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# Cryptosporidium spp. Infection in Solid Organ Transplantation: The Nationwide “TRANSCRIPTO” Study

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**Background.** Diarrhea is a frequent complication of solid organ transplantation. Cryptosporidiosis is classically reported in patients with acquired immunodeficiency syndrome and emerged as a cause of persistent diarrhea in solid organ transplant patients.

**Methods.** Through the ANOFEL Cryptosporidium National Network and the French Transplantation Society, we collected all cryptosporidiosis cases identified in solid organ transplanted patients between 2006 and 2010 in France. **Results.** We reported 47 solid organ transplant recipients (41 kidneys) with cryptosporidiosis, mostly men (68%), with a median age of 52 (6-70) years old. Five patients had additional immunodepression favoring cryptosporidiosis (CD40 ligand deficiency [n = 1], human immunodeficiency virus infection [n = 4]). Cryptosporidiosis occurred at a median time of 3.4 (0-19.8) years posttransplant. Exposure to environmental risk factors was found before infection onset in 18 patients. Time between first symptoms and diagnosis was 10 (2-110) days. Four patients had associated extraintestinal location (biliary tract [n = 3] and lung [n = 1]). Thirty-five patients received specific therapy against cryptosporidiosis ie nitroimidazole, 25 in monotherapy, and 10 in association with azithromycin, 13 in association with immunosuppression (IS) reduction. Four patients were cured with IS treatment tapering only. The others patients had neither IS reduction nor specific therapy against cryptosporidiosis. Cryptosporidiosis was complicated by renal failure in 15 patients. Symptoms resolved after a median of 10 days of treatment. Six patients relapsed and 3 died, 1 with evolutive infection.

**Conclusions.** Cryptosporidiosis is a late posttransplant infection that disseminated to biliary duct or lung in 9% of patients. When limited to digestive tract, infection may resolve without IS reduction.

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Cryptosporidium spp. is a protozoan-causing diarrhea after the ingestion of contaminated food products or water.<sup>1,2</sup> Disease severity and duration vary with host immune status.<sup>3,4</sup> Whereas infection is self-limited in immunocompetent hosts, it can be responsible for severe and/or disseminated disease in the immunocompromised. Cryptosporidiosis has been reported in patients with acquired immunodeficiency syndrome (AIDS), and more recently emerged as

a cause of severe and persistent diarrhea in solid organ transplant (SOT) patients.<sup>5-8</sup> One fifth of SOT will develop diarrhea in 3 years posttransplant.<sup>9,10</sup> The most frequently reported pathogens responsible for persistent diarrhea are by far *Cryptosporidium difficile* and Norovirus.<sup>10,11</sup> However, cryptosporidiosis can be responsible diarrhea in this setting.<sup>7,10,12-14</sup> Most reports are confined to single patients or small series. One study was conducted in an endemic area in India evidencing *Cryptosporidium* spp. being responsible for 28% of diarrhea

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F.L. designed the study, analyzed the results, wrote the article, K.A. collected the data, analyzed the results, and wrote the article. L.F. revised the article. M.-F.M.-B. designed the study. H.A. performed the statistical analysis. J.T. participated in data collection and revised the article. S.D. participated in data collection and revised the article. J.Z. revised the article. A.S. revised the article. C.L. revised the article. O.L. designed the study and wrote the article. M.-E.B. designed the study and wrote the article.

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in transplant patients (34 patients).<sup>6</sup> Clinical presentation, outcome, and treatment of cryptosporidiosis in SOT patients are yet poorly described.

At the request of the Institut National de Veille Sanitaire, the French center for disease control, a Cryptosporidium National Network has been set up in 2006 in France to provide data on the epidemiology of human cryptosporidiosis. A third of reported cases of cryptosporidiosis in France occurred in immunocompromised patients without human immunodeficiency virus (HIV) infection.<sup>15</sup> We retrospectively collected information on history, treatment, and outcome of cryptosporidiosis in SOT recipients.

## MATERIALS AND METHODS

The ANOFEL Cryptosporidium National Network (ACNN) was set up to provide public health authorities with data on the incidence and epidemiology of human cryptosporidiosis in France. The operating of the network has been described.<sup>16</sup> Through the ACNN and by contact with French Transplantation Society, we retrospectively collected all cryptosporidiosis cases identified in SOT recipients between 2006 and 2010. Cases were defined by the presence of diarrhea (ie,  $\geq 3$  liquid stools per day) and detection of oocysts of *Cryptosporidium* sp. by a microscopic examination of fecal smears after staining (modified acid-fast Ziehl-Neelsen or auramine). Lung cryptosporidiosis was assessed by presence of cryptosporidies at the site of infection. Biliary cryptosporidiosis was assessed by compatible images on magnetic resonance imaging or cholangiography associated with confirmed digestive location. We retrospectively collected clinical information regarding the patient, the transplant, induction and maintenance immunosuppressive regimens, clinical presentation, environmental characteristics, treatment, and outcome. Ethical board approval was centralized and obtained for the multicenter study.

