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ORIGINAL ARTICLE

Clostridium difficile infection mimics intestinal acute cellular rejection in pediatric multivisceral transplant—A case series

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Abstract

Clostridium difficile infection (CDI) is the most common health care-associated infection in the United States. Thirty-nine percent of intestinal transplant recipients may develop CDI. Induction of rejection has been reported as a rare event. To our knowledge, this will be the second report of an association between CDI and rejection in the literature. We describe our experience with four pediatric MVT recipients, three of whom on treatment of their CDI alone had resolution of biopsy findings of intestinal ACR. Our patients were males aged 2-5 years old who had their first CDI post-MVT occurring from 2 months to 15 months post-transplant. All first episodes of CDI were treated with a 10-14 day course of metronidazole with one additionally receiving vancomycin. All four recipients had recurrent CDI, and two recipients had septic shock as a manifestation of their CDI. Three recipients had biopsies showing mild rejection during episodes of CDI, and treatment of the CDI resulted in resolution of biopsy findings of rejection. Our case series suggests CDI may mimic ACR on intestinal biopsy. Treatment of rejection during active CDI carries the risk of oversuppression and worsening of CDI. Our experience has taught us that surveillance endoscopy for rejection may be deceiving during an active CDI, and if mild acute rejection is noted during active CDI, treatment of rejection can be safely delayed and potentially avoided.

KEYWORDS

Clostridium difficile, multivisceral transplant, rejection

1 | INTRODUCTION

CDI is the most common health care-associated infection in the United States. Incidence in children, like that of adults, has been on the rise. Transplant recipients are an at-risk population. They often have multiple inherent risk factors like antibiotic exposure, hospitalization, usage of acid-suppressing medications, tube feeding, and immunosuppression.[1,2] One of eight recipients who undergo transplantation with more than one organ will develop CDI.[3] In pediatric SOT, CDI rates are highest among recipients receiving intestines, pancreas, or more than one organ.[4] A little is known about the impact of CDI on multivisceral transplantation. Adult data suggest increased risk of graft loss and worse outcomes after CDI in SOT.[5,6] A recent study by Duclaux-Loras et al found a higher prevalence of CDI after pediatric intestinal transplant recipients compared to other SOT with a prevalence of 39%. They reported the induction of rejection as a rare

Abbreviations: ACR, acute cellular rejection; *C diff*, *Clostridium difficile*; CDI, *Clostridium difficile* infection; CLABSIs, central line-associated blood stream infections; EIA, toxin enzyme immunoassay; GDH, glutamate dehydrogenase; IFALD, intestinal failure-associated liver disease; MVT, multivisceral transplant; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PTLD, post-transplant lymphoproliferative disease; SOT, solid organ transplantation.

event.[7] To our knowledge, this will be the second paper to describe this association.

2 | METHODS

In this case series, we describe our experience with four pediatric MVT recipients who had both CDI and biopsy findings of intestinal ACR. After treatment of the CDI alone, 3 patients no longer showed findings of ACR. Our case series review was approved by the Institutional Review Board of the University of Miami. The review period was from January 1, 2013 to June 30, 2018. Inclusion criteria consisted of the following: (a) age <18 years at time of transplantation, (b) recipient of intestinal or MVT, (c) CDI post-transplant, and (d) biopsy proven intestinal ACR. There were only four recipients that were eligible for inclusion in this case series, and the guardians of all four recipients gave written consent.

2.1 | Definitions

2.1.1 | Acute cellular rejection

The diagnosis of ACR was made according to the grading system outlined at the 2003 8th International Small Bowel Transplant Symposium.[8] The grading system is as follows: Grade 0 (no evidence of acute rejection), Grade IND (indeterminate for acute rejection), Grade 1 (ACR, mild), Grade 2 (ACR, moderate), and Grade 3 (ACR, severe). Only Grades 1, 2, and 3 were included in our definition of ACR.

2.1.2 | Multivisceral transplant

MVT includes en bloc transplantation of stomach, duodenum, pancreas, small intestine with or without large intestine, and liver. A modified MVT occurs without liver transplantation.[9] At our institution, large intestine transplantation is routinely included in MVT and modified MVT.

