Clostridium difficile in haematological malignancy

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SUMMARY Twenty patients with haematological malignancies who developed Clostridium difficile bowel infection or colonisation are described. All isolates of C difficile were toxigenic in vitro and faecal cytotoxin (toxin B) was detected in 20/26 episodes. Ten of 20 episodes with detectable faecal cytotoxin were associated with typical antibiotic associated diarrhoea. In the other 10 episodes (nine patients), there was a severe unusual illness which was associated with detection of C difficile. The unusual features of the illness were pronounced jaundice (total bilirubin ≥ 44 μmol/l), abdominal pain and distension, and initial constipation followed either by diarrhoea or by large bowel stasis. Four of these patients died within seven days. Bacteraemia was often a presenting feature in neutropenic patients subsequently shown to have C difficile. This was not the case in non-neutropenic patients. Bacteraemia was commonly polymicrobial and in two cases C difficile was isolated from blood culture.

The clinical implications of recognition of this atypical C difficile associated syndrome are discussed.

Patients who are treated for haematological malignancies form an important group of immunocompromised patients who are particularly susceptible to opportunist infections. They require many courses and varying combinations of antibiotics together with frequent and often prolonged admissions to hospital. Such treatment makes them liable to acquire hospital strains of bacteria, including Clostridium difficile.

This paper attempts to evaluate the significance of colonisation or infection with C difficile, or both, in relation to various clinical features and to treatment in 20 patients. In recent years this organism has emerged as one causing increasing and unusual problems in our patients with haematological malignancies.

Methods

We began examining faecal samples for the presence of C difficile in July 1979. Until December 1981 faeces were examined for C difficile cytotoxin (toxin B) and cultured only when clinical features suggested infection with C difficile. Since January 1982 samples of faeces have been sent to the laboratory from all neutropenic leukaemic patients included in formal antibiotic trials either when symptoms suggested C difficile colitis or routinely after five days of antibiotic treatment. No specific protocol has been adopted for examining faeces from non-neutropenic patients or from neutropenic patients not included in antibiotic trials.

DETECTION OF C DIFFICILE CYTOTOXIN

A 1/5 dispersion of each faecal sample was made in phosphate buffered saline (pH 7.3) and centrifuged at 1500 g for 30 min to deposit bacteria and debris. Supernatant fluid was inoculated into a culture of Hep 2 cells so as to give a final dilution of 1/50. The cells were held as a monolayer in maintenance medium in wells of microtitre plates and examined microscopically after 18 h for a cytopathic effect which could be neutralised by C sordellii antitoxin (Wellcome Research Laboratories). Positive faecal samples were then titrated in order to estimate the concentration of cytotoxin present.

CULTURE OF C DIFFICILE

Faecal samples were cultured on prerduced cefoxitin cycloserine fructose agar (Oxoid CM 601) containing 8% horse blood and incubated in an atmosphere of 80% nitrogen, 10% hydrogen, 10% carbon dioxide either in anaerobic jars or in an anaerobic incubator (Don Whitley Scientific Ltd) at 37°C for
48 h. Strains with colonial characteristics of *C. difficile* were identified by gas-liquid chromatography and results of biochemical tests. Isolates were also tested for their ability to produce neutralisable cytotoxin when cultured anaerobically in tryptic nitrate medium (Difco 0367-01) for four days.

Other bacterial enteric pathogens including campylobacter, shigella, and salmonella but not *Aeromonas* sp were specifically sought but not found in the patients described in this paper.

**Ward environment and ward policies**

Throughout the period of the study patients were nursed in a single medical ward with four single rooms, two three bedded units, and a ten bedded unit. Each multiple bedded unit and two of the single bedded rooms have their own toilet facilities. The ward had a heated bedpan washer without temperature control. This was replaced by a bedpan macerator (Haigh Sluicemaster S900) in July 1982 as a measure for controlling *C. difficile*. Protective isolation techniques that require the use of face masks, gowns, aprons, or gloves are not used. About 50 new adult cases of acute leukaemia are treated in the ward each year. Mean bed occupancy by all haematological patients is 12. About 60 cases of bacteraemia a year are confirmed, with an average of 1-5 per patient each year. Patients with lymphoma, myeloma, or chronic leukaemia requiring intensive cytotoxic therapy are also admitted to the ward.

