Open Forum Infectious Diseases

MAJOR ARTICLE

Resolution of Cryptosporidiosis in Transplant Recipients: Review of the Literature and Presentation of a Renal Transplant Patient Treated With Nitazoxanide, Azithromycin, and Rifaximin

Ewa Tomczak, April N. McDougal, A. Clinton White, Jr.,

Infectious Disease Division, Department of Internal Medicine, University of Texas Medical Branch, Galveston, Texas, USA

Background. *Cryptosporidium* is a major cause of diarrheal disease worldwide, including chronic disease in malnourished children and patients with acquired immune deficiency syndrome. There are increasing reports of cryptosporidiosis in transplant patients, especially from middle-income countries.

Methods. The literature on treatment of cryptosporidiosis in transplant patients was reviewed and included no controlled trials but only small case series. Nitazoxanide, azithromycin, spiramycin, and combination therapies have been used, but none are consistently efficacious.

Results. We present a case of chronic diarrhea from cryptosporidiosis in a renal transplant patient. His illness resolved with decreasing immunosuppression and treatment with the 3-drug combination of nitazoxanide, azithromycin, and rifaximin.

Conclusions. Although current therapies are not reliably effective in the absence of an effective cellular immune response, combination therapies hold promise for improved responses.

Keywords. azithromycin; cryptosporidiosis; *Cryptosporidium*; nitazoxanide; transplant recipient.

Cryptosporidiosis has been recognized as a cause of diarrhea in immunocompromised hosts for over 40 years, particularly in patients with acquired immunodeficiency syndrome (AIDS) [1]. However, the burden of disease due to this organism in other patient groups has been largely overlooked due to infrequent use of appropriate diagnostic tests and the poor sensitivity of tests that were used. With improved testing, the number of cases reported in the United States has tripled [1]. Over the past decade, *Cryptosporidium* has been recognized as a major cause of diarrheal disease in children in resource-poor countries [2–4]. Organ transplantation is increasingly performed, including in middle-income countries. There are also increasing reports of cryptosporidiosis in organ transplant recipients [5–9].

Management of cryptosporidiosis is problematic [10, 11]. Nitazoxanide is a US Food and Drug Administration-approved treatment for cryptosporidiosis in normal hosts, based on randomized trials demonstrating more rapid resolution of symptoms and oocyst shedding [12, 13]. A trial in hospitalized children in Africa, most of whom were malnourished, noted an incomplete clinical response but improved survival with treatment [14]. However, nitazoxanide was not better than placebo in 2 placebo-controlled trials in children with AIDS [14, 15]. By contrast, restoration of the cellular immune response in response to effective antiretroviral therapy is now recognized as the mainstay for therapy in AIDS [16].

Data on management of cryptosporidiosis in transplant recipients are more limited [17, 18]. There are no controlled trials of anti-parasitic drugs. Case series have described a number of different approaches to cryptosporidiosis in transplant recipients. Nitazoxanide has been used with reported success but also high rates of treatment failure [6]. Others have been treated with combinations of nitazoxanide with azithromycin or other agents. We hypothesized that combination therapy with multiple drugs may be more effective than dual antiparasitic agents. In this manuscript, we report a case with rapid resolution after therapy with a 3-drug combination of nitazoxanide, azithromycin, and rifaximin and review the literature on treatment of cryptosporidiosis in transplant recipients.

Received 27 September 2021; editorial decision 24 November 2021; accepted 2 December 2021; published online 4 December 2021.

