Eur J Vasc Endovasc Surg **14**, 217–220 (1997)

Clostridium difficile Colitis After Aortic Surgery

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Objective: *To determine the incidence and outcome of* Clostridium difficile *colitis (CDC) following aortic surgery.*
Design: *Retrospective clinical study, and case-note review.*
Patients: *Of 180 patients undergoing aortic surgery for either aneurysmal or occlusive disease between 1 September 1994 and 31 August 1996 (24 months), 15 (8.4%) developed CDC. There were 12 male and three female patients of median age 65 (range 46–84).*
Results: *Two patients died from multiple organ failure in association with CDC, one of whom underwent negative re-laparotomy for suspected ischaemic bowel because the diagnosis of CDC had not been entertained. Previously identified risk factors for CDC comprised: age >65 (eight); renal impairment (four); chronic obstructive airways disease (seven); coexistent malignancy (three); admission from another hospital (four); H_2 antagonist therapy (13); ITU (nine); and/or HDU care (14). Diarrhoea commenced a median of 9 (range 5–26) days, and CDC, was diagnosed a median of 14 (range 10–26) days after operation. All patients received intravenous Cefuroxime, originally prescribed as prophylaxis, for a median of 6 (range 3–16) days prior to onset of CDC. Two patients received 1 additional antibiotic; one received 2; two received 3; and one received 4 prior to onset of CDC.*
Conclusions: *CDC is a common and potentially serious complication of vascular, and in particular, aortic surgery. Although such patients often possess several risk factors for CDC, colitis frequently follows prolonged 'prophylactic' cephalosporin administration, which should therefore be avoided.*

Key Words: Clostridium difficile *colitis; Aortic surgery; Nosocomial infection.*

Introduction

Over the last 10 years there has been a marked increase in the number of surgical patients developing symptomatic *Clostridium difficile* (CD) infection.[1] This is due to several factors: heightened awareness of the condition; better methods of diagnosis; more widespread use of antibiotics for treatment and prophylaxis; and the increasing numbers of elderly and immunocompromised patients with malignancy, sepsis, and (multi) organ failure being cared for within intensive therapy (ITU) and high dependency units (HDU).[2] In addition to morbidity and mortality, the economic burden of CD infection in terms of delayed discharge is considerable. Although elderly patients with peripheral vascular disease undergoing aortic surgery are likely to be at increased risk of CD colitis (CD) for a variety of reasons, this has not been previously studied. The aim of this paper, therefore, was to review the incidence, diagnosis, treatment, and clinical significance of CDC in patients undergoing aortic surgery for aneurysmal or occlusive disease.

Patients and Methods

Patients with CDC were identified by interrogating a prospectively completed database of all patients testing positive for CD toxin within the department of microbiology. Patients undergoing aortic surgery were identified from a prospectively completed vascular surgery unit database. Case notes of patients undergoing aortic surgery who developed clinically apparent, CD toxin-positive diarrhoea during the same admission were then reviewed. Between 1 September 1994 and 31 August 1996, 180 patients underwent aortic surgery for occlusive or aneurysmal disease.

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1078–5884/97/090217+04 $12.00/0

Table 1. CDC in patients undergoing aortic surgery.

Day of event related to day of admission (day 1)	Median (days)	Range (days)
Aortic operation	3	1–11
Commencement of diarrhoea	9	5–26
Diagnosis of CDC	14	10–26
Treatment for CDC commenced	14	11–32
Delay between events in days	**Median (days)**	**Range (days)**
Aortic operation and onset of diarrhoea	6	4–19
Onset of diarrhoea and diagnosis of CDC	1	0–9
Onset of diarrhoea and treatment	2	1–9
Commencement of treatment and cessation of diarrhoea (or death)	5	1–11

Unit policy stipulated that patients undergoing aortic surgery should receive prophylactic Cefuroxime 750 mg (Glaxo UK, Greenford, Middx., U.K.) intravenously thrice daily and Ranitidine 50 mg (Glaxo UK, Greenford, Middx., U.K.) intravenously twice daily for 5 days postoperatively.

Results

Patients with CDC

Of 180 patients undergoing aortic surgery between 1 September 1994 and 31 August 1996, 15 (8.3%) developed clinically significant, toxin-positive CDC. There were 12 male and three female patients of median age 65 (range 46–84). There was no significant difference in the incidence of CDC between those operated for occlusive (2/45) and those operated for aneurysmal disease (13/135, $p=0.52$, Fisher's exact test). Despite a reduction in CDC in the hospital as a whole over the period of the study, there has been a significant increase in the proportion of patients with CDC who had undergone a vascular surgical procedure. Thus, between 1 September 1994 and 31 August 1995 there were six vascular patients (three aortic procedures) out of a total of 271 patients with CD-positive stool samples (2.2%) compared to 16 (12 aortic procedures) out of 217 CD-positive patients (7.4%) between 1 September 1995 and 31 August 1996 ($p<0.05$, Fisher's exact test). Patients were operated on a median of 3 (range 1–11) days after admission. The timing of onset of diarrhoea, diagnosis and commencement of treatment in relation to the day of operation is shown in Table 1.

