Extraintestinal *Clostridium difficile* Infections

Eero Mattila,¹ Perttu Arkkila,² Petri S. Mattila,³ Eveliina Tarkka,⁴ Päivi Tissari,⁴ and Veli-Jukka Anttila¹

Departments of ¹Infectious Diseases, ²Gastroenterology, and ³Otorhinolaryngology, and ⁴Division of Clinical Microbiology, Helsinki University Central Hospital Laboratory Diagnostics, Finland

**Background.** *Clostridium difficile* causes diarrhea that ranges from a benign, self-limiting antibiotic use-associated disease to a life-threatening pseudomembranous colitis. *Clostridium difficile* has rarely been isolated in extraintestinal infections. Our objective was to characterize clinical features and risk factors of these infections.

**Methods.** Extraintestinal *C. difficile* infections (CDIs) were searched for in an electronic database of all *C. difficile*-positive isolates found during a 10-year period. The medical records were reviewed retrospectively. Disease severity and comorbidities of the patients were evaluated using Horn disease severity and Charlson comorbidity indexes.

**Results.** Extraintestinal CDI was found in 31 patients who comprised 0.17% of all CDIs. Two patients had bacteremic infections, 4 had abdominal infections without any prior surgery, 7 had abdominal infections after surgery, 4 had perianal abscesses, 13 had wound infections, and 1 had *C. difficile* in a urinary catheter. In most cases (85%), *C. difficile* was isolated together with other microbes. Most (81%) patients developed the infection when hospitalized and many had severe comorbidities. Sixteen (52%) had diarrhea. The 1-year mortality rate was 36% and it correlated with the severity of underlying diseases.

**Conclusions.** Extraintestinal CDIs occur mainly in hospitalized patients with significant comorbidities. Extraintestinal CDIs in the abdominal area may result from either intestinal perforation after infection or after intestinal surgery. Wound infections may result from colonization by feces. *Clostridium difficile* may reach distant sites via bacteremia. Mortality in extraintestinal CDIs is associated with the severity of underlying diseases.

**Keywords.** *Clostridium difficile*; bacteremia; postoperative complications; abscess; wound infection.

*Clostridium difficile* colonizes the colon of 1%–3% of asymptomatic healthy adults. Antibiotic use and hospitalization increase the risk of colonization, and stool carriage rate can reach 35% among inpatients [1, 2]. Colonization may lead to enteritis and its severity ranges from a benign, self-limiting antibiotic use–associated disease to a life-threatening pseudomembranous colitis [3, 4]. In recent years the incidence and mortality of *C. difficile* enteritis have increased [5].

Although *C. difficile* enteritis is the most frequent presentation of *C. difficile* infection (CDI), *C. difficile* causes infections also outside the intestine. These infections are rare but have been reported as early as 50 years ago [6], which is well before the recognition of *C. difficile* colitis in the late 1970s [7]. *Clostridium difficile* bacteremias [8–10], isolated case reports of extraintestinal CDIs, and few series of extraintestinal CDIs have been reported [11–13]. In clinical practice, a finding of *C. difficile* in an extraintestinal site is often a surprise. Evaluation of the significance of the finding may not always be straightforward, especially when *C. difficile* is found in conjunction with other microbes. We therefore performed a systematic analysis of all consecutive extraintestinal CDIs during 10 years’ time to characterize predisposing factors, clinical features, and outcomes of these infections.

**PATIENTS AND METHODS**

Patients with extraintestinal CDIs were searched for in the electronic data files of the Division of Clinical
Microbiology, Helsinki University Central Hospital Laboratory Diagnostics. The laboratory receives microbiologic samples from a population of approximately 1.5 million and it analyzes all samples from patients that are covered by the community. The inclusion criterion was detection of *C. difficile* in an extraintestinal sample analyzed between January 2002 and September 2012. Individual patient records were evaluated retrospectively in the archives of our hospital district. The study was approved by the institutional review board of Helsinki University Central Hospital.

*Clostridium difficile* was isolated in extraintestinal sites using conventional anaerobic bacteriologic techniques. These were not specifically designed to detect *C. difficile* but rather designed to detect all anaerobic microbes. After transportation in Stuart transportation media, the samples were streaked on plates with Fastidious Anaerobe Agar (Lab M, Bury, United Kingdom) that were supplemented with 5% defibrinated horse blood. The plates were then incubated in anaerobic jars at 35°C.

