

Extracolonic manifestations of *Clostridioides difficile* infection: Thinking Beyond the Gut

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INTRODUCTION

Clostridioides difficile (*C. difficile*) is a Gram-positive, spore-forming anaerobic bacterium that is widely recognized as the leading cause of antibiotic-associated diarrhea and pseudomembranous colitis [1]. Although *C. difficile* primarily affects the colon, cases of extraintestinal manifestations are increasingly reported in the medical literature [2]. These manifestations include both infectious and non-infectious complications and account for less than 1% of all reported *C. difficile* infections [3].

Risk factors and pathogenesis

Prior exposure to broad-spectrum antibiotics remains the most important predisposing factor, as disruption of the normal intestinal microbiota facilitates colonization and overgrowth of *C. difficile* [4].

Advanced age, prolonged hospitalization, proton pump inhibitor use, immunosuppression, malignancy, diabetes mellitus, chronic liver and kidney disease, cardiovascular disease, and sickle cell disease are other significant risk factors [5].

The development of extraintestinal manifestations is thought to result primarily from disruption of the

intestinal mucosal barrier, as occurs in severe colitis, inflammatory bowel disease, intestinal surgery, bowel perforation, and gastrointestinal malignancies, which facilitates the translocation of *C. difficile* and other microorganisms of the normal intestinal microbiota into the bloodstream, enabling their subsequent dissemination to distant organs [6]. In some cases, however, extraintestinal manifestations occur in the absence of gastrointestinal disease, suggesting that additional mechanisms may be involved [2,7]. These mechanisms may include hematogenous spread from asymptomatic intestinal colonization, toxin-mediated effects, or direct inoculation of the bacterium into tissues during trauma, surgery, or invasive medical procedures [2,6].

Bacteremia and sepsis-like syndrome

Bacteremia is the most frequently reported extraintestinal manifestation of *C. difficile* infection [2]. Underlying malignancy and chronic liver disease are frequently identified in affected patients [8]. Although monomicrobial bacteremia can occur, it is considerably less common than polymicrobial bacteremia and may reflect the presence of an extraintestinal infectious focus [5,6]. The development of sepsis-like syndrome may be attributed to toxin A-induced neutrophil chemotaxis and intestinal barrier dysfunction, which allows toxins and microbes to enter the bloodstream.

Abdominal and pelvic infections and abscesses

Abdominal and pelvic infections represent the most common extraintestinal *C. difficile* infections [2]. These infections occur predominantly in patients with underlying

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Received: 14 Jun 2026; Accepted: 15 Jul 2026

ing immunosuppression or conditions that compromise the intestinal barrier [2]. Splenic abscesses may arise through hematogenous dissemination, trauma, or splenic infarction [2]. Clinical manifestations are often nonspecific and include fever, abdominal pain, weight loss, leukocytosis, and elevated inflammatory markers [2]. Liver and pancreatic abscesses are rare [2]. Many intra-abdominal infections are polymicrobial, with *Escherichia coli* and *Enterococcus* species frequently isolated alongside *C. difficile* [2,9]. Hypervirulent ribotype 027 strains have also been implicated in several cases [7].

Central nervous system infections and abscesses

Only a few cases of brain abscesses caused by *C. difficile* have been reported [10,11]. In one case, the infection developed secondary to suppurative otitis media, while another case occurred in a patient with a history of subdural hematoma and asymptomatic intestinal carriage of *C. difficile* [10,11]. Interestingly, some reported CNS infections involve non-toxigenic strains, suggesting that strains with lower intestinal virulence may persist in the gut and cause opportunistic infections [11]. Patients with central nervous system infections and abscesses may present without gastrointestinal symptoms, making diagnosis particularly challenging [2].

Pleuropulmonary infections

Pleuropulmonary infections associated with *C. difficile* include pleural effusions, empyema, and, in severe cases, necrotizing pneumonia [2]. Most reported cases have occurred following thoracic surgery, thoracentesis, chest trauma, or other invasive procedures, suggesting direct inoculation into the respiratory tract as the primary mechanism [12,13]. Patients may present with fever, chest pain, and dyspnea [2].

Bone and joint infections

Bone and joint infections are frequently reported extraintestinal manifestations [2]. Septic arthritis may affect both native and prosthetic joints, although prosthetic joint infections are considerably more common [2]. Native joint infections have been particularly documented in patients with sickle cell disease, where intestinal ischemia and immune dysfunction may facilitate bacterial translocation into the bloodstream [2,14].

Prosthetic joint infections are believed to result mainly from direct contamination during surgery [2]. These infections are usually monomicrobial, supporting

the hypothesis of direct inoculation rather than hematogenous spread [2]. Clinical manifestations include joint pain, swelling, fever, and elevated inflammatory markers [2].

Osteomyelitis caused by *C. difficile* is rare but tends to become chronic [15]. Cases usually involve long bones, often following trauma, surgery, or previous hospitalization [2].

Soft tissue and surgical site infections

Soft tissue infections caused by *C. difficile* include cases of cellulitis, wound infections, abscesses, and necrotizing fasciitis [2]. Trauma and surgical interventions are major predisposing factors, with direct wound contamination from environmental or nosocomial sources of *C. difficile* representing the most likely pathogenic mechanism [2].

Published case reports have identified toxigenic strains in infected wounds, whereas different strains were isolated from the patients' gastrointestinal tracts [16,17]. This observation suggests that infection may originate from environmental contamination [2]. Nevertheless, intestinal colonization may also contribute to infection during abdominal surgical procedures [2].

Clinical presentations range from localized wound infections to rapidly progressive necrotizing soft tissue infections [2].

Cardiovascular infections

Cardiovascular manifestations are rare but potentially life-threatening [2]. Reported cases include mycotic aneurysms, infected vascular grafts and endovascular prostheses, intracardiac vegetations, pericarditis, epicardial patch infections, and pacemaker-associated infections [2].

The most widely accepted pathogenic mechanism involves hematogenous dissemination following bacterial translocation across the gastrointestinal mucosal barrier [2]. Many affected patients have concurrent intestinal disease and positive stool toxin tests [2]. Previous vascular interventions may further increase susceptibility to infection by creating localized anaerobic conditions that favor bacterial proliferation [18].

Reactive arthritis and other non-infectious manifestations

The most common non-infectious extraintestinal manifestation of *C. difficile* infection is reactive arthritis [2].

Reactive arthritis typically develops within days to weeks after the onset of diarrhea and commonly affects the knees, ankles, and wrists [6].

Underlying pathogenesis is believed to result from increased intestinal permeability, which facilitates systemic exposure to bacterial antigens and triggers an aberrant immune response [6]. More than half of affected patients are positive for the HLA-B27 antigen, although its precise role remains uncertain [19].

Other rare non-infectious manifestations include Takotsubo syndrome, leukocytoclastic vasculitis, and syndrome of inappropriate antidiuretic hormone secretion (SIADH), underscoring the potential systemic effects of *C. difficile* toxins and associated immune dysregulation [2,20].

CONCLUSION

Although *C. difficile* is primarily recognized as an intestinal pathogen responsible for pseudomembranous colitis, it may occasionally cause a wide spectrum of extraintestinal manifestations. Increased awareness of these rare manifestations is essential for timely diagnosis and appropriate management, and further research is needed to elucidate their pathogenesis, identify prognostic markers, and optimize therapeutic strategies.

Conflict of interest: None to declare

Declaration of funding sources: None to declare

Author contributions: The authors were responsible for the conception, writing, and revision of the manuscript.

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