multiple debridements. Extended use of postoperative prophylactic oral cefadroxil may increase the risk of *C. difficile*-associated diarrhea. Additionally, our case suggests that *C. difficile* infection may subsequently increase the risk of bacteremia which could lead to prosthetic joint infection. More evidence is required to further define this risk.


## Introduction

Total knee arthroplasty (TKA) is one of the most successful operations in orthopedic surgery and allows patients with incapacitating degenerative joint disease to return to a functional level of activity. However, foreign implants come with an increased risk of deep surgical site infection and a need for a perioperative strategy for infection prophylaxis [1].The incidence of prosthetic joint infection (PJI) after primary TKA in the United States is approximately 2% and thought to be rising [2].

Most surgeons and institutions have developed their own infection prophylaxis protocols based on operative environmental factors, host risk factors, and wound care [3]. One universally agreed upon initiative is that of perioperative intravenous (IV) antibiotics [4,5]. Recently, there has been evidence that supports the use of an extended course of oral antibiotics postoperatively for PJI prophylaxis in select high-risk patients (obesity with body mass index [BMI] >35 kg/m$^2$, diabetes mellitus, chronic kidney disease, autoimmune disease, active smoker) following total joint arthroplasty (TJA) [6–8]. However, there is no overwhelming consensus regarding the timing, dosage, or antibiotic that is to be used in this manner. This strategy remains controversial as a course of extended oral antibiotics is not without risk. Among these risks are drug-drug interactions, anaphylaxis, hepatotoxicity, tendon rupture, neuropathy, skin hyperpigmentation and/or rash, development of antibiotic resistance, and *C. difficile* colitis. The incidence of these complications is dependent upon on the duration, number, and type of antibiotic(s) used [9–11]. There is also counterevidence to suggest that an extended course of oral/per Os (PO) antibiotics after TJA, specifically in morbidly obese patients, does not in fact confer a reduced rate of wound infection or early PJI [12].

Despite prophylaxis efforts, PJI remains a significant complication following TKA. Revision surgery for infection imparts a significant financial burden on patients, orthopedic surgeons, and hospital systems and is expected to rise as the total number of TKAs performed annually increases [2,13]. Effectiveness of an extended course of oral antibiotics after TKA has yet to be demonstrated by randomized controlled trials. To our knowledge, there is only one such protocol which details a specific

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postoperative oral cefadroxil regimen for PJI prophylaxis after primary TKA [7]. Their group conducted a large retrospective study examining the implementation of this protocol in high-risk patients following TJA. In their study, there were no reported cases of *C. difficile* infection in 1196 patients who received a 7-day course of oral cefadroxil after primary TKA [8]. Following the accolades these papers received at the 2020 American Association of Hip and Knee Surgeons Annual Meeting, our institution implemented a cefadroxil protocol as a postoperative extended antibiotic regimen for these "high-risk" TJA patients [7,8]. We describe a novel case of a patient who developed *C. difficile* infection after the use of this oral cefadroxil protocol in the postoperative period. This emphasizes the importance of recognizing possible complications associated with the use of extended oral antibiotics after primary TKA.

## Case history

The patient was informed that details about the case would be submitted for publication, and written permission was obtained. A 69-year-old male, currently smoking, with a medical history of obesity (BMI 33 kg/m$^2$) and type II diabetes mellitus presented with knee pain secondary to severe tricompartmental osteoarthritis (Fig. 1). He had failed an extensive course of conservative management and elected to proceed with joint replacement. He underwent a left TKA at our institution in 2021 (Fig. 2). The patient had no other medical conditions causing immunosuppression, and he was not taking any immunosuppressive medications. There were no intraoperative complications. He received 1 dose of 2-g IV cefazolin preoperatively and 2 doses of 2-g IV cefazolin postoperatively 8 hours apart. The patient was discharged on postoperative day two and, based on his medical comorbidities (type II diabetes mellitus), was scheduled to start oral cefadroxil on the day of discharge [7,8].

