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Clostridium difficile bacteremia: report of two cases in French hospitals and comprehensive review of the literature

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Abstract

We report two cases of bacteremia due to *Clostridium difficile* from two French hospitals. The first patient with previously diagnosed rectal carcinoma underwent courses of chemotherapy, and

antimicrobial treatment, and survived the *C. difficile* bacteremia. The second patient with colon perforation and newly diagnosed lung cancer underwent antimicrobial treatment in an ICU but died shortly after the episode of *C. difficile* bacteremia. A review of the literature allowed the identification of 137 cases of bacteremia between July 1962 and November 2016. Advanced age, gastro-intestinal disruption, severe underlying diseases and antimicrobial exposure were the major risk factors for *C. difficile* bacteremia. Antimicrobial therapy was primarily based on metronidazole and/or vancomycin. The crude mortality rate was 35% (21/60).

Keywords: *Clostridium difficile* Bacteremia; Toxin; Treatment; Outcome.

Introduction

Clostridium difficile is an anaerobic gram-positive bacterium responsible for diarrhea. Spectrum of disease ranges from mild diarrhea to severe and complicated colitis, including pseudomembranous colitis, toxic megacolon and death[1–3]. *C. difficile* has been identified as the leading cause of healthcare-associated diarrhea among adults in industrialized countries. Increasing incidence of *C. difficile* infection (CDI) and large hospital outbreaks have been described worldwide[4–7]. This trend is assumed to be due in part to the emergence and rapid spread of a highly virulent strain known as BI/NAP1/027 strain[8–10].

The main risk factors for CDI are antimicrobial exposure, prolonged hospitalization and age over 65 years. Severe underlying diseases are also commonly mentioned as predisposing situations to CDI developing. Any factors that disturb the host-microbiota homeostasis can promote *C. difficile* colonization and infection[11–17]. The most commonly incriminated antimicrobials are cephalosporins and fluoroquinolones but all antimicrobial classes are associated with a risk of CDI and the

antimicrobial stewardship programmes may play a key role in CDI prevention[18–23]. Metronidazole (MTZ), vancomycin (VA) and fidaxomicin (FDX) are the drugs of choice to treat CDI[24,25].

Although *C. difficile*-associated diarrhea incidence is increasing worldwide, extracolonic infections with *C. difficile*, including bacteremia (CDB), remain uncommon. The most commonly reported extraintestinal infections include abdominopelvic abscesses, peritoneal and pleural infections, visceral abscess, as well as bacteremia[26–28]. Here we report two cases of CDB in two French hospitals and give a review of the literature to comprehensively present the clinical features of CDB.

Case report 1

A 54-year-old man was admitted with severe sepsis to the hepato-gastro-enterology unit at Tenon University Hospital, Paris, France, on 10 July 2012. He was febrile and blood cultures were taken during the fever. His blood pressure was 87/55 mm Hg and his pulse rate 83 beats per min; the white blood cell count was 15,200/mm^3 with 12,050/mm^3 neutrophils; the hemoglobin level was 10.3 g/L and that of C-reactive protein was 276 mg/L; urinalysis was unremarkable. His medical history included a rectal adenocarcinoma diagnosed in June 2010. At that time, he underwent surgical resection of the rectosigmoid colon and of hepatic metastases followed by multiple courses of chemotherapy. Postoperatively, a colostomy bag was required. He also underwent radiation therapy. During that period, he had recurrent episodes of urinary tract infections treated with multiple courses of antimicrobials including cefixime, nitrofurantoin and amoxicillin-clavulanate. Five months prior to his admission in July 2012, he developed an abdominal abscess with iliac vein thrombosis that was treated with ceftazidime and MTZ and then with piperacillin-tazobactam and amikacin. In the month preceding his admission, he had sepsis due to extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* that was treated with imipenem.

Blood cultures taken at admission grew an anaerobic gram-positive bacillus identified as *C. difficile* by mass spectrometry (MALDI-TOF, Bruker). A stool sample from the colostomy bag was examined for *C.*

difficile a few days after the blood culture and was found to be positive. It also tested positive for glutamate dehydrogenase antigen (C DIFF Quick Chek® Alere™). A cytotoxicity assay using MRC-5 cells in order to detect free toxins was negative but culture of on selective TCCA (taurocholate, cycloserine, cefoxitin agar) was positive for toxigenic *C. difficile*. The bacteremia was treated with 500 mg intravenous MTZ every eight hours for three days. Repeated blood and stool cultures were negative and the treatment was switched to 500 mg oral MTZ every twelve hours for seventeen days. The patient recovered and was discharged to a palliative-care unit. *C. difficile* isolates from stool and blood cultures were sent to the National Reference Laboratory for *C. difficile* (Saint Antoine Hospital, Paris, France). Both isolates were toxigenic but did not produce the binary toxin. Their PCR ribotypes were identical, did not belong to the 25 most commonly identified PCR ribotypes (i.e., 070, 078/126, 002, 012, 029, 053, 075, 005, 018, 106, 131, 117, 003, 019, 046, 050, 014/020/077, 001, 015, 017, 023, 027, 056, 081 and 087) and were both susceptible to erythromycin, moxifloxacin, VA and MTZ.

