

Deadly Diarrhea Caused by Co-Infection of *Clostridium perfringens* Type ST-865 and *Clostridium difficile*: A Case Report and Review of the Literature

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Purpose: There is a paucity of evidence regarding the occurrence of fatalities resulting from diarrhea due to co-infection with *C. perfringens* and *C. difficile*. Here, we report a rare case of severe diarrhea caused by a novel ST-865 type of *C. perfringens* in conjunction with *C. difficile* to draw the attention of clinicians and microbiology laboratory staff.

Case Descriptions: The patient is male, 69 years old and one month before admission, there was diarrhea without fever. The doctor administered anti-infective treatments such as levofloxacin, ceftriaxone, minocycline, gentamicin and tinidazole, and sent fecal samples for anaerobic culture. Two colonies, *Clostridium perfringens* and *Clostridium difficile*, were cultivated and identified by sequencing as type F-*Clostridium perfringens* of ST-865 and *Clostridium difficile* carrying toxins A and B.

Conclusion: The case we reported, which involved a severe case of diarrhea caused by a combined infection of ST-865 type F-type *Clostridium perfringens* and *Clostridium difficile* carrying both A and B toxins, and resulting in eventual death, is extremely rare. Such cases should draw the attention of clinicians and microbiology laboratory personnel.

Keywords: *Clostridium perfringens*, *Clostridium difficile*, diarrhea

Introduction

Clostridium perfringens and *Clostridium difficile* are anaerobic gram-positive bacilli that form spores that are highly resistant to environmental assaults, thus complicating their treatment. Both bacilli can cause bloodstream infections and diarrhea. *C. perfringens* is the second leading cause of foodborne bacterial illness in the United States, resulting in approximately one million cases annually;¹ the fourth most common in Europe,² and among the top six in Japan.³ *C. difficile* causes antibiotic-associated diarrhea (AAD) and severe infectious colitis, resulting in high morbidity and mortality on a global scale. *C. difficile* has also been associated with gastroenteritis-related mortality in North America and Europe for several decades.⁴ However, there is a paucity of evidence regarding the occurrence of fatalities resulting from diarrhea due to co-infection with *C. perfringens* and *C. difficile*. A novel ST-type *C. perfringens* strain was recently isolated from the feces of a patient presenting with diarrhea, a condition not previously documented in the medical literature. Here, we report a rare case of severe diarrhea caused by a novel ST-865 type of *C. perfringens* in conjunction with *C. difficile* to draw the attention of clinicians and microbiology laboratory staff.

Case Description

A 69-year-old male presented with diarrhea without an identifiable trigger a month prior to admission. Diarrhea was characterized by mucopurulent and bloody stools accompanied by nausea and vomiting but no fever. The patient was admitted to a local hospital 25 days before presentation and was diagnosed with infectious diarrhea. The three stool cultures yielded negative results. An anti-infection regimen of levofloxacin, ceftriaxone, minocycline, gentamicin, and

tinidazole was initiated, which notably improved his symptoms. Seven days previously, the patient presented with mucopurulent bloody stools accompanied by abdominal pain and diarrhea. His abdominal discomfort intensified, prompting admission as an outpatient for further treatment of infectious diarrhea.