Correspondence: A. Clinton White, Jr., MD, Infectious Disease Division, Department of Internal Medicine, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0435, USA (acwhite@utmb.edu)

Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab610

CASE DESCRIPTION

In October 2020, a 24-year-old Hispanic male presented to our hospital with chronic watery diarrhea. He was born with congenital renal dysplasia and had received a deceased donor kidney transplant in early childhood (2002). His posttransplant course was complicated by graft failure in 2017, requiring hemodialysis. In January 2020, he underwent a second kidney transplant from a deceased donor. Approximately 1 month after the second transplant, he developed watery diarrhea, which was initially attributed to his immunosuppressive medications, mycophenolate and tacrolimus. However, the symptoms did not respond to dose reduction. He was subsequently diagnosed with antibody-mediated rejection and received treatment with intravenous immunoglobin with increased doses of mycophenolate and tacrolimus. This was followed by worsening diarrhea, which eventually led to his hospital presentation. He was admitted to an outside facility, complaining of 12 episodes a day of watery stool associated with nausea. He denied fevers, chills, or abdominal pain. Initial laboratory findings included negative tests for *Clostridioides difficile* toxin, bacterial culture, and microscopy for ova and parasites. Colonoscopy with biopsy revealed moderate to severe chronic active colitis with rare organisms morphologically consistent with *Cryptosporidium*. No cytomegalovirus (CMV)-positive cells were identified. He was treated with a 7-day course of nitazoxanide, 500 mg twice daily, and his mycophenolate was stopped and azathioprine started. When the diarrhea persisted, he was transferred to our institution. Upon arrival, he was afebrile and hemodynamically stable. Physical examination showed signs of volume depletion, and a benign abdominal exam revealed a healing surgical incision. Laboratory results included mild leukopenia ($3.83 \times 10^3/\mu L$), hyponatremia (131 mmol/L), elevated serum creatinine level (1.79 mg/dL), and mildly elevated liver enzymes (*aspartate aminotransferase* 43 U/L; *alanine aminotransferase* 62 U/L). Cryptosporidiosis was confirmed by antigen detection (TECHLAB Giardia/Cryptosporidium CHEK test; TECHLAB, Blacksburg, VA). Since he had failed nitazoxanide monotherapy, he was started on a combination regimen with oral nitazoxanide (1 gram twice daily), azithromycin (600 mg daily), and rifaximin (550 mg twice daily) as well as intravenous fluids and diphenoxylate-atropine. Azathioprine was stopped. The tacrolimus level was 17 ng/mL, and it was discontinued and later restarted at a lower dose. Diarrhea resolved within 48 hours. The patient was discharged home after initial clinical improvement. He was observed in Infectious Diseases clinic and reported complete resolution of his diarrhea within 10 days without recurrence. He reported no medication side effects.

METHODS

Data Analysis

We searched the PubMed database to find articles on cryptosporidiosis in organ transplant recipients. We used search terms "cryptosporidium + transplant, "cryptosporidiosis + transplant" and found 129 articles between years 1979 and 2021. Most of them were limited to case reports or small case series. Because individual case reports are likely to be biased, we only included articles with at least 5 patients in the sample size, which analyzed antiparasitic treatment and outcome. With these criteria, we were able to identify 9 articles published between 1989 and 2017 that contain 158 cases (Table 1) [6, 7, 19–25]. There were no controlled trials and few prospective studies. Thus, the quality of evidence is poor. Kidney transplant recipients

Table 1. Case Series of Antiparasitic Therapy for Cryptosporidiosis in Transplant Patients

Author (Ref.)	Organ Transplanted (N)	Treatment	Respond/Total	Relapsed/Responded
Lanternier et al [6]	Kidney (41), Heart (3), 1 each Liver/Kidney, Liver Pancreas	Nitazoxanide Nitazoxanide+Azithromycin	16/25 7/10	4/16 2/7
Bhadauria et al [7]	Kidney (34)	Nitazoxanide Nitazoxanide+Ciprofloxacin	5/13 18/34	2/5 2/18
Gentile et al [23]	Hematopoietic stem cell (20)	Spiramycin	9/11[a]	4/9
Ok [20]	Kidney (13)	Secnidazole Spiramycin	0/2 2/4	N/A
Udgiri et al [21]	Kidney (12)	Spiramycin	2/2	N/A
Roncoroni et al [19]	Kidney (11)	Spiramycin	0/1	N/A
Bonatti et al [24]	Kidney (8), Liver (1), Lung (1)	Nitazoxanide Nitazoxanide+Azithromycin Azithromycin Azithromycin+Paromomycin	3/3[b] 3/3 2/2 1/1	N/A
Krause et al [25]	Kidney (4), Liver/Kidney (1), Heart (1)	Nitazoxanide Nitazoxanide+Azithromcyin	5/5 1/1	2/5 0/1
Legrand et al [22]	Hematopoietic stem cell (5)	Nitazoxanide+Azithromycin	5/5[c]	N/A