Isolation of *C. difficile* from peripheral blood samples was performed using the BacT/ALERT Culture Media system for blood samples (bioMérieux, Marcy l’Etoile, France). Isolation of *C. difficile* in stool samples was performed using *C. difficile*-selective cycloserine-cefoxitin-fructose-egg yolk agar at 35°C for 42 hours in anaerobic atmosphere. Colonies with typical morphology, fluorescence, and odor were presumptively identified as *C. difficile*. Bacterial isolates were identified by biochemical tests. *Clostridium difficile* toxins were detected directly from *C. difficile* colonies by the Premier Toxins A&B-test kit (Meridian; Bioscience Inc, Cincinnati, Ohio) during 2007–2010 according to the manufacturer’s instructions. From 2011 onward, the toxin genes were analyzed from *C. difficile* colonies with multiplex polymerase chain reaction (PCR) [14]. Strain typing when done was performed by DNA analysis using multiplex PCR [14].

We categorized the severity of the disease using the Horn index [15] that rates disease severity in categories from 1 to 4 on the basis of clinical judgment: mild (single mild illness), moderate (more severe illness but uncomplicated recovery expected), severe (major complications or multiple conditions requiring treatment), and fulminant (catastrophic life-threatening illness). The severity of the underlying disease was scored using the Charlson index [16] as follows. One point was added from each of the below listed comorbidities unless otherwise noted: myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes mellitus (1 point uncomplicated, 2 points if end-organ damage), moderate to severe chronic kidney disease (2 points), hemiplegia (2 points), leukemia (2 points), malignant lymphoma (2 points), solid tumor (2 points, 6 points if metastatic), liver disease (1 point mild, 3 points if moderate to severe), and AIDS (6 points). In addition, points were given according to age: 41–50 years (1 point), 51–60 years (2 points), 61–70 years (3 points), and 71 years or older (4 points).

**RESULTS**

Extraintestinal CDI was found in 31 patients during the 10-year study period. During the same time, fecal samples of 18,570 patients were positive for *C. difficile*. Thus, only 0.17% of all CDIs were extraintestinal. The number of extraintestinal CDIs ranged from none to 6 cases per year, with a mean of 3.1 cases annually. All patients had received antibiotics before developing an extraintestinal CDI and most had received multiple courses. Analysis of prior antibiotic use did reveal any clear predisposing pattern regarding the type of antibiotics. Only 6 of 31 patients were outpatients. All the other patients (81%) developed the infection when hospitalized. The 1-year mortality rate was 36% (11/31).

We categorized the 31 patients into 5 groups: bacteremic infections (2 patients), abdominal infections without any prior surgery (4 patients), abdominal infections after surgery (7 patients), perianal abscesses (4 patients), wound infections (13 patients), and urinary catheter colonization (1 patient) (Table 1).

Both of the 2 patients with bacteremic CDIs had diarrhea and severe conditions affecting the colon. The older patient had an advanced colon cancer with peritoneal carcinosis. She underwent palliative resection of the tumor that obstructed the colon but subsequently developed colon fistulas to the skin and bladder. She became febrile, developed *C. difficile* diarrhea and bacteremia, and died shortly after. The other patient had paraparesis with recurrent urinary tract infections that had been treated with multiple courses of antibiotics. He had developed ischemic colitis that required intensive care treatment with ionotropic medication and ventilatory support. Six months after resolution of the colitis, he got abdominal pain with fever and diarrhea. Blood cultures were positive for *C. difficile*. Investigations of the abdominal pain revealed an abdominal aortic aneurysm. The aneurysm was operated and reconstructed with a graft. The consistency of the resected aneurysm was abnormal and suspicious of an infection. *Clostridium difficile* was isolated in the resected aneurysm and also in an adjacent abdominal lymph node. The patient recovered without any apparent development of infection in the abdominal vascular graft.