Case report 2

A 62-year-old woman was admitted to Pitié-Salpêtrière University Hospital, Paris, France, on 26 June 2013 for fatigue, weight loss and arthralgia. On 27 June, computed tomography (CT) of the chest, abdomen and pelvis revealed a malignant lung lesion associated with pleural effusion and putative secondary cancerous lesions of liver, vertebrae and pelvis. Two days later, the patient was transferred to an intensive care unit because of acute respiratory distress syndrome due to massive pleural effusion and acute pneumonia. Antimicrobial treatment associating cefotaxime (1g three times a day) and spiramycin (3 MIU twice a day) was initiated. On 5 July, the patient developed a distended abdomen and guarding of the left upper and lower quadrants, associated with tachypnea and mottled skin. Abdominal CT showed a pneumoperitoneum. During tomography, a perforation (1 cm) of the sigmoid colon was found and a left hemicolectomy and terminal colostomy were performed. No evidence of peritoneal carcinomatosis was found. Following the operation, the

patient became hypotensive and required fluid resuscitation and vasopressor therapy and she was transferred to an intensive care unit.

On admission to the ICU, she had sepsis-induced tissue hypoperfusion with hypothermia (33.6°C), tachycardia (heart rate, 110 beats per min), leucocytosis (19,000/mm^3), hyperlactatemia (5.6 mmol/L), mottled skin of the lower limbs and cyanosis of the soles of the feet. She was initially given intravenous piperacillin-tazobactam (4 g three times a day); 24 hours later, intravenous ciprofloxacin was added (400 mg twice a day). Peritoneal fluid cultures were positive with polymorphic flora and ESBL-producing *E. coli*. Blood cultures performed between 5 and 7 July were positive with *Bacteroides fragilis* and *C. difficile*. The *C. difficile* toxins A and B were detected with the enzyme immunoassay ImmunoCard® Toxins A&B test (Meridian Bioscience, Cincinnati, OH, USA) directly from colonies. The *C. difficile* isolate was resistant to moxifloxacin and erythromycin and was sent to the National Reference Laboratory for further investigations. Antimicrobial therapy was changed to imipenem (500 mg four times a day) and VA with a loading dose (1 g) followed by continuous infusion (1 g per day). On 10 July, a ventilator-associated pneumonia due to *Stenotrophomonas maltophilia* was diagnosed and treated with intravenous trimethoprim-sulfamethoxazole (400 mg twice a day) and ciprofloxacin (400 mg twice a day). Following five days of treatment with intravenous VA, the treatment was switched to oral MTZ (500 mg three times a day) for 5 additional days. On 21 July, the patient developed rectal ischemia, her general condition worsened and she died on 25 July. Stools collected 48 hours before her death were positive for the toxigenic *C. difficile* strain of PCR ribotype 078/126. The strain was resistant to moxifloxacin and erythromycin but susceptible to VA and MTZ.

Systematic review

Search strategy and selection criteria

The PubMed database was searched using the keywords "*Clostridium* difficile infection", "extraintestinal *C. difficile* infection" (ECD), "*Clostridium difficile* bacteremia" (CDB), and *C. difficile* pathogenesis. Pertinent references included in some of the search results were also reviewed. Relevant articles and abstracts published in English, French and Japanese between 1962 (the first published CDB case) and November 2016 were selected. Among these articles, about 28 with descriptive cases of CDB and 10 other reports including other CDB cases were retrieved. The published reports were heterogeneous. The majority were published as case reports and the others were epidemiological or retrospective studies. The other main publications were related to CDB subject or to the particular features of *Clostridium difficile* pathogenesis. A single author (MD) reviewed the relevant articles and abstracts. A description of the patients' clinical features, treatment and/or outcome was often lacking. The reported cases with missing clinical data about the analyzed parameter were not included in the statistical analysis.

Descriptive statistics were used to determine the mean age and to summarize the distribution of CDB among the cohort of report cases in literature. Statistical analysis was performed using StatView software, version 5.0.0.0 (SAS Institute Inc). Categorical variables were compared using the chi-square test or two-tailed Fisher's exact test where applicable. For all statistical comparisons, results were considered significant when the p value was < 0.05.

Frequency of CDB

To date, 137 CDB cases have been reported in the literature comprising 60 cases (including the 2 cases presented in this report) with detailed clinical patient characteristics. Most commonly reported information included age, sex, underlying diseases, toxinogenicity of the strain, antimicrobial therapy and clinical outcome. Apart from the 60 cases, 77 have been identified in epidemiological reports

