

Fidaxomicin Use in the Pediatric Population with *Clostridioides difficile*

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Abstract: *Clostridioides difficile* infection (CDI) remains a devastating infection both in hospital settings and in the community. While a number of antibiotics have anti-*C. difficile* activity, fidaxomicin is unique as a minimally absorbed antibiotic with narrow spectrum of activity. These features make it an appealing option for pediatric CDI to balance safety and efficacy. The purpose of this structured review was to outline the clinical evidence for safety and efficacy of fidaxomicin for pediatric CDI. A structured literature search was performed to identify relevant clinical data. Fidaxomicin is similarly effective to oral vancomycin with a lower rate of recurrent CDI. There were no serious safety signals reported with fidaxomicin. In conclusion, fidaxomicin is a safe and effective treatment option for pediatric CDI.

Keywords: Dificid, diarrhea, colitis, microbiota

Introduction

Clostridioides difficile infection (CDI) is a leading cause of nosocomial infection with a devastating impact on patients and the health-care system. While initially thought limited to hospital settings, it is clear that CDI occurs in the community as well. This trend holds true for both adults and children. In fact, most pediatric CDI appears to arise in the community setting.^{1,2} The incidence of pediatric CDI is estimated around 17–24 per 100,000 children, about 8-fold lower than adults over the age of 65.³ Importantly, the incidence of pediatric CDI appears to be increasing, although changes in the diagnosis of CDI likely contribute.⁴ The bulk of treatment data for CDI is from adult populations, particularly adults aged over 65, based on the distribution of CDI. As such, it is not clear how to translate recommendations from adults.

C. difficile is an opportunistic infection that arises when the host intestinal microbiota is damaged, typically in the setting of systemic antibiotics. As with adults, the main cause of dysbiosis leading to CDI is antibiotics in the pediatric population, although the specific antibiotic risks are slightly varied.^{3,5} A healthy human intestinal microbiota is capable of colonization resistance against *C. difficile*.^{6,7} With loss of diversity and function of the microbiota (dysbiosis), colonization resistance is lost, and *C. difficile* spores can germinate, produce toxin, and cause clinically significant inflammation in the colon. The importance of the microbiota in CDI is highlighted in very young children. Children under the age of 1 year do not develop CDI despite near ubiquitous colonization with *C. difficile*. Children aged 1–3 are remain likely to be colonized, although at some point, colonization rates drop, and infection is possible.⁴ Changes in the intestinal microbiota in early childhood development are likely the reason for this effect.

As the key pathophysiology of CDI is dysbiosis, then antibiotics that perpetuate dysbiosis present an inherent problem. Oral vancomycin, commonly used in adults and pediatric populations has a devastating effect on the colonic microbiota.^{8–10} While effective at treating acute CDI, the resulting intestinal microbiota is damaged. Fidaxomicin is a narrow spectrum macrolide antibiotic that has minimal systemic absorption and no effect on gram-negative aerobes or gram-negative anaerobes. Fidaxomicin was first FDA approved in 2011 for the treatment of *C. difficile*-associated

diarrhea in adults and received orphan drug designation for the treatment of pediatric CDI December 2010.¹¹ Fidaxomicin was approved for the treatment of CDI in children aged 6 months or greater in 2020.¹² However, its use often remains limited to multiple CDI recurrences.¹³ It was only in 2021 that IDSA/SHEA updated the adult CDI guidelines to favor fidaxomicin for first-line therapy.¹⁴ This structured review will highlight the role of Fidaxomicin in the treatment of pediatric CDI summarizing the pharmacology of fidaxomicin in CDI and the clinical efficacy.

Methods

A librarian from the University of Minnesota Library Services performed the literature search. The aim of the review was a structured review of the clinical fidaxomicin use in pediatric CDI. The goal was to synthesize all clinical controlled data. In order to comprehensively search the published and grey literature, we first developed the search strategy in Ovid MEDLINE using a combination of index terms and natural language to encompass the concepts of fidaxomicin and *C. diff* and their iterations and a pediatric patient population. Search terms included: fidaxomicin (Dificid or Lipiamycin or tiacumicin or PAR-101 or PAR101), *Clostridium* Infections or *Clostridium difficile* (*clostridium* or *Clostridioides* or *Peptoclostridium* or *difficile* or infection or “*c diff*” or “*c difficile*”), Pediatrics or Infant or Child or Adolescent (pediatric or paediatric or infant or baby or babies or child or children or adolescent or teenage). The search was then additionally translated and executed in Embase, Scopus, and the Cochrane Library, for a total of 183 articles after deduplication. All titles were reviewed by both authors and relevant clinical data was summarized.