Seventeen of the 20 patients described here had acute leukaemia. All except patient 14 were treated with combination cytotoxic chemotherapy of daunorubicin, an anthracycline, with cytotoxic arabinoside and 6-thioguanine (DAT) or DAT combined with other cytotoxic drugs. Patient 14 was given another anthracycline, adriamycin, combined with BCNU (1,3-bis[2-chloroethyl]-1-nitrosoureia), cyclophosphamide, and prednisolone. As a result of the underlying disease and intensive chemotherapy, all patients underwent prolonged periods of neutropenia, although not all were neutropenic when evidence of the presence of *C. difficile* was found.

Management of infection during the first and subsequent episodes of induced remission in such patients remains controversial. In many centres selective gut decontamination is attempted using oral antibiotics, especially cotrimoxazole, with or without other non-absorbable agents, with the aim of preventing bacteraemia of gut origin. We did not introduce antibacterial prophylaxis when this might have been favoured because, over a period of two years, fatal infections on our unit were almost always associated with trimethoprim resistant organisms. We do give oral antifungal drugs. Systemic use of antibiotics is restricted to a five to seven day course, if the patient's fever subsides with chemotherapy, rather than continuing to give antibiotics throughout the neutropenic episode.

In January 1982, having briefly assessed the combined use of piperacillin and gentamicin, we began to compare cefotaxime plus gentamicin with ceftazidime (alone or with parenteral vancomycin), thus converting our previous penicillin usage progressively to cephalosporin usage.

**Distribution of cases from 1979 to 1982 and cross infection**

During this period 26 episodes of *C. difficile* infection or colonisation affecting 20 patients were recorded. Five patients relapsed with recurrence of *C. difficile* after becoming free of symptoms with culture and toxin negative faeces. One patient relapsed twice. Intervals between the date of first detection and relapse varied from three weeks to one year.

Case clustering in 1980 and 1982 suggested that there was cross infection, and by 1981 we began to suspect that patients who were on the ward at the same time as others with *C. difficile* colitis might have become carriers of an epidemic strain of the organism.

Patient 7 presented in February 1982 with symptoms of a relatively mild colitis, after which vigorous attempts were made to prevent cross infection. These included the closing of the ward so that all surfaces and equipment could be cleaned or soaked in a solution of glutaraldehyde. When the ward was reopened the only patients admitted were those newly referred or those who had received a course of antibiotics and had had three faecal samples examined for *C. difficile* with negative results. Known positive patients or those who had been positive in the past were nursed elsewhere in isolation. In spite of these measures, two more cases rapidly appeared and it proved impossible to sustain necessary care for patients located on several wards. The attempt at segregation was therefore abandoned only to be followed by a total of 11 more infected patients in 1982. Recently, some of our strains have been typed by two different methods and we have evidence that at least seven different types were involved. It is likely that there were some minor incidents of cross infection—for example, between cases 1 and 2 and between cases 16 and 18, but it is now certain that our experience does not reflect a single common source outbreak (Table 2).
Case histories of patients with Clostridium difficile

Tables 1 and 2 outline the main details of all the patients who were known to have *C difficile* in the period from August 1979 to December 1982 inclusive.

Faecal cytotoxin was detected in 20/26 episodes tested. All strains of *C difficile* produced cytotoxin in vitro. Abdominal symptoms and signs were present in 23/26 episodes, but in three of the six episodes without detectable faecal cytotoxin (affecting patients 11, 13, and 20) the clinical significance of the positive culture for *C difficile* is in doubt. Patient 11 died with *Pseudomonas aeruginosa* septicaemia and extensive perirectal cellulitis on the day of admission and no history was available. The colon appeared normal at postmortem examination. Patient 13 had severe ulcerative colitis and systemic mucormycosis. *Absidia corymbifera* was isolated and hyphae were seen at necropsy in rectal sections. Patient 20 did not have diarrhoea or abdominal discomfort. The three other faecal cytotoxin negative episodes in patients 6, 10, and 14 were associated with definite symptoms and signs of gastrointestinal upset.

