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ORIGINAL ARTICLE

Outcome of *Clostridium difficile*-associated disease in solid organ transplant recipients: a prospective and multicentre cohort study

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Abstract

Clostridium difficile-associated disease (CDAD) is the most common cause of nosocomial diarrhea. Information about CDAD in solid organ transplant (SOT) recipients is scarce. To determine its epidemiology and risk factors, we conducted a cohort study in which 4472 SOT patients were prospectively included in the RESITRA/REIPI (Spanish Research Network for the Study of Infection in Transplantation) database between July 2003 and July 2006. Forty-two episodes of CDAD were diagnosed in 36 patients. The overall incidence was 0.94%. Median onset of infection was 31.5 days (range 6–741); in half the cases, onset occurred during the first month after transplantation. In 26% of cases, there was no previous antibiotic use. Independent risk factors for CDAD using Cox regression analysis were previous use of first- and second-generation cephalosporins (HR 3.68; 95%CI 1.8–7.52; $P < 0.001$), ganciclovir prophylactic use (HR 3.09; 95%CI 1.44–6.62; $P = 0.004$) and corticosteroid use before transplantation (HR 2.95; 95%CI 1.1–7.9; $P = 0.031$). There were no deaths related to CDAD. In summary, the incidence of CDAD in SOT was low, most cases were diagnosed soon after transplantation and the prognosis was good.

Introduction

Clostridium difficile-associated disease (CDAD) has become the most common nosocomial infection of the gastrointestinal tract in healthy and immunocompromised patients, with a reported incidence density rate of 4.1 cases per 10 000 patient-days per hospital [1]. The clinical manifestations of CDAD range from asymptomatic

colonization of the gastrointestinal tract and mild diarrhea to diarrhea with colitis, which can progress to toxic dilatation, sepsis, intestinal perforation, and death. Recent antibiotic use is the most important risk factor for the development of CDAD, although the condition can also occur in patients who have not received these drugs [2–6]. Other recognized risk factors include lengthy hospital stay, advance age, recent surgery, and immunosuppression [7,8]. Solid organ transplant (SOT) recipients are among the highest risk groups for this infection because of impaired defense mechanisms resulting from immunosuppressive therapy, and perioperative antibiotic use [9,10]. The estimated reported incidence of CDAD in SOT recipients ranges from 3 to 7% in liver recipients to 2.1–31% in lung transplantation [7,11–18]. The aim of this study was to characterize the epidemiology and risk factors for the development and to assess the outcome of CDAD in a large cohort of patients undergoing SOT.

Patients and methods

Study population

From July 2003 to July 2006, all consecutive SOT recipients were prospectively included in a database within the Spanish Research Network for the Study of Infection in Transplantation (RESITRA/REIPI), involving 16 transplant centers throughout Spain. Pretransplant, peritransplant, and follow-up data (days 0, 7, 14, 30, 60, 90, 180, 270, 360, and 720 after transplantation) as well as all infections (diagnostic workup, clinical presentation, therapy, and outcomes) and rejection episodes were prospectively recorded in the database. In the case of infection caused by *Clostridium difficile* (CD), the treatment data included the type of drug (metronidazole, vancomycin), route of administration (oral or intravenous), dose, duration, and reason for switching from one drug to another (failure, toxicity, or other) and, lastly, surgery requirement. The data were collected with PDF e-forms, which were sent to a Structured Query Language (SQL) server database located on a Web site. The data were handled with the help of managerial and statistical databases generated from the SQL server database after a validation process performed by each hospital coordinator. The surgical transplantation procedure and perioperative management were performed according to standard techniques. Perioperative antimicrobial prophylaxis varied between centers and type of solid organ transplantation. Seronegative cytomegalovirus (CMV) recipients from a seropositive donor and all lung transplant recipients were administered prophylaxis with either iv ganciclovir or po valganciclovir for at least 3 months.

The study was approved by the Institutional Review Board of all the participating hospitals. All patients gave written informed consent for participation in the study.

Definition

A CDAD case was established when a patient had diarrhea and positive enzyme immunoassay testing for CD toxins A and B in stool specimens. No screening of stool for CD carriage was carried out prior to transplantation. Patients with confirmed CDAD were compared with those without to identify risk factors for the development of CDAD.

Microbiological procedure

Clostridium difficile toxin A and B detection was performed with a rapid enzyme immunoassay (Premier Toxins A & B; Meridian Diagnostics Inc., Cincinnati, OH, USA). Testing for the hypervirulent CD strain, NAP1/BI/027, was not being performed during the study period.