Results

Pediatric Pharmacokinetics and Dosing

Safety and pharmacokinetic (PK) data in the pediatric population were not published until 2017 to support a dosing regimen in children. Fidaxomicin’s PK profile in pediatrics is similar to that observed in adults.^{15,16} Fidaxomicin and its primary active metabolite (OP-1118) exhibit minimal systemic absorption and are largely confined to the gastrointestinal tract following oral administration, regardless of age and weight. Transformation to its active metabolite occurs in the gut and is independent of cytochrome P450 enzymes. Fecal excretion is the main mode of elimination and detectable levels of fidaxomicin and its metabolite are identified in the majority of pediatric fecal samples. Mean stool concentrations of fidaxomicin in pediatrics exceeded the 90% minimum inhibitory concentration of 0.125 mg/L for *C. difficile* and were generally higher (2700–3227.9 ug/g) compared to stool concentrations described in adults (1225.1 ug/g).^{17,18} However, no correlation between fecal fidaxomicin concentration and efficacy has been observed. The pediatric dosing regimen used in these clinical trials ultimately informed current dosing recommendations in pediatric patients down to 6 months of age (Table 1).

Fidaxomicin was FDA approved for use in pediatric patients 6 months to <18 years of age on January 27, 2020.¹¹ No dose adjustments are required in patients with renal or hepatic impairment and no clinically significant drug interactions are known to occur.¹⁹ Fidaxomicin is supplied as a 200 mg oral film-coated tablet or granule formulation for reconstitution in suspension (40 mg/mL). Either formulation can be taken with or without food.

Table 1 FDA-Approved Fidaxomicin Dosing in Pediatric Patients 6 Months to <18 Years of Age

| Weight | Dose | Volume of 40 mg/mL suspension PER DOSE |
|--------------------------------------|--|--|
| ≥12.5 kg and able to swallow tablets | One 200 mg tablet orally twice daily for 10 days | N/A |
| ≥12.5 kg and prefer oral suspension | 200 mg orally twice daily for 10 days | 5 mL |
| 9 to <12.5 kg | 160 mg orally twice daily for 10 days | 4 mL |
| 7 to <9 kg | 120 mg orally twice daily for 10 days | 3 mL |
| 4 to <7 kg | 80 mg orally twice daily for 10 days | 2 mL |

Efficacy

The first pediatric case report of successful fidaxomicin therapy was published in 2013 describing a 10-year-old male with a history of chromosomal disorder, microcephaly, seizures, gastric tube feeding, and recurrent CDI related to multiple pneumonia treatment courses with antibiotics.²⁰ After five previous instances of CDI, he was initiated on a 10-day course of fidaxomicin (200 mg twice daily) and remained symptom free at 1-month follow-up.

Prior to the publication of pediatric data, physicians were recommending fidaxomicin off-label in the pediatric setting. Sammons et al described pediatric infectious disease (ID) physician recommendations for pediatric CDI management through a web-based national survey in 2013.²¹ Of the 125 pediatric ID responders who recommended alternative therapies for the management of severe or recurrent CDI in pediatrics, 20 (16%) recommended fidaxomicin. The majority (80%) of physicians who recommend fidaxomicin recommend it at or beyond the third recurrence. However, 4 (20%) physicians recommended fidaxomicin for severe disease and 3 (15%) at first recurrence. Off-label fidaxomicin prescribing was occurring prior to the availability of pharmacokinetic or outcomes data in the pediatric population.