Unfortunately, the patient had a mechanical ground-level fall at home on the day of discharge. He presented to the emergency department where radiographs were obtained and found to be negative for fracture. He was subsequently readmitted for ambulatory dysfunction in order to improve strength, balance, and safety awareness with physical therapy. At this point, he had not started cefadroxil. He was eventually discharged 3 days later (postoperative day 5) to a rehab facility where he began taking cefadroxil by mouth (PO) 500 mg twice daily for 7 days [7,8]. He was discharged from rehab to home after 5 days.

The patient presented to an outpatient family medicine physician with diarrhea 9 days after completing cefadroxil. He was diagnosed with *C. difficile* colitis after a *C. difficile* toxin DNA PCR test was found to be positive. He had received no other antibiotics at this time other than the previously mentioned perioperative IV cefazolin. He was then started on PO vancomycin 125 mg every 6 hours for 10 days as treatment for *C. difficile* colitis. Three days after being diagnosed with *C. difficile* colitis, he fell at home again, and his wound dehisced for which he was readmitted. He also reported a fever of 102°F at home on the day of the fall. Blood cultures were drawn and found to be positive for multidrug-resistant *Escherichia coli* (*E. coli*). He was started on prophylactic IV vancomycin and cefepime, and PO vancomycin for *C. difficile* infection was continued. A wound vac was applied at bedside.

The patient underwent 3 formal irrigation and debridement surgeries with polyethylene exchange and wound vac exchange over the course of a 15-day period (approximately 1 month postoperatively). Surgical cultures grew multidrug-resistant *E. coli* consistent with blood cultures and *Bacteroides thetaiotaomicron*. Antibiotics were managed by an infectious disease team throughout the course of his admission. At 2 months postoperatively, he required an explant with placement of a static antibiotic spacer and a medial gastrocnemius flap with split-thickness skin graft by plastic surgery (Fig. 3). The spacer was subsequently revised after the patient failed to clear the infection. The patient was sent to an outside facility where a MicroGenDX (Orlando, FL) quantitative PCR DNA diagnostic study was performed to accurately identify the microbial profile of the *E. coli* responsible for the continued infection. Based on these results, the antibiotic spacer was revised to include gentamicin-impregnated cement. The patient was eventually transitioned to long-term PO antibiotics for suppression and continues to be monitored with his static antibiotic spacer.

## Discussion

In light of recent evidence, several institutions have adopted a postoperative protocol for PJI prophylaxis in high-risk patients undergoing primary TJA that includes an extended course of oral antibiotics [7,8,14,15]. There has been no consensus in the literature