Statistical analysis

Categorical variables are expressed as percentages, and numerical data as the mean ± SD for variables with a normal distribution or the median and IQR for those with a skewed distribution. Categorical variables were compared with the chi-squared test or Fisher exact test and continuous variables with the Student *t*-test. All statistical tests were two-tailed, and the threshold of statistical significance was $P < 0.05$.

To calculate the incidence of CDAD in SOT patients, day 0 corresponded to the date when SOT was performed. Patients were observed until they developed CDAD, death occurred, or the follow-up period ended.

Crude and adjusted hazard ratios (HRs) were calculated using Cox regression analysis to identify risk factors. Variables showing statistically significant differences between patients with or without CDAD in the univariate analysis were then tested in multivariate models. Models were performed in a sequential fashion beginning with the variable most strongly associated with CDAD and continuing until no other variable reach significance or changed the HRs of variables already in the model. In addition, clinically relevant factors with *P*-values <0.1 that were considered to be potential confounders on the basis of experience and data in the literature were forced into the multivariate model to investigate their effect. Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL, USA).

Results

Study population, clinical presentation, and treatment

During the study period, 4472 consecutive patients underwent SOT in the RESITRA/REIPI transplant centers:

2057 (46%) kidney, 1570 (35%) liver, 406 (9%) heart, 310 (7%) lung, and 128 (3%) pancreas. Patients were followed for a median of 360 days after transplantation (IQR, 180–720). Among the total of SOT recipients, 36 (median age 56 years, IQR 39–65 years, 26 male) developed 42 episodes of CDAD. There was no cluster detected in any institution. Median onset was 25.5 (IQR, 13–58.5) days after the procedure for the first episode of infection and 31.5 (IRQ, 13–74) days considering all episodes. The overall incidence was 0.94% and the global incidence density rate was 0.25 episodes per 10000 patient-days of follow-up. Incidence and incidence density rates sorted by type of transplantation are shown in Table 1, and the demographic, clinical, and outcome data are presented in Table 2.

In our series, 38 (90%) episodes were detected during the first 6 months after transplantation, including 20 (48%) in the first month. Only 2 (4.8%) cases were documented after the first year. Fifteen of the 42 episodes (35.7%) were related to the prophylaxis with antibiotics for the transplant procedure, whereas 16 (38.1%) occurred after a bacterial infection treated with a course of antibiotics. In 11 episodes (26.2%), there was no antibiotic use in the previous 30 days. The most common antimicrobial agents used before development of CDAD were first- and second-generation cephalosporins (18 episodes). Fluorquinolones were administered before CDAD in four cases (Table 3).

Immunosuppressive therapy was mainly based on corticosteroids, calcineurin inhibitors, and mofetil mycophenolate (Table 2). Induction treatment with basiliximab was used in 12 (33.3%) patients and thymoglobulin in 4 (11.1%). Eleven (30.6%) recipients were started on prophylaxis for CMV disease.

All CDAD patients presented with abdominal pain and watery diarrhea. Fulminant disease requiring colectomy occurred in one case. Treatment consisted of fluid and electrolyte replacement and oral metronidazole, with vancomycin added in two cases because of poor response. Metronidazole was for used a median of 10 days (IRQ 9–14). In 30 episodes (71.4%), metronidazole was administered at a dose of 500 mg tid. In the other 12 patients, a dose of 250 mg q6 h was used. The cases treated with vancomycin 125 mg q6 h during 8 days were first given metronidazole 500 mg tid for 7 and 10 days, respectively. No cases were initially managed on an outpatient setting.

One liver transplant recipient developed fulminant colitis during his first episode of CDAD and required subsequent colectomy. There were no deaths directly attributed to CD infection in our series. Relapse was diagnosed in 6 (16.7%) patients, 2 renal, 1 heart, 1 lung, 1 pancreas, and 1 liver recipient. The median time to recurrence was 45 days (IQR, 28–94) and all patients had only one recurrent infection. In three of the recurrences, no previous antibiotic use was recorded. Treatment of recurrent disease consisted in repeating oral metronidazole, with clinical resolution of all episodes.

No statistically significant differences in 1-year mortality were found between patients with CDAD (8.3%; 3 of 36 patients) and patients without (7%; 311 of 4436 patients).

Risk factor analysis

Crude and adjusted HRs are shown in Table 4. Overall, the adjusted model showed that the variable most closely related to development of CDAD was the administration of first- and second-generation cephalosporins within 30 days before CDAD (HR 3.68; 95%CI 1.8–7.52; $P < 0.001$). Other risk factors were ganciclovir prophylaxis use (HR 3.09; 95%CI 1.44–6.62; $P = 0.004$) and corticosteroid use within the 3 months before transplantation (HR 2.95; 95% CI 1.1–7.9; $P = 0.031$).