2.1.3 | *Clostridium difficile* infection

Per Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines,[1] our institution employs a two-step diagnostic algorithm using GDH plus EIA arbitrated by nucleic acid amplification test (PCR). Only liquid stool is tested per our prearranged institutional stool submission criteria. Diagnosis of CDI was made by the managing physician based on clinical signs and symptoms with a corresponding positive (a) GDH and toxin EIA, (b) GDH and PCR, or (c) toxin EIA and PCR.

3 | RESULTS

3.1 | Case 1

Patient 1 was a 6-year-old African American male who had a history of intestinal failure secondary to gastroschisis, IFALD, and multiple drug-resistant infections. He had his first MVT at 3 years which he lost from severe intestinal cellular rejection refractory to medical therapy with stricturing disease. A second MVT was complicated in

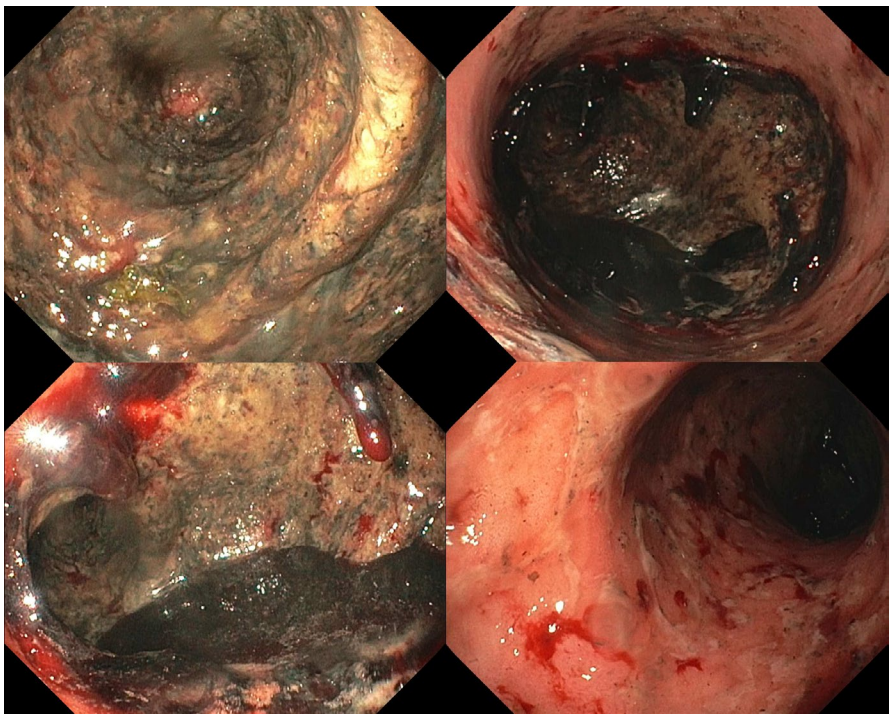

FIGURE 1 Endoscopy findings of severe pseudomembranous colitis in patient 1

the early post-operative period by enterocutaneous fistulas. He received a third MVT at 5 years old.

His first CDI post-transplant occurred 15 months after his third MVT. He presented with a 1-day history of fever, an oral aphthous ulcer, and abdominal pain. He had a partial sepsis workup done and was started empirically on antibiotics. On the third day of admission, he was febrile and had three episodes of hematochezia for which he underwent urgent endoscopy. He was found to have severe pseudomembranous colitis (see Figure 1). Stool studies returned positive for *C diff* GDH and toxin EIA. The remainder of infectious stool studies was negative. There was no rejection on biopsies (Grade 0 ACR of transplant stomach and duodenum; Grade IND ACR of transplant colon). No biopsies were obtained from the transplant terminal ileum as his severe colitis made it difficult to identify the ileocecal valve. He was started on IV metronidazole and oral vancomycin. Repeat colonoscopy 5 days later showed significantly improved mucosa, and the transplant terminal ileum was intubated. On biopsy, there was now Grade 1 ACR of transplant terminal ileum and colon with mild-to-moderate lymphoplasmacytic infiltrate with effacement and lymphocytic cryptitis (see Figure 2A,B). The decision was made to hold off on treatment for rejection, and no additional immunosuppression was given. His repeat endoscopy 6 days later (day 11 of CDI treatment) showed resolution of his rejection (Grade IND ACR of biopsied transplant terminal ileum and colon). Despite initially having biopsy findings of intestinal rejection, his biopsy findings resolved without any treatment for rejection (on medications for CDI only).

