Case report

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

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A B S T R A C T

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).

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I n t r o d u c t i o n

*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, extraintestinal 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.

C a s e   r e p o r t

A 54-year-old man was admitted with severe sepsis to the hepatogastronenterology 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/mm³ with 12,050/mm³ 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 anti-microbials 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 cefazidime 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 cytotoxic 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, 065, 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 (1 g 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), leukocytosis (19,000/mm³), 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 h 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 h before her death were positive for the toxigenic C. difficile strain of PCR.

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

| Period     | Country | Number of CDB cases | Incidence | Reference |
|------------|---------|---------------------|-----------|-----------|
| 1962–1969  | USA     | 3 Isolates/86 nonhistotoxic clostridial bacteremias (laboratory isolates) | 0.4       | [42,52]   |
| 15 months  | USA     | 1 Blood culture isolate (AnaeroDE study) | 0.8       | [53]      |
| 14 months  | USA     | 1 CDB/2168 bacteremias | 0.9       | [30]      |
| 1985–1995  | USA     | 3 CDB/14 ECD² | 0.3       | [31]      |
| 1990–1997  | USA     | 1/164 304 hospitalizations | 0.13      | [32]      |
| 1990–2000  | Spain   | 2 CDB/21 ECD (50 000 admissions/year) | 0.2       | [33]      |
| 1988–2003  | USA     | 2 Blood culture isolates/25 ECD | 0.2       | [34]      |
| 2000–2006  | Canada  | 11 CDB/12 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 | 0.6       | [43]      |
| 2002–2012  | Finland | 2 CDB/31 ECD | 0.2       | [54]      |
| 2004–2013  | USA     | 11 CDB/40 ECD/6525 CDB | 1.1       | [28]      |
| 1962–2016  | All countries | Total: 117 (the 58 published cases, the two present cases and 77 cases in other reports) | Present review | |
| Age/sex | Underlying conditions | Clinical presentation | Antimicrobial exposure¹ | 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 abscesses | None | NR/NR² | None | Penicillin G, DAT | Died | 1983 | [55] |
| Neonate/M | Prematurity, neonatal NEC | None | Ampicillin + kanamycin | Yes³/NR | S. epidermidis³ (contaminant) | Ampicillin + kanamycin Surgery, DAT | Died | 1984 | [56] |
| 65/M | Arteritis of legs and gangrene | Diarrhea and colitis | 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., G. D streptococci | iv MTZ + oral VA | Died | 1985 | [58] |
| 69/F | Acute lymphoblastic leukemia, chemotherapy corticosteroids | Abdominal distension, peritonitis, toxic megacolon, bilateral posas abscesses | Yes | Yes/Yes | Colistin, Co, iv MTZ, ampicillin, gentamicin | Died | 1985 | [58] |
| 62/M | Hypertension, coronary surgery, appendectomy, cholecystectomy, aortofemoral bypass, C. difficile septicaemia 5 months before | None | Piperacillin, netilmicin | NR/No | None | Splenectomy MTZ, cefoxitin | Recovered | 1987 | [59] |
| 39/M | Oropharynx cancer | Left mandible radionecrosis, hypotension, fever, acute diverticulitis, recurrent diarrhea, fever hypotension | Cefuroxime, vancomycin | 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 | None | 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 | 1996 | [60] |
| 3/M | Thalassemia minor, 5 episodes of tonsillitis | Fever, odynophagia, acute pericarditis, pericardial effusion, mild GI signs fluus with small-bowel obstruction | Amoxicillin-clavulanic acid, cefixime, cefotaxime | Yes/NT | None | iv VA | Discharged | 1998 | [61] |
| 17/M | Duchenne muscular dystrophy | Pelvic abscesses, recto-vaginal fistula after radiotherapy | Yes | NT/NT | Candida parapsilosis, C. caudaveris, B. melaninogenicus, Fusobacterium species | NR | Recovered | 1998 | [31] |
| 33/F | Metastatic cervical cancer | Yes | NT/NT | Escherichia coli, E. faecium, B. fragilis | Impenem | Died | 2001 | [33] |
| 77/M | Severe emphysema, corticosteroid therapy | Perforated sigmoid diverticulitis | Yes | NT/NT | E. coli, E. faecium, B. fragilis | imipenem | Died | 2001 | [33] |
| 66/M | Infiltrating bladder cancer | Intestinal invasion of the advanced bladder cancer, pyelonephritis | NR | NT/NT | Ceftriaxone, ciprofloxacin | Died | 2001 | [33] |
| 65/M | Obesity | Ischemic colitis after cardiac surgery, bacterial peritonitis | NR | NT/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/No | None | Ofloxacin, MTZ, abscess drainage | Recovered | 2001 | [62] |
Table 2 (Continued)

