Safety of Fecal Transplantation in Pediatric Inflammatory Bowel Disease

Therapeutic manipulation of the intestinal microbiome using fecal microbiota transplantation (FMT) has the potential to treat various diseases, including inflammatory bowel disease (IBD). However, the efficacy of FMT in the treatment of IBD, including Crohn disease and ulcerative colitis, is unclear and this aspect is especially true in pediatric patients. The authors of this study performed an open-label prospective trial at a single children's hospital in the United States. Patients between 2 and 22 years of age with Crohn disease, ulcerative colitis, and indeterminate colitis were included in the study. Study subjects were recruited if they needed a medically indicated colonoscopy, were showing no improvement in IBD symptoms with medical therapy, and had mild to moderate disease. Worsening disease activity was determined by an elevated Pediatric Crohn's Disease Activity Index (PCDAI), an elevated Pediatric Ulcerative Disease Activity Index (PUCAI), or an elevated fecal calprotectin or lactoferrin level. Donors for FMT were first-degree relatives or friends who had no contraindications for donation. Exclusion criteria included an active GI infection, severe IBD, use of high-dose steroids combined with a biologic agent, presence of a central line, requirement of ICU care, Crohn disease limited to the small intestine only, abscess or stricture, or a change in medical therapy within 4 weeks of potential recruitment. Study subjects were given metronidazole or vancomycin as well as omeprazole and loperamide prior to the procedure. A single FMT consisted of 150 grams of stool mixed in 250 to 300 milliliters of saline given via the distal duodenum / proximal jejunum and terminal ileum / right colon. Clinical response was defined as a decrease in PCDAI of 12.5 points, a decrease in PUCAI of 15 points, or normalization of fecal biomarkers. Additionally, bacterial 16S rRNA gene sequences were amplified and sequenced to identify microbiome changes at one week, one month, and six months after FMT.

Twenty-one patients were included in this study with 34% of patients having Crohn disease, 57% having ulcerative colitis, and 9% having indeterminate colitis. At the one month follow-up assessment, 71% of patients with Crohn disease had a clinical response while 50% of ulcerative colitis and indeterminate colitis patients had a clinical response. It should be noted that patients with ulcerative colitis and indeterminate colitis were combined due to low patient numbers. At 6 months post-FMT, no patients with ulcerative colitis or indeterminate colitis were in clinical remission and only 2 patients with Crohn disease were in clinical remission. No difference in age, disease duration, disease location, disease severity, or medication use before FMT existed between responders and non-responders. No serious adverse events occurred with FMT use.

An intestinal microbiome analysis demonstrated lower within-sample taxonomic diversity (alpha diversity) in stool samples of IBD patients prior to FMT compared to donor samples. Patients with IBD had higher amounts of *Enterobacteriaceae* and less *Lachnospiraceae* (which has been demonstrated to occur in other IBD microbiome studies). Alpha diversity of stool microbiome samples improved in patients with IBD at one week and one-month post-FMT although diversity patterns normalized to pre-FMT patterns at 6 months. Alpha diversity appeared to be lower in patients who responded to FMT compared to patients who did not respond; however, the difference was not significant.

This study demonstrates that FMT is safe in pediatric patients with IBD and there are possible short-term clinical improvements that can occur possibly associated with microbiome changes. Long-term treatment outcomes are still unknown.

Goyal A, Yeh A, Bush B, Firek B, Siebold L, Rogers M, Kufen A, Morowitz M. Safety, clinical response, and microbiome findings following fecal microbiota transplant in children with inflammatory bowel disease. Inflammatory Bowel Diseases 2018; 24: 410-421.

Colonic Eosinophilia in Children

Children who undergo endoscopy for gastrointestinal issues often have eosinophils noted in colonic biopsies. However, the presence of eosinophils as a cause of gastrointestinal disease in children is unknown, and the authors of this study performed a retrospective study of all patients with colonic eosinophilia at a tertiary children's hospital with expertise in allergic gastrointestinal disease. An analysis of pathology specimens over an 8-year period was performed to identify any colonic pathology specimen with eosinophils mentioned in a pathology database. This cohort of specimens was labeled as "colonic eosinophilia", and the group was compared to control subjects with no colonic eosinophils or inflammation noted using the same database. Patients under one year of age with biopsy-proven allergic colitis, history of bone marrow transplantation, or history of a parasitic infection were excluded from analysis. The electronic medical record was used to determine clinical features of both

(continued on page 62)

(continued from page 60)
groups, including symptoms, laboratory testing, and potential final diagnosis.