Patient 6 had already suffered once from toxin positive *C difficile* diarrhoea when three weeks later she developed severe illness with fever, abdominal distension, paralytic ileus, jaundice, and renal failure. Klebsiella and faecal streptococci were isolated from her blood; she died four days later and a request for necropsy was refused. Patient 10 had mild diarrhoea, which was treated promptly with vancomycin because *C difficile* had been isolated previously. Patient 14 had diarrhoea, which improved on treatment with vancomycin.

Ten of 20 episodes with detectable faecal cytotoxin were associated with typical signs and symptoms of antibiotic associated diarrhoea, which improved after treatment with vancomycin. Five of these patients were not neutropenic at the time (patients 1, 3, 5, 9, and 16). Three were having relapse of *C difficile* infection (patients 1, 9, 16).

In 10 of 20 episodes, affecting nine patients (nos 1, 2, 4, 8, 9, 12, 15, 16, and 18) with detectable faecal cytotoxin, there was severe illness with unusual clinical features which coincided with the detection of *C difficile*. These unusual features were

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Date</th>
<th>Sex/Age (yr)</th>
<th>Cytotoxic therapy</th>
<th>Diarrhoea</th>
<th>Other signs</th>
<th>Pronounced jaundice</th>
<th>Death within 7 days</th>
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<tbody>
<tr>
<td>Neutropenic at first diagnosis (white cell count &lt; 1 x 10^9/l)</td>
<td></td>
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<tr>
<td>1 (AML)</td>
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<td>+</td>
<td>Distension</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>2 (AML)</td>
<td>16.9.80</td>
<td>F/17</td>
<td>DAT, FOP</td>
<td>+</td>
<td>Distension</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3 (AML)</td>
<td>17.9.80</td>
<td>F/35</td>
<td>DAT</td>
<td>+</td>
<td>Distension, ascites</td>
<td>+</td>
<td>+</td>
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<tr>
<td>4 (AML)</td>
<td>13.6.81</td>
<td>M/45</td>
<td>DAT</td>
<td>+</td>
<td>Distension, stasis</td>
<td>–</td>
<td>–</td>
</tr>
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<td>8.7.81</td>
<td>M/49</td>
<td>DAT</td>
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<td>Distension, peritonism</td>
<td>–</td>
<td>+</td>
</tr>
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<td>6 (AML)</td>
<td>1.2.82</td>
<td>M/55</td>
<td>DAT, FOP</td>
<td>+</td>
<td>Distension, peritonism</td>
<td>–</td>
<td>+</td>
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<tr>
<td>7 (ALL)</td>
<td>16.2.82</td>
<td>M/69</td>
<td>DAT</td>
<td>+</td>
<td>Distension, peritonism</td>
<td>–</td>
<td>+</td>
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<tr>
<td>8 (ALL)</td>
<td>7.3.82</td>
<td>M/17</td>
<td>DAT</td>
<td>+</td>
<td>Distension, peritonism</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>9 (ALL)</td>
<td>31.3.82</td>
<td>M/17</td>
<td>DAT, FOP</td>
<td>+</td>
<td>Distension, peritonism</td>
<td>–</td>
<td>+</td>
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<tr>
<td>10 (ALL)</td>
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<td>M/45</td>
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<td>F/55</td>
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<td>F/78</td>
<td>DAT</td>
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<td>Distension, peritonism</td>
<td>–</td>
<td>–</td>
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<tr>
<td>17 (AML)</td>
<td>25.10.82</td>
<td>M/29</td>
<td>DAT</td>
<td>+</td>
<td>Distension, peritonism</td>
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<tr>
<td>Not neutropenic at first diagnosis</td>
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<tr>
<td>3 (AML)</td>
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<td>+</td>
<td>Distension</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>5 (AML)</td>
<td>27.11.80</td>
<td>F/65</td>
<td>DAT + Mtx</td>
<td>+</td>
<td>Distension, peritonism</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12 (CML)</td>
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<td>F/55</td>
<td>DAT</td>
<td>+</td>
<td>Distension, peritonism</td>
<td>–</td>
<td>+</td>
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<td>14 (Myeloma)</td>
<td>8.6.82</td>
<td>F/66</td>
<td>Adriamycin, BCNU, etc+</td>
<td>–</td>
<td>Distension, peritonism</td>
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<td>–</td>
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<td>19.6.82</td>
<td>F/45</td>
<td>DAT</td>
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<td>–</td>
<td>+</td>
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<td>20 (CML)</td>
<td>1.12.82</td>
<td>M/25</td>
<td>DAT</td>
<td>–</td>
<td>Distension, peritonism</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AML = acute myeloid leukaemia; ALL = acute lymphoblastic leukaemia.
DAT = daunorubicin, cytosine arabinoside, 6-thioguanine.
FOP = 5-fluorouracil, vincristine, 6-mercaptopurine.
Mtx = methotrexate.
BCNU = (1,3-bis[2-chloroethyl]-1-nitrosourea).
NT = not tested.
pronounced jaundice (total bilirubin concentration \( \geq 44 \text{ mmol/l, normal range 2–17 mmol/l} \), abdominal distension and pain, most striking in the right iliac fossa or epigastrium, as well as initial constipation followed either by diarrhoea or by large bowel stasis with diminished bowel sounds. Sometimes ascites was suspected. Four of these nine patients died within seven days of \( C \text{ difficile} \) being found in their faeces; five recovered. All were treated with oral vancomycin or vancomycin plus parenteral metronidazole. In the first five episodes with one or other of these unusual clinical features, the patient also had concurrent bacteraemia (Table 2). Four of these bacteraemias were polymicrobial and \( C \text{ difficile} \) was a component of two.