aiming at determining the incidence of CDB (Table 1 and 2). The first case of CDB was described in 1962 in a 5-month-old male infant with a 3-week history of coryza, cough, and anorexia[29]. In 1975, Gorbach *et al.* reported one *C. difficile* isolate found among 2,168 positive blood cultures (0.05%) in one general hospital over a 14-month period[30]. During a 10-year period (1985–1995), Wolf *et al.* identified three patients with CDB among 14 patients with ECD in a tertiary-care hospital[31]. Rechner *et al*. identified one isolate of *C. difficile* when retrospectively reviewing the blood cultures positive for *Clostridium* species in two teaching hospitals of ca. 300 and 200 beds, respectively, representing a total of 164,304 hospitalizations[32]. Garcia-Lechuz *et al.* reported two episodes of CDB during a 10-year period (1990–2000) in a large tertiary-care teaching hospital serving a population of approximately 650,000 with an average of 50,000 admissions per year[33]. This corresponds to an incidence of 0.4 cases per 100,000 admissions. Among 25 extraintestinal *C. difficile* infections recorded between 1988 and 2003, Zheng *et al.* found out two isolates from blood cultures but did not report clinical features[34]. Another epidemiological study covering a large Canadian health region (population 1.2 million) conducted over a six-year period (2000–2006) reported a CDB incidence of 0.08 per 100,000 residents per year[35]. This study reported a CDB prevalence of 5% among clostridial bacteremias, which is in line with that of 7% (3/42) reported by McGill *et al.* in England. In this latter study, the rate of CDB between 2004 and 2008 was estimated to be about 0.01% to 0.02% among a total of 320,371 bacteremias[36]. Thus, the National Health Protection Agency in the UK registered 62 CDB cases during 2003-2008 (range: 9-17 per annum) with a tendency for decreasing incidence (no CDB case was reported in the period 2008-2012 and 2010-2014) in England, Wales and Northern Ireland[37–39]. A recent retrospective medical record review conducted from January 1, 2004 through December 31, 2013 as a single-center experience exposed 40 ECD with 11 *C. difficile* bloodstream infections identified among 6525 CDI cases[28]. Other cases have been reported as individual cases and are summarized in the present review (Table 2).

Patient characteristics

Analysis of the 58 cases described in the literature and of the two cases presented here showed that CDB affected male as well as female (33/59, [56%] and 26/59, [44%] respectively). Excluding two neonates, two infants (5 months and 19 months), and one 3-year-old child, the mean age (± standard deviation) was 56.1 ± 19.7 years (range, 12 to 88 years). Concerning infants or neonates, they may have inflammatory intestinal conditions favoring CDI[40,41]. About 47% (28/60) of the described patients are over sixty and among them 35% (21/60) are between 60 and 79 years old. The data suggest that advanced age may be a risk factor for CDB (Figure 1).

Analysis of the data from the combined 60 cases showed that 93% (56/60) of patients had severe underlying diseases (e.g. colon carcinoma, liver cirrhosis, leukemia, cardiovascular disease), 85% (41/48) had abdominal setting (e.g. abdominal pain, diarrhea, bowel surgery, colitis), and 84% (36/43) had previous antibacterial treatment. Interestingly, only three patients (6%) presented diarrhea as the single abdominal symptom, 17% (8/48) developed this symptom with other abdominal disturbances, 62% (30/48) had abdominal signs without diarrhea and the others (7/48, [15%]) presented other clinical features (Table 3). The cases described in the recent experience of Gupta *et al.*, not included in analysing proportions of CDB associated symptoms, were globally reported to have diarrhea for 10 patients of 11 and 3 of 11 with inflammatory bowel disease without specifying if the concerned patients presented other abdominal symptoms. Concerning diarrhea, there was a significant difference between Gupta *et al.* patients and the other literature cases (10/11, [91%] vs. 11/48, [23%]; $p < 0.0001$). However, there was no difference between Lee *et al.* series and the other literature cases with or without Gupta *et al.* cases (4/12 [33%] vs. 7/36 [19%]; $p = 0.43$, and 4/12 [33%] vs. 17/47 [36%] respectively; $p = 1.0$). These data show that CDB is not systematically associated with documented diarrhea while the presence of other abdominal symptoms was associated with bacteremia. Usually CDB was often preceded by gastrointestinal

disorders (e.g. abdominal pain, enterocolitis or surgical and spontaneous disruption of the colon), or by previous exposure to cytotoxic drugs or antimicrobials.

It may be assumed that the bowel is the primary site of clostridial colonization which may predispose *C. difficile* to spread by translocation or intestinal perforation[17,42]. Indeed, monomicrobial CDB was present as frequently as CDB associated with additional pathogens to *C. difficile* (30/60, [50%]), which is similar to the 50% (6/12) of Lee *et al.* series, even if it has been reported that CDB were rather polymicrobial infections probably because of the small number of cases recorded at that time[27,43–45]. In CDB, isolates other than *C. difficile* are often also from the gut flora. This indicates the ability of intestinal bacteria to translocate in patients with bowel damage. However, it is still unclear whether intestinal infection with *C. difficile* is the primary infection that promotes bacterial translocation or whether an underlying disease (e.g. colonic ischemia, intestinal tract disorders or disruption of mucosal barriers) is the initial step that facilitates bacteria dissemination. The use of proton pump inhibitor (PPIs) was not mentioned in the majority of published reports except in one recent study where 9 of 11 patients with CDB (82%) had received PPI for various indications[28].

Strain toxin Production

The potential of *C. difficile* isolates from blood to produce toxins A and B *in vitro* has been rarely investigated. Among the 23 CDB cases where the toxigenic status of blood strains was mentioned, 16 stains were toxigenic (70%) and 7 (30%) were non-toxigenic (Table 3). The direct detection of toxins in blood has never been reported. One bacteremia due to binary-toxin producing strain was reported by Elliott *et al.*[46].

In 26 of the 60 cases, the stools of patients with CDB were tested for *C. difficile*. In ten cases (38%) the isolate was non-toxigenic while in 16 cases (62%) it was toxigenic. Among the 16 patients with CDB due to a toxigenic strain isolated in blood, six had a toxigenic and two a non-toxigenic strain in their stools, the latter suggesting the presence of two different strains in the gut. It is still unknown

whether toxigenic strains may translocate more easily into the blood than non-toxigenic strains. In addition, the rare patients who had only diarrhea, toxin is positive in stools as well as negative but the presence of abdominal symptoms with or without diarrhea appear more common with the presence of toxigenic strain. This data need to be further investigated.