Abbreviations: N/A, information not available; Ref., reference.

[a]An additional patient was asymptomatic before treatment.

[b]Includes 1 patient treated with nitazoxanide plus trimethoprim-sulfamethoxazole.

[c]Two patients died of concomitant fungal infections.

represented most of the population (125), but studies included hematopoietic stem cell, liver, lung, heart, or pancreas transplant recipients. The most common antiparasitic treatment used was nitazoxanide (46), or a combination of nitazoxanide with azithromycin (19), and spiramycin (18). Other treatment regimens were azithromycin, nitazoxanide with fluoroquinolone, or paromomycin with azithromycin. Reduction of immunosuppression was implemented in many cases; however, specific data whether alone or in combination with antiparasitic treatment were often lacking. A substantial number of patients (27) suffered graft dysfunction. There were several fatalities, but none were believed to be due to cryptosporidiosis. All studies included are detailed in Table 1.

Patient Consent Statement

The material in this report includes only anonymized data collected for other purposes and therefore meets criteria of being exempt from review according to the Institutional Review Board of the University of Texas Medical Branch

RESULTS

In the largest study, Lanternier et al [6] identified 47 transplant recipients with cryptosporidiosis from a French national database. Patients were mainly treated with nitazoxanide alone or a combination of nitazoxanide with azithromycin. In 4 patients, reduction of immunosuppression alone led to resolution of symptoms. Of 25 cases treated with nitazoxanide, 16 resolved compared with 7 of 10 treated with the combination of nitazoxanide and azithromycin. Many cases received a prolonged course of antimicrobials. Four cases that relapsed after treatment with nitazoxanide were treated successfully with combination therapy.

In a retrospective study of 34 renal transplant recipients, Bhadauria et al [7] noted that only 5 of 13 patients responded to nitazoxanide. By contrast, patients treated with nitazoxanide combined with a fluoroquinolone had significantly higher response to treatment compared with nitazoxanide alone. However, bacterial coinfections, which might explain effectiveness of fluoroquinolone, were not studied.

Gentile et al [23] identified 20 patients with hematologic malignancies (including 11 hematopoietic stem cell transplant recipients) who were found to be shedding *Cryptosporidium* oocysts. One case was fatal and the others all resolved eventually, although 4 died of unrelated fungal infections. Of 11 initially treated with spiramycin, 9 resolved with therapy, as did 3 of 4 not initially receiving spiramycin. Of the 9 responding to spiramycin, 4 developed recurrent diarrhea. Legrand et al [22] reported 5 hematopoietic stem cell transplant recipients with cryptosporidiosis. All cases were treated with nitazoxanide plus azithromycin. Two patients died of disseminated fungal infections whereas the remaining 3 showed symptom resolution.

In a study of 10 solid organ transplant (SOT) recipients (8 kidney, 1 liver, 1 lung) by Bonatti et al [24], all patients recovered. Two cases resolved with reduction in immunosuppression without antiparasitic therapy. The other 8 resolved after a 1- to 3-week course of antiparasitic treatment, including nitazoxanide alone (3), nitazoxanide plus azithromycin (3), azithromycin (2), or azithromycin plus paromomycin (1). Other small case series are listed in Table 1 [19–21, 25].