None of the patients who were not neutropenic at the time of \( C \text{ difficile} \) detection had concurrent bacteraemia, but 9\text{17} \( C \text{ difficile} \) episodes with neutropenia were associated with bacteraemia. Organisms recovered from the blood in five episodes included penicillin resistant \( Bacteroides \) sp. and group D streptococci, which are unusual isolates in our patients. In general, the organisms recovered were not correlated with the known enteric flora and were resistant to the antimicrobial drugs most recently used.

Details of four of the unusual cases are given below in greater detail in order to illustrate difficulties in diagnosis and management. Interestingly, two of the four patients (nos 12 and 15) were not neutropenic at the time they developed their \( C \text{ difficile} \) infection. Two other cases, patients 1 and 9, have already been documented in detail elsewhere.

Patient 4, a 35 year old woman, who was neut-
rerenic after cytotoxic therapy for newly diagnosed acute myeloid leukaemia, became ill with abdominal pain. She was febrile, jaundiced (total bilirubin 44 μmol/l; alkaline phosphatase and alanine trans-
ferase normal), and had guarding in the right iliac fossa and slight diarrhoea, which was rapidly followed by abdominal distension and more grosse diarrhea. She was treated for seven days with cefotaxime and gentamicin. These antibiotics were then stopped and intravenous metronidazole and oral vancomycin were given because C. difficile and its toxin were detected in faeces. She continued to deteriorate, developed paralytic ileus with ascites, and died six days later. C. difficile, Bacteroides sp, and group D streptococci were subsequently grown from a blood culture taken four days after detection of C. difficile cytotoxin in the faeces. There was no postmortem examination.

Patient 8, a 69 year old woman, had acute lymphoblastic leukaemia first diagnosed in 1973. She had relapsed with involvement of the central nerv-
ous system in 1980 and again in January 1982, when she was admitted for more intrathecal methotrexate, cranial irradiation, and systemic chemotherapy, which included prednisolone 40 mg daily. After this she had local staphylococcal skin sepsis as well as E. coli and Bacteroides sp bacteraemia on more than one occasion. On 16 February a clostridium species, two strains of E.coli, and Bacteroides sp were isolated from a blood culture. At the time the patient was not feverish and was relatively well, and it was thought that the blood culture might have been contaminated during collection. She continued to deteriorate slowly, despite treatment with a sequence of antibiotics that included cloxacin, co-
trimoxazole, metronidazole, ampicillin, and gen-
tamicin. We then suspected that she had an intra-
abdominal abscess. On 3 March Clostridium sp and E.coli were again isolated from the blood. On this occasion the clostridium and that isolated on 16
February was identified as C. difficile. She had no diarrhoea or abdominal symptoms and results of liver and renal function tests were normal. Her faeces were not examined for C. difficile until the blood culture isolate had been identified. At this time, on 17 March, the patient suddenly became acutely ill with abdominal distension, peritonitis, and toxic megacolon. C. difficile and its toxin were then detected in the faeces while Bacteroides sp and two strains of E.coli were isolated from blood cul-
tures.