Physical examination upon admission revealed a body temperature of 36.4°C, respiratory rate of 20 bpm, heart rate of 112 bpm, blood pressure of 111/89 mmHg, flat abdomen, normal respiratory movement, soft abdominal wall, and abdominal pressure without a palpable mass. Laboratory test results indicated a C-reactive protein content of 201.50 mg/L (normal value, 0–8 mg/L), white blood cell count of $1.42 \times 10^9/\text{L}$ (normal value, $4.0\text{--}10.0 \times 10^9/\text{L}$), red blood cell count of $2.63 \times 10^{12}/\text{L}$ (normal value, $4.0\text{--}5.5 \times 10^{12}/\text{L}$), absolute neutrophil count of $1.19 \times 10^9/\text{L}$ (normal value, $1.5\text{--}7.0 \times 10^9/\text{L}$), and procalcitonin content of 2.12 ng/mL (normal value, <0.15 ng/mL). The fecal sample was watery and was positive for occult blood and transferrin. These findings suggested the presence of intestinal infection, and a stool sample was sent for culture (Figure 1A). Gram staining of the stool samples revealed the presence of predominantly gram-positive cocci with a minor population of large gram-positive rods (Figure 1B), suggesting an imbalance in the microbial community. After 48 h of aerobic incubation, there was no growth of pathogenic bacteria. However, anaerobic culture yielded two presumptive pathogenic bacterial colonies. The first colony, measuring 2–4 mm in diameter, exhibited a white, round, elevated, smooth surface and a neat edge, with evident hemolysis (Figure 1C). This colony was identified as *C. perfringens* using mass spectrometry. The second colony, measuring 2–3 mm in diameter, displayed a grayish-white coloration with irregular edges and no hemolysis and was identified as *C. difficile* by mass spectrometry (Figure 1C). Both bacterial strains were tested for susceptibility to imipenem, metronidazole, meropenem, vancomycin, ceftriaxone, penicillin, and piperacillin/tazobactam using the E-test method. The results demonstrated that *C. perfringens* was susceptible to antimicrobials, whereas *C. difficile* was resistant to ceftriaxone and penicillin (Table 1). Bacteriophage DNA was extracted and sequenced, which demonstrated that *C. difficile* harbors two toxin genes: TcdA and TcdB. Multilocus sequence typing (MLST) identified the strain as ST-81. The *S. perfringens* isolate carried two major toxin genes (*plc* and *cpe*) and 22 other toxin genes (*nagH*, *nagI*, *nagJ*, *nagL*, *colA*, *cloSI*, *entA*, *entB*, *entD*, *pilB*, *pilM*, *pilT*, *pilC*, *pilN*, *pilA1*, *pilA2*, *fbpA*, *CBO*, *CPF*, *hlyB*, *virS*, and *virR*). Notably, the sequencing results demonstrated the absence of a corresponding ST type in the public database, indicating that the *C. perfringens* isolate was a newly discovered ST type. The housekeeping gene sequence was uploaded to the PubMLST database (<https://pubmlst.org/multilocus-sequence-typing>) and designated ST-865.

During hospitalization, 10 g of human albumin was administered via intravenous drip to treat hypoproteinemia. Acid suppression and rehydration have been used to treat electrolyte disorders. Following admission, cefoperazone sulbactam was administered at 3.0 g every 12 h via an intravenous drip as an anti-infective agent. However, after a 3-day period, there was no improvement, and the patient's condition deteriorated rapidly, progressing to acute necrotizing enterocolitis 4 days post-admission. On post-admission day 3, in accordance with the stool culture results, penicillin was administered intravenously at 4,000,000 U every 6 h, along with oral vancomycin at 0.125 g every 6 h. On post-admission day 4, the patient's body temperature was 39.2°C. Thus, aspirin DL-lysine was initiated at 0.9 g as an antipyretic and the anti-infective regimen was continued. However, the patient's condition did not improve. On the morning of post-admission day 5, the patient was discharged and died 1 day later.

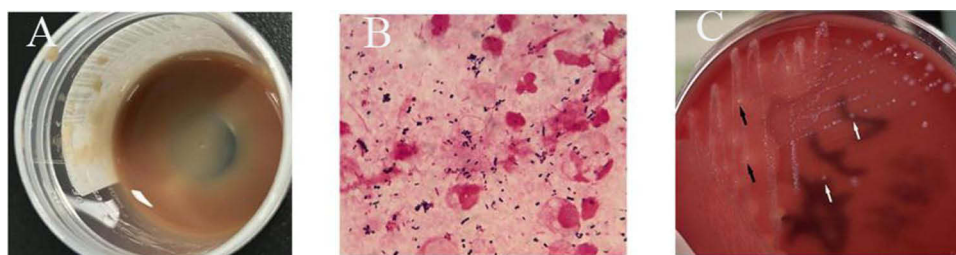


Figure 1 (A) A watery fecal sample. (B) A large number of Gram-positive cocci and a small number of Gram-positive bacilli observed at high magnification of a Gram-stained fecal smear ($\times 1000$). (C) Two distinct colonies were observed: one with irregular edges and no hemolysis, identified as *C. difficile* (white arrow), and a second that was round with a raised, smooth surface, neat edges, and obvious hemolysis, identified as *C. perfringens* (black arrow).

Table 1 Details of Simultaneous Detection of *C. perfringens* and *C. difficile* as Described in the Literature

	Age	Sex	<i>C. perfringens</i> Genotype	<i>C. perfringens</i> Isolation	<i>C. difficile</i> Isolation	Clinical History	Outcome
Gianerilli et al⁵ 1 Patient	19 months	—	—	+	+	Chronic diarrhea	—
Borriello et al⁶ 1 Patient	—	—	—	+	+	Loose stools	Recovery
Abrahao et al⁷ 1 Patient	—	—	—	CPE ⁺	+	—	Diarrhea after antibiotic and immunotherapy
Banaszkiewicz et al⁸ 2 Patients	12 years	female	—	CPE ⁺	+	—	—
Pituch et al⁹ 16 Patients	—	—	—	CPE ⁺	A+B+/A-B+	—	—
Heimesaat et al¹⁰ 26 Patients	—	—	—	+,CPE [—]	A+B+	—	—
Forero et al¹¹ 143 Patients	—	—	—	+	+	—	—
Pituch et al¹² 4 Patients	—	—	—	+,CPE [—]	A-B+/A+B+	—	—
Joshy et al¹³ 1 Patient	—	—	A	+,CPE [—]	+	—	—
Ackermann et al¹⁴ 3 Patients	>60 years	—	—	+	+	—	—
Tonooka et al¹⁵ 4 Patients	30 days	—	—	+	+	—	—

Notes: +, Carry toxin or toxin gene; -, No toxin or toxin gene; —,Data not shown.