DISCUSSION

Diarrhea is a common problem in SOT recipients. Bunnapradist et al [26] estimated the prevalence of diarrhea in SOT recipients to be 20%–50% [27]. Medications, including immunosuppressives such as mycophenolate and tacrolimus, may directly cause diarrhea. There are also several infections associated with gastrointestinal illness. In wealthy countries, the most commonly reported infectious causes of diarrhea in transplant patients are *C difficile*, norovirus, and CMV [28].

There has been increasing recognition of cryptosporidiosis in transplant recipients with diarrhea. The French national network on surveillance of human cryptosporidiosis reported 210 cases of cryptosporidiosis in immunodeficient individuals, 49% of which were SOT recipients and 30% had human immunodeficiency virus (HIV) [9]. The shift from AIDS-associated cases to transplant patients likely reflects the increasing number of transplant recipients and the improvements in combination antiretroviral therapy. In addition, there have been major paradigm shifts in diagnostic methods. *Cryptosporidium* is not detected with routine parasitologic studies. Acid-fast staining, which has been used to detect cryptosporidiosis, is thought to miss many cases [10, 29]. In recent years, increased use of antigen-detection assays and nucleic acid amplification are revealing more cases [29, 30].

Most immunocompetent patients will recover from cryptosporidiosis without treatment [10]. A short course of nitazoxanide is associated with a shorter duration of symptoms and oocyst shedding. It is unfortunate that treatment of immunocompromised hosts continues to be challenging for clinicians. Supportive therapy with fluid resuscitation, electrolyte repletion, and antimotility medications remain the first-line symptomatic treatment for cryptosporidiosis. Because cell-mediated immunity plays a key role in host defense, efforts should be made to minimize immunosuppression in transplant recipients with cryptosporidiosis.

Several studies suggested increased risk of cryptosporidiosis with mycophenolate and tacrolimus use [7, 24]. Bhadauria et al [7] showed a significantly higher risk of developing *Cryptosporidium* infection in patients using a tacrolimus-based regimen compared with a cyclosporine-based regimen for immunosuppression. Bonatti et al [24] demonstrated elevated tacrolimus levels and transient decrease in renal

function in SOT recipients with cryptosporidiosis. This phenomenon was not observed among transplant recipients with community-acquired *C difficile* infection. Decreased intestinal metabolism or hepatic excretion of tacrolimus associated with cryptosporidiosis-related enteritis may explain this finding. Regardless of cause, there is a vicious cycle of volume depletion and increasing tacrolimus levels, leading to acute kidney injury and worsening infection.

Adjusting immunosuppression and monitoring immunosuppressant levels is crucial in both management and prevention of cryptosporidiosis. The American Society of Transplantation Infectious Diseases Community of Practice recommends both reduction of immunosuppression and nitazoxanide as initial treatment for SOT recipients with cryptosporidiosis [18]. Nevertheless, data supporting antiparasitic drugs in transplant recipients are very limited.

Nitazoxanide has been evaluated in 3 randomized controlled trials involving immunocompetent patients in developing countries [12–14]. In 2 placebo-controlled trials conducted in Egypt, including both children and adults, a 3-day course of nitazoxanide was proven to be more effective than placebo in both clinical response and oocyst clearance [12, 13]. Another placebo-controlled trial in Zambia demonstrated both clinical and parasitological response in HIV-negative children [14]. Studies involving immunocompromised hosts have been less impressive. Nitazoxanide showed no benefit compared with placebo in 2 trials of HIV-seropositive children in Zambia [14, 15]. Likewise, in a meta-analysis including 130 HIV-positive adults, nitazoxanide failed to demonstrate effect on duration of diarrhea and oocyst clearance. There is also evidence that other antimicrobials might play a role in resolution of cryptosporidiosis. As noted, there are only limited and poor-quality data on the use of nitazoxanide in transplant recipients. The published results demonstrate some evidence of efficacy, but they clearly document that responses to nitazoxanide are inconsistent (Table 1). However, all available data come from case reports and small case series (mostly retrospective). Thus, the risk of publication bias is high, such that efficacy may be overstated.