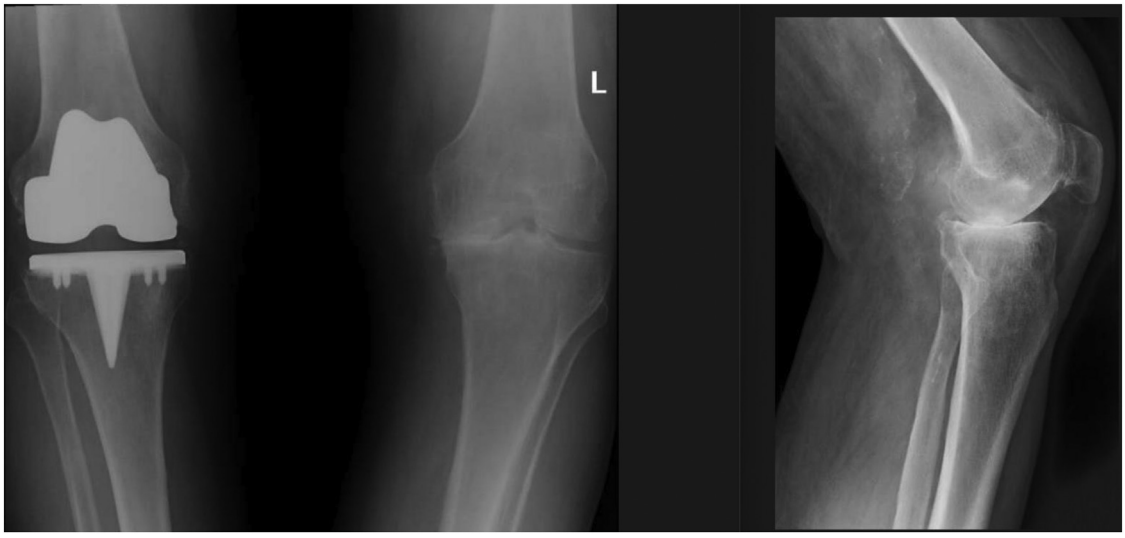


**Figure 1.** Preoperative plain radiographs (standing posteroanterior and lateral) demonstrating primary, severe tricompartmental osteoarthritis of the left knee.

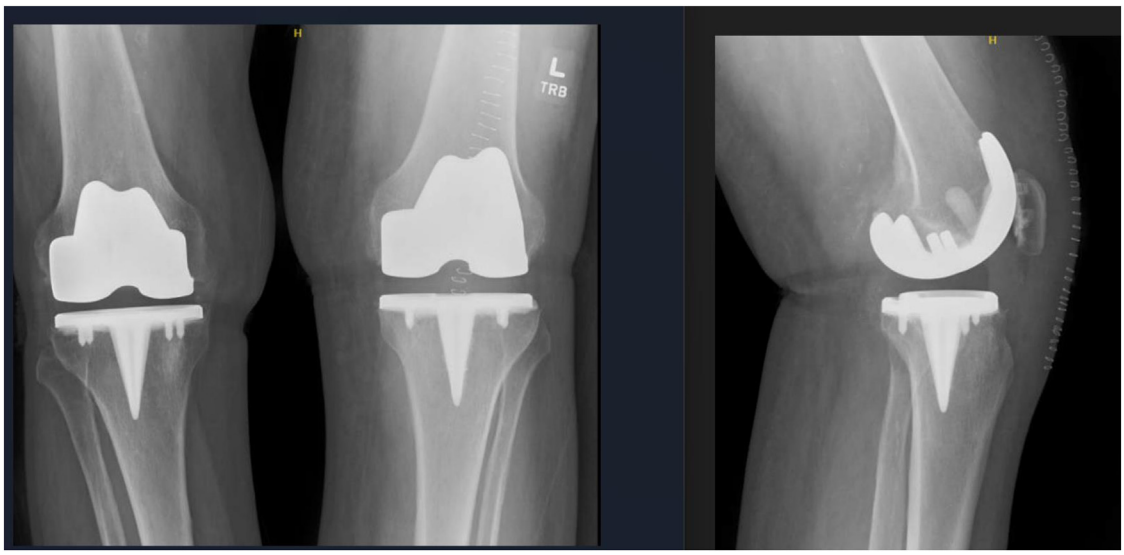


**Figure 2.** Postoperative plain radiographs (standing posteroanterior and lateral) demonstrating left total knee arthroplasty.

regarding the antibiotic of choice, duration of treatment, or patient demographic that would optimize this regimen [9,16]. Inabathula et al. proposed and implemented the use of a specific oral antibiotic and a set of indications for its use in the postoperative setting [7]. The authors report included 2181 primary TKA cases that received a 7-day course of PO cefadroxil 500 mg twice daily for 7 days. Patients who were deemed "high risk" and received cefadroxil were those with a BMI $\geq$35 kg/m$^2$, diabetes, who are active smoker, with chronic kidney disease, autoimmune disease, and nasal colonization with Methacillian-Sensitive Staphylococcus *aureus*. They found that a previous cohort of similar patients that did not receive an extended course of postoperative oral antibiotics was 4.9 times more likely to develop PJI after TKA than those that did receive oral antibiotics. While Inabathula et al. discussed the possibility of contributing to antimicrobial resistance by implementing a protocol for an extended course of postoperative oral antibiotics, they did not discuss the potential risk regarding *C. difficile* colitis [7]. They also did not report any of the patients in their study having this complication [7]. To the best of our knowledge, this is the first case report on a patient who underwent TKA and developed *C. difficile* colitis after following this cefadroxil protocol without receiving any other perioperative antibiotics other than IV cefazolin.

