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Clostridium difficile colitis in patients after kidney and pancreas–kidney transplantation

Key words:
Clostridium difficile; kidney; pancreas–kidney; transplantation

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Abstract: Limited data exist about *Clostridium difficile* colitis (CDC) in solid organ transplant patients. Between 1/1/99 and 12/31/02, 600 kidney and 102 pancreas–kidney allograft recipients were transplanted. Thirty-nine (5.5%) of these patients had CDC on the basis of clinical and laboratory findings. Of these 39 patients, 35 have information available for review. CDC developed at a median of 30 days after transplantation, and the patients undergoing pancreas–kidney transplantation had a slightly higher incidence of CDC than recipients of kidney alone (7.8% vs. 4.5%, $P > 0.05$). All but one patient presented with diarrhea. Twenty-four patients (64.9%) were diagnosed in the hospital, and CDC occurred during first hospitalization in 14 patients (40%). Treatment was with oral metronidazole (M) in 33 patients (94%) and M + oral vancomycin (M + V) in 2 patients. Eight patients had recurrent CDC, which occurred at a median of 30 days (range 15–314) after the first episode. Two patients (5.7%) developed fulminant CDC, presented with toxic megacolon, and underwent colectomy. One of them died; the other patient survived after colectomy. CDC should be considered as a diagnosis in transplant patients with history of diarrhea after antibiotic use, and should be treated aggressively before the infection becomes complicated.

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Infections are the leading cause of morbidity and mortality in the early post-transplant period. More than 80% of recipients suffer at least one episode of infection in the first year (1, 2). The occurrence of infectious complications is closely related to immunosuppressive treatment, including induction, maintenance, and the treatment of acute rejection.

Although, many viral and bacterial opportunistic infections are well known in kidney and pancreas–kidney allograft recipients, *Clostridium difficile* colitis (CDC) is a less frequently described gastrointestinal infection in these patients. *Clostridium difficile* (CD) is one of the most common hospital-acquired (nosocomial) infections causing antibiotic-associated colitis (3). CDC has been defined as the existence of diarrhea and CD toxin in the stool.

In this study, we identified our patients with CDC after kidney and pancreas–kidney transplantation and report the clinical presentation,

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timing of infection, risk factors, recurrence, and treatment. We also report two patients with fulminant CDC (FCDC) after kidney transplantation.

Material and methods

Between 1 January 1999 and 31 December 2002, 702 adults underwent kidney and pancreas–kidney transplantation at University of Pittsburgh Medical Center. Of these, 600 were kidney alone and 102 patients were pancreas–kidney allograft recipients. All patients with a diagnosis of CDC at discharge from hospital and with a positive assay for CD toxin in stool during this period were identified. A detailed computer-assisted chart review, through the University of Pittsburgh Medical Archive and Retrieval System (MARS) and the Electronic Data Interface for Transplantation (EDIT) of the Thomas E. Starzl Transplantation Institute, was used to study the patients who had CDC during this period. Demographic features and the immunosuppressive regimen of all patients with CDC were reviewed. All patients' records were also evaluated for clinical presentation of the infection, fever, white blood cell count, history of antibiotic use in the past 1 month, recurrence of the infection, treatment of the CDC, and presence of FCDC.

Review was made of the clinical course, including laboratory values, dosage and trough levels of immunosuppressive agents, and steroid and antibody treatments for rejection episodes. Data were collected by two physicians (KK and LR). The data collection was approved by the Institutional Review Board (IRB) of the University of Pittsburgh Medical Center.

Immunosuppression was tacrolimus and mycophenolate mofetil and steroids in 12 patients; tacrolimus, sirolimus, and steroids in 3; tacrolimus and steroids in 6; and preconditioning (Thymoglobulin-14, Campath-1, OKT3–1) with tacrolimus monotherapy in 14 patients (4). The initial treatment of acute rejection was with a steroid bolus for patients receiving the preconditioning regimen and with a steroid bolus and recycle for traditionally immunosuppressed patients. Steroid-resistant acute rejections and high-grade rejections were treated with antibody therapy. All kidney allograft recipients received cefazolin 1.0 g intraoperatively and on the first postoperative day. All pancreas–kidney allograft recipients received cefotetan 1.5 g intraoperatively and on the first 2 postoperative days. Pancreas–kidney recipients underwent preoperative bowel preparation with enemas. All patients were started on oral nystatin (antifungal), trimethoprim–sulfamethoxazole (for *Pneumocystis carinii*), and cytomegalovirus prophylaxis for 3–6 months.

