8. LaRovere KL, Raju GP, Gorman MP. Postvaricella acute transverse myelitis in a previously vaccinated child. *Pediatr Neurol*. 2008;38:370–372.
9. Ben-Amor S, Lammouchi T, Benslamia L, et al. Post varicella zoster virus myelitis in immunocompetent patients. *Neurosciences (Riyadh)*. 2011;16:156–158.
10. Nagel MA, Cohrs RJ, Mahalingam R, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology*. 2008;70:853–860.
11. Haug A, Mahalingam R, Cohrs RJ, et al. Recurrent polymorphonuclear pleocytosis with increased red blood cells caused by varicella zoster virus infection of the central nervous system: Case report and review of the literature. *J Neurol Sci*. 2010;292:85–88.
12. Ong OL, Churchyard AC, New PW. The importance of early diagnosis of herpes zoster myelitis. *Med J Aust*. 2010;193:546–547.
13. Outteryck O, Deramecourt V, Bombois S, et al. [VZV-related myelitis: a pathophysiological hypothesis]. *Rev Neurol (Paris)*. 2007;163:89–92.
14. Frohman EM, Wingerchuk DM. Clinical practice. Transverse myelitis. *N Engl J Med*. 2010;363:564–572.
15. Kim MY, Suh ES. A case of acute transverse myelitis following chickenpox. *Korean J Pediatr* 2009; 3:380–384.
16. de Silva SM, Mark AS, Gilden DH, et al. Zoster myelitis: improvement with antiviral therapy in two cases. *Neurology*. 1996;47:929–931.

FECAL MICROBIOTA TRANSPLANTATION IN CHILDREN WITH RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION

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Abstract: *Clostridium difficile* eradication using fecal microbiota transplantation (FMT) has been successful in adults but little information is available in pediatrics. We report 6 pediatric patients with refractory *C. difficile* cured by FMT with no recurrences to date. Our results demonstrate that FMT can be an effective treatment for refractory *C. difficile* infection in pediatrics. Long-term safety and efficacy need to be studied.

Key Words: microbiome, stool infection, colonoscopy

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Fecal microbiota transplantation (FMT) for the treatment of recurrent *Clostridium difficile* infection (CDI) is the subject of significant interest, although little information are available in children. *C. difficile* is carried asymptomatically in the intestine of up to 60–70% of infants <1-month of age, with a diminished carriage rate of 10% by age 1, decreased to 0–3% by adulthood.[1] Symptomatic CDIs among children are increasing, with a 10-fold rise in incidence from 1991 to 2009.[2] Although antibiotics are the first-line treatment, there are few Food and Drug Administration approved drugs for CDI in children. Similar to adults, children have a 30% risk of recurrence after initial CDI treatment, with diminished cure rates with each subsequent recurrence.[3]

FMT has been used successfully to cure recurrent CDI with data almost exclusively derived from adult populations. In this case series, we present data and follow up of 6 children successfully treated with FMT for recurrent CDI using a uniform protocol.

MATERIALS AND METHODS

Patient Selection

Patients included in this series had a history of recurrent and refractory CDI, defined as at least 3 CDIs that failed or relapsed within 2 weeks after withdrawal of antibiotic therapies and were subsequently treated with FMT. Six patients were identified retrospectively (Table 1), 4 in whom other gastrointestinal disorders coexisted including inflammatory bowel disease, Hirschprung disease and gastrostomy tube dependence. Informed consent was obtained from each subject. This study was approved by the Institutional Review Board of Columbia University Medical Center.

Protocol

Potential donors were screened for a history of the following: irritable bowel syndrome, idiopathic chronic constipation, chronic diarrhea, autoimmune disease of any kind, gastrointestinal malignancy or known polyposis, antibiotic use within the preceding 3 months, immunosuppressive or antineoplastic medication use, recent ingestion of an allergen of the recipient, high-risk sexual behaviors and illicit drug use. If the donor was still eligible after the initial screen, he or she underwent the following serum and stool examinations within 2 weeks of FMT: serum HIV, RPR, Hepatitis A, B and C and stool *C. difficile* polymerase chain reaction (once) and toxin (twice), ova and parasites and acid fast stain for *Cyclospora, Isospora* and *Crypotosporidium*. Donors, all parents of recipients, received 17 g of polyethylene glycol-3350 twice daily for 2 days. Stool was collected no more than 18 hours before FMT. Recipients discontinued anti-CDI antimicrobials 24 hours before FMT and underwent bowel lavage with standard laxatives in preparation for colonoscopy.