He had another episode of CDI almost 2 years after his last MVT. He presented with fever. Stool studies returned positive for GDH and a toxigenic *C diff* strain on PCR. He was given a 10-day course of oral metronidazole and a 6-week tapering vancomycin course. At time of this manuscript, he is over 2 years post-transplant and is doing well as an outpatient.

3.2 | Case 2

Patient 2 was a 2-year-old Caucasian male who had a history of extrahepatic biliary atresia with failed Kasai for which he received two prior orthotopic liver transplants at 9 months of age at another institution. The second transplant occurred 2 days after the first for graft loss secondary to hepatic artery thrombosis. He presented to us at 1.5 years of age in end stage liver disease with progressive cholestasis of unknown origin for re-transplant evaluation. He was listed for MVT because of extensive portal vein thrombosis and was transplanted at 2.5 years of age.

Thirty days post-transplant, he had Grade 1 ACR of transplant duodenum and colon for which he needed a steroid pulse of intravenous (IV) methylprednisolone and the addition of sirolimus to his maintenance oral tacrolimus. He received rituximab on day 50 post-transplant when high donor-specific antibodies were detected in his serum. He developed diarrhea 2 days after being given rituximab and was found to have first episode of CDI with positive *C diff* GDH and toxin EIA. He was started on a 14-day course of IV metronidazole. Rejection was documented to have resolved on duodenal and colonic biopsies 4 weeks after its initial diagnosis (on day 9 of CDI treatment). He had his second CDI 7 months post-transplant (a month after initiating chemotherapy for PTLD diagnosed on biopsies of cervical lymph node and colon). He was treated with 14 days of IV metronidazole and a tapering oral vancomycin course. His endoscopy, 2 weeks after diagnosis of CDI, did not show rejection.

His third episode of CDI occurred 9 months post-transplant. He presented with fever and bloody diarrhea. Norovirus was also detected in his stool this time. His endoscopy 6 days after presentation noted a few small ulcers at the anastomotic site which, on biopsy, showed Grade 1 ACR. Transplant duodenum, stomach, terminal ileum, and remainder of colon were all Grade IND ACR. At the time of diagnosis of PTLD, there were multiple ulcers with rolled edges upon a normal base at the anastomotic site. Appearance of ulcers was much improved compared to previous scopes. Given the isolated location of findings of rejection at the anastomotic site, no treatment for intestinal rejection was given. His treatment for CDI this episode was a 14-days course of both oral metronidazole and vancomycin. Without treatment for rejection and only treatment for his CDI, he clinically improved, and there was no rejection shown on his next set of biopsies 3 months later.

At time of this manuscript, he is almost 2 years post-transplant and has not had any further episodes of CDI.

3.3 | Case 3

Patient 3 was a 5-year-old African American male who received an MVT with a history of intestinal failure secondary to gastroschisis complicated by IFALD, multiple central line-associated blood

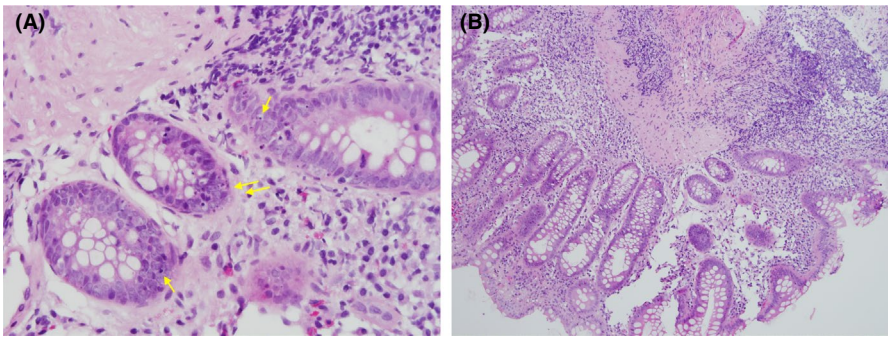

FIGURE 2 A, Biopsies showing mild Grade 1 intestinal rejection in patient 1 (arrows pointing at apoptosis bodies) H&E stains 400×. B, Biopsies showing mild Grade 1 intestinal rejection in patient 1 H&E stains 100×