Treatment of CDC was with oral metronidazole for 15 days or until diarrhea subsided; oral vancomycin was added if metronidazole was not effective in controlling diarrhea. Recurrent CDC was also treated with metronidazole, and additional agents such as oral vancomycin, cholestyramine, or intravenous immunoglobulin. Beginning in January 2003, all kidney and pancreas–kidney transplant recipients have been prophylactically treated with metronidazole in the early post-transplant period.

Data are expressed as mean ± SD and median with a range for highly skewed distributions. Parametric and non-parametric tests including Student's *t*-test, Wilcoxon signed rank test and χ^2 test were used as appropriate. A probability value of $P<0.05$ was considered as statistically significant. Statistical analysis was done using SPSS for Windows version 11.0 (Chicago, IL, USA).

Results

Among the 702 recipients, 39 (5.5%) patients were found to have CDC by laboratory and clinical findings. Thirty-five (mean age 53 ± 14 years, 26 male, 9 females) patients have data available for review. Twenty-seven of them were kidney and 8 patients were pancreas–kidney allograft recipients (Table 1). The etiology of renal failure was diabetes mellitus in 15, chronic tubulointerstitial nephritis in 6, chronic glomerulonephritis in 4, unknown in 3, polycystic kidney disease in 3, hypertension in 2, and systemic lupus erythomatosus (SLE) in 2 patients. Nine patients underwent living-related kidney transplantation, and 26 underwent cadaveric kidney and pancreas–kidney transplantation. Although, CDC was seen slightly more often in pancreas–kidney allograft recipients than in kidney recipients (7.8% vs. 4.5%), the difference was not statistically significant ($P>0.05$).

CDC occurred at a median of 30 days (range: 3–819) after transplantation, and 75% of the cases manifested within 4 months after the operation. CDC occurred during the initial hospitalization in 14 (40%) patients, and 22 (62.9%) patients developed the infection as inpatients. The main clinical presentation of CDC was with diarrhea, which occurred in all but one patient (97.1%). Abdominal pain and fever (> 38.5 °C) were other accompanying symptoms seen in 16 (45.7%) and 4 (11.4%) patients, respectively, and one patient presented with ileus. Leukocytosis (> 10,000/mm^3) developed in 16 (45.7%) patients. Fifteen patients had a stool test for white blood cells, and only 2 (13.3%) had white blood cells in the stool. As a risk factor, 31 (88.6%) patients had a history of antibiotic use in previous 1 month. The main treatment was with oral metronidazole in 33 patients (94.3%) and with oral metronidazole and oral vancomycin in 2 patients (5.7%). The patients who had preconditioning had a slightly higher incidence of CDC than those not receiving preconditioning, but this difference was not statistically significant (7.3% vs. 4.2%, $P>0.05$). Eight patients (22.9%) had recurrent infection (Table 2). The median time to recurrence was 30 days after the first episode of CDC (range: 15–314), and most recurrences (75%) occurred within 40 days after the first

CDC in kidney and pancreas-kidney allograft recipients

	Kidney ($N = 27$)	Pancreas–kidney ($N = 8$)	P
Incidence	4.5%	7.8%	NS
Age (mean ± SD)	54.1 ± 14.9	50.0 ± 6.9	NS
Sex (M/F)	19/8	7/1	NS
Antibody preconditioning	12/27 (44%)	4/8 (50%)	NS
Time to CDC after transplantation (median, range: min–max days)	30 (3–819)	28 (10–520)	NS
CDC occurrence during initial hospitalization	10/27 (37%)	4/8 (50%)	NS
Recurrent CDC	7/27 (25%)	1/7 (12.5%)	NS
Fulminant CDC	2/27 (7.4%)	0%	NS
Death	2/27 (7.4%)	0%	NS

CDC, *Clostridium difficile* colitis; NS, not significant.

Table 1

Recurrent and non-recurrent CDC

	Patients with recurrent CDC ($N = 8$)	Patients without recurrence ($N = 27$)	P
Age (mean ± SD)	54.8 ± 12.4	52.0 ± 14.0	NS
Sex (M/F)	6/2	20/7	NS
Cadaveric/living donor	7/1	19/8	NS
Kidney/pancreas–kidney	7/1	20/7	NS
Antibody preconditioning	5/8 (62.5%)	10/27 (37%)	NS
Steroid avoidance	5/8 (62.5%)	11/27 (40.7%)	NS
Time to CDC after transplantation (median, range: min-max days)	20 (11–819)	43 (3–690)	NS
Previous acute rejection	4/8 (50%)	14/27 (51.8%)	NS
CDC occurrence during initial hospitalization	3/8 (37.5%)	11/27 (40.7%)	NS

CDC, *Clostridium difficile* colitis; NS, not significant.