Over the last several decades, there has been an increased incidence of *C. difficile*-associated diarrhea (CDAD) as well as a

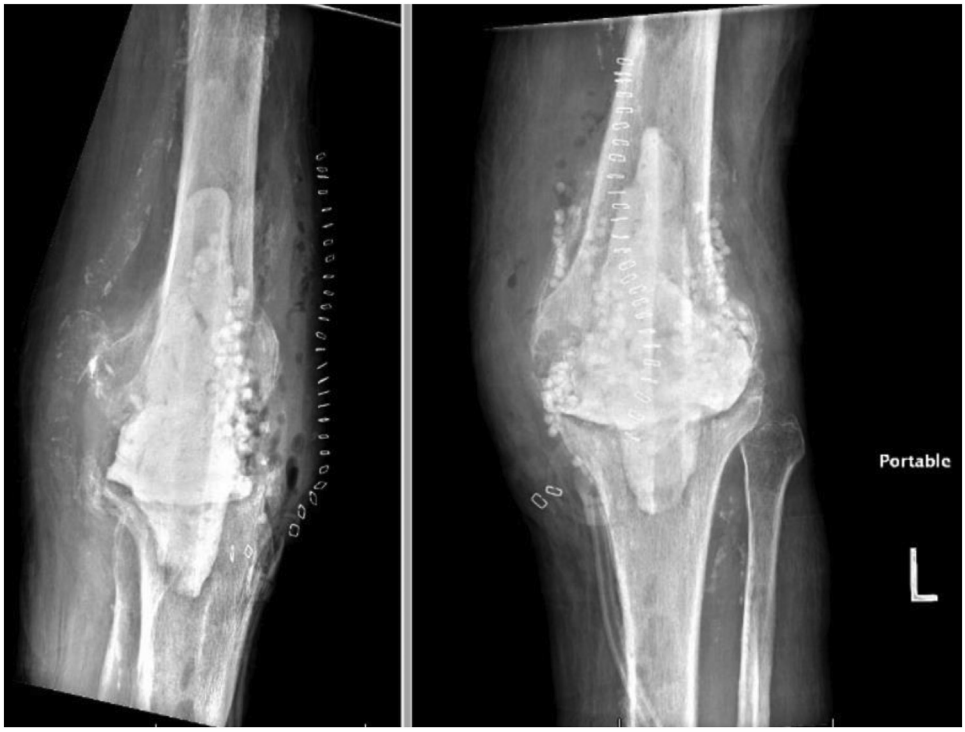


**Figure 3.** Postoperative plain radiographs demonstrating left knee static antibiotic spacer using a carbon fiber external fixator rod.

significant increase in mortality from this complication during inpatient admission [17–22]. *C. difficile* is a gram-positive, anaerobic, spore-forming bacillus found in the intestines of humans. It is associated with the development of diarrhea after antibiotic administration. Clinical symptoms may range from mild diarrhea to pseudomembranous colitis or toxic megacolon which can be life-threatening [23]. The pathogenesis of this infection includes alteration in the intestinal microbial composition brought about by previous antibiotic therapy which enables *C. difficile* colonization and subsequent toxin production. This leads to disruption of the epithelial lining of the colon [24]. Not all antibiotics carry the same risk of enabling *C. difficile* colonization and leading to CDAD [25]. However, it has been observed that overgrowth of *C. difficile* occurs commonly after cephalosporin therapy [26]. It has also been demonstrated that almost all healthy patients receiving oral cephalosporins excrete *C. difficile* after 10 days of therapy [27].