stream infections (CLABSIs), and multiple central venous thrombi. His post-operative course was complicated by bacterial peritonitis, *Stenotrophomonas* CLABSI, and an intra-abdominal abscess, for which he received additional antibiotics. Given his complicated course, he spent 24 days in the PICU and was still inpatient two months post-transplant when he developed foul smelling diarrhea. At the onset of diarrhea, he was on continuous enteral feeds at goal, and his parental nutrition was being weaned. His stool infectious evaluation, including *C diff* was negative. His upper and lower endoscopy was visually normal. There was no rejection on biopsy (Grade IND ACR of transplant duodenum and terminal ileum biopsies). His formula was switched to a lower osmolality formula, and trial of bolus tube feeds was attempted. A week later, his diarrhea, though improved in frequency, had persisted. His infectious stool studies were repeated, revealing his CDI with a positive GDH and toxigenic *C diff* strain isolated on PCR. Oral metronidazole was initiated. Two days later, he had his surveillance endoscopy for rejection. Grossly, his mucosa appeared normal, but he now had intestinal rejection with Grade 1 ACR of transplant duodenum. Biopsies of his transplant stomach, cecum, and colon showed Grade IND ACR. The decision was made to hold off on treatment for rejection, and no additional immunosuppression was given. He completed a 14-days course of metronidazole. His endoscopy was repeated 2 weeks later and showed resolution of his intestinal rejection. His biopsy findings of intestinal rejection resolved without any treatment for rejection (on medications for CDI only). Mucosa was visually normal, and biopsy of transplant duodenum was Grade 0 ACR and that of transplant cecum and colon were Grade IND ACR.

His stool infectious studies included campylobacter antigen, rotavirus antigen, viral cultures, and bacterial cultures, which were all negative. The guidelines do not recommend testing for cure as toxigenic *C diff* often persists after infection.[1] However, taking into account his unique scenario, repeat *C diff* testing was sent on day 10 of his metronidazole course and was negative. This was his first documented case of CDI. Three months after his first case of CDI, he presented to another institution with vomiting and diarrhea. He was found to have recurrent CDI. He was started on oral metronidazole and vancomycin but later went into septic shock with severe metabolic acidosis for which he was transferred to our PICU. Endoscopy was done 9 days after diagnosis and initiation of therapy for CDI. He did not have any biopsy findings of intestinal ACR. He clinically improved and completed a course of oral metronidazole and vancomycin taper. At time of this manuscript, he is 2 years post-transplant and has not had any further episodes of CDI but had another bout of intestinal ACR 20 months post-transplant which responded to a steroid pulse.

3.4 | Case 4

Patient 4 was a 5-year-old Caucasian male who had a history of intestinal failure secondary to total aganglionosis complicated by IFALD, multiple CLABSIs including fungemia, and multiple central venous thrombi including portal vein and inferior vena cava thrombi, for which he received his MVT at 3 years of age. Given aganglionosis, with his transplant, he had colostomy creation.

Eleven months post-transplant, he had his first case of CDI. He presented with a one-day history of fever, increased ostomy output, and lethargy. On day 2 of admission, his stool studies came back positive for GDH and a toxigenic *C diff* strain isolated on PCR. The remainder of his infectious workup also revealed norovirus in his stool. Empiric antibiotics were discontinued, and he was given a 10-day course of oral metronidazole. Endoscopy on day 2 of admission (before diagnosis of CDI) showed an enteritis with erythema and blunting of villi in the transplant duodenum and ileum with normal appearing colon. There was no rejection on biopsies (Grade 0 ACR transplant stomach, duodenum, and transverse colon; Grade IND ACR of transplant ileum and cecum).