About a third of the reviewed cases have non documented toxin status for both blood and stool (19/60, 32%). In blood, most toxigenic status of isolated strains (37/60, 62%) was lacking, possibly due to the non-systematic toxin search in extra-intestinal samples. Indeed, stools were not tested in more than half of cases (34/60, 57%), which is perhaps likely due to the absence of diarrhea.

Typing of strains isolated from blood culture has been rarely reported, probably because molecular typing was uncommon when CDB cases were described in the early 1990s. Gérard *et al.* characterized a serogroup C strain and McGill *et al.* reported two ribotype 106 strains and one ribotype 001[36,47]. Another case report detected a ribotype 106 from bacteremia and breast abscess[48]. One of two bacteremia cases recently reported by Hemminger *et al.* was due to the epidemic and hypervirulent NAP1 strain (027/BI, toxinotype III, binary toxin-positive), and the other was due to NAP-4[49]. In the present series, Case 2 was due to a strain of ribotype 078/126 which is one of the ribotypes most frequently found in France[50]. So far, there is no evidence indicating that one specific ribotype may be more often responsible for CDB than another.

Mortality

CDB-associated mortality rates vary among studies. The present comprehensive review indicates a crude mortality rate of 35% (n = 21/60) which is in line with the early reviews of Jacobs *et al.* and Libby *et al.* (20% [2/10], p = 0.48; 53% [8/15], p = 0.19 respectively), with that reported by Lee *et al.* (41.7%, 5/12, p = 0.75) and also similar to the recent study of Gupta *et al.* (27% [3/11], p = 0.74)[27,28,43,44]. The latest review of Kazanji *et al.* concluded to the same rate (39%, p = 0.68)[51].

However, the mortality attributable to CDB remains difficult to assess because many patients with CDB have severe co-morbidities and underlying conditions.

Treatment

Antimicrobial therapy for CDB was highly variable and most of the time adapted to cover polymicrobial bacteremia. As CDB is a rare infection, there are no studies or specific guidelines for the appropriate therapy, but metronidazole (MTZ) and vancomycin (VA) are the commonly treatment options used to deal with CDB[27,28,43]. In CDB Case 1 we reported here, the patient was treated first with intravenous (IV) and then oral MTZ, and the septicemia rapidly resolved. Most commonly used treatments include VA or MTZ alone or in combination and in this review about 67% (35/52) had one of these two antimicrobials or both and eight patients had their therapeutic coverage not specified (Table 4). Treatment was usually started intravenously and continued orally. Sixteen patients were treated with MTZ (one IV and orally, one orally, not specified in the remaining cases), ten with VA (three IV, two orally and IV, one orally, four not specified) and nine with VA or MTZ sequentially or simultaneously (usually IV initially, then orally). These specific treatments against *C. difficile* were used alone or associated with other antimicrobials and surgery. MTZ and VA are usually associated with other antimicrobials with extended spectrum and against anaerobes according to the clinical setting. Of note, patients with MTZ, VA or both had a reduced rate of mortality than those with other antimicrobials (22% [6/27], 75% [6/8]; p = 0.011). The crude mortality rate in patients managed with associated medical and surgical therapy was 20% (7/35) compared to 59% (10/15) in those who did not receive antimicrobial therapy including MTZ or VA or both (p = 0.005). Therefore, management with medical therapy involving drugs against *C. difficile* appears to prevent death during CDB episode. Hence, the choice of treatment, the way the drugs are administered and the treatment duration may change but early patient management and antibacterial coverage may critically influence outcome.

In conclusion, CDB remains uncommon. It occurs mostly in patients with risk factors such as chronic underlying diseases, advanced age, coexisting gastrointestinal pathologic conditions and antimicrobial exposure. Outcome depends on various factors including early diagnosis, severity of the underlying conditions and antimicrobial therapy. MTZ and VA are the two drugs currently used to cover CDB. However, it is difficult to assess the most effective treatment since data on outcome are not systematically reported.

Contributors

M. DOUFAIR, reviewed the literature, wrote the text and set figure and tables. F. BARBUT and C. ECKERT provided help and advices for writing. C. AMANI-MOIBENI and J-D. GRANGE wrote the case 1 whereas L. DRIEUX and L. BODIN wrote the second case. M. DENIS gave advices concerning clinical management.