Review and Discussion

A review of the relevant published literature using the keywords “Clostridium perfringens” and “Clostridium difficile” returned 11 articles, but there were no case reports of diarrhea and death due to co-infection with *C. perfringens* and *C. difficile*. The retrieved articles are summarized in Table 1. In a report to determine the role of *C. difficile* in the upper gastrointestinal tract of children, 19 specimens from patients with chronic diarrhea were positive for both bacteria.⁵ In one case of AAD, both *C. perfringens* and *C. difficile* were detected.⁶ In a prospective study of patients with AAD, 10 fecal specimens were positive for the *C. difficile* enterotoxin A and one was positive for both the *C. perfringens* enterotoxin and *C. difficile* toxin.⁷ In a study investigating the prevalence of *C. perfringens* infection in pediatric patients with inflammatory bowel disease, two (2.2%) of 91 stool specimens were positive for both the *C. difficile* toxin and *C. perfringens* enterotoxin.⁸ A pilot study on the clinical correlation between *C. difficile* toxin and *C. perfringens* conducted in Poland found that 16 (30.8%) of 52 stool samples were positive for both *C. perfringens* and *C. difficile*.⁹ A prospective study of patients with AAD reported that 26 (3.8%) of 693 stool specimens were positive for *C. difficile* toxins A and B.¹⁰ A study conducted in Bogotá, Columbia, found that 143 (65%) of 220 stool samples were positive for both *C. perfringens* and *C. difficile*.¹¹ In a study of 158 patients to explore the role of enterotoxin-producing anaerobes, other than *C. difficile*, in the etiology of AAD, found that four specimens were positive for both *C. perfringens* and *C. difficile*.¹² A prospective study conducted in India on the prevalence and characterization of *C. perfringens* reported that only one (0.07%) of 150 stool specimens was positive for both *C. perfringens* and *C. difficile*.¹³ Another study evaluating the prevalence of different bacteria in the stools of patients with AAD reported that 89 diarrhea specimens were positive for *C. perfringens*, *C. difficile*, and *Staphylococcus aureus*.¹⁴ Lastly, an investigation of the prevalence of the genus *Clostridium* in infants identified both *C. perfringens* and *C. difficile* in four (18.2%) of 22 fecal samples.¹⁵

A combination of *C. perfringens* and *C. difficile* can cause severe intestinal infections. Although both *C. perfringens* and *C. difficile* can cause diarrhea, co-infection is uncommon and the underlying mechanisms are distinct. *C. perfringens* is capable of secreting nearly two dozen different toxins and can be categorized into seven distinct toxin types (A–G) based on