The patient died four days later and at postmor-
tem examination bilateral psoas abscesses adjacent to perforations of the colon were found. E.coli and Bacteroides sp were isolated from the pus. Mucosal and serosal petechial haemorrhages were present throughout the colon and the lumen was filled with blood. The mucosa of the terminal ileum and ascending colon contained many raised reddish nodules with a flat ulcerated surface. Sections showed autolysis of the mucosa with submucosal haemorrhage but no inflammation or secondary oedema. Organisms were not seen.

Patient 12, a 55 year old woman with chronic myeloid leukaemia, was in blast crisis (white cell count 43 × 10^9/l, neutrophil count 21 × 10^9/l) two weeks after being neutropenic following cytotoxic therapy. She had had multiple courses of antibiotics for infections. Treatment included oral van-
comycin for suspected, but not confirmed, C. difficile diarrhoea. Six days after stopping treatment with vancomycin the patient became clinically shocked, but blood cultures taken at the time were negative. She had abdominal distension with tenderness and guarding. Over the next 24 h her condition became worse, and she developed paralytic ileus and acute renal failure (serum urea 30–80 mmol/l; normal up to 6–6 mmol/l; serum creatinine 272 mmol/l; normal 35–90 mmol/l). Although the bilirubin and alanine transferase were normal, alkaline phosphatase was raised (251 U/l; normal 30–135 U/l). C. difficile and cytotoxin were detected in faeces collected on the first day of this acute illness. Despite treatment with intravenous metronidazole and cefotaxime plus oral vancomycin, she died four days later.

As with patient 8, the colon at postmortem examination was filled with blood; the colon and terminal ileum contained reddish mucosal nodules with a flat ulcerated surface. Sections of these areas showed mucosal ulceration and infiltration by leukemic cells but bacteria were not seen in the gut wall.

Patient 15, a 45 year old woman, had presented with acute myeloid leukaemia five weeks previously. After cytotoxic treatment she was in remission but had been troubled since the start of her illness by a discharging abscess on her anterior abdominal wall from which Pseudomonas aeruginosa was grown and now had a leucocytosis (white cell count 27 × 10^9/l, neutrophil count 21 × 10^9/l). She had received multiple courses of antibiotics and suddenly developed fever, abdominal distension (without diarrhoea), paralytic ileus, jaundice (total bilirubin 80 μmol/l, alkaline phosphatase 174 U/l, alanine transferase normal) and acute renal failure, which required dialysis (serum urea 32 mmol/l, serum creatinine 712 mmol/l). Blood cultures were negative but C. difficile and its toxin were detected in her faeces. Computer assisted axial tomography showed thick-
ening of the wall of the ascending colon but no abs-
cess. She was treated with intravenous metronidazole, vancomycin, and piperacillin plus oral
vancomycin and recovered completely over a period of almost three months.

Discussion

The following points emerge from our survey:
1. Twenty patients developed one or more infections with *C. difficile*. At least seven different types of the organism were involved.
2. Symptoms and signs were not always typical of pseudomembranous colitis or antibiotic associated diarrhoea. Often the patients who were most severely ill did not have diarrhoea but definite gastrointestinal signs and symptoms were strikingly associated with the presence of *C. difficile*.
3. Sigmoidoscopy and biopsy were not done on any of these patients because of the risk of complications. We do not know, therefore, if any had typical pathology of pseudomembranous colitis. Pathological findings in those patients who died and had postmortem examinations were not typical of pseudomembranous colitis.
4. Two patients developed *C. difficile* bacteraemia. Bacteraemia with other gut organisms, including *Bacteroides* sp and group D streptococci, was often a presenting feature in neutropenic patients subsequently shown to have *C. difficile*.
5. In 1982 a prospective survey began. Colonisation of the gut with *C. difficile* was then detected in 13/55 (23%) of the patients treated for acute leukaemia. Ten of 13 of these had appreciable gastrointestinal disturbance but they were identified and treated early; few developed bacteraemia.