Declaration of interests

We declare that we have no competing interests

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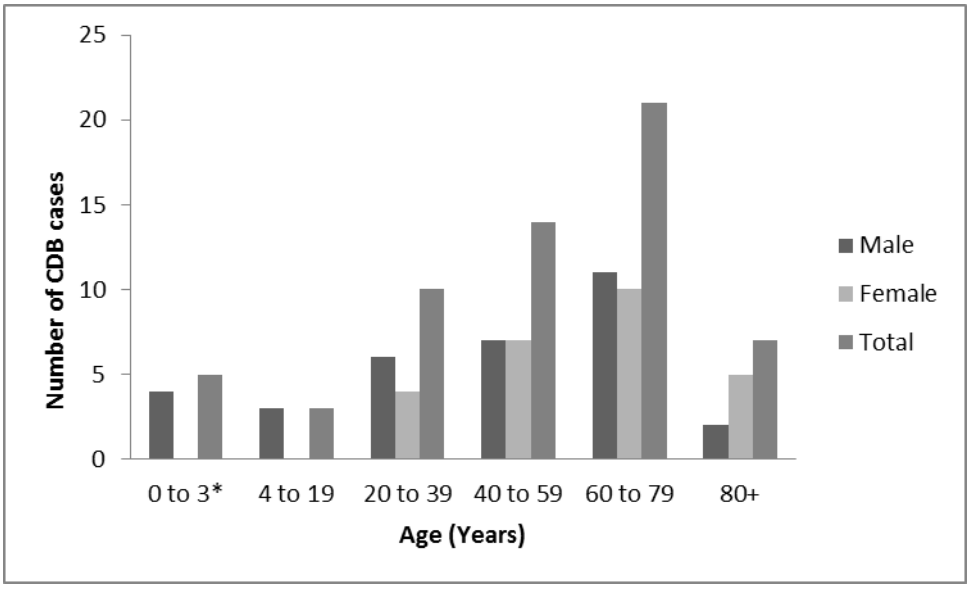

Figure 1. Distribution of the 60 recorded CDB cases according to age and sex. (*: 1 neonate with not reported sex by Bergamo *et al.*)

Table 1. Epidemiology of *C. difficile* bacteremias reported in the literature

Period	Country	Number of CDB cases[a]	Incidence	Reference
1962-1969	USA	3 Isolates/86 nonhistotoxic clostridial bacteremias (laboratory isolates)*	0.4	[42,52]
15 months	USA	1 Blood culture isolate (Anaerobe study)*	0.8	[53]
14 months	USA	1 CDB/2168 bacteremias*	0.9	[30]
1985-1995	USA	3 CDB/14 ECD[2]	0.3	[31]
1990-1997	USA	1/164 304 hospitalizations*	0.13	[32]
1990-2000	Spain	2 CDB/21 ECD (50 000 admissions/year)[b]	0.2	[33]
1988-2003	USA	2 Blood culture isolates/25 ECD*	0.2	[34]
2000-2006	Canada	7 CDB/1.2 million residents*	1	[35]
2004-2008	UK	62 CDB/320 371 bacteremias*	9 to 17	[36,37]
2008-2012	UK	0	0	[38]
2010-2014	UK	0	0	[39]
1989-2009	Taiwan	12 CDB/2 medical centers[b,c]	0.6	[43]
2002-2012	Finland	2 CDB/31 ECD[b]	0.2	[54]
2004-2013	USA	11 CDB/40 ECD/6525 CDI[b]	1.1	[28]
1962-2016	All countries	Total: 137 (the 58 published cases[b], the two present cases[b] and 77* cases in other reports)		Present review

[a]: CDB cases of each study or literature review when clearly mentioned in articles or reports. [b]: Cases with clinical data reported in table 2. [c]: 1,100-bed and 2,800-bed tertiary-care hospitals in Taiwan. *: cases not available with clinical data but exposed in other reports in the reviewed literature.

Table 2. Summary of the 58 well-documented *C. difficile* bacteremia cases (1962–2016) reviewed in this study and the present two cases.

Age/sex	Underlying conditions	Clinical presentation	Antimicrobial exposure[1]	Strain toxicity from blood/stool	Other organisms in blood culture	Clinical management	Outcome	Year[Reference]
5 months/M	None	Cough, coryza, anorexia	NR	NR/NR	None	NR	NR	1962[29]
19 months/M	Pseudomembranous NEC, systemic carnitine deficiency (recurrent hypoglycemia and cirrhosis)	Frequent sepsis, diarrhea, vomiting, peritonitis	ampicillin + gentamicin	Yes/NR	None	NR	Died	1982[40]
68/M	Cirrhosis, chronic pancreatitis	Jaundice, ascites, encephalopathy, splenic abscess	None	NR/NR[2]	None	Penicillin G, DAT	Died	1983[55]
Neonate/M	Prematurity, neonatal NEC	Fever, respiratory distress, abdominal distension, necrotic bowel, peritonitis	Ampicillin + kanamycin	Yes[3]/NR	*S. epidermidis*[3] (contaminant)	Ampicillin + kanamycin Surgery, DAT	Died	1984[56]
65/M	Arteritis of legs and gangrene	Diarrhea and colitis 6th day, septicemia 10th day postoperative	Cefuroxime, vancomycin	Yes/No	*B. fragilis*	Cefuroxime, **MTZ**	Recovered	1984[57]

35/F	AML, neutropenia	Fever, abdominal pain, diarrhea	Cefotaxime + gentamicin	Yes/Yes	*Bacteroides sp., Gr. D streptococci*	iv **MTZ** + oral **VA**	Died	1985[58]
69/F	Acute lymphoblastic leukemia, chemotherapy corticosteroids	Abdominal distension, peritonitis, toxic megacolon, bilateral psoas abscesses	Yes	Yes/Yes	*Bacteroides sp., E.coli*	Cloxacillin, Co, iv **MTZ**, ampicillin**,** gentamicin	Died	1985[58]
62/M	Hypertension, coronary surgery, appendectomy, cholecystectomy, aortofemoral bypass, *C. difficile* septicemia 5 months before	Fever, nausea, vomiting, left pleural effusion, splenic abscess	Piperacillin, netilmicin	NR/NR	None	Splenectomy **MTZ**, cefoxitin	Recovered	1987[59]
39/M	Oropharynx cancer	Left mandible radionecrosis, hypotension, fever, acute diverticulitis	NR	Yes/Yes	*E. coli, E. faecalis, B. vulgatus*	iv **MTZ**, iv and oral **VA**, pefloxacin	Recovered	1989[47]
85/F	Chronic pulmonary disease, heart failure, dementia, sinus bradycardia, ischemic attack, pneumonia	Recurrent diarrhea, fever hypotension	VA	NR/Yes	*E. faecalis*	iv **VA**, gentamicin	Recovered	1995[26]