Literature pertaining to CDAD in orthopedic patients is limited. In the late 20th century, the association between prophylactic antibiotic use and CDAD was discovered. This contributed to the recommendation of 3 doses or less of preoperative antibiotics [28,29]. This was later confirmed by a study in which a cohort of patients who underwent internal fixation for intertrochanteric femoral fractures were given prophylactic antibiotics that were found to be strongly associated with the incidence of CDAD [30]. More recently, it has been suggested that 1 dose of perioperative IV antibiotics is just as effective as multiple doses without increasing the risk of infection, even in high-risk patients [31].

Today, CDAD is recognized as a complication in the postoperative period following hip and knee arthroplasty [10,11,32]. Kurd et al. found that overall health status, based on American Society of Anesthesiologists score, number of antibiotics used ($\geq$2 antibiotics), and duration of hospital stay were strongly associated with the development of CDAD after TJA [11]. This study did not specify whether "number of antibiotics" included those provided via IV and/or PO routes. To our knowledge, there is no such study investigating the use of perioperative IV antibiotics with the subsequent use of PO antibiotics and the association with CDAD in patients who underwent TKA.

We hypothesize that our patient developed *C. difficile* colitis as a result of the use of multiple perioperative antibiotics, including the extended postoperative course of oral cefadroxil. He subsequently developed multidrug-resistant *E. coli* bacteremia and a PJI consistent with this bloodborne bacteria. *E. coli* is commonly found as commensal intestinal flora and is also found on the floors of hospitals and long-term care facilities. It can also cause urinary tract infections, pneumonia, and peritonitis among other infections [33–35]. The TKA was also found to be concomitantly infected with *Bacteroides thetaiotaomicron*, another common commensal intestinal flora [36]. Because our patient had no evidence of concomitant *E. coli* infection of the genitourinary, respiratory, or gastrointestinal tract, it is possible that the source of *E. coli* bacteremia which led to PJI was commensal intestinal bacteria that was introduced into the bloodstream as a result of *C. difficile* toxin production affecting intestinal epithelial cells. There is evidence to suggest that *C. difficile* toxin can augment bacterial penetration of intestinal epithelium and facilitate bacterial translocation in vitro [37]. This may have also allowed translocation of *B. thetaiotaomicron* from the gut flora.

Our patient unfortunately sustained 2 falls after his primary TKA. The second fall resulted in a wound dehiscence without disruption of the arthrotomy. Retrospective evidence has demonstrated increased risk of PJI in knees that underwent primary TKA after acute, traumatic wound dehiscence [38]. Our patient's wound dehiscence certainly increases his risk of infection and potentially confounds the findings related to the etiology of his PJI. However, he did note a previous fever of 38.9°C and incisional drainage prior to the wound dehiscence. Furthermore, the fact that the subsequently identified microbes were *E. coli* and *B. thetaiotaomicron* leads us to believe that the source of infection was more likely translocation of commensal organisms from the gut facilitated by *C. difficile* toxin, rather than external bacteria introduced through wound dehiscence.

## Summary

Perioperative prophylactic antibiotic therapy remains an important strategy for reducing the risk of PJI. While administration of prophylactic perioperative antibiotics is endorsed by most current guidelines, the postoperative duration of antibiotics and the use of an extended course of oral antibiotics remain controversial [4,5]. An extended course of postoperative oral cefadroxil is not without risk and may contribute to the development of CDAD in TKA patients. This may subsequently facilitate bacteremia with commensal gastrointestinal organisms which can in turn seed a prosthesis and cause PJI. Further studies are needed in order to elucidate the true incidence of CDAD in TKA patients after the use of oral cefadroxil as well as the possible mechanism linking *C. difficile* toxin production to subsequent development of bacteremia and PJI.

## Conflicts of interest

The authors declare there are no conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2022.08.016.

## Informed patient consent

The authors confirm that informed consent has been obtained from the involved patient or if appropriate from the parent, guardian, power of attorney of the involved patient; and, they have given approval for this information to be published in this article.

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