Three of the 4 patients who had abdominal infections without any prior surgery had intestinal perforation due to either diverticulitis or appendicitis. The fourth patient had liver cirrhosis with ascites. He became disoriented, and *C. difficile* was isolated in the ascites fluid. The 7 patients who had abdominal infections after surgery either had infections after leakage of colon anastomosis or had a presumed peritoneal
<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Number</th>
<th>Age</th>
<th>Sex</th>
<th>Underlying Disease</th>
<th>Clinical History</th>
<th>Site of Isolation</th>
<th>Other Microbes</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremic</td>
<td>1</td>
<td>72 y</td>
<td>Female</td>
<td>Colon cancer with peritoneal carcinosis</td>
<td>Tumor resection, colon fistula to skin and bladder, diarrhea</td>
<td>Blood</td>
<td>Bacteroides fragilis</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>69 y</td>
<td>Male</td>
<td>Paraparesis, recurrent UTI</td>
<td>Ischemic colitis, diarrhea, operation for abdominal aneurysm</td>
<td>Blood, abdominal aneurysm, lymph node</td>
<td>No</td>
<td>Recovered</td>
</tr>
<tr>
<td>Abdominal without prior surgery</td>
<td>3</td>
<td>97 y</td>
<td>Female</td>
<td>Breast cancer, dementia</td>
<td>Appendicitis, perforation, peritonitis, diarrhea</td>
<td>Peritoneal fluid</td>
<td>Escherichia coli, anaerobes</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>74 y</td>
<td>Female</td>
<td>Sarcoiosis, cortisone treatment, pulmonary thrombosis</td>
<td>Diverticulitis with perforation and peritonitis, diarrhea</td>
<td>Peritoneal fluid</td>
<td>E. coli, anaerobes</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>59 y</td>
<td>Female</td>
<td>Epilepsy</td>
<td>Periappendicular abscess</td>
<td>Drain discharge</td>
<td>E. coli, anaerobes</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>59 y</td>
<td>Male</td>
<td>Alcoholism, liver cirrhosis with marked ascites</td>
<td>Disorientation, diarrhea</td>
<td>Ascites fluid</td>
<td>No</td>
<td>Recovered</td>
</tr>
<tr>
<td>Postoperative abdominal</td>
<td>7</td>
<td>74 y</td>
<td>Female</td>
<td>Rectum stricture</td>
<td>Diarrhea, rectum resection, anastomosis leakage, abscess</td>
<td>Abscess fluid</td>
<td>B. fragilis, Prevotella intermedia</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>53 y</td>
<td>Male</td>
<td>Pancreas cancer</td>
<td>Pancreatocoduodenectomy, anastomosis leakage</td>
<td>Peritoneal fluid</td>
<td>Enterococci, Candida</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>50 y</td>
<td>Male</td>
<td>Alcohol pancreatitis</td>
<td>Pancreas and colon resection, psoas abscess</td>
<td>Abscess fluid</td>
<td>Staphylococcus epidermidis</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>49 y</td>
<td>Male</td>
<td>Alcoholism, chronic pancreatitis</td>
<td>Pancreas pseudocyst, colon and pancreas resection, diarrhea</td>
<td>Abscess fluid</td>
<td>Enterococcus faecium</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>44 y</td>
<td>Female</td>
<td>Crohn’s disease, cortisone treatment</td>
<td>Hemicolectomy, anastomosis leakage, diarrhea</td>
<td>Abscess fluid</td>
<td>No</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>40 y</td>
<td>Female</td>
<td>Alcoholism, rectum perforation</td>
<td>Colostomy reversal, anastomosis leakage</td>
<td>Abscess fluid</td>
<td>No</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>17 y</td>
<td>Female</td>
<td>Crohn’s disease, cortisone treatment</td>
<td>Hemicolectomy, anastomosis leakage</td>
<td>Abscess fluid</td>
<td>Enterococcus faecalis, Staphylococcus epidermidis</td>
<td>Recovered</td>
</tr>
<tr>
<td>Perianal abscess</td>
<td>14</td>
<td>39 y</td>
<td>Male</td>
<td>None</td>
<td>Perianal abscess, diarrhea</td>
<td>Abscess fluid</td>
<td>E. faecium, Pseudomonas aeruginosa</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>36 y</td>
<td>Male</td>
<td>None</td>
<td>Perianal abscess</td>
<td>Abscess fluid</td>
<td>Enterococci, anaerobes</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>26 y</td>
<td>Male</td>
<td>None</td>
<td>Perianal abscess</td>
<td>Abscess fluid</td>
<td>E. faecalis, Klebsiella pneumoniae</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>21 y</td>
<td>Female</td>
<td>None</td>
<td>Perianal abscess</td>
<td>Abscess fluid</td>
<td>Bacteroides spp</td>
<td>Recovered</td>
</tr>
<tr>
<td>Wound infection</td>
<td>18</td>
<td>85 y</td>
<td>Male</td>
<td>Arteriosclerosis, cardiac insufficiency, COPD</td>
<td>Decubitus ulcer of the buttock, diarrhea</td>
<td>Wound discharge</td>
<td>B. fragilis, P. aeruginosa</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>81 y</td>
<td>Male</td>
<td>Arteriosclerosis, Alzheimer disease</td>
<td>Decubitus ulcer of the sacrum, diarrhea</td>
<td>Wound discharge</td>
<td>Coliforms, anaerobes</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>79 y</td>
<td>Female</td>
<td>Arteriosclerosis, coronary heart disease</td>
<td>Leg ulcer discharge</td>
<td>Wound discharge</td>
<td>Wound staphylococci koag. neg.</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>74 y</td>
<td>Female</td>
<td>Arteriosclerosis, coronary heart disease</td>
<td>Open heart surgery, sternum wound</td>
<td>Wound discharge</td>
<td>E. faecium</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>69 y</td>
<td>Female</td>
<td>Arteriosclerosis, diabetes, lymphoma</td>
<td>Pneumonia, leg amputation</td>
<td>Wound discharge</td>
<td>E. faecalis</td>
<td>Died</td>
</tr>
</tbody>
</table>
contamination during intestinal surgery. Four patients had C. difficile in perianal abscess.