Macrolides, including azithromycin and spiramycin, have activity against *Cryptosporidium* and showed promising results in transplant recipients and in AIDS patients [19, 20, 23, 31–33]. Some early studies reported outcomes with spiramycin, most of them are small case series [20, 21]. Failure of spiramycin treatment was noted in 1 patient by Roncoroni et al [19]. Gentile et al [23] report resolution of symptoms in 9 of 12 leukemic patients treated with spiramycin; however, most of the other patients recovered without specific treatment according to the study [28]. Azithromycin monotherapy has been tried as a treatment for cryptosporidiosis, but it has mostly been used in combinations with other antiparasitic drugs. However, there was no significant difference in symptoms, oocyst shedding, and weight loss in a placebo-controlled multicenter trial involving AIDS patients with cryptosporidiosis treated with azithromycin monotherapy [34].

Combination therapy has been proposed as treatment of cryptosporidiosis in AIDS patients and transplant recipients [6, 22, 35, 36]. For example, in a prospective open-label trial in AIDS patients, more patients had resolution with the combination of paromomycin and azithromycin than in a prior study of patients treated with paromomycin alone [35]. There are limited data to support this in transplant recipients. Lanternier et al [6] conducted a prospective study in which 10 patients received combination therapy of azithromycin and nitazoxanide, and outcomes seemed to be better than with nitazoxanide alone.

Rifamycins have some activity against *Cryptosporidium*. For example, 2 randomized trials of rifabutin for prevention of *Mycobacterium avium* complex infections demonstrated fewer cases of cryptosporidiosis in those receiving rifabutin [37, 38]. Giacometti et al [39] demonstrated additive activity of nitazoxanide, azithromycin, and rifabutin against *Cryptosporidium* in vitro. Rifaximin is a poorly absorbed rifamycin, used for treatment and prevention of traveler's diarrhea. There are case series that suggest its effectiveness in cryptosporidiosis in HIV patients [40, 41]. However, there are no controlled trials evaluating rifaximin for treatment of cryptosporidiosis. In a study of 48 HIV-positive patients, rifaximin was effective in patients with CD4 counts greater than or equal to 200/mm^3, which may have been due to self-limited disease [40]. There is a report of a transplant recipient in whom cryptosporidiosis resolved with treatment with rifaximin [42].

We hypothesize that combinations of antiparasitic drugs may improve response to cryptosporidiosis in patients lacking an effective immune response. In our case report, resolution of diarrhea was achieved by combining high-dose nitazoxanide with rifaximin and azithromycin along with lowering levels of tacrolimus. This may have been due to reduction of immunosuppression. Further studies of combination treatment are needed to determine its efficacy. In the meantime, combination therapy may offer improved results in difficult cases.

CONCLUSIONS

In summary, effective treatment of cryptosporidiosis in immunocompromised hosts (especially the growing population of organ transplant recipients) remains unclear, and evidence to support antiparasitic regimens is limited. Our case report supports a growing body of evidence that suggests that combination therapy might be superior to nitazoxanide alone in challenging patients. We emphasize that cryptosporidiosis is likely underestimated in organ transplant recipients; hence, it is important to recognize its risk factors, establish early diagnosis, and prevent grave complications. Antiparasitic treatment and immunosuppression reduction is recommended for all symptomatic organ transplant recipients. In cases of prolonged

cryptosporidiosis, combination therapy and longer duration of treatment should also be considered.

Acknowledgments

Author contributions. All authors were involved in management of this patient as well as revision and approval of the final manuscript. E. T. performed the literature review and drafted the initial manuscript. A. N. M. assisted with the literature review and revised the manuscript. A. C. W. conceived of the study, assisted with the literature review, and revised the manuscript.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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