18/M	None	Treated for exudative sore throat, fever, chills, abdominal pain, vomiting, diarrhea	Erythromycin, lincomycin	NR/Yes	None	Oral **VA**	Recovered	1996[60]
78/M	None	Trauma; pneumonia, fever, watery diarrhea	Ofloxacin, clindamycin, cefuroxime, amikacin	NR/No	None	Oral and iv **VA**	Recovered (died from nosocomial pneumonia)	1996[60]
3/M	Thalassemia minor, 5 episodes of tonsillitis	Fever, odynophagia, acute pericarditis, pericardial effusion, mild GI signs	Amoxicillin-clavulanic acid, cefixime, cefotaxime	Yes/NT	None	iv **VA**	Discharged	1998[61]
17/M	Duchenne muscular dystrophy	Ileus with small-bowel obstruction	Yes	NT/NT	*Candida parapsilosis*	NR	Recovered	1998[31]
33/F	Metastatic cervical cancer	Pelvic abscesses, recto-vaginal fistula after radiotherapy	Yes	NT/NT	*C. cadaveris, B. melaninogenicus, Fusobacterium species*	NR	Died	1998[31]
77/M	Severe emphysema, corticosteroid therapy	Perforated sigmoid diverticulum	Yes	NT/NT	*Eubacterium lentum*	NR	Died	1998[31]

66/M	Infiltrating bladder cancer	Intestinal invasion of the advanced bladder cancer, pyelonephritis	NR	NR/NT	*E. faecium, B.fragilis*	Imipenem	Died	2001[33]
65/M	Obesity	Ischemic colitis after cardiac surgery, bacteremic peritonitis	NR	NR/NT	*E. faecium, B. ovatus*	Ceftriaxone, ciprofloxacin	Died	2001[33]
66/M	AML, immunodepression, chemotherapy	Fever, pancytopenia, anal margin abscess and diarrhea	C3G+ FQ	NR/NR	None	Ofloxacin, **MTZ**, abscess drainage	Recovered	2001[62]
69/F	3rd degree burn injuries	Skin operation, fever, abdominal pain and severe diarrhea	Cefazolin, flomoxef	Yes/Yes	*E. faecalis, E.casseliflavus*	oral and iv **VA**	Recovered	2004[63]
50/M	Crohn's disease with chemotherapy	Nausea, abdominal abscess, small-bowel obstruction, bowel surgery, jejunum adenocarcinoma	Ampicillin /sulbactam + gentamicin	NR/No	None	Pip-Taz	Recovered	2009[45]
40/F	AML, Dermatomyositis, corticosteroid treatment	Fatigue, weight loss, fever, tachycardia	Yes, unknown antimicrobials	NR/NT	None	Cefepime, **MTZ**, iv **VA**	Died	2009[27]

40/M	Alcoholism, liver failure, bone marrow suppression, pancreatitis, and recurrent pneumonia.	Vomiting, diarrhea, abdominal pain, fever	Cephalexin	No[4]/NR	*Staphylococcus epidermidis* (contaminant)	Ceftriaxone	Discharged[5]	2009[46]
1989-2009	**Taiwan, 12 patients[43]:**							
69/F	Liver cirrhosis	NR (Dead on arrival)	NR	Yes/NR	None	None	Died	2010
38/M	Wilson's disease	Abdominal pain	NR	No/NR	None	Cefmetazole	Died	2010
65/F	Perforated peptic ulcer	Fever, abdominal pain	NR	NR/NR	None	**MTZ**	Died	2010
58/M	Liver cirrhosis	Fever, abdominal pain	NR	No/NR	None	**MTZ**	Recovered	2010
12/M	Biliary atresia, liver transplantation	Fever, dyspnea	NR	No/NR	None	Pip-Taz, **VA**	Recovered	2010
41/F	Pulmonary fibrosis	Fever, dyspnea	NR	No/NR	None	Ceftazidime, gentamicin, **VA**	Recovered	2010
45/M	Liver cirrhosis	Abdominal pain	NR	Yes/NR	*CNS spp.*	Ceftriaxone	Died	2010
83/M	None	GI bleeding , hypovolemic shock, fever, bloody stool	NR	No/NR	*E. coli*	Imipenem	Died	2010