the production of six major exotoxins, which include α (CPA), β (CPB), ϵ (ETX), iota (ITX), enterotoxin (CPE), and necrotizing enteritis B-like (Net-B).¹⁶ In the present case, *C. perfringens* carried two major toxin genes, *cpe* and *plc* (also known as *cpa*), and was therefore classified as type F. This classification is associated with both food poisoning and AAD.¹⁶ CPE, the primary toxin produced by *C. perfringens*, is responsible for gastrointestinal symptoms¹⁷ via a mechanism of action that involves binding to the tight junction protein receptor, which is a crucial component of the tight junctions on the surfaces of epithelial and endothelial cells. This binding process not only facilitates the formation of pores in the plasma membrane, but also the removal of claudin proteins from the cell membrane, thereby disrupting the tight junctions between cells, thereby increasing barrier permeability and impairing absorption in the small intestine and colon, leading to diarrhea.^{18,19} Isolates of the F-type carrying the chromosomal *cpe* gene are reportedly more likely to cause foodborne gastrointestinal disorders, whereas most isolates of the F-type carrying the plasmid *cpe* gene are mainly associated with non-foodborne gastrointestinal disorders.²⁰ Furthermore, strains carrying the plasmid *cpe* gene exhibit greater heat resistance than strains with the chromosomal *cpe* gene.²¹ This enhanced heat resistance enables the former to survive in food, thereby increasing the likelihood of food poisoning. Sequencing analysis revealed that the *cpe* gene of *C. perfringens* in this case was located on the chromosome, which may provide more favorable conditions for food-borne infection. Furthermore, our findings revealed that this particular strain of *C. perfringens* contained 22 paratoxin genes, including *colA*, which has been associated with avian necrotizing enterocolitis and degradation of the extracellular matrix.²² The *nagH*, *nagI*, *nagJ*, and *nagL* genes have been demonstrated to promote the diffusion of tissue-damaging α -toxins, degrade hyaluronic acid cell surface coatings, and increase the permeability of connective tissues, which collectively elevate the risk of airborne gangrene. Given their destructive impact on the intestine,^{23,24} we postulate that these toxins may facilitate further invasion of *C. difficile* and provide favorable conditions for co-infection with *C. perfringens* and *C. difficile*, although this hypothesis requires further confirmation. A total of 186 *C. perfringens* isolates were obtained from nine provinces in China between 2013 and 2021. Human isolates were characterized by four predominant types:²⁵ ST-221, ST-62, ST-408, and ST-493. In a separate study, 195 ST types were identified in 372 isolates from diverse sources. The most common subtypes are ST-147, ST-248, ST80, ST251, and ST-73. However, isolates within these STs tended to share the same toxin type. For instance, 14 F-type isolates obtained from food and human sources in the United States and Italy between 2017 and 2019 were classified as ST-147, while 13 F-type isolates from dogs and horses in Canada and the United States were classified as ST-80.²⁶ Notably, this is the first report of diarrhea caused by the novel ST-865 type. The housekeeping gene sequence of this new ST type was uploaded to the PubMLST database for reference. Although the origin of this strain was not traced in detail, these new typing results may serve to enhance the *C. perfringens* database and provide a theoretical foundation for future epidemiological investigations of this bacterium.

Diarrhea caused by *C. difficile* is a direct consequence of the disruption of the intestinal flora following antibiotic administration. In this case, the *C. difficile* infection produced two toxins, A and B, which are encoded by *tcdA* and *tcdB*, respectively, within the pathogenicity locus. The pathogenesis of diarrhea caused by *C. difficile* is primarily driven by the activity of enterotoxin A and cytotoxin B, which are internalized by intestinal epithelial cells, resulting in the glycosylation of small Rho proteins in the cell membrane, ultimately leading to cell death and a loss of intestinal barrier function.^{4,27} Furthermore, the host immune response intensifies the symptoms of infection, including an acute intestinal inflammatory response and neutrophil infiltration, which exacerbate damage to epithelial cells.²⁸ A number of studies have demonstrated that individuals who are particularly susceptible to *C. difficile* infection include those who are hospitalized and have recently undergone antibiotic exposure, as well as those aged ≥ 65 years.²⁹ The risk factors for *C. difficile* infection in these individuals include the elimination of protective gut flora by antibiotics^{29–31} and a diminished immune response to *C. difficile* due to age and medical comorbidities.^{32,33} In this case, the patient was aged ≥ 65 years and had been treated with antibiotics, including tinidazole, gentamicin, and minocycline, at the onset of diarrhea, which markedly elevated the likelihood of *C. difficile* infection.

Search Strategy and Selection Criteria

Articles were retrieved from the MEDLINE (PubMed), SPRINGER NATURE LINK, Web of Science, and EBSCO databases until December 29, 2024, with the key words “*Clostridium perfringens*” and “*Clostridium difficile*”, and no restrictions on language, in addition to the reference lists of the retrieved publications.

Conclusion

We postulated that our patient had a diet-induced *C. perfringens* infection, and that the extensive use of antimicrobials during treatment resulted in intestinal flora dysbiosis and *C. difficile* co-infection, which ultimately progressed to severe hemorrhagic necrotizing enterocolitis. Despite our best efforts to identify the causative pathogen, the patient's condition ultimately deteriorated, resulting in his demise 1 day after the administration of penicillin for *C. perfringens* and vancomycin for *C. difficile*. To the best of our knowledge, this is the first reported death caused by a co-infection with *C. perfringens* and *C. difficile*. In particular, an ST-865 type *C. perfringens* was identified. It remains unclear whether the large number of toxin genes carried by this F-type strain is associated with the severe symptoms observed in this patient. Furthermore, it is unclear whether this strain is more likely to occur with *C. difficile*. These research avenues warrant further investigation.

Ethical Approval

This report has been approved by The Affiliated Hospital of Chengde Medical University's ethics committee to publish the case details and conducted in accordance with the ethical principles for medical research involving human subjects, as described in the Declaration of Helsinki. Written informed consent to have the case details published has been provided by the patient's family.

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Disclosure

The authors declare no competing interests in this work.

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