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Current Challenges in Fecal Microbiota Transplantation for *Clostridioides difficile* Infection in Children

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Abstract

Background: The impact of the 2019 Food and Drug Administration safety alert involving transmission of multi-drug resistant organisms through fecal microbiota transplantation (FMT), and the COVID-19 pandemic on the use of FMT in children, is unknown

Methods: A survey of pediatric gastroenterologists performing FMT for *Clostridioides difficile* infection was conducted.

Results: Of 36 respondents, 17 (47%) and 30 (83%) changed their FMT practices related to the FDA safety alert and COVID-19 pandemic, respectively, with 22 (61%) of programs halted.

Conclusions: The FDA safety alert and COVID-19 pandemic have substantially influenced the availability and access of FMT for children.

Keywords

fecal microbiota transplantation; *Clostridioides difficile* ; diarrhea; safety; pediatrics

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• **Specific author contributions:** MRN initiated the study, created the data abstraction instrument, and drafted the initial manuscript. MRN, MC, AG, KJ, SKH, JK, MK, MW, and SK designed the study, performed data interpretation, reviewed, edited, and approved the final manuscript as submitted.

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Introduction

Fecal microbiota transplantation (FMT) has been well studied for the treatment of *Clostridioides difficile* infection (CDI) in children and adults[1,2] and is included in recent practice guidelines for the treatment of recurrent CDI.[3] Despite this, FMT remains a relatively unregulated therapeutic and is deemed investigational by the Food and Drug Administration (FDA). In June 2019, the FDA released a safety alert after the development of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* in two immunocompromised recipients who had received FMT from an ESBL *E.coli* positive donor, with subsequent fatality in one.[4] Based on this safety alert, additional donor screening for multi-drug resistant organisms (MDROs) was recommended.[5] In addition, as it became evident in 2020 that SARS-CoV-2 could be detected in the feces of infected individuals, additional FMT donor screening was necessary.[6] There has been growing concern regarding the evolving risk of FMT, increasing the difficulty in striking the balance of accessibility and safety.[7] We surveyed the pediatric gastroenterology community to determine the impact of both the 2019 FDA safety alert and the COVID-19 pandemic on the use of FMT for CDI in children.

Methods

Pediatric gastroenterologists were invited to participate in an online survey evaluating FMT practices for the treatment of CDI prior to and post the FDA alert and during the COVID-19 pandemic. The survey was administered via REDCap[8] from December 19, 2020- February 1, 2021 and approved by the Institutional Review Board at the sponsoring institution, Vanderbilt University Medical Center. Each provider could contribute to the survey once. Multiple providers from a single institution were permitted; institutional data was combined so that an institution was not over-represented. Surveys were excluded if they were from a non-United States (US) site, the site was not providing FMT prior to 2019, or if more than one survey was completed per individual.

Results

Forty-five surveys were completed. Surveys excluded were: non-US site (n=3), center initiated FMT for the treatment of CDI after 2019 (n=5) or survey completed more than once per individual (n=1). There were 36 survey responses representing 32 institutions. These institutions provided FMT for the treatment of CDI to between 135 and 330 pediatric patients per year prior to 2019. The majority of institutions were academic (88%), and most used material from a commercial stool bank prior to June 2019 (81%) (Table 1).

There were 17 providers (47%) who changed their FMT practices related to the FDA safety alert, 18 (50%) who did not change their practice, and one (3%) who was unaware of the safety alert. Those who changed their practice made one or more of the following adjustments: 7 (41%) changed to a commercial stool bank, 5 (29%) increased use of oral vancomycin, 5 (29%) increased use of fidaxomicin, 4 (24%) avoided FMT in immunocompromised hosts, 3 (18%) added additional donor screening, and 3 (18%) put their program on hold. Most participants (89%) agreed with the recommendations

of the FDA safety alert. However, one did not agree and two were uncertain. These individuals cited concerns that the alert was applied to all FMT recipients instead of only immunocompromised patients and noted difficulties in obtaining clinical MDRO donor screening, thereby limiting use of donor-directed FMT.

The majority (83%) of providers performing FMT for CDI in children changed their practice in relation to the COVID-19 pandemic. One provider (4%) moved to a local stool bank, three (11%) did additional screening for directed-donors, 22 (61%) put their programs on hold, 9 (32%) increased vancomycin use, 12 (43%) increased fidaxomicin use, 4 (14%) avoided FMT in immunocompromised hosts, and 2 (7%) increased use of non-procedural FMT (i.e. capsules, feeding tubes, and enemas). Four individuals also reported the use of FMT for non-CDI research-related indications; two were affected by the 2019 FDA alert and all four were affected by the COVID-19 pandemic and their FMT research projects were placed, at least temporarily, on hold.

Discussion

Over the last two years there have been immense challenges and alterations in the use of FMT for CDI, but there is little information on the impact of the 2019 FDA safety alert and the COVID-19 pandemic on pediatric providers. Through our survey of pediatric gastroenterologists, we identified that, among responding individuals, nearly 50% performing FMT for pediatric CDI changed their practice based on the FDA safety alert with 41% moving to the use of commercial stool banks. Even more pronounced, the majority (83%) of pediatric providers changed their practice patterns based on the COVID-19 pandemic with 61% of providers placing their programs on hold.

A notable limitation of this study is potential response bias with survey responders more likely to be those with larger volume programs and clinical interest in FMT. It is possible that smaller programs may have been less influenced by recent guidance. However, despite a relatively small sample size, this likely represents a meaningful representation of pediatric centers providing FMT, as a 2018 study identified 45 pediatric centers providing FMT in the US.[9]

Importantly, for the majority of 2020 and 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 safety concerns. Although their product became recently available, they expect to provide access to FMT material only through 2021, due to promising bio-therapeutics for the treatment of CDI currently undergoing phase III trials.[10] Unfortunately, the pediatric population will less likely to be eligible for these bio-therapeutics in the near future given the oral administration that is difficult for children, lack of pediatric clinical trials, and inherent delays in the FDA approval process and insurance coverage.[11]

The 2019 FDA safety alert and the COVID-19 pandemic have both negatively influenced the availability of pediatric FMT for CDI with long-lasting consequences. These recent events highlight the need for approval of a safe, highly refined, and reproducible pediatric-friendly

bio-therapeutic product for the treatment of CDI. Until there is an approved pediatric product, enabling access to safe and well screened FMT material for children with recurrent CDI is vital.

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Abbreviations:

FMT	fecal microbiota transplantation
CDI	*Clostridioides difficile* infection
MDRO	multi-drug resistant organism

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Table 1.

Fecal Microbiota Transplantation Center Characteristics

Institution Characteristics	**N= 32 centers**
Institution type	
Academic	28 (88%)
Private Practice	3 (9%)
Hospital-owned Practice	1 (3%)
FMT donor prior to June 2019 *	
Directed Donor	13 (41%)
Commercial Stool Bank	26 (81%)
Local Stool Bank	3 (9%)
FMT delivery prior to June 2019 *	
Upper delivery via NG/NJ	15 (47%)
Upper delivery via endoscopy	5 (16%)
Upper delivery via capsule	5 (16%)
Lower delivery via colonoscopy	32 (100%)
Lower delivery via enema	1 (3%)
Number of FMT/center/year prior to June 2019	
0–5	16 (50%)
5–10	9 (28%)
10–20	5 (16%)
20–30	2 (6%)

* Multiple responses allowed so totals >100%

FMT=Fecal Microbiota Transplantation

NG=nasogastric tube

NJ=nasojejunal tube