87/F	Congestive heart failure, end-stage renal disease, pseudomembranous colitis	Bloody stool	NR	Yes/NR	*P. aeruginosa, E.faecium, E. coli, ESBL-K. oxytoca*	**VA**, meropenem	Recovered	2010
80/F	Liver cirrhosis, pseudomembranous colitis	Bloody stool	NR	Yes/NR	*CNS spp.*	**MTZ**	Recovered	2010
66/F	Femoral neck fracture (hip replacement with prosthetic infections), chronic kidney disease	Fever, lower GI bleeding, abdominal pain	NR	No/NR	*E. cloacae*	Debridement cefepime, **MTZ**	Recovered	2010
75/F	Lymphoma, biliary tract infection	Fever, chills, nausea, vomiting, abdominal pain	NR	NR/NR	*K. pneumoniae, C.perfringens*	Cefepime, **MTZ**	Recovered	2010
39/M	Alcohol dependency	Jaundice, vomiting, fecal incontinence	None	NR/NR	None	Cefuroxime, **MTZ**	Discharged	2011[36]
20/M	Juvenile polyposis syndrome, elective subtotal colectomy	UTI, small-bowel resection and end-ileostomy, CD ileitis	Cephradine, Pip-Taz	NR/Yes	None	Oral **VA**, meropenem, iv **MTZ**	Discharged	2011[36]
67/M	Ulcerative colitis	GI bleed	None	NR/Yes	None	None	Discharged	2011[36]
39/F	Chronic hepatitis,	Menorrhagia,	Cefotaxime	NR/NR	None	**MTZ** +	Recovered	2011[48]

	chronic alcoholic liver disease	spontaneous bruising, jaundice. 3rd week: fever, rectal bleed, varices, gastritis, breast abscess				amoxicillin /clavulanic		
83/M	CAD, chronic hemodialysis, diverticulitis and peptic ulcer disease	Fever, abdominal pain, nausea, vomiting, bleeding post gastrostomy tube placement	Amikacin, VA, Pip-Taz	Yes/No	None	**MTZ**	Recovered	2011[49]
39/M	Gastric adenocarcinoma, chemotherapy and chemoradiation	Abdominal pain, vomiting and obstipation	None	Yes/NT	*Candida glabrata*	NR	Recovered then discharged	2011[49]
60/M	Metastatic prostate cancer	Fever, abdominal pain, hematochezia, hydronephrosis, rectal stricture, loop ileostomy	VA + meropenem, ticarcillin, piperacillin + MTZ	NR/No	None	NR	Discharged	2013[64]
72/F	Colon cancer with peritoneal carcinosis	Tumor resection, colon fistula to skin and bladder, diarrhea	NR	NR/NR	*B. fragilis*	NR	Died	2013[54]

69/M	Paraparesis, recurrent UTI	Ischemic colitis, diarrhea, operation for abdominal aneurysm	Yes for UTI	NR/NR	None	Surgery (Aneurysm prosthesis)	Recovered	2013[54]
57/M	Mantle cell lymphoma	Abdominal pain, intra-abdominal tumor and cecum perforation	None	NR/NR	None	iv **VA** + **MTZ**	Recovered then discharged	2013[65]
2004-2013	**USA, 11 patients:**	**10/11 had diarrhea**	**All of them**	**11NT/5Yes** **(10 stools tested)**	**3 Monomicrobial**	**1 ATB/10 surgery+ATB**	**3 Died/8 Recovered**	**2014**[28]
88/F	Peptic ulcer disease after partial gastrectomy	*C. difficile* colitis, lower gastro-intestinal bleed	Yes		*B. fragilis, E. coli, P. aeruginosa*	oral **MTZ**, iv cefepime, iv ciprofloxacin	Recovered	2014
75/F	Squamous cell carcinoma of mouth after resection	Cecal impaction and rupture after laparotomy	Yes		*Candida tropicalis*	Abdominal washouts, meropenem	Died 17 days later	2014
46/F	Hepatic adenoma after resection	Alcoholic hepatitis and ascites	Yes		*Enterococcus* species, *Candida* species, *Klebsiella* species	Paracentesis, **MTZ**, cefepime	Recovered	2014
41/F	Alcohol abuse after inguinal hemia repair	Recurrent groin cellulitis	Yes		*Clostridium orbiscindens*	Debridement of groin infection, meropenem, linezolid	Recovered	2014

47/F	Crohn disease, multiple suicide attempts after self-stab to abdomen leading to liver laceration	Self-inflicted abdominal wounds, suspicion for factitious contamination	Yes		*Enterococcus* species, *Clostridium ramosum*, *Bacteroides* species	Wound debridement Pip-Taz	Recovered	2014
79/F	Colorectal cancer after resection, *C. difficile* colitis	Ovarian cyst after oophorectomy, postoperative confusion, ascites	Yes		None	Paracentesis, **VA**, Pip-Taz	Died 7 days later	2014
80/F	Diabetes mellitus, congestive heart failure, COPD, stroke	Diverticulitis after laparotomy	Yes		*E. coli*	Abdominal washout, cefepime	Died 6 days later	2014
51/F	Ileal neuroendocrine tumor, Crohn disease after ileal and sigmoid resection, *C. difficile* colitis	Anastomotic breakdown and postoperative fever	Yes		None	Anastomotic takedown, colostomy, washout, levofloxacin, **MTZ**	Recovered	2014
35/M	Congenital pancreatic duct abnormality after pancreatectomy, splenectomy, *C. difficile* colitis	Recurrent polymicrobial bacteremia and skin abscesses	Yes		*Blautia coccoides*, *K. pneumoniae*, *E. coli*	Skin debridement meropenem, linezolid	Recovered	2014