Table 2

episode. Six patients had 1 recurrent infection after the first episode, one patient had 2, and one had 5 recurrent episodes. All patients with recurrent infection presented with diarrhea. The treatment of recurrent disease was with oral metronidazole in four, oral vancomycin in two, and oral metronidazole plus vancomycin in two patients. One patient developed chronic recurrent CDC and was treated with metronidazole plus vancomycin and additional cholestyramine and intravenous immunoglobulin; however, the patient did not respond to treatment and ultimately succumbed to inanition. No statistically significant difference was noted between the patients with primary and with recurrent CDC (Table 2).

Fulminant colitis developed in two kidney allograft recipients (5.7%) during their first episode of infection when they were in hospital. Both patients underwent colectomy for toxic megacolon. Fever and leukocytosis (17,400/mm^3, and 67,400/mm^3) were the striking features in both patients. While one patient survived, the other (who had a previous liver transplant) died after operation. The pathological specimens of the colon were consistent with necrotizing colitis secondary to CDC.

Since 1/1/03, only two (1.1%) cases of CDC have been observed in 178 transplant recipients (Table 3). These 178 patients received prophylactic metronidazole in the early post-transplant period.

Discussion

CDC is a well-known nosocomial infection causing diarrhea, most commonly secondary to antibiotic use. Although its incidence varies in different centers, CDC has been reported to occur in 1–4% of general surgery patients (5, 6). CDC can spread primarily by the fecal–oral route in hospitalized or nursing home patients and may cause severe morbidity and mortality, especially in elderly hospitalized patients. In hospitalized

CDC and fulminant CDC between 1999 and 2003

	1999 *N* (%)	2000 *N* (%)	2001 *N* (%)	2002 *N* (%)	2003 *N* (%)
Patients with CDC	6 (3.1%)	5 (3.3%)	5 (2.7%)	19 (10.6%)	2 (1.1%)
Patients with fulminant CDC	0	0	1	1	0
Patients with recurrent CDC	2 (33%)	2 (40%)	0	4 (21%)	0
CDC episodes	7	6	5	29	2

CDC, *Clostridium difficile* colitis.

Table 3

patients, CDC has been reported to be more frequent in general surgery patients than in other hospitalized patients, with an association between CDC and prior CD diarrhea, prior antibiotic treatment, renal insufficiency, recent hospitalization, age of patient, and length of total hospital stay (5, 6). In their study, West et al. (7) found that CDC is not an uncommon infection in patients after kidney and pancreas–kidney transplantation and reported an incidence of 8%. Pediatric patients (16%) and pancreas–kidney recipients (15.5%) had a higher incidence of CDC than kidney alone (3.5%) recipients (7). In our patients, the overall incidence was 5.5%. The incidence tended to be higher in patients receiving antibody preconditioning than in those who did not; however this difference was not statistically significant.

FCDC refers to any patient with a systemic inflammatory syndrome (fever, hypotension, tachypnea, leukocytosis, and/or a requirement for volume resuscitation) that results in death or an illness severe enough that death is likely without urgent colectomy (8). However, it is unclear why some patients develop a fulminant course despite appropriate treatment, while others do not. It may be related to the host's capability to mount an efficient antibody-mediated response to clostridial toxins. While West et al. (7) did not report any patient with FCDC, Dallal et al. (8) reported higher incidence of FCDC in lung allograft recipients. However, there are few reports about the occurrence of FCDC in kidney and pancreas–kidney transplantation. FCDC developed in two patients (5.7%) and one survived after colectomy.

The time interval between transplantation and the development of CDC can vary considerably (7, 9, 10). We found that CDC occurred relatively early after transplantation (median 30 days) and within 4 months in 75% of our patients. West et al. (7) reported a significant difference in timing of the CDC in pediatric, adult kidney, and pancreas–kidney patients. Adult kidney allograft recipients developed CDC an average of 15 months after transplantation, while in pancreas–kidney recipients CDC occurred 6 months after the operation. In our patients, CDC occurred at a similar time interval after kidney and pancreas–kidney transplantation; it occurred during the initial hospital stay in 40% of the patients and in a total of 62% of the patients during an in-hospital stay. West et al. (7) reported that 26% of the adult kidney and 54% of the pancreas–kidney patients developed the infection during the initial hospital stay. Nosocomial transmission, frequent antibiotic use, and immunosuppression may be factors leading to the occurrence of CDC in the hospital. However, why some patients develop CDC, while others do not, and why some patients develop FCDC is not known.