Most of the patients became colonised with *C. difficile* after remission induction therapy for newly diagnosed or relapsed acute myeloid or acute lymphoblastic leukaemia. They had had several stays in hospital, during which they had been at risk of acquiring *C. difficile* from the environment. Both cytotoxic drugs and antibiotics are known to predispose to gut colonisation with *C. difficile*, so it is not surprising that this was common despite attempts to prevent cross infection. The association of an increasing incidence of *C. difficile* infection with progression to greater use of third generation cephalosporins may not be a coincidence. These antibiotics selectively reduce the numbers of enterobacteriaceae in the gastrointestinal flora and may thereby permit emergence of *C. difficile*.

Although some of our patients had relatively mild and clinically typical antibiotic associated diarrhoea, many had unusual features such as fever, constipation, abdominal distension, and pronounced jaundice. It is difficult to assess the significance of jaundice in patients who have had cytotoxic drugs and are neutropenic and highly susceptible to concurrent bacteraemia. Two groups of controls were available for comparison with the 18 episodes of neutropenia/*C. difficile* infection. In 1982 82 febrile episodes in neutropenic patients were treated in a comparative trial of cefotaxime and ceftazidine. Faeces from all these patients were tested for *C. difficile* after five days of treatment. Between July 1979 and December 1981 another group of 139 episodes was treated in our cefotaxime/carbenicillin and piperaclillin trials. Only faeces from patients with diarrhoea, however, were tested for *C. difficile*. We may therefore have missed the diagnosis in some of these patients. Mildly abnormal total bilirubin values ≤43 μmol/l were not unusual in either group and were noted in 45% of all febrile episodes. In 1982 pronounced jaundice (bilirubin >44 μmol/l) accompanied 8/18 (44%) of all episodes of diagnosed *C. difficile* infection in trial patients compared with only 12/70 (17%) of febrile episodes in trial patients without *C. difficile* infection. An association between pronounced jaundice and bacteraemia in the absence of *C. difficile* was not evident.

The other unusual features such as severe right sided abdominal pain with distension and bowel stasis are more typical of neutropenic enterocolitis than of classic pseudomembranous colitis. Patient 9, who underwent laparotomy, had all the features of neutropenic enterocolitis. We now know that *C. septicum* was also present in the affected bowel wall. We have seen two other patients with neutropenic enterocolitis with classic histopathological findings and evidence of *C. septicum* infection but none of *C. difficile*.

One patient, no 17, however, had a history of recent *C. difficile* diarrhoea. Since faecal culture for other clostridia was not carried out at the same time as examination for *C. difficile* throughout this series, we cannot tell if atypical clinical features were associated with colonisation by more than one clostridial species.

Other workers have found that *C. difficile* colitis is a serious complication in immunosuppressed patients undergoing chemotherapy for cancer or bone marrow transplantation and some have noted that the clinical presentation may be unusual. Our experience confirms this. *C. difficile* toxins probably cause mucosal damage from which bacteraemia may arise. Greater attention should therefore be given to such colonic disease as an additional cause of fever in neutropenic patients even in the presence of bacteraemia. Early recognition and treatment with appropriate antibiotics may prevent a serious or fatal outcome. But, as patient 4 illustrates, complete withdrawal of parenteral antibiotics is hazardous because of the risk of bacteraemia from the ulcerated colon.
**Clostridium difficile in haematological malignancy**

Since the beginning of 1983 18 more of our patients undergoing treatment for haematological malignancy have had a total of 25 episodes of *C. difficile* infection or colonisation. We have pursued a policy of early treatment with oral vancomycin and most of these patients have had relatively mild illnesses. There have not been any associated deaths.

We are grateful to Dr R Fekety and Dr S Tabaqchali, who arranged for typing of some of the isolates of *C. difficile*. We are also indebted to Dr C E D Taylor for helpful editorial suggestions and to Mrs M Bailey for typing the manuscript.

**References**


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