Discussion

Clostridium difficile infection is a potentially severe complication following SOT with a reported estimated overall incidence ranging from 3% to 16% [7,9,15,17], and an annual incidence reported by type of transplantation of 2.1–31% in lung recipients, 3–7% in liver recipients,

Table 1. Annual incidence of CDAD in the RESITRA patient cohort, sorted by type of transplant.

Type of transplant	Total number of transplants	Total CDAD cases	Incidence (%)	Incidence density rate*
Liver	1570 (35)	10 (23.7)	0.63	0.16
Kidney	2057 (46)	16 (38)	0.77	0.2
Heart	406 (9)	5 (12)	1.23	0.33
Lung	310 (7)	6 (14.3)	1.93	0.71
Pancreas	128 (3)	5 (12)	3.9	1.62
Global	4472 (100)	42	0.94	0.86

CDAD, *Clostridium difficile*-associated disease.
Data are *n* (%) of patients, unless otherwise indicated.
*Expressed as episodes/10 000 patient-days of follow-up.

Table 2. Demographics and clinical data of patients diagnosed with CDAD and controls.

	CDAD	Controls	
	36 (0.8)	4436 (99.2)	*P*
Patient data			
Median age (IRQ), years	56 (39–65)	53 (42–61)	0.38
Male gender	26 (72.2)	2953 (66.6)	0.48
Diabetes mellitus	12 (33.3)	821 (18.5)	0.02
Peptic ulcer	3 (8.3)	287 (6.5)	0.65
HIV infection	0 (0%)	63 (1.5%)	0.48
CMV D+/R–	3 (8.3)	376 (8.5)	0.97
Previous transplant	4 (11.1)	515 (11.7)	0.91
Corticosteroids 3 months before Tx	31 (86.1)	4183 (94.3)	0.03
Antibiotics 3 months before procedure	31 (86.1)	3997 (90.1)	0.42
Type of transplantation			
Kidney	14 (39)	2043 (46)	0.39
Liver	9 (25)	1561 (35.2)	0.2
Heart	4 (11)	402 (9.1)	0.67
Lung	5 (13.9)	305 (6.9)	0.09
Pancreas	4 (11.1)	124 (2.8)	0.03
Procedure data			
Emergent transplant	5 (13.9)	302 (6.8)	0.09
Mean (SD) cold ischemia, min	737 (672)	630 (513)	0.33
Mean (SD) surgery time, min	261 (113)	279 (216)	0.63
Two or more antibiotics as prophylaxis	18 (50)	1807 (40.7)	0.26
Prophylaxis against CMV disease	11 (30.6)	521 (11.7)	0.001
Immunosuppression			
Induction with anti-CD25 antibodies	12 (33.3)	1264 (28.5)	0.52
Induction with thymoglobulin	4 (11.1)	164 (3.7)	0.02
Corticosteroids in main regimen	32 (88.9)	4001 (90.2)	0.85
Calcineurin inhibitors in main regimen	27 (75)	3859 (87)	0.07
MMF in main regimen	30 (83.3)	3024 (68.2)	0.03
mTOR inhibitors in main regimen	2 (5.5)	236 (5.3)	0.88
Evolution			
Glycopeptide use 30 days before CDAD	8 (22.2)	833 (18.8)	0.59
Carbapenem use 30 days before CDAD	0	138 (3.1)	0.28
1st/2nd generation CF 30 days before CDAD	17 (47.2)	1137 (25.6)	0.003
Quinolone use 30 days before CDAD	1 (2.8)	489 (11)	0.11
Acute rejection	9 (25)	881 (19.9)	0.44
CMV disease	4 (11.1)	459 (10.3)	0.88
Outcome			
One-year overall mortality	3 (8.3)	311 (7)	0.76

CDAD, *Clostridium difficile*-associated disease; CF, cephalosporin; CMV, cytomegalovirus; CMV D+/R–, donor seropositive/recipient seronegative for cytomegalovirus infection; HIV, human immunodeficiency virus; MMF, mycophenolate mofetil; SD, standard deviation; Tx, transplantation.
Data are *n* (%) of patients, unless otherwise indicated.