Immediately before the procedure, the physician agitated donor stool with non-bacteriostatic saline to create a 250–500 mL slurry, which was subsequently strained through gauze. Approximately 60 mL of donor solution were instilled through colonoscope into the cecum of the recipient, and 20–30 mL every 5–10 cm thereafter upon withdrawal, with the final sample deposited in the descending colon. One dose of loperamide was administered to the recipient in the recovery room post-procedure and recipients were asked to continue loperamide for 24 hours. Patient 6 was not given loperamide because of a history of Hirschsprung disease with surgical resection and reanastamosis.

Cure was defined as clinical resolution of patient symptoms (diarrhea, pain, failure to gain weight) attributed to CDI, without further dependence on anti-CDI antimicrobials.

RESULTS

All patients were cured of CDI following FMT, with results described in Table 1. Of note, after FMT, patient 2 was treated with multiple courses of antibiotics for possible infections not related to the gastrointestinal tract without our knowledge, but she remained asymptomatic without CDI recurrence.

Patient 4 had visual evidence of uncontrolled Crohn's disease (ulcerations, purulence, diseased ileocecal valve) at the time of FMT. While reporting diminished diarrhea and abdominal pain 1 week post-FMT, he presented 2 weeks after his procedure with an acute abdomen and was diagnosed with appendicitis by computed tomography scan. After appendectomy, pathologic examination showed acute appendicitis with multifocal granulomas. His inflammatory bowel disease therapy was subsequently optimized, his *C. difficile* toxin remained negative after 9 weeks post-FMT, his weight percentiles increased from the 35th to the 52nd percentile, and he had no reported gastrointestinal symptoms at 12 weeks post-FMT.

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TABLE 1. Patient Characteristics at the Time of Fecal Transplantation

	Age	Gender	Comorbidities/Additional Therapies	Donor	Number/Length of Time With *C. difficile* Infection	Previous Failed Therapeutic Agents
1.	7 yr	Male	Muscular dystrophy, gastrostomy-dependent	Mother	>10 infections, 5 years, was on vancomycin for 1 year before transplant	Metronidazole, vancomycin, IVIG
2.	21 yr	Female	Indeterminant colitis, on 6-mercaptopurine and infliximab	Mother	5 infections	Metronidazole, vancomycin with subsequent rifaximin twice
3.	21 mo	Male	Asthma	Father	5 infections	Metronidazole, vancomycin with subsequent rifaximin twice
4.	12 yr	Male	Crohn's disease, on adalimumab	Father	4 infections	Metronidazole, vancomycin 3 times with nitazoxanide once
5.	4 yr	Female	None	Father	6 infections	Metronidazole, vancomycin 4 times and with rifaximin once
6.	7 yr	Male	Emmanuel syndrome, Hirschsprung disease	Mother	4 infections	Metronidazole, vancomycin, fidaxomicin

DISCUSSION

This is one of the first case series of children treated with FMT for recurrent CDI. Our results demonstrated a cure rate of 100%. Studies evaluating the efficacy of FMT for refractory CDI in adults show eradication of the infection in up to 95% of patients treated.[4–8] Few other pediatric cases have been published and no unified protocol has previously been available.[9,10]

Community-acquired CDIs are increasing in children and may be more prone to complications and recurrence.[11] The American Academy of Pediatrics recommends metronidazole as first-line therapy for children with CDI and suggests vancomycin for relapses.[12] Treatment for pediatric patients who fail these treatments has not been standardized pediatric providers may prescribe fidaxomicin or nitazoxanide once initial therapies have failed, although outcomes for these drugs in children are not well-studied. For patients with relapsing CDI who fail both traditional and unconventional therapies, FMT offers an opportunity for cure.

Various methods of FMT exist athough each of our patients received treatment through colonoscopy. The indication for colonoscopy in each case was diarrhea and refractory *C. difficile* colitis. Nasogastric infusion was offered in all cases to avoid procedural and anesthetic risks, but each patient and/or the patient's parent in our cohort preferred infusion through colonoscopy in each instance. We adopted our methods from previously published protocols and used similar stool volumes,[13,14] although the amount of donor stool required for FMT is unknown. Successful CDI eradication using a small volume infusion of donor stool through a nasogastric tube has been reported without a preceding bowel lavage.[10] Currently, no studies have been performed comparing the efficacy of different FMT protocols, including whether a large infusion volume is necessary if given by colonoscopy, and whether a bowel preparation is indeed necessary if stool is administered through a route other than colonoscopy.