The C. difficile wound infections included wounds that presumably had poor circulation, such as an amputation wound and decubitus wounds, but also wounds that presumably had rather good circulation, such as sternum and thoracotomy wounds. Six of the 13 patients with wound infections had generalized arteriosclerosis. Five of these 6 patients died shortly after isolation of C. difficile. Four of all wound infections were decubitus ulcers. One patient developed a wound infection after correction of a nonmedical circumcision after delivery.

In 1 patient, C. difficile was isolated in a urine catheter. She had undergone cardiac transplantation and had a urine catheter during the immediate postoperative period. At the time of isolation, she also had C. difficile diarrhea, suggesting that the stools may have contaminated the catheter. In addition to C. difficile, enterococci and Staphylococcus haemolyticus were isolated in the catheter.

In most instances, C. difficile was isolated together with other microbes. In only 5 (15%) of the infections, C. difficile was the sole microbe isolated. Strain typing was done of 9 isolates, and 2 (22%) of these had a DNA profile compatible with the BI/NAP1/027 ribotype. Toxin genes were tested of 9 isolates, and 8 (89%) of them carried toxin genes. Of the total 16 patients with diarrhea, 11 underwent stool testing, but only 5 had a positive C. difficile fecal sample. Of the 31 patients, 9 (29%) were alcohol abusers to the extent that they had severe adverse effects related to alcohol abuse such as liver cirrhosis or pancreatitis.

Most patients had a severe underlying disease. The majority (24 of 31 [77%]) had a Horn index 3 or 4 indicating a severe or fulminant disease. Many patients had severe underlying diseases, and the mean Charlson index was 5.2. Patients with perianal abscesses had lower Horn and Charlson indexes than the other patients (analysis of variance [ANOVA], \( P < .05 \)). They also tended to be younger than the other patients (ANOVA, \( P < .05 \)).

One-year mortality was associated with both the Horn (\( P = .01 \)) and Charlson indexes (\( P < .001 \)). The mean Horn and Charlson indexes of the 8 patients who had died during the 1-year follow-up were 4.0 and 9.4, respectively, compared to the 23 surviving patients who had mean Horn and Charlson indexes of 3.0 and 3.7, respectively.

**DISCUSSION**

Extraintestinal CDIs were rare. Only 31 cases were found during the 10-year period studied in our hospital district that provides healthcare to a population of approximately 1.5 million. The number of cases was low (0.17% of all CDIs) compared to all patients with CDI during the same time period.
The numbers of extraintestinal \textit{C. difficile} cases observed would translate to a mean incidence of 0.2 per 100,000 person-years. This may, however, be an underestimate as \textit{C. difficile} may be difficult to isolate and the rate of recovery may vary depending on the isolation method [2]. It should be noted that \textit{C. difficile} was isolated in most cases together with other microbes, which may make the isolation of \textit{C. difficile} even more demanding. Detection of \textit{C. difficile} in extraintestinal sites remains a challenge and emphasizes the need for sensitive microbiologic detection methods.

A common feature of extraintestinal CDIs was that most patients were hospitalized and had received antibiotics, which increases the risk of \textit{C. difficile} carriage. The patients may or may not have clinical symptoms of diarrhea but many had severe comorbidities, previous surgery, or intestinal infection. Such characteristics have also been observed in previous reports [11, 17]. Most of the patients in our series had high Charlson comorbidity and Horn disease severity indexes, which reflect the morbidity of our patients. Mortality was high and it correlated with these indexes.

