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Updates and Challenges in Fecal Microbiota Transplantation for *Clostridioides difficile* Infection in Children

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Abstract

Fecal microbiota transplantation (FMT) is currently the most effective, but loosely regulated therapy, for recurrent *Clostridioides difficile* infection (rCDI) in pediatrics. Over the last two years, there have been mounting challenges in the ability to provide FMT to pediatric patients. Firstly, an FDA safety alert in 2019 reported transmission of a multi-drug resistant organism from FMT donor to recipient resulting in the death of one patient. Secondly, the COVID-19 pandemic induced further safety and regulatory challenges. Biotherapeutics are promising and more readily regulated treatment options for rCDI, which may replace FMT in the near future for adults upon regulatory agency approvals. Such approvals, however, are expected to be significantly delayed for children, raising concerns for limited access to effective treatment for children with rCDI. In this commentary, we discuss the recent challenges and future directions of FMT and microbial therapeutics in children with rCDI.

Keywords

fecal transplant; pediatric; microbial therapeutics

Introduction

Fecal microbiota transplantation (FMT) is currently the most effective microbial therapy for recurrent *Clostridioides difficile* infection (rCDI) in children and adults[1,2] and is now included in recent practice guidelines for the treatment of rCDI in pediatric patients.[3] Our large multi-center pediatric study found a single FMT to be 81% successful in treating rCDI.[1] However, recent events including an Food and Drug Administration (FDA) safety alert and the COVID-19 pandemic, have brought into question the safety of FMT and also

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made this unconventional treatment less accessible for our pediatric population with rCDI. Here we discuss the current challenges in providing FMT and other microbial therapeutics to children with rCDI.

Safety of FMT in children

Despite its efficacy, FMT remains a poorly standardized and relatively unregulated therapeutic strategy with ongoing concerns regarding its safety. We reported that in children, the most common adverse events are diarrhea, pain, and bloating.[1] However in the same pediatric study, there were two serious adverse events thought to be related to FMT: 1) aspiration pneumonia and 2) hospital admission for vomiting and diarrhea after FMT.[1]

Long term safety outcomes of FMT remain unknown. This is especially relevant for our pediatric population in which the intestinal microbiome is still undergoing critical development, which may later be associated with protection from or susceptibility to adverse health outcomes including chronic inflammatory, allergic, and autoimmune diseases.[4,5,6] As FMT changes the intestinal microbiome and metabolome, the potential risk for the development of future microbiome-associated chronic diseases warrants attention. While there is a paucity of literature, FMT has been associated with durable transmission of pro-carcinogenic bacteria from adult donors to pediatric recipients, for example, although the long-term consequences of such transfer are unknown.[7]

2019 FDA Safety Alert

Compounding safety concerns, an FDA safety alert was released in June 2019, describing the acquisition of extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* upon FMT in two immunocompromised adult recipients, one of whom died. The FMT donor was found to be positive for ESBL *Escherichia coli* with clonality confirmed.[8] Given this, the FDA determined that additional precautions for FMT were needed, specifically including donor screening and testing for multi-drug resistant organisms (MDRO).[8] This additional testing can be expensive, difficult to access and most are not certified through Clinical Laboratory Improvement Amendments (CLIA). Our yet unpublished survey of pediatric gastroenterologists in the United States (US) revealed that the FDA safety alert changed the FMT practice of 47% of reporting providers, including moving to a commercial stool bank and avoiding FMT in immunocompromised hosts. No direct transmission of MDROs by FMT causing adverse effects has been shown in children. In prior studies, however, while FMT generally decreased the abundance of multidrug resistance genes in recipient microbiomes, there was acquisition of certain antimicrobial resistance genes after FMT from adult donors to pediatric recipients.[9] This highlights the need for optimized and standardized FMT donor screening.