Hospitalization because of CDC has been reported to be increased in recent years (8). The incidence of CDC in hospitalized patients increased from a baseline of 0.68% (1989–1999) to 1.2% (2000), and incidence of FCDC increased from 0% (1990) to 3.2% (2000). The mortality for patients diagnosed with CDC was 13.5%, and this is greater than the overall hospital death rate of 3.4% (8). CDC thus increases mortality, even if it does not cause life-threatening complications such as toxic megacolon in most patients. In their study, Dallal et al. (8) found that CDC was quite a common infection after lung transplantation; 78 (31%) patients out of 250 were reported to have CDC between 1990 and 2000. Ten (13%) developed FCDC, a significantly higher incidence than for other hospitalized patients (1.6%). Although immunosuppression seems to be a risk factor for development of FCDC, immunosuppressed patients had a better survival (58% vs. 37%) after development of FCDC than non-immunosuppressed patients. In our study, we found that adult kidney and pancreas–kidney recipients had a 5.5% incidence of CDC during 1999–2002, and it was significantly higher than the overall incidence in our hospital (0.68%, $P<0.001$). Among kidney and pancreas–kidney allograft recipients, 2 (5.7%) patients of 35 developed FCDC, which is higher than the 1.6% overall incidence described by Dallal et al. (8), but it was lower than the lung allograft recipients (13%). Both of our patients with FCDC underwent surgery, and one survived (50%). Regarding the higher incidence of CDC and FCDC after lung transplantation as compared to kidney and pancreas–kidney transplantation, it can be speculated that longer hospital stay and more frequent antibiotic usage for repeated lung infection may be contributing factors. On the other hand, in their study, Dallal et al. (8) showed that patients with a prior history of successfully treated CDC seemed to be at highest risk for FCDC. In our study, both patients developed FCDC during their first episode of CDC. While West et al. (7) did not report any cases of FCDC in their kidney and pancreas–kidney transplant recipients, Mistry et al. (9) and Altiparmak et al. (10) reported one and two cases of FCDC in their kidney allograft recipients, respectively.

The treatment of FCDC is surgical, and total abdominal colectomy and ileostomy can be life saving; however, if the operation takes place after vasopressors are needed, the mortality rate increases significantly (7). Therefore, early recognition of FCDC is very important. In their study, Altiparmak et al. (10) described two patients who developed FCDC; both died without surgical intervention. One patient survived after surgery for FCDC in the report of Mistry et al. (9). Although data are limited, FCDC seems to be associated with a high mortality rate in kidney and pancreas–kidney allograft recipients.

Several reasons are likely for the increased susceptibility to CDC among solid organ transplant patients, including the frequent use of antibiotics, suppression of anti-inflammatory cytokines, suppression of antibody-mediated response to toxins, and longer and more frequent hospital admissions. Although no data have shown any association between specific immunosuppressive agents and CDC infection, we found that the patients receiving antibody induction might be more prone to develop CDC than those not receiving antibody induction; however, this difference was not statistically significant. In addition to host and environmental factors, recent antibiotic use is one of the well-known risk factors for CDC. In our study, we found that CDC was associated with current antibiotic use in 31 patients (88%), while West et al. (7) reported that 60% of the cases with CDC were related to antibiotic use. Despite appropriate treatment, it has been reported that the recurrence rate in non-immunosuppressed patients varies between 10% and 30%; West et al. reported a 13% incidence of recurrent CDC in their pancreas–kidney patients. We found a 22.8% incidence of recurrent CDC. No statistically significant differences were found between kidney and pancreas–kidney allograft recipients with recurrent CDC (Table 2). Metronidazole is a very effective therapy for CDC, even in recurrent disease, and it can be combined with oral vancomycin. Although frequent relapse is not a common problem, some patients can have multiple episodes of CDC. In our study, one patient had 6 CDC episodes, resulting in chronic diarrhea and CD colitis. This patient showed no response to metronidazole plus vancomycin, not even to the addition of cholestyramine and intravenous immunoglobulin, which can be effective for patients with multiple episodes of CDC (11, 12). Eventually, this patient succumbed to inanition. It was reported that asymptomatic carriers of CD have high serum antibody levels against toxin A, and patients with relapsing CDC have lower anti-toxin antibody levels than patients with a single, brief episode of diarrhea (13). Thus, it seems that an adequate immune response to CD appears to be an important mechanism for controlling infectious episodes and relapsing diarrhea.

Measures to prevent CDC include institution of contact isolation precautions, and hand washing before and after patient contact. An important reduction has been noted in the incidence of CDC in our transplant patients receiving prophylaxis with metronidazole (1.1% vs. 5.5%, $P = 0.009$). This practice merits further study.

CDC is not an uncommon problem after kidney and kidney-pancreas transplantation. Aggressive measures to confirm the diagnosis and treat the infection are necessary to prevent development of the potentially fatal fulminant form of the disease. Contact precautions have to be implemented to prevent spread to other patients who are susceptible. The use of metronidazole prophylaxis early in the post-transplant course may be effective in reducing the incidence of CDC.

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