| Age/sex | Underlying conditions                                                                 | Clinical presentation                                                                 | Antimicrobial exposure\(^1\)                                                                 | Strain toxicity from blood/stool | Other organisms in blood culture | Clinical management | Outcome | Year | Reference |
|---------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|---------------------|---------|------|-----------|
| 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, jejenum 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                                              | Cephalixin                                                                                 | No\(^4\)/NR                     | Staphylococcus epidermidis (contaminant) | Ceftriaxone          | Discharged\(^3\) | 2009 | [46]      |
| 1989–2009 | Taiwan, 12 patients \([43]\):                                                       |                                                                                        |                                                                                             |                                 |                                 |                     |                     |      |           |
| 69/F    | Liver cirrhosis Wilson’s disease                                                      | Abdominal pain, Fever, abdominal pain                                                 | NR                                           | (Dead on arrival)                | None                            | None                | Died               | 2010 |           |
| 65/F    | Perforated peptic ulcer                                                                | Abdominal pain, Fever, abdominal pain                                                 | NR/No                                        | None                            | None                            | Cefmetazol           | Died               | 2010 |           |
| 58/M    | Liver cirrhosis                                                                          | Fever, abdominal pain                                                                  | NR                                           | No/No                           | None                            | MTZ                 | Recovered          | 2010 |           |
| 12/M    | Biliary atresia, liver transplantation                                                  | Fever, dyspnea                                                                         | NR                                           | No/No                           | None                            | Pip-Taz, VA          | Recovered          | 2010 |           |
| 41/F    | Pulmonary fibrosis                                                                       | Fever, dyspnea                                                                         | NR                                           | No/No                           | None                            | Cefazidime, gentamicin, VA | Recovered          | 2010 |           |
| 45/M    | Abdominal pain                                                                          | GI bleeding, hypovolemic shock, fever, bloody stool                                    | NR                                           | No/No                           | CNS spp.                       | MTZ                 | Recovered          | 2010 |           |
| 83/M    | Liver cirrhosis                                                                          | Abdominal pain                                                                        | NR                                           | Yes/No                          | E. coli                        | Ceftriaxone Imipenem | Died               | 2010 |           |
| 87/F    | Congestive heart failure, end-stage renal disease, pseudomembranous colitis            | Bloody stool                                                                          | NR                                           | Yes/No                          | P. aeruginosa, E. faecium, E. coli, ESBL-K. oxyroca | VA, meropenem         | Recovered          | 2010 |           |
| 80/F    | Liver cirrhosis, pseudomembranous colitis                                              | Bloody stool                                                                          | NR                                           | Yes/No                          | CNS spp.                       | MTZ                 | Recovered          | 2010 |           |
| 60/F    | Femoral neck fracture (hip replacement with prosthetic infections), chronic kidney disease | Fever, lower GI bleeding, abdominal pain                                              | NR                                           | No/No                           | 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, falc Incontinence, ascites, Billerlysis, CD ileitis                 | None                                          | NR/NR                          | None                            | Cefuroxime, MTZ      | Recovered          | 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, chronic alcoholic liver disease                                      | Menorrhagia, spontaneous bruising, jaundice, 3rd week: fever, rectal bleed, varices, gastritis, breast abscess | Cefotaxime                                  | NR/NR                          | None                            | MTZ + amoxicillin/oral | Recovered          | 2011 | [48]      |
| 83/M    | CAD, chronic hemodialysis, diverticulitis and peptic ulcer disease                      | Fever, abdominal pain, nausea, vomiting, bleeding post gastroscoy tube placement       | Amikacin, VA, Pip-Taz                      | Yes/No                          | None                            | MTZ                 | Recovered          | 2011 | [49]      |
| 39/M    | Gastric adenocarcinoma, chemotherapy and chemorporation                                 | 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                                                    | NR/NR                                        | None                            | None                            | NR                   | Discharged          | 2013 | [64]      |
| Age/sex | Underlying conditions | Clinical presentation | Antimicrobial exposure | Strain toxicity from blood/stool | Other organisms in blood culture | Clinical management | Outcome | Year | Reference |
|---------|-----------------------|-----------------------|------------------------|----------------------------------|----------------------------------|----------------------|---------|------|----------|
| 72/F    | Colon cancer with peritoneal carcinoma | Hydronephrosis, rectal stricture, loop ileostomy | VA + meropenem, ticarcillin, piperacillin + MTZ | NR/NR | B. fragilis | NR | Died | 2013 | [54] |
| 69/M    | Paraparesis, recurrent UTI | Tumor resection, colon fistula to skin and bladder, diarrhea | Yes for UTI | Yes | None | None | Surgery (Aneurysm prosthesis) | Recovered | 2013 | [54] |
| 57/M    | Mantle cell lymphoma | Ischemic colitis, diarrhea, operation for abdominal aneurysm | None | None | None | iv VA + MTZ | Recovered then discharged | 2013 | [65] |
| 2004–2013 USA, 11 patients: | 10/11 had diarrhea | All of them | 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 gastrointestinal 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 | Entercoccus species, Clostridium perfringens | Paracentesis, MTZ, cefepime | Recovered | 2014 |
| 41/F    | Alcohol abuse after inguinal hema | Recurrent groin cellulitis | Yes | | Clostridium orboscedens | 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 perfringens, Bacteroides species | Enterococcus species, Clostridium perfringens | Paracentesis, VA, Pip-Taz | Recovered | 2014 |
| 79/F    | Colorectal cancer after resection, C. difficile colitis | Ovarian cyst after oophorectomy, postoperative confusion, ascites | Yes | | Clostridium perfringens | Paracentesis, VA, Pip-Taz | Died 7 days later | 2014 |
| 80/F    | Diabetes mellitus, congestive heart failure, COPD, stroke | Diverticulitis after laparotomy | Yes | None | Enterococcus species, Clostridium perfringens | Paracentesis, VA, Pip-Taz | 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 | 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 | None | None | Anastomotic takedown, washout, MTZ, VA, meropenem | Recovered | 2014 |
| 56/F    | COPD, concurrent C. difficile colitis, small intestinal bowel obstruction after adhesiolysis | Abdominal compartment syndrome, surgical wound infection | Yes | None | None | Wound debride, MTZ, VA | Recovered | 2014 |
| 27/F    | Crohn disease, recurrent C. difficile colitis | Previous right hemicolectomy and ileostomy | Yes | None | None | Anastomotic takedown, washout, MTZ, VA, ertapenem | Recovered | 2014 |
| 40/M    | Alcohol liver disease | Abdominal pain, vomiting, cirrhosis, gastrohepatic varices, colitis | None | None | None | iv VA + Pip-Taz | Died | 2015 | [51] |
| Neomate/ | NEC | Large bowel wall pneumatisis with perforation | None | None | None | VA + MTZ + gentamicin, Pip-Taz + MTZ | Recovered | 2016 | [66] |
| 54/M    | | Severe sepsis | Imipenem | Yes/Yes | None | iv and oral MTZ | Recovered | | | |
Table 2 (Continued)