### Statistical Analysis

Continuous variables are described as means ( $\pm$  standard deviation) and/or medians (range) and categorical variables are presented as numbers and frequencies (percentages).

## RESULTS

### Characteristics of the Patients

Forty-seven SOT recipients developed cryptosporidiosis between 2006 and 2010 in France. Patients were from 17 centers. The patients' characteristics are reported in Table 1. Most patients were men (68%), with a median age of 52 (6-70) years. Seven patients were younger than 15 years, all were from the same center.<sup>15</sup> The kidney was the most frequently transplanted organ ( $n = 42$ , 47%). A single patient received kidney and liver transplant. Five patients had additional immunodepression favoring cryptosporidiosis: 1 patient had CD40 ligand deficiency and was a liver transplant recipient and 4 had HIV infection (3 had received kidney transplant and 1 heart transplant).

### Clinical Characteristics

Cryptosporidiosis occurred at a median time of 3.4 (0-19.8) years posttransplant (1.4 [0.4-4.3] years posttransplant for the 4 HIV infected patients). It occurred within 6 months posttransplant in 10 patients. Time between first symptoms

**TABLE 1.**

**Characteristics of the 47 transplanted patients with cryptosporidiosis in France from 2006 to 2010**

Characteristics	Value
Age: median (range), y	52 (6-70)
Sex (female)	15 (32)
Type of organ transplantation	
Kidney only	41 (88)
Liver/Kidney	1 (2)
Liver	1 (2)
Heart	3 (6)
Pancreas*	1 (2)
First transplant	43 (93)
Immunosuppressive regimen	
Induction regimen	
ATG only	13 (65)
Anti-CD25 only	20 (57)
Both	2 (10)
Immunosuppressive regimen in last 3 mo	
Corticosteroids	42 (89)
Tacrolimus	32 (68)
Cyclosporin	9 (19)
MMF	42 (89)
Sirolimus	4 (8)
Organ rejection before cryptosporidiosis	13 (32)
Corticosteroids bolus for rejection	12 (92)
ATG for rejection	2 (15)
HIV-infected patients	4 (8%)
Coinfection	4 (8%)
Median time interval between transplantation and infection (range), y	3.4 (0-19.8)

ATG, antithymoglobulin; MMF, mycophenolate mofetil.  
Data are n (%) unless otherwise indicated.

and diagnosis was 10 (2-110) days (Table 2). Two patients had coinfection, one with enterovirus and one with *Giardia intestinalis*. Two patients had mucus or blood in stool without any coinfection.

Four patients had associated extraintestinal location (biliary tract [ $n = 3$ ] and lung [ $n = 1$ ]); 3 were kidney and 1 liver transplant recipient. In these patients, median time from transplant to cryptosporidiosis was 0.5 (0.2-4) years. Furthermore, 2 patients with biliary cryptosporidiosis experienced acute rejection treated with corticosteroids before cryptosporidiosis: 1 patient with *Cryptosporidium* cholangitis had CD40 ligand deficiency; he never cleared the infection and died, and the second patient relapsed.

Four patients had HIV infection; all with CD4 cell counts greater than 300/mm<sup>3</sup> at time of cryptosporidiosis diagnosis. Median age was 45.6 (27.3-49.6) years. None of them had extraintestinal location. Diagnostic delay was 9 days.<sup>6-20</sup> Diarrhea duration was 12 (10-40) days. All 4 patients were treated with nitoxoxanide for a median time of 30 days (21-90 days) and one relapsed.