0.5–16% in kidney recipients, 1.5–7.8% in pancreas–kidney recipients, 9% in intestinal recipients, and 1.4–15% in heart recipients. The overall incidence in our series was 0.94%, a value lower than previously reported percentages. However, our incidence rates sorted by type of transplantation are in keeping with previous reported results, with the exception of liver recipients, in whom the risk was lower in our series. An accurate antibiotic policy and perhaps rifaximin prophylaxis, given to some cirrhotic patients to prevent hepatic encephalopathy, might have contributed to our lower incidence of CDAD. Unfortunately, we do not have precise data on the number of patients treated with rifaximin. Pancreas recipients presented the highest risk (3.9%), in accordance with reported results. It has been speculated that the longer hospital stay and more frequent antibiotic use for repeated infections in these patients may be contributing factors to the high incidence of CDAD in pancreas transplant recipients [16].

The time interval between transplantation and the development of CDAD varies considerably. In our series, 38 (90%) of episodes appeared within 6 months after

Table 3. Antibiotic use in 42 episodes of *Clostridium difficile*-associated disease.

	Antibiotic prophylaxis (*n* = 15)	Antibiotic therapy (*n* = 16)	No previous antibiotic use (*n* = 11)
CD infections/organ			
Kidney	5 (33.3)	8 (50)	3 (27.3)
Liver	5 (33.3)	1 (6.3)	4 (36.4)
Heart	1 (6.7)	3 (18.8)	1 (9.1)
Lung	3 (20)	3 (18.8)	0
Pancreas	1 (6.7)	1 (6.3)	3 (27.3)
Antibiotic prior to CD infection			
Cephalosporins	12 (80)	6 (37.5)	0
Penicillins	3 (20)	2 (12.5)	0
Quinolones	0	4 (25)	0
Carbapenems	0	3 (18.8)	0
Glycopeptides	0	1 (6.3)	0

CD, *Clostridium difficile*.
Data are *n* (%) of patients, unless otherwise indicated.

transplantation, 20 (48%) of them in the first month. These data are consistent with findings from other series, which showed the highest incidence of CDAD within the first 3 months post-transplant, in relation to surgery and antibiotic prophylaxis. Late-onset CDAD, occurring later than 6 months post-transplant, may be associated with antimicrobial exposure or intensified immunosuppression to treat graft rejection [15,18]. Based on this observation, some authors have proposed treating transplants recipients prophylactically with metronidazole in the early post-transplant period to reduce the incidence of CDAD [16]. Although implementation of this measure showed a reduction in the incidence of CDAD in kidney and pancreas–kidney transplant recipients [16], we believe that the available evidence does not suffice to apply this strategy as common practice in all SOT patients. Of note, in our series, there were no CDAD-related deaths.

Diarrhea, as a side effect of immunosuppressive therapy, is a frequent clinical symptom in SOT patients. The presumed disruption of the intestinal microflora because of immunosuppression, enteral nutrition, and antimicrobial therapy can facilitate CD growth and toxin production [12,13,15]. Although nearly all the antimicrobial classes have been associated with CDAD, clindamycin, cephalosporins, fluoroquinolones, and penicillins have been implicated as high-risk agents. In our series, the antimicrobial agents most commonly associated with CDAD were cephalosporins (18 cases), followed by penicillins (5), fluorquinolones (4), and carbapenems (3). On multivariate Cox analysis, treatment with first- and second-generation cephalosporins was a significant risk factor for CDAD. However, in nearly one-third of our cases, there had been no antibiotic exposure within 30 days prior to the CDAD diagnosis.

Other unknown factors, such as the effect of immunosuppressive agents, might be involved in these cases. In our series, none of the immunosuppressive therapies was significantly associated with the development of CDAD, but Keven *et al.* [16] observed that the incidence of CDAD tended to be higher in patients receiving antibody preconditioning than in those who did not. Other authors have recommended CDAD prophylaxis at every reintroduction of tacrolimus and/or rapamycin, arguing that patients receiving these treatments are at a higher risk of developing the infection [19,20]. Conversely, in the univariate analysis, patients administered calcineurin inhibitors as a part of the immunosuppressive therapy seemed protected against the development of CDAD. Hence, again, we believe that the available evidence does not suffice to warrant prophylaxis use of any kind as common practice. Nonetheless, early screening for CD should be carried out in patients with diarrhea, and a longer treatment course could be considered in high-risk patients.

The reason why some patients develop CDAD and others do not remain uncertain. It has been proposed that CDAD development greatly depends on the host capability to produce an efficient antibody-mediated response to clostridial toxins [16], and because of their immunosuppression, SOT patients might be more vulnerable to CD.

Table 4. Cox regression results for risk factors of CDAD.