The lack of definite complications of FMT among our patients is promising; however, the risks and overall safety of FMT is still largely unknown. Patient 4 in our series had appendicitis 2 weeks after FMT and although we cannot exclude this incident as a complication of FMT, it was likely related to Crohn's disease. We found no other reported cases of appendicitis after FMT, although this unanticipated outcome highlights the need for larger controlled studies. It is also unknown if donors should be screened for other pertinent past medical or social histories or if additional infectious blood or stool studies should be collected from the donors.

The lack of uniformity in FMT administration is apparent from the Food and Drug Administration's classification of stool as a biologic. Currently, Food and Drug Administration oversight for FMT therapy for refractory CDI is recommended and is required when used for other indications. This inconsistency in regulations speaks to overwhelmingly positive outcomes reported for patients undergoing FMT for CDI, with a lack of such data for other conditions. Clinical trials evaluating the applicability of FMT in a variety of conditions and administration techniques are ongoing and will undoubtedly yield important data regarding its safety and additional applications.

Although our series was limited because of its retrospective design, this report is one of the first of its kind and demonstrated a 100% cure rate for pediatric patients with recurrent CDI. Future and larger prospective studies will add important information regarding predictors of cure with FMT and are needed to better assess the safety and risks associated with FMT.

REFERENCES

1. Janqi S LJ. Asymptomatic colonization by *Clostridium difficile* in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr*. 2010;51:2–7.
2. Khanna S, Baddour LM, Huskins WC, et al. The epidemiology of *Clostridium difficile* infection in children: a population-based study. *Clin Infect Dis*. 2013;56:1401–1406.
3. Morinville V, McDonald J. *Clostridium difficile*-associated diarrhea in 200 Canadian children. *Can J Gastroenterol*. 2005;19:497–501.
4. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol*. 2012;107:1079–1087.
5. Jorup-Rönström C, Håkanson A, Sandell S, et al. Fecal transplant against relapsing *Clostridium difficile*-associated diarrhea in 32 patients. *Scand J Gastroenterol*. 2012;47:548–552.
6. MacConnachie AA, Fox R, Kennedy DR, et al. Faecal transplant for recurrent *Clostridium difficile*-associated diarrhoea: a UK case series. *QJM*. 2009;102:781–784.
7. Rohlke F, Surawicz CM, Stollman N. Fecal flora reconstitution for recurrent *Clostridium difficile* infection: results and methodology. *J Clin Gastroenterol*. 2010;44:567–570.
8. Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infect Dis*. 2003;36:580–585.
9. Kahn SA, Young S, Rubin DT. Colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection in a child. *Am J Gastroenterol*. 2012;107:1930–1931.
10. Russell G, Kaplan J, Ferraro M, et al. Fecal bacteriotherapy for relapsing *Clostridium difficile* infection in a child: a proposed treatment protocol. *Pediatrics*. 2010;126:e239–e242.
11. Tschudin-Sutter S, Tamma PD, Naegeli AN, et al. Distinguishing community-associated from hospital-associated *Clostridium difficile* infections in children: implications for public health surveillance. *Clin Infect Dis*. 2013;57:1665–1672.

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12. Schutze GE, Willoughby RE; Committee on Infectious Diseases; American Academy of Pediatrics. *Clostridium difficile* infection in infants and children. *Pediatrics*. 2013;131:196–200.
13. Bakken JS, Borody T, Brandt LJ, et al.; Fecal Microbiota Transplantation Workgroup. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol*. 2011;9:1044–1049.
14. Brandt LJ, Reddy SS. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *J Clin Gastroenterol*. 2011;45 Suppl: S159–S167.

USE OF XPERT FOR THE DIAGNOSIS OF PULMONARY TUBERCULOSIS IN SEVERELY MALNOURISHED HOSPITALIZED MALAWIAN CHILDREN

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Background : Pulmonary tuberculosis contributes to increased morbidity and mortality in severely malnourished children in endemic settings. Despite high clinical suspicion, few tuberculosis prevalence estimates exist in malnourished African children. Diagnostics such as Xpert MTB/RIF may help to determine pulmonary tuberculosis prevalence, however its performance in severely malnourished children is largely unknown.