### Treatment and Outcome

Thirty-five patients received specific therapy against cryptosporidiosis, that is, nitoxoxanide, 25 in monotherapy for a mean duration of 19 days (2-35 days) and 10 in association with azithromycin for a median duration of 10 days (8-60 days), 13 in association with immunosuppression (IS) tapered or

**TABLE 2.**  
**Clinical presentation of cryptosporidiosis and laboratory characteristics in the 47 solid organ transplant patients**

Characteristics	Value
Median duration of cryptosporidiosis symptoms before diagnosis, d	10 (2-110)
Symptoms	
Fever	
Nausea	26 (59)
Abdominal pain	31 (77)
Blood in stool	1 (3)
Stool's nb/d	6 (3-20)
Mucus in stool	1 (3)
Weight loss	38 (95)
Weight loss (kg)	4 (0-15)
Cryptosporidiosis location	
Digestive	47 (100)
Biliary	3 (7)
Lung	1 (2)
Time from first symptoms to treatment start, d	10.5 (0-25)
Biological characteristics at diagnosis	
Median lymphocyte count, /mm <sup>3</sup>	1200 (500-3070)
Median CD4 count, /mm <sup>3</sup>	426 (124-1101)
<i>Cryptosporidium</i> genotype (n = 6)	
<i>Cryptosporidium parvum</i>	2 (33)
<i>Cryptosporidium hominis</i>	4 (67)

Data are n (%) unless otherwise indicated.

stopped (mean treatment duration of 19 days (4-60 days). Treatment and outcome are summarized in Figure 1. Finally, 4 patients had IS treatment tapering only. Three patients had neither tapering of IS treatment or specific therapy against cryptosporidiosis. Diarrhea resolved 11 (2-25) days after treatment onset when treated with antiparasitic treatment and 9 (1-53) days when antiparasitic treatment was

associated with IS reduction. Interestingly, the 7 patients who did not receive antiparasitic treatment or/and reduction of immunosuppressive regimen cleared *Cryptosporidium* spp. without any relapse. Among all patients, 86% patients had stool negative after a median duration of 14 (1-53) days. Cryptosporidiosis was complicated with renal failure in 15 patients. One 10-year-old kidney transplant had organ rejection secondary to cryptosporidiosis.

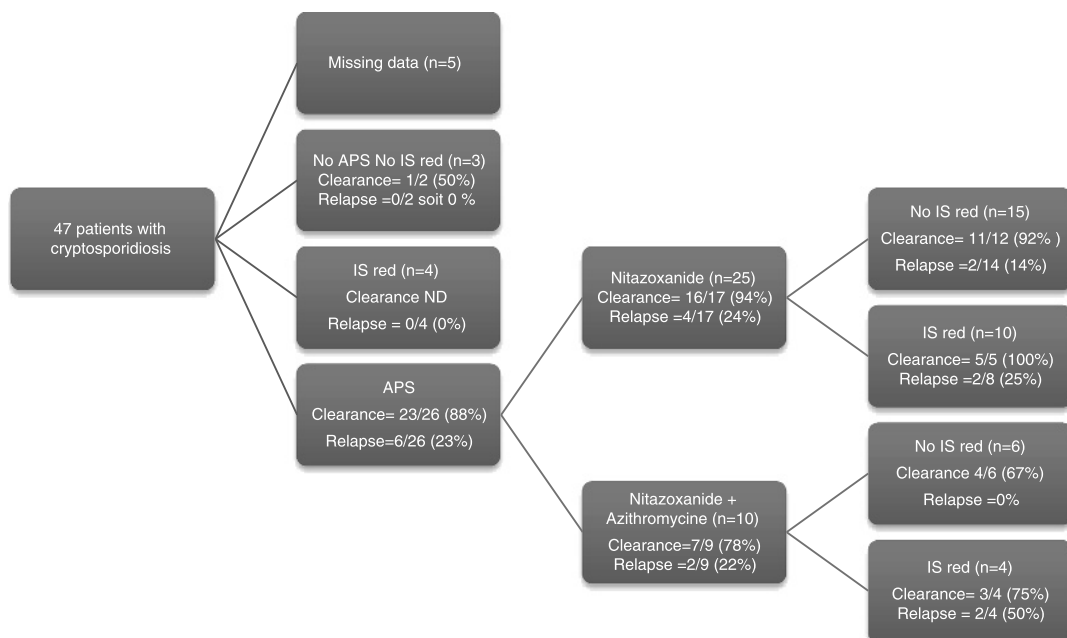
Six patients relapsed, all were renal transplant, 1 had lung location. Two had a history of recent acute rejection. All were treated with an association of nitazoxanide and azithromycin, 4 in association with reduction of immunosuppressive regimen. Three patients died, 1 from biliary and profuse digestive cryptosporidiosis associated with CD40 ligand deficiency although careful investigations were performed at the onset of transplant procedure. Oocysts of *Cryptosporidium* sp. were present in stool. However, no autopsy was performed.

**Epidemiological Risk**

Exposure to environmental risk factors was found before infection onset in 18 patients. We found epidemiological information that could be associated with the occurrence of cryptosporidiosis in 6 patients from rural areas, 2 that were in contact with farm animals, 2 drank nonpotable water, 4 used recreational water, and 10 traveled recently in endemic areas. Diarrhea was reported in siblings for 4 patients.