O’Gorman et al were one of the first to describe fidaxomicin outcomes data in pediatric patients in 2017.¹⁵ In their phase 2a trial, clinical response occurred in 92.1% of patients (35 of 38) within 2 days after completing fidaxomicin therapy. Twenty-five (65.8%) patients demonstrated sustained clinical response 28 days after fidaxomicin. Recurrence occurred in 11 (31.4%) patients among the 35 who demonstrated an initial clinical response. This recurrence rate was initially concerning given it is higher than recurrence rate associated with fidaxomicin in adult Phase 3 studies (12.7–15.4%) when using similar definitions of recurrence.^{18,22} However, this pediatric study included a small number of patients (n = 38) with the majority (60.5%) having a past history of CDI and this study was not powered to detect accurate estimates of recurrence.

The SUNSHINE trial is the first and only prospective multicenter randomized single blind, phase 3 clinical trial to evaluate the safety and efficacy of fidaxomicin in pediatric patients with a CDI diagnosis.¹⁶ Pediatric patients were randomized 2:1 to 10 days of treatment with either fidaxomicin (suspension or tablets, twice daily) or vancomycin (suspension or tablets, 4 times daily) if they had ≥ 3 unformed bowel movements (or watery diarrhea if < 2 years old) within 24 hours and positive for toxin A/B or toxigenic *C. difficile* within 72 hours before randomization. Clinical response two days post therapy was not significantly different between the two groups (77.6% vs 70.5%; adjusted treatment difference, 7.5%; 95% CI, -7.4–23.9%). However, global cure (30 days after completing therapy) was significantly higher in patients receiving fidaxomicin (68.4% vs 50%; adjusted treatment difference, 18.8%; 95% CI, 1.5–35.3%). CDI recurrence was not statistically significant between groups among those who achieved confirmed clinical recurrence, although trended towards a benefit with fidaxomicin (11.8% vs 29%; adjusted treatment difference, -15.8%; 95% CI, -34.5–0.5%). However, cumulative incidence of recurrence was significantly higher in the vancomycin group (log-rank P = 0.02). The number needed to treat with fidaxomicin was 5.3 (95% CI, 2.8–66.7) to prevent 1 additional treatment failure or recurrence.

Safety

Fidaxomicin is well tolerated in pediatric patients. The most common adverse reactions in pediatric patients receiving fidaxomicin include pyrexia (13.3%), vomiting (7.1%), diarrhea (7.1%), abdominal pain (5.1%), constipation (5.1%), increased aminotransferase (5.1%), rash (5.1%), pruritus (3.1%), and oral candidiasis (3.1%).¹⁶ However, of the seven events of increased aminotransferases, only one (1%) occurrence (elevated alanine aminotransferase) was classified as possibly related to CDI therapy. Fidaxomicin therapy was not related to any serious adverse event.^{15,16} Fidaxomicin was discontinued in 2.9% (4 of 136) of pediatric patients in the following scenarios: moderate colitis, fidaxomicin-related urticaria, gas pain considered unrelated to fidaxomicin, and increased body temperature with tachycardia considered possibly related to therapy.^{15,16} The incidence of treatment-related adverse events is similar between pediatric patients receiving fidaxomicin (7.1%) and vancomycin (11.4%).¹⁶

Incorporation into Guidelines

Society guidelines from around the world have recently commented on fidaxomicin’s place in therapy (Table 2). Since 2018, many guidelines recommend fidaxomicin for initial CDI episode (except for fulminant CDI) as well as for first or subsequent CDI recurrence in adults. However, guidelines providing pediatric CDI recommendations do not recommend

Table 2 International Guideline Comparison of Fidaxomicin Place in CDI Management