| Age/sex. | Underlying conditions | Clinical presentation | Antimicrobial exposure | Strain toxicity from blood/ stool | Other organisms in blood culture | Clinical management | Outcome | Year | Reference |
|----------|-----------------------|-----------------------|------------------------|----------------------------------|----------------------------------|---------------------|---------|------|-----------|
| 62/F     | Rectal adenocarcinoma, colostomy, chemotherapy of colon cancer with invasive lesions of liver, vertebral and pelvic area | Colon perforation, hemicolectomy and end colostomy | Cefotaxime + spiramycin, Pip-Taz, ciprofloxacin | Yes/Yes | B. fragilis | iv VA, oral MTZ, other antimicrobials | Died | Present | Case 1 |

NR (Not reported), NT (Not tested). 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.

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 homogeneous. 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 (Tables 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 2168 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 from 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 11C. 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.
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 strains were toxigenic (78%) 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)/

### Table 3

Overview of the *C. difficile* toxigenic 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                           | –                 | –             | –   | –                 | 2     |
| Yes/NR                      | –        | 1                           | 6                 | –             | 1   | –                 | 8     |
| No/NR                       | –        | 1                           | 4                 | 2             | –   | –                 | 7     |
| NT/Yes                      | 1        | 1                           | 3                 | –             | –   | 5                 | 10    |
| NT/No                       | 1        | 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.

| Medical Management | MTZ or/and VA | Other ATB | Other ATB and Surgery | Surgery alone | No therapy | NR* | Total† |
|--------------------|--------------|-----------|-----------------------|---------------|------------|------|--------|
|                    | Type         | CD therapy | CD therapy and surgery |               |            |      |        |
| No. of patients (No. of death) | MTZ ≤ 5 (1) | 0 | 8 (6) | 0 | 2 (1) | 2 (1) | 8 (4) | 60 (21) |
|                    | MTZ + ATB = 6 | (1) | 5 (0) | | | | 0 | 20% |
|                    | VA ≤ 4 | 0 | | 0 | | | | |
|                    | VA + ATB = 5 | (1) | 1 (1) | | | | 0 | 20% |
|                    | MTZ + VA = 2 | (1) | 1 (0) | | | | 0 | 20% |
|                    | MTZ + VA + ATB = 5 | (2) | 1 (0) | | | | 0 | 20% |

Rate of mortality, p value

- 22% (6/27) 13% (1/8) 75%
- 20% (7/35) vs. 62% (8/13), p = 0.012 40%
- 20% (7/35) vs. 60% (9/15), p = 0.009 50%
- 20% (7/35) vs. 59% (10/17), p = 0.005 50%
- 35% (42/121) 50% |

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).

**Bl, 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% [210], 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 Kazanjí 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% (10/17) 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. DOUAIR, reviewed the literature, wrote the text and set figure and tables. F. BARBUT and C. ECKERT provided help and advice for writing. C. AMANI-MOIBENI and J-D. GRANGE wrote the case 1 whereas L. DRIEU and L. BODIN wrote the second case. M. DENIS gave advices concerning clinical management.

**Declaration of interests**

We declare that we have no competing interest.

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