**DISCUSSION**

We report 47 cases of cryptosporidiosis in solid organ transplanted patients between 2006 and 2010 in France. In our cohort, cryptosporidiosis is a late posttransplant infection, occurring a median time of 3 years after transplant. Whereas in HIV infection low CD4 cell count, below 50 is the determinant of symptomatic cryptosporidiosis,<sup>17</sup> SOT patients developing cryptosporidiosis in our study had a median CD4 cell count over 400 cells/mm<sup>3</sup>. All patients had diarrhea, most of them associated with abdominal pain. Fever



**FIGURE 1.** Flowchart of cryptosporidiosis treatment and outcome.

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and blood or mucus in stool could also be present in the absence of any evidenced coinfection. Cryptosporidiosis has therefore to be discussed in case of any form of diarrhea in SOT. Diarrhea duration reported for cryptosporidiosis in immunocompetent children is 7 days.<sup>1</sup> In our SOT patients, digestive cryptosporidiosis is also quite acute with a median duration of symptoms of 10 days compared with 8.7 months for Norovirus and 1 month for bacterial infection as reported previously by our group.<sup>11</sup>

Infection severity is reflected by hospitalization rate and duration. Impact on renal function was important as half of patients developed renal insufficiency. However, only 1 organ rejection complicated the infection. We report extra intestinal location in 9% of patients, 7% developing biliary location. Among the 3 patients with biliary cryptosporidiosis, 1 had CD 40 ligand deficiency and liver transplantation, whereas the other 2 were kidney transplant. In immunocompetent patients, cryptosporidiosis is associated with diarrhea without extra intestinal location, whereas sclerosing cholangitis is frequent in patients with AIDS (17% or CD40 ligand deficiency (10%).<sup>18</sup> Sclerosing cholangitis was previously reported in 6.1% of pediatric SOT developing cryptosporidiosis.<sup>19</sup>

Cryptosporidiosis treatment is not always mandatory in immunocompetent individuals, despite association with relapse of digestive symptoms.<sup>20</sup> For immunocompromised individuals, cellular immunity improvement is the key of cryptosporidiosis management. Indeed, in HIV-infected patients, it was evidenced that highly active antiretroviral therapy treatment, as single therapy, was associated with favorable evolution of cryptosporidiosis.<sup>21</sup> In our report, half of the patients had a reduction of IS regimen. However, we cannot assess that this reduction was necessary to cure the infection. Despite IS reduction and antiparasitic treatment, 4 patients relapsed.

Antiparasitic regimen for cryptosporidiosis treatment in SOT is not well defined. Nitazoxanide was previously evidenced to reduce diarrhea duration in non-HIV infected individual, but not in HIV-infected individuals.<sup>22-24</sup> Azithromycin was not effective in cryptosporidiosis treatment in AIDS patients.<sup>25</sup> In an Indian study of *Cryptosporidium* infection in SOT recipients, prolonged course from 16 to 60 days of nitazoxanide alone in combination with fluoroquinolone in 21 patients were used. 16% patients had relapse. Combination therapy was more effective than nitazoxanide treatment alone.<sup>6</sup> Our data suggested that antiparasitic treatment is not required to cure all SOT patients with cryptosporidiosis, because 7 patients were cured without antiparasitic treatment. Only 1 patient had refractory infection despite IS reduction and antiparasitic combination, due to additional underlying immunodeficiency with CD40 ligand deficiency. We can assume that depending on infection severity, renal impairment and symptoms duration, antiparasitic treatment could be postponed. Relapse was quite frequent with 6 patients that relapsed. However, in immunocompetent patients, up to 40% of patients had recurrence of intestinal symptoms.<sup>20</sup> Majority of patients were on tacrolimus that was reported to be protective in Bhaduria study.<sup>6</sup> However, we did not study risk factor of cryptosporidiosis.

We could find environmental exposure at risk to develop cryptosporidiosis in some patients as contact with farm animals, recreational waters or travel in endemic countries. Recommendations could be given to SOT patients to avoid

contact with recreational water and drink mineral water while traveling in tropical areas to reduce cryptosporidiosis risk.

In conclusion, cryptosporidiosis is a late and severe post-transplant infection. Clinical presentation associates digestive symptoms and can be complicated with biliary duct or lung location. Symptoms resolve after a median of ten days of treatment. When limited to digestive tract, infection might resolve without specific antiparasitic treatment. Exposures to environmental risk factors are quite frequently found before infection onset and should be explained to patients.

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