56/F	COPD, concurrent *C. difficile* colitis, small intestinal bowel obstruction after adhesiolysis	Abdominal compartment syndrome, surgical wound infection	Yes		None	Wound debride, **MTZ**, **VA**	Recovered	2014
27/F	Crohn disease, recurrent *C. difficile* colitis	Previous right hemicolectomy and ileostomy	Yes		*Citrobacter* species, *Streptococcus anginosus*	Anastomotic takedown, washout, **MTZ**, **VA**, ertapenem	Recovered	2014
40/M	Alcohol liver disease	Abdominal pain, vomiting, cirrhosis, gastrohepatic varices, colitis	None	NR/Yes	None	iv **VA** + Pip-Taz	Died	2015[51]
Neonate/NR	NEC	Large bowel wall pneumatosis with out perforation	None	NT/NT	None	**VA**+ **MTZ** +gentamicin, Pip-Taz + **MTZ**	Recovered	2016[66]
54/M	Rectal adeno-carcinoma, colostomy, chemotherapy	Severe sepsis	Imipenem	Yes/Yes	None	iv and oral **MTZ**	Recovered	Present Case 1
62/F	Lung cancer with cancerous lesions of liver, vertebrae and	Colon perforation, hemicolectomy and end colostomy	Cefotaxime + spiramycin, Pip-Taz,	Yes/Yes	*B. fragilis*	iv **VA**, oral **MTZ**, other antimicrobials	Died	Present Case 2

	pelvis		ciprofloxacin					

NR (Not reported), NT (Not tested), [1]: Antimicrobial exposure in the 3 months preceding CDB. [2]: Abscess toxin +, [3]: Heart Blood (Autopsy), [4]: A-B- Binary toxin +, [5]: Discharged: Home or hospice care. CNS: Coagulase-negative *Staphylococcus spp.*, DAT: diagnosis at autopsy, UTI: urinary tract infection, iv: intravenous, GI: gastrointestinal, NEC: Necrotizing enterocolitis, AML: Acute myeloid leukemia, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, VA: Vancomycin, MTZ: Metronidazole, Co: Cotrimoxazole, Pip-Taz: Piperacillin – Tazobactam, C3G: Third cephalosporin generation, FQ: Fluoroquinolone, ATB: antibacterial.

Table 3. Overview of the *C. difficile* toxinogenic status both in blood and in stools and its relationship with the clinical setting

Toxin status in Blood/Stools	Diarrhea	Diarrhea and abdominal signs	Abdominal features	Other symptoms	NR*	Gupta *et al. cases*	Total
Yes/Yes	-	2	3	1	-	-	6
Yes/No	-	1	1	-	-	-	2
Yes/NR	-	1	6	-	1	-	8
No/NR	-	1	4	2	-	-	7
NT/Yes	1	1	3	-	-	5	10
NT/No	1	-	2	-	-	5	8
NR, NT/NR, NT	1	2	11	4	-	1	19
Total	3	8	30	7	1	11	60

NR (Not reported), NT (Not tested), * One of Lee *et al.* cases: dead on arrival

Table 4. Clinical management of the 60 patients with CDB and the crude rate of mortality

<table>
<tr><td rowspan="2">Medical Management</td><td colspan="3">MTZ or/and VA</td><td rowspan="2"></td><td rowspan="2">Other ATB</td><td rowspan="2">Other ATB and Surgery</td><td rowspan="2">Surgery alone</td><td rowspan="2">No therapy</td><td rowspan="2">NR*</td><td rowspan="2">Total*</td></tr>
<tr><td>Type</td><td>CD therapy</td><td>CD therapy and surgery</td></tr>
<tr><td rowspan="6">No. of patients (No. of death)</td><td>MTZ</td><td>5 (1)</td><td>0</td><td rowspan="6"></td><td rowspan="6">8 (6)</td><td rowspan="6">5 (2)</td><td rowspan="6">2 (1)</td><td rowspan="6">2 (1)</td><td rowspan="6">8 (4)</td><td rowspan="6">60 (21)*</td></tr>
<tr><td>MTZ + ATB</td><td>6 (1)</td><td>5 (0)</td></tr>
<tr><td>VA</td><td>4 (0)</td><td>0</td></tr>
<tr><td>VA + ATB</td><td>5 (1)</td><td>1 (1)</td></tr>
<tr><td>MTZ + VA</td><td>2 (1)</td><td>1 (0)</td></tr>
<tr><td>MTZ + VA + ATB</td><td>5 (2)</td><td>1 (0)</td></tr>
<tr><td rowspan="4">Rate of mortality, p value</td><td></td><td>22% (6/27)</td><td>13% (1/8)</td><td></td><td>75%</td><td>40%</td><td rowspan="2">50%</td><td rowspan="3">50%</td><td rowspan="3">50%</td><td rowspan="3">35%*</td></tr>
<tr><td colspan="6">20% (7/35) vs. 62% (8/13), p = 0.012</td></tr>
<tr><td colspan="7">20% (7/35) vs. 60% (9/15), p = 0.009</td></tr>
<tr><td colspan="8">20% (7/35) vs. 59% (10/17), p = 0.005</td></tr>
</table>

MTZ: Metronidazole, VA: Vancomycin, ATB: other antibacterial, CD therapy: *C. difficile* therapy (MTZ or/and VA), NR (Not reported). * The case reported by Smith *et al.* with NR therapy and NR outcome status, accounted in mortality rate, did not change the conclusion. Surgery included all operations and other procedures used to resolve CDB and the implicated source of bacteria dissemination (e.g. abdominal washout, debridement).