Clinical consequences of CDC

Two patients died from multiple organ failure (MOF) in association with CDC, one of whom underwent negative re-laparotomy for suspected ischaemic bowel because the diagnosis of CDC had not been entertained. This patient had been operated on for ruptured abdominal aortic aneurysm and on the third postoperative day was making an uneventful recovery when he developed abdominal distension, pain, and profuse diarrhoea. On examination the patient was dehydrated and exhibited lower abdominal tenderness. Investigation revealed a leukocytosis and a metabolic acidosis; plain abdominal radiograph showed distended loops of bowel. A provisional diagnosis of ischaemic bowel was made and the patient taken to theatre. At laparotomy, the small and large bowel were diffusely distended and oedematous but there was no evidence of ischaemic or other intra-abdominal pathology and no surgical procedure was undertaken. Forty-eight hours later the stool tested positive for CD toxin and the patient was commenced on vancomycin via nasogastric tube.

Antibiotic exposure prior to onset of CDC

All patients had received Cefuroxime 750 mg intravenously thrice daily. In all cases this had orginally been prescribed as prophylaxis to cover insertion of a prosthetic aortic graft and potential infection arising from central venous cannulae in the early postoperative period. Unit policy stipulated that this antibiotic should be prescribed for 5 postoperative days and then discontinued. However, patients with CDC had received this 'prophylactic' antibiotic for a median of 6 (range 3–16) days prior to onset of diarrhoea. In most cases the antibiotic had been continued without any microbiological evidence of infection sensitive to Cefuroxime. Eight patients received one antibiotic (Cefuroxime) only, while the other patients had received multiple antibiotics prior to the onset of diarrhoea (Table 2).

Risk factors of CDC

The majority of patients possessed several previously identified risk factors for CDC,[2] including age >65 ($n=8$); renal impairment ($n=4$); chronic obstructive airways disease ($n=7$); coexistent malignancy ($n=3$); admission from another hospital ($n=4$); H_2 antagonist

Table 2. Antibiotic exposure prior to the development of CDC and treatment administered.

Patient	*Day of operation	*Day symptoms commenced	Antibiotic exposure (drug, route, and days)	Treatment (drug and days)
1	1	11	Cefuroxime, IV, 1–8 Benzyl penicillin, IV, 1–25 Metronidazole, IV, 1–25 Ceftazidime, IV, 6–25 Clarithromycin, IV, 13–25 Vancomycin, IV, 21–45	Metronidazole, NG, 26–27
2	1	11	Cefuroxime, IV, 1–12 Metronidazole, IV, 1–20 Ceftazidime, IV, 20–25 Clarithromycin, IV, 13–21	Vancomycin, O, 14–17 Metronidazole, O, 19–50
3	5	9	Cefuroxime, IV, 2–11	Metronidazole, O, 14–18
4	7	26	Cefuroxime, IV, 6–10 Metronidazole, IV, 7–10, 14–17 Ceftazidime, IV, 14–17	Vancomycin, O, 32–44 Metronidazole, O, 45–53
5	4	10	Cefuroxime, IV, 4–12	Metronidazole, O, 12–15
6	11	16	Cefuroxime, IV, 11–16 Metronidazole, IV, 4–12	Withdrawal of antibiotic
7	9	21	Cefuroxime, IV, 9–23 Vancomycin, IV, 14–21	Metronidazole, O, 23–26
8	3	9	Cefuroxime, IV, 3–7	Withdrawal of antibiotic
9	2	12	Cefuroxime, IV, 2–10	Withdrawal of antibiotic
10	1	5	Cefuroxime, IV, 1–3 Metronidazole, IV, 1–32 Vancomycin, IV, 14–51	Vancomycin, O, 22–32
11	3	9	Cefuroxime, IV, 3–8	Metronidazole, O, 11–25
12	1	6	Cefuroxime, IV, 1–6	Withdrawal of antibiotic
13	3	9	Cefuroxime, IV, 3–9	Metronidazole, IV, 11–14
14	7	12	Cefuroxime, IV, 7–11	Withdrawal of antibiotic
15	7	13	Cefuroxime, IV, 7–14 Erythromycin, IV, 9–15 Amoxicillin, IV, 9–15 Vancomycin, IV, 14–22	Metronidazole, O, 15–24

* Day 1 is taken as the day of admission to our hospital; IV = intravenous; O = oral; NG = nasogastric tube administration.

therapy ($n=13$); ITU care ($n=9$) and/or HDU care ($n=14$).