He had a tumultuous year following his first CDI episode with four admissions for recurrent CDI, three of which involved septic shock secondary to CDI. His recurrent episodes occurred at intervals 13 months, 18 months, 21 months, and 25 months post-transplant. With his first recurrence, he presented with fever, abdominal pain, and lethargy and was given a 14-days course of oral vancomycin. For his second recurrence, he presented in septic shock with fever, lethargy, and profuse diarrhea. He was initiated on IV metronidazole and oral vancomycin. He completed a 14-days course of vancomycin followed by a 6-week taper. The remainder of his infectious workup was negative. For his third recurrence, he presented with fever and progressed to septic shock. He had pseudomembranous pan-colitis. His stoma over time had started to close on its own and now had an abscess in that location with enterocutaneous fistula formation which was incised and drained. Treatment of his third recurrent episode of CDI included IV immunoglobulin, 14 days of IV metronidazole, 10 days of rifaximin, and 6 weeks of oral vancomycin. He was stabilized and discharged home with his temporary stoma. Four months later he presented with fever, abdominal pain, emesis, and diarrhea which again progressed to septic shock. His abdominal computerized tomography showed pan-colitis with massive colonic dilation. He had an exploratory laparotomy for his bowel obstruction with bowel decompression and new ostomy creation. His functional obstruction was believed to be secondary to his CDI compounded by a short remaining segment of aganglionic bowel. He was treated with 14 days of oral vancomycin and metronidazole, followed by 7 days of nitazoxanide.

For his episodes of recurrence, stool was positive for GDH and a toxigenic strain isolated on PCR with the exception of the second recurrence which was GDH and toxin EIA positive. He had biopsies from the second and third recurrent episodes with no intestinal rejection. Seven months after his fourth recurrent CDI, he had removal of remaining native colon, pull through operation with transplant colon-anal anastomosis. He had Grade 1 ACR of the transplant colon at that time and received a methylprednisolone course. His fifth recurrent episode of CDI occurred with GDH and toxin EIA positivity 5 months later (3 years 1 month post-transplant) and was treated with 14 days of oral metronidazole and vancomycin, followed by 7 days of nitazoxanide. At the time of this manuscript, he has not

had any other episodes of CDI or rejection and he is over 3 years post-transplant.

4 | DISCUSSION

The incidence of CDI has been on the rise, making it ever more likely that we will encounter this infection in a recipient of an MVT.[1] The last meta-analysis in 2015 reported a prevalence of 12.7% for SOT recipients receiving more than one organ but the true prevalence in the MVT subset is likely higher.[3] A decade and a half ago the prevalence of bacterial infection after intestinal and MVT was over 90%.[10,11] With advances in the field, this number has drastically reduced but remains relatively high. There are still reports of over 90% of recipients developing an infection, with half being bacterial in origin.[12] In the 2003 study, 3 CDI cases were reported among the 327 infections in their cohort of 124 patients.[10] Although the incidence of bacterial infections has been on the decline, the incidence of CDI has been rising; thus, the incidence of CDI in this population is now much higher. A 2016 study looking at CDI rates in pediatric SOT reported an incidence of 5% in 329 intestinal transplants.[4] A 2018 study from our institution reported an even higher incidence of 20%. Over a 2-year period at our institution, 10 out of 51 intestinal, MVT, and modified MVT recipients developed CDI in the first year post-transplant.[13] Forty percent of the cases were pediatric recipients, and 40% of the cases were severe. Post-intestinal transplant CDI prevalence rate has been reported to be as high as 39% in children in a 2019 study from France.[7]

Our case series further supports that there can be significant morbidity from CDI in this population. All 4 of our recipients had recurrent CDI which resulted in numerous hospitalizations, and two recipients had septic shock as a manifestation of their CDI. Patient 4, who had total aganglionosis disease, had a particularly difficult course which we suspect was partly because of colonic stasis from his remaining short segment of native aganglionic bowel combined with his multiple risk factors from being a post-transplant recipient. After two episodes of septic shock from CDI, patient 4 had removal of remaining native colon, and his subsequent recurrent episode of CDI was more benign. Prior to colon-anal anastomosis, he was having CDI recurrence at intervals of 2-5 months, but he has now had 7 months without recurrence at the time of this manuscript. Our experience from this case has changed how we surgically approach intestinal and MVT in patients with total aganglionosis. Pseudomembranous colitis is known to be a life-threatening condition in Hirschsprung's disease with an associated mortality rate of 50%.[14] Post-transplant 2 of our patients had life-threatening septic shock, and patient 4, who had total aganglionosis, presented in septic shock for 2 of his 6 episodes of CDI.