In total, 72 study subjects with colonic eosinophilia were compared to 35 control patients. Patients with colonic eosinophilia had significantly more eosinophils per high-power field (eos/HPF) throughout the colon compared to the control group. The three most common gastrointestinal complaints for patients with colonic eosinophilia were abdominal pain (59%), hematochezia (47%), and diarrhea (39%). The final diagnosis of patients with colonic eosinophilia included eosinophilic gastrointestinal disease (including eosinophilic colitis) (37%), inflammatory bowel disease (IBD) (36%), and various other disorders (49%) such as toddler's diarrhea, constipation, or no disease. There was some overlap between diagnoses.

Patients with colonic eosinophilia and IBD were significantly older at time of biopsy, had significantly lower hemoglobin levels and significantly higher erythrocyte sedimentation rates, and were significantly more likely to have hematochezia and chronic colitis noted on biopsy. Patients with eosinophilic colitis were significantly more likely to be male and to have higher mean peripheral blood eosinophil counts compared to patients with no IBD and no eosinophilic colitis. Many of these patients (68%) had a change in diagnosis after two or more colonoscopies.

This study demonstrates our lack of understanding about colonic eosinophilia in the pediatric population, and the authors are to be commended for making a database to follow such patients in a long-term manner. The authors have recognized three clinical phenotypes of colonic eosinophilia, and further research is needed to predict how such patients will progress clinically over time.

Mark J, Fernando S, Masterson J, Pan Z, Capocelli K, Furuta G, de Zoeten E. Clinical implications of pediatric colonic eosinophilia. Journal of Pediatric Gastroenterology and Nutrition 2018; 66: 760-766.

Probiotics and Necrotizing Enterocolitis: Still Confusion

Necrotizing enterocoliltis (NEC) is a significant cause of mortality in premature infants. Probiotics have been proposed as a potential preventative therapy for NEC by theoretically changing the intestinal microbiome to a more protective profile; however, research outcomes are unclear, as different probiotic strains, dosing, and timing of administration have been used. The authors of this retrospective observational study at a single newborn intensive care unit (NICU) evaluated the effect of one probiotic, *Lactobacillus rhamnosus* GG (LGG). LGG was given at a standardized dosing of 2.5×10^9 colony forming units (CFU) once per day, which was then increased to 5×10^9 CFU once feeds were advanced. Infants were included in the study if they weighed less than 1500 grams, had no congenital abnormalities, were in the NICU greater than 3 days, and were admitted to the NICU less than 7 days of age. Primary outcome analysis was development of NEC, defined as modified Bell stage IIA or greater.

This study occurred over an 8-year duration, and 640 infants met study criteria (175 infants received LGG; 465 infants received no LGG). The median gestational age of study infants was 28.7 weeks with a median birth weight of 1070 grams. Both gestational age and birth weight were significantly lower in infants who had NEC and in those infants that received LGG. Maternal age was significantly higher in mothers of infants who received LGG. No significant difference was present between the groups in the percentage of infants who received breast milk. Seventy-eight infants (12%) developed NEC during the study with 19% of infants receiving LGG developing NEC compared to 10% of infants not receiving probiotics. An epoch analysis demonstrated that 17% of infants developed NEC after LGG supplementation compared to 10% of infants before LGG was introduced in the study. No infant had *Lactobacillus* sepsis, and there was no difference in culture-positive sepsis between the two groups. A multivariable analysis demonstrated that LGG supplementation alone was associated with an increased risk of NEC.

This is a retrospective study, so these findings do not account for potential NICU clinical practice changes over time. However, LGG given at a standardized dosing regimen did not appear to prevent NEC in this study suggesting much more research is needed to determine the potential benefit of probiotic use in relation to strain, dosing, and timing of administration.

Kane A, Bhatia A, Denning P, Shane A, Patel R. Routine supplementation of Lactobacillus rhamnosus GG and risk of necrotizing enterocolitis in very low birth weight infants. Journal of Pediatrics 2018; 195: 73-79.

John Pohl, M.D., Book Editor, is on the Editorial Board of *Practical Gastroenterology*