| Reference | Society Endorsement | Year | Country | Population | Fidaxomicin Place in Adult Therapy | Fidaxomicin Place in Pediatric Therapy |
|------------------------------|---|------|---------------|--|--|---|
| Schutze et al ⁴² | American Academy of Pediatrics (AAP) | 2013 | USA | Pediatrics only | N/A | Criteria for optimal use in pediatrics is unknown |
| Diorio et al ²³ | American Society of Clinical Oncology | 2018 | International | Pediatric hematology/ oncology and HSCT patients | N/A | Consider in the setting of recurrent CDI |
| Van Prehn ⁴³ | European Society of Clinical Microbiology and Infectious Disease: | 2021 | Europe | Adults | Recommended for initial and first recurrence when available and feasible | N/A |
| McDonald et al ²⁴ | IDSA/SHEA | 2018 | USA | Adults and pediatrics | Recommended for initial episode (non-severe, severe) and first or subsequent recurrences but not fulminant CDI | Not recommended for routine use as not FDA approved at the time of guideline publication |
| Wu et al ⁴⁴ | Infectious Diseases Society of Taiwan (IDST) | 2020 | Taiwan | Adults and pediatrics | Suggested for initial episode (non-severe, severe) and first or subsequent recurrences but not fulminant CDI Suggests an extended regimen for patients with first recurrence who are high risk for subsequent recurrence or second and subsequent recurrences | Not recommended for routine use as not approved by FDA in Taiwan at time of publication |
| Nana et al ⁴⁵ | South African Society of Clinical Microbiology | 2020 | South Africa | Adults and pediatrics | Recommended for initial episode (non-severe, severe) first or subsequent recurrences but not fulminant CDI | Not currently recommended, although preliminary data are encouraging. Seek subspecialist input in exceptional cases |
| Langer et al ⁴⁶ | Gemeinsamer Bundesausschuss, Federal Joint Committee of Germany | 2020 | Germany | Pediatrics only | N/A | Additional benefit is not proven for treatment of mild CDI, there is a hint for considerable additional benefit for severe and/or recurrent CDI |
| Johnson et al ¹⁴ | IDSA/SHEA | 2021 | USA | Adult focused update | Preferred over vancomycin for initial episode (non-severe, severe) and first CDI recurrence Recommended for second or subsequent recurrences but not fulminant CDI | N/A |

(Continued)

Table 2 (Continued).

| Reference | Society Endorsement | Year | Country | Population | Fidaxomicin Place in Adult Therapy | Fidaxomicin Place in Pediatric Therapy |
|---------------------------|--|------|---------|-------------|---|--|
| Kelly et al ²⁵ | American College of Gastroenterology (ACG) | 2021 | USA | Adults only | Recommended for initial episode (non-severe, severe) and first recurrence but not fulminant CDI | N/A |

Abbreviations: HSCT, Hematopoietic stem cell transplant; CDI, *Clostridioides difficile* infection; IDSA, Infectious Disease Society of America; SHEA, Society for Healthcare Epidemiology of America.

fidaxomicin in treatment algorithms given these were published prior to pediatric FDA approval of fidaxomicin and availability of SUNSHINE Trial results. Despite not including fidaxomicin in pediatric recommendations, many create a discussion around the off-label use of fidaxomicin and the encouraging preliminary data to support its use in pediatrics. One of the stronger recommendations for fidaxomicin in pediatrics came from a clinical practice guideline from an international panel of pediatric experts who say to consider fidaxomicin for pediatric hematology/oncology and HSCT patients in the setting of recurrent CDI.²³ The 2017 IDSA/SHEA and ACG 2021 guidelines do not address fidaxomicin's place in pediatric CDI.^{24,25} However, for adults, the IDSA/SHEA 2021 clinical practice guidelines focused update favor earlier use of fidaxomicin (conditional recommendation, moderate certainty of evidence).¹⁴

Discussion

While *C. difficile* is susceptible to many antibiotics,^{26,27} many individuals develop recurrent CDI (rCDI).²⁸ In this case, following antibiotic treatment of CDI, patients have recurrence of symptoms and *C. difficile* toxin production. The pathogenesis of rCDI is mediated by ongoing dysbiosis and failure of the hosts microbiota diversity of and function to return.²⁹ As dysbiosis is an essential component of CDI, the presence of *C. difficile* alone is insufficient for diagnosis. Clinicians must astutely be aware of other causes of pediatric diarrhea with *C. difficile* colonization.³⁰ When treating CDI, providers should also consider the underlying dysbiosis that predisposes to CDI. This may be more important in children. In pediatric and adult populations dysbiosis is associated with many chronic diseases. It is possible that recurrent antibiotic burden in early life and subsequent dysbiosis increases the risks of chronic diseases later in life such as inflammatory