Treatment of CDC

Five patients were treated by withdrawal of antibiotic only. These patients had mild disease and all were receiving Cefuroxime only at the time diarrhoea commenced. The remaining patients were treated with either Metronidazole or Vancomycin (Table 2).

Conclusions

CD infection may be a trivial and self-limiting condition in otherwise healthy persons undergoing antibiotic therapy for minor infection. However, in patients undergoing major surgery, CDC is an important cause of morbidity and a significant contributor to mortality.[3] Although virtually every field of surgery appears affected by this nosocomial disease, patients undergoing vascular operations have not previously been specifically studied.[4] Many studies examining the effectiveness of broad spectrum cephalosporins as prophylaxis describe an association with CD-related postoperative diarrhoea.[5] Even when only one to three doses of antibiotic are given, the risk of CD infection is apparent, and increases markedly when therapy is continued in to the postoperative period,[6] an observation that is confirmed by the present study. Patients on prolonged, combination antimicrobial therapy are at greatest risk. Diagnosis of CDC may be a particular problem following aortic surgery, because diarrhoea is often thought to represent colonic ischaemia rather than infection. While ischaemia usually manifests itself within 48 h of surgery, the present

study indicates that diarrhoea due to CDC nearly always has a later onset. Prompt diagnosis and treatment of CD infection in surgical patients is crucial if morbidity and mortality are to be minimised.[7] For example, in a recent series of 201 patients with CD colitis, the overall mortality was 3.5%. Surgical intervention was required in 5% of cases and was associated with a mortality of 30%. The only discriminative factor in this large study between patients who died and those who survived was length of time from symptoms to treatment – 6 days for survivors vs. nearly 11 days for those who died.[1] In a series of 710 mixed medical and surgical patients, factors that significantly predisposed to the development of severe CD colitis included malignancy, chronic obstructive airways disease, immunosuppressive and antiperistaltic medications, and renal failure.[8] Twenty-one (3%) of these patients required admission to ITU or died as a result of their CD infection. In a series of over 200 surgical patients who developed CDC,[9] diarrhoea developed on average 10 days postoperatively and patients had received an average of three to four different antibiotics before the diagnosis was made. The overall mortality was 8%. Five patients (2%) developed toxic dilatation, of whom four died. Twenty-five per cent of all deaths were thought to be directly attributable to the effects of CD infection. Six variables were identified as predictive of increased mortality rate: administration of laxatives and steroids, length of preoperative stay in hospital, postoperative interval before onset of symptoms, use of total parenteral as opposed to enteral nutrition, and abdominal distension. Lipsett and colleagues reviewed all adult patients undergoing surgical intervention for CD-related infection over a 6-year period.[10] In that time 37 000 CD toxin assays had been performed, of which 3300 were positive. Thirteen adults (0.39% of all affected patients) required surgical intervention for their CD infection, of whom 38% died.

It is important to remember that the first presentation of CD infection may be as a surgical emergency with a clinical picture more commonly associated with fulminant ischaemic or ulcerative colitis; namely toxic dilatation and perforation.[11] Patients presenting in this way may undergo emergency laparotomy to their detriment before the true diagnosis is established, as in the case of our patient who was incorrectly diagnosed as having ishaemic colitis.

In summary, CD colitis is a common and potentially serious nosocomial infection following aortic surgery. Although many of the affected patients were on multiple antibiotics and had several other risk factors, in the majority of cases CDC follows prolonged cephalosporin therapy which has originally been prescribed as prophylaxis. It was also evident that prior treatment with intravenous Metronidazole or vancomycin (usually prescribed for Methicillin-resistant *Staphylococcus aureus*) did not prevent the onset of CD colitis. In addition to morbidity, CDC contributed to the death of two patients. CDC should be considered high in the differential in any patient developing diarrhoea after major vascular surgery.[12]

This study has prompted us to change the prophylacitc antibiotic strategy in patients undergoing aortic surgery. Patients now receive only three doses of Cefuroxime 750 mg 8-hourly, and two doses of Vancomycin 1 g, adjusted to take into account renal function, 12-hourly postoperatively. Prolonged courses of postoperative cephalosporin treatment are avoided and every attempt is made to base continuing antibiotic therapy upon microbiological evidence of infection and sensitivity testing.

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Accepted 17 February 1997