Methods: We conducted a prospective observational study evaluating Xpert compared to smear microscopy and liquid culture on induced sputums among severely malnourished children (aged 6 to 60 months) at Kamuzu Central Hospital in Lilongwe, Malawi. From February 1 to May 30, 2012, children who met World Health Organization 2006 guidelines for severe acute malnutrition were evaluated using clinical symptoms, tuberculin skin tests, chest radiographs, and induced sputums. National Institute of Health (NIH) consensus case definitions were used to estimate tuberculosis prevalence.

Results: Three hundred severely malnourished children (median age 18.5 months, IQR 12.1-25.6) had one induced sputum performed; 295 (98.3%) received two. Fifty-two (17.6%) were HIV-infected. Over 25% had tuberculosis exposure with 48/297 (16.2%) reporting contact and 40/287 (13.9%) with positive TST. Two (0.7%) patients had confirmed tuberculosis by Xpert and culture, but only one had positive smear microscopy. Twenty (6.7%) patients fulfilled probable and 97 (66%) met possible tuberculosis NIH case definitions. Overall mortality was 9.7%.

Conclusions: Microbiologic confirmation likely underestimates the prevalence of pulmonary tuberculosis in severely malnourished children. In our study, Xpert on induced sputums did not increase case finding. Future studies are needed using Xpert among targeted groups of severely malnourished children and on non-sputum specimens.

Key Words: pediatric tuberculosis, malnutrition, Xpert MTB/RIF

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Preliminary data were presented at the 17th Annual Conference of the Union Against TB and Lung Disease-North America Region, Vancouver, 2013 and included in the WHO 2013 Xpert guidelines for the diagnosis of pulmonary and extrapulmonary tuberculosis in adults and children.

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Of the nearly 9 million annual tuberculosis diagnoses, one-fourth occur in Africa, with approximately 530,000 among children.[1] Pediatric tuberculosis diagnosis is challenging because of protean presentation, sample collection difficulties, paucibacilliary disease and limited availability of microbiologic culture.[2] Malnourished children are at increased risk of tuberculosis infection, disease progression and worse outcomes.[3] HIV further increases mortality in this highly vulnerable group.[4,5] Nevertheless, few tuberculosis prevalence estimates exist in malnourished African children.[4,6–8]

The complex triad of HIV, tuberculosis and malnutrition exists in Malawi where approximately 180,000 children are HIV-infected and mortality among HIV-infected malnourished children is high.[5] Children account for 11% of new tuberculosis diagnoses annually (Malawi National Tuberculosis Program, unpublished).

Xpert MTB/RIF (Xpert, Cepheid, Sunnyvale, CA) is a polymerase chain reaction-based rapid tuberculosis diagnostic test and the World Health Organization (WHO) recommends its use in children suspected of tuberculosis.[9] In 2012, the WHO began reporting global pediatric tuberculosis incidence; however, improved estimates are needed.[1] Testing induced sputums of high-risk children with Xpert may help determine pulmonary tuberculosis prevalence in high-HIV burden areas and better target treatment.[10–14] Xpert's performance in severely malnourished children is largely unknown.

We aimed to determine pulmonary tuberculosis prevalence among hospitalized severely malnourished Malawian children with Xpert compared with smear and culture on induced sputums and characterize patients by National Institutes of Health (NIH) consensus case definitions (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B907).[15] We hypothesized that severely malnourished children would have a high tuberculosis prevalence and Xpert would be superior to smear and similar to culture on induced sputums.

METHODS

We conducted a prospective observational study at Kamuzu Central Hospital, a tertiary referral center serving central Malawi, from February 1 to May 30, 2012. Enrollees met WHO severe acute malnutrition criteria for children aged 6–60 months with: weight-for-height z-score ≤−3 standard deviations below the median, mid-upper arm circumference (MUAC) ≤115 mm or bilateral pedal edema.[16] Weight-for-height was not calculated in children with edema because this can falsely elevate weight. We excluded patients already receiving tuberculosis treatment, those with conditions (besides malnutrition) causing edema, and if induced sputums were contraindicated.

After informed consent was obtained from a guardian, a tuberculin skin test (TST, Tubersol, Sanofi Pasteur, Swiftwater, PA) and anterior–posterior and lateral digital chest radiograph were performed. Radiographs were read by 2 blinded reviewers per a

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