Of the 31 extraintestinal CDIs, 14 (45\%) were associated with intestinal surgery, with perianal abscesses, or with intestinal perforations resulting from intestinal infections. In these infections, \textit{C. difficile} likely spreads directly from the intestinal lumen. Direct spread of \textit{C. difficile} from the intestine has also been reported in several previous cases of extraintestinal CDI [13, 18, 19]. \textit{Clostridium difficile} may also cause infections after transient bacteremia. One of our patients, who had liver cirrhosis and ascites, had \textit{C. difficile} in the ascites fluid but he had no obvious intestinal perforation. \textit{Clostridium difficile} has also been found in prosthetic joint infections [20, 21], osteomyelitis [22, 23], spondylodiscitis [24], splenic abscess [25–27], brain abscess [28], pericardial fluid [29], and pleural empyema [30], which implies that \textit{C. difficile} may enter distant sites through blood circulation.

We found 2 cases of \textit{C. difficile} bacteremias. One patient had \textit{C. difficile} in an abdominal aneurysm. In addition to the aneurysm and blood, \textit{C. difficile} grew in an adjacent lymph node. No other microbes were found. The patient had an episode of fulminant colitis 6 months before the infection, suggesting that \textit{C. difficile} may have reached the aneurysm via transient bacteremia already and then remained relatively dormant for months. Subsequently, the patient underwent correction of the aneurysm with a prosthesis and recovered. This case resembles a previously reported patient who had \textit{C. difficile} in an abdominal aneurysm [31]. It is possible that an anaerobic thrombus promotes the survival of \textit{C. difficile} in the aneurysm. The second patient with \textit{C. difficile} bacteremia had advanced colon cancer, developed bacteremia after palliative surgery, and subsequently died. Her bacteremia was polymicrobial. Previously reported cases of \textit{C. difficile} bacteremia have often been polymicrobial or have usually occurred in patients with underlying conditions, such as inflammatory bowel disease or malignancy, or in patients who have undergone intestinal surgery [9, 10, 12, 27, 32]. These previously reported bacteremic cases have also had high mortality.

Extraintestinal CDIs occurred also in wounds and especially in decubitus ulcers. It is possible that \textit{C. difficile} had reached the wounds via contamination by stools. Many of our patients had generalized arteriosclerosis and died shortly after detection of \textit{C. difficile}. This may imply that in many cases the wounds had poor circulation or were otherwise compromised, and that this might have predisposed to CDI. \textit{Clostridium difficile} has also been reported in previously healthy trauma patients who had developed deep wound infections [33], fascitis, and gas gangrene [6, 34, 35]. A case of perineal necrotizing fascitis has also been reported in a patient with \textit{C. difficile} pseudomembranous colitis [36]. These infections had required extensive surgical debridement, suggesting that \textit{C. difficile} can be highly pathogenic in a wound infection.

There have been reports of reactive arthritis after \textit{C. difficile} enteritis [37–40]. Although the synovial fluids of inflamed joints in reactive arthritis are sterile, reactive arthritis after CDI can be considered as an extraintestinal manifestation of CDI. Because we searched for CDIs in extraintestinal sites, cases of reactive arthritis after CDI enteritis could not be detected in our study.

A significant proportion of our patients were alcohol abusers. Alcohol abuse has also been reported in previous reports of an extraintestinal CDIs [13, 32]. It has recently been found that a subgroup of alcoholics has dysbiosis with an altered colonic microbiota with lower median abundances of Bacteroidetes and higher ones of Proteobacteria [41]. Lower abundances of Bacteroidetes have also been observed in the intestinal flora of patients with CDI enteritis [42], suggesting some similarity in the intestinal flora of alcohol abusers and patients with CDI. Such changes in the intestinal microbiota of alcohol abusers may increase the risk of \textit{C. difficile} colonization. It is also possible that alcohol abuse or diseases due to alcohol abuse may suppress immune responses, which could increase the risk of \textit{C. difficile} colonization and infection.

It can be concluded that extraintestinal CDIs are rare and occur in hospitalized patients who often have severe comorbidities. \textit{Clostridium difficile} is usually isolated together with other microbes but may also be the single microbe of the infection. Most extraintestinal CDIs are localized in the abdominal area and result either from intestinal perforation after infection or leakage after surgery. \textit{Clostridium difficile} wound infections may result from contamination by feces. \textit{Clostridium difficile} can cause bacteremia and may enter distant sites through transient bacteremia. Mortality in these patients was high and associated with severe comorbidities.