	Crude hazard ratio	Adjusted hazard ratio
Diabetes mellitus	2.22 (1.11–4.45); 0.024	
Corticoids 3 months before procedure	2.9 (1.13–7.48); 0.027	2.95 (1.1–7.9); 0.031
Pancreas transplantation	4.92 (1.74–13.94); 0.003	
1st or 2nd generation CF use 30 days before CDAD	2.64 (1.37–5.08); 0.004	3.68 (1.8–7.52); <0.001
Prophylaxis with ganciclovir	3.4 (1.67–6.91); 0.001	3.09 (1.44–6.62); 0.004
Induction with thymoglobulin	3.31 (1.17–9.36); 0.024	
Calcineurin inhibitors as main immunosuppressants	0.41 (0.18–0.9); 0.027	

CDAD, *Clostridium difficile*-associated disease; CF, cephalosporin.
Numbers expressed as hazard ratio (95% confidence interval); *P*.

The responsibility of hypogammaglobulinemia as a predisposing condition has not been extensively studied, although some authors have suggested that it has an important role [21]. Although, in our study, we did not have data about hypogammaglobulinemia, gammaglobulin administration did not play any role in preventing the development of CDAD. However, recipients receiving pretransplant corticosteroids seemed prone to this condition, supporting the causal hypothesis of lower immune status. In contrast, as some authors have argued [7], a diminished inflammatory response together with close follow-up might contribute to improving the outcome in SOT patients compared with other CD cohorts.

Surprisingly, ganciclovir prophylaxis was found to be a risk factor for CDAD. Some authors have described an association between CMV mismatch, and consequently ganciclovir use, with severe progression of CDAD [13], although we did not observe this link. In our case, the significance of CMV prophylaxis could be related to its universal prescription in lung transplantation, in which the incidence of CDAD is higher, or to a drug-induced leukopenia, but, unfortunately, these data were not collected.

The crude HRs showed other conditions associated with CDAD, such as diabetes mellitus (HR 2.22, 95% CI 1.11–4.45; $P = 0.041$) and induction with thymoglobulin (HR 3.31, 95% CI 1.17–9.36; $P = 0.024$), supporting the hypothesis of weaker immune capability as responsible for developing CDAD.

Current CDAD treatment focuses on metronidazole and vancomycin [22]. Early studies showed equivalence of these drugs, but more recent reports indicate that oral vancomycin is preferred for severe CDAD [5,22]. All of our patients were initially treated with metronidazole; in the two cases with a poor response, vancomycin was added and the episode resolved.

Our patients had a good prognosis, with only one colectomy requirement, despite the use of oral vancomycin and iv metronidazole, and no related 30-day mortality. Furthermore, there were no differences in 1-year mortality. The reported incidences of fulminant CDAD vary from 1.6 to 5.7% [7,16], and an infection-related mortality rate of 2.3% has been described [13]. Recent CD epidemics caused by NAP1 strains have been associated with a severe presentation and increased risk of death [23]. We do not know whether any of our patients had this specific strain because the isolates were not typed, but NAP1 isolation has not been reported in Spain [24]. We believe that our cases were likely caused by other less virulent CD-ribotypes and not by NAP1 CD-strains.

The observations in our study are subject to limitations. First, all patients were diagnosed by positive enzyme immunoassay testing, but stools were not analyzed using multiplex real-time PCR or cultured for CD detection; thus, it is likely that some cases were missed. Second, RESITRA/REIPI was conceived as a general database for all transplant procedures, and information on specific risk factors associated with CDAD, such as previous history of CDAD, use of proton pump inhibitors, H2 blockers, laxatives, and enteral feeding, was not included. However, the management of SOT patients is highly standardized on our setting, and no significant differences would be anticipated between recipients with and without CDAD. The strengths of our study are its prospective nature and the large number of cases included.

In summary, CDAD is a potentially severe complication following SOT, with an incidence of 0.94% and an incidence density rate of 0.25 episodes per 10 000 patient-days of follow-up in our setting. Most cases were diagnosed in the early post-transplant period and two-thirds of affected patients had prior antibiotic exposure. Although CDAD is a potentially lethal condition, the prognosis was good in the RESITRA/REIPI cohort.

Authorship

LO, RPD and GJ: Conception and design. LO, AJM, BM, BN, BG, CJ, CJM, FJ, GM, MM, CC, MP, AA, and TCJ: Acquisition of data. LO and RPD: Analysis and interpretation of data. LO and RPD: Drafting the article. All authors: Revising the article. All authors: Final approval of the version to be published.

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