Intestinal and MVT recipients are an at-risk population for colonization and CDI. Specific data on risk factors in pediatric recipients are limited. Unlike in adults, one single-center pediatric study reported that in children recent hospitalization and antibiotic exposure did not increase the risk of CDI in SOT. This study also found acid suppression protective, which also differs from adult data. Their study consisted of 202 children but only seven were intestinal/MVT recipients.[15] A case-control study by Guzman et al looked at risk factors for CDI, specifically in pediatric intestinal transplant. They, interestingly, found administration of proton pump inhibitors protective, but they were not able to demonstrate statistical significance of any other risk/protective factors.[16] Their study included 29 infected pediatric intestinal transplant recipients matched to a control group of 87 pediatric intestinal transplant recipients without CDI. These two pediatric studies suggest that we may not be able to extrapolate risk factors from adult data.

While acid suppression, hospitalization, and antibiotic exposure were not independently found to be important in those studies, perhaps they may prove statistically significant when combined with concomitant risk factors. In children, pancreatic and intestinal transplantation have been shown to have the highest incidence of CDI among SOT,[4] suggesting that there are inherent risk factors that are likely putting these children at greater risk, but more studies are needed to identify what these risks are. Some risk factors worth exploring include the surgical manipulation of the gastrointestinal tract, post-transplant hypogammaglobulinemia, prolonged enteral tubes, presence of ostomies, and the type of immunosuppression unique to intestinal/MVT leading to dysbiosis. Our patients with MVT generally have all the aforementioned potential risk factors. Furthermore, monoclonal antibodies have been shown to increase the risk of CDI[16] and rituximab (a monoclonal antibody) is part of the induction regimen post-MVT at our institution. Duclaux-Loras et al's study which identified 22 of 57 pediatric intestinal transplant recipients with CDI did not detect any risk factors for CDI in their univariate analysis.[7]

Though acid suppression may be protective in pediatrics, three of our recipients were on a proton pump inhibitor at the time of their first CDI. Our recipients were also identified to have had recent antibiotic exposure, manipulation of gastrointestinal tract, hospitalization, enteral tube feeds, and immunosuppression. Only one recipient had received monoclonal antibodies immediately prior to his first CDI, but all had received rituximab as part of their induction therapy. None had hypogammaglobulinemia at the time of their first CDI, but all were known to have had post-transplant hypogammaglobulinemia.

Prevention of recurrence in this population may be especially challenging because inherent risk factors for CDI remain constant post-transplant. All four recipients had recurrence, including the recipient who was a year out from transplantation and the recipient who received vancomycin with the first CDI episode. The latest guidelines recommend vancomycin or fidaxomicin for initial CDI episodes in adults as studies showed superior efficacies compared to metronidazole for sustained resolution. As pediatric data are lacking, the guidelines recommend either metronidazole or vancomycin in children with non-severe CDI.[1] Of Duclaux-Loras et al's 22 intestinal transplant recipients with CDI, nine had recurrence with seven being symptomatic. Six had received metronidazole for their first episode. Duclaux-Loras et al's study concluded that standard treatment was

effective in most cases.[7] Given the adult data and our experience from this case series, it may be worth exploring if there is a subset in this at-risk population that may benefit from vancomycin as first line therapy for CDI.

Our case series suggests there may be an association between CDI and biopsy findings of intestinal rejection. Three recipients had biopsies showing mild ACR during episodes of CDI, and treatment of the CDI alone resulted in resolution of the biopsy findings. This occurred in patients 1, 2, and 3. In patient 1 and 3, this occurred in their first CDI episodes, and in patient 2, it was with his third CDI episode. This resolution—without treating for rejection—leads us to believe that these were not true cases of rejection but rather that CDI may mimic intestinal biopsy findings of ACR *C diff* is known to cause disruption of cytoskeletal architecture and cell death[17]; findings that are considered classic in intestinal transplant rejection.