The Covid-19 pandemic effects on FMT

Additional safety concerns surfaced in 2020 during the COVID-19 pandemic, when it was discovered that the SARS-CoV-2 viral RNA could be detected in feces.[10] This raised apprehensions for the potential transmission of the SARS-CoV-2 virus from donor to

recipient via FMT. A case report has found infectious SARS-CoV-2 in the feces of a patient with severe COVID-19,[11] but detailed virologic examinations in a case series of hospitalized patients with a mild course of the disease failed to identify infectious viruses from stool.[12] Importantly, we and others have not found any published evidence for fecal transmission of SARS-CoV-2 infection so far.[13] Nevertheless, the FDA released a further safety alert in March 2020, which was revised in April 9th 2020, advising for additional precautions including testing donors and/or donor stool for SARS-CoV-2 prior to FMT.[14] To date, however, there are no molecular tests with stool as the specimen type which have received an emergency use authorization to screen for SARS-CoV-2.[15] Likely due to these challenges, our yet unpublished survey mentioned above also found that 83% of pediatric gastroenterologists in the US performing FMT changed their practice as a result of the COVID-19 pandemic, with 61% of reporting providers placing their FMT program on hold as of January 2021.

Access to FMT in children

Prior to the FDA safety alerts, most pediatric providers in the US were delivering FMT using thawed, previously frozen, stool from a stool bank (as opposed to a patient selected donor).[1] Critically, for the majority of 2020 and into early 2021, the largest stool bank in the US, OpenBiome, which provided much of the donor material for pediatric FMT, halted distribution for non-emergent FMT to address the safety concerns listed above. Although their product became recently available, they expect to only be able to provide access to FMT donor material through 2021, due to 1) the increased costs of the additional donor screening required and 2) promising biotherapeutics for the treatment of rCDI currently undergoing phase III trials.[16]

The future of FMT in children

Over the last 2 years, there have been tremendous challenges in providing FMT for rCDI. Alternative strategies include the use of fidaxomicin, which has been shown to be effective in children for CDI and is now approved for use in patients 6 months and older.[17] However, some children with rCDI, after careful assessment that there are no other causes for their symptoms, will still have a need for FMT if fidaxomicin fails. [18,19] Given both the lack of standardization and safety concerns of FMT, biotherapeutics (loosely defined as drug therapy products where the active substance is extracted from a biological specimen) are likely the way of the future for treating rCDI. Biotherapeutics have the potential for increased standardization, safety and practicality compared with FMT. Phase III studies are underway for some of these products for rCDI (e.g. SER-109, an investigational microbiome drug consisting of a consortium of bacterial spores from healthy donors in oral capsule form (NCT02437487) and RBX2660, a suspension of standardized intestinal microbes delivered by enema (NCT03244644)), with some products given a fast track designation by the FDA.

While these biotherapeutics are very promising, the pediatric population will be less likely to benefit from these in the near future given the lack of clinical trials in children and the inherent delays to reach this point.[20] To date, we are unaware of a phase III biotherapeutic trial enrolling pediatric patients with CDI. Additionally, the oral (capsule) and enema route,

currently used for these therapeutics, are less feasible for pediatric use. This is evidenced by our multi-center pediatric FMT study, where of the 372 children included (median age 10 years, interquartile range 3–15 years), oral capsules for FMT were only used in 14/372 (3.8%) and enemas in 4/372 (1.1%).[1] This leaves children with rCDI and their providers in quite a predicament; there will be little access to safe FMT donor material from stool banks beyond 2021, yet biotherapeutics to treat rCDI for children are unlikely to be available soon. Providers of FMT will then face the dilemma of: 1) returning to donor directed FMT, which is now significantly more challenging given the additional donor screening recommended by the FDA, and which is costly and frequently not available in a certified, standardized fashion; 2) setting up local stool banks, which is usually impractical outside of research studies given the relatively low number of FMTs in any given geographic location; and 3) not providing FMT and running the risk of families self-administering the treatment at home (example https://www.youtube.com/watch?v=xLIndT7fuGo; over 129,000 views) with its associated inherent safety risks. Given these considerations, we imminently face lack of access to FMT without viable options for the treatment of recurrent rCDI in children. Our pediatric gastroenterology community needs to advocate industry, legislature and regulatory agencies toward safe, effective and widely accessible microbial therapeutics for children with rCDI with clinical trials and rapid FDA approval.

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What is known:

- Fecal microbiota transplantation (FMT) is the most effective, but relatively unregulated, therapy for recurrent *Clostridioides difficile* infection (rCDI) in children.

What is new:

- New safety concerns arose concerning FMT upon the 2019 FDA safety alert and the COVID-19 pandemic.
- There is currently limited access to FMT for children with rCDI.
- While biotherapeutics may be available for adults soon to treat rCDI, these are unlikely to be approved for children in a timely fashion.