Our assumption is that these episodes were not true episodes of rejection. To our knowledge, antibiotics alone have not been shown to treat rejection. CDI could theoretically induce ACR either from its effects on local gut inflammation, dysbiosis, or decreased effectiveness of oral immunosuppression from associated diarrhea. Oh et al have shown that certain alterations in the microbiome are sensitive and specific indicators of rejection.[18] Similar alterations in the microbiome have been seen in patients with recurrent CDI.[19] It is not yet clear whether this altered microbiome plays a causative or exacerbating role in rejection, or if it represents a consequence of rejection. If the microbiome does play a causative or exacerbating role in rejection, it is reasonable to think that antibiotics could play a role in treating rejection. It is also possible that by treating CDI with antibiotics, the diarrhea and absorption of tacrolimus improves, allowing for slightly higher immunosuppression that could be sufficient to treat mild rejection. More studies are needed to explore these theories. Of note, immunosuppression was not reduced by the medical team during bouts of CDI.

Germination of *C diff* spores and growth of vegetative forms occur only in the colon because the lumen there is anoxic.[17] The findings of rejection, however, were found in the transplant duodenum in patient 3 and in the terminal ileum in patient 1. For the theory that CDI mimics intestinal biopsy findings of ACR to explain these findings, the small intestine would have to be infected by *C diff*. *C diff* enteritis has been reported in the literature but represents a rare clinical entity.[20] Certain risk factors appear to predispose patients to *C diff* enteritis such as altered intestinal anatomies and immunosuppression. It is plausible that intestinal and MVT recipients are at a higher risk for *C diff* enteritis than the general population. In the pediatric case-control study assessing CDI in intestinal transplantation by Guzman et al, the authors suspected that a high percentage of their 29 intestinal transplant recipients had *C diff* enteritis.[16] Two of the episodes of CDI in patient 4 had documented small bowel involvement on either endoscopy or imaging.

Guzman et al further reported rejection rates in the first year post-transplant of 24.14% in the CDI group vs 20.69% in the non-infected group. They, however, did not find any statistical significance. We would have expected a statistically significant higher rate of rejection in the infected group if CDI does mimic intestinal biopsy findings of ACR, especially since in their study biopsies appeared to have been done during infection. No concurrent episodes of CDI and rejection were explicitly reported. Perhaps greater numbers are needed in the CDI group to show statistically significant differences. It is also possible that the timing of endoscopy may affect the presence of biopsy findings of rejection from CDI. In patient 1, when CDI was initially diagnosed, there were no biopsy findings of rejection, but these findings were noted 5 days later. In their study, it appears that endoscopy was done at the onset of symptoms.

In the study by Duclaux-Loras et al, three of the 22 CDI in intestinal transplant recipients had ACR. Two had concomitant CDI and ACR, and the third had rejection 3 years after their CDI. Of the two with concomitant CDI and ACR, one received treatment for both CDI and ACR, and the other only received antimicrobials with no change in immunosuppression. The latter had also received cidofovir for their adenovirus infection. Both recipients, including the recipient who had no change in immunosuppression, recovered.

We believe that CDI may mimic ACR on intestinal biopsy, and further studies are warranted. Treatment of rejection during active CDI carries the risk of over-suppression and worsening of CDI. We believe that surveillance endoscopy for rejection during an active bout of CDI may be deceiving. If mild ACR is noted during active CDI, treatment of rejection can be safely delayed and potentially avoided. It may be prudent to avoid decreasing immunosuppression during active CDI until studies are done to prove that CDI does not induce or exacerbate rejection.

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AUTHORS' CONTRIBUTIONS

Donna Ann Cheung, Thiago Beduschi, and Jennifer Garcia: Conceived of the presented idea; Donna Ann Cheung and Jennifer Garcia: Worked on IRB approval; Donna Ann Cheung, Phillip Ruiz, and Jennifer Garcia: Acquired the data; Donna Ann Cheung, Thiago Beduschi, Akin Tekin, Gennaro Selvaggi, Phillip Ruiz, Rodrigo M. Vianna, and Jennifer Garcia: Assisted in analysis and interpretation; Donna Ann Cheung, Thiago Beduschi, and Jennifer Garcia: Drafted the work; Akin Tekin, Gennaro Selvaggi, Phillip Ruiz, and Rodrigo M. Vianna: Critically reviewed and revised; Donna Ann Cheung, Thiago Beduschi, Akin Tekin, Gennaro Selvaggi, Phillip Ruiz, and Rodrigo M. Vianna, and Jennifer Garcia: Approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the

accuracy or integrity of any part of the work are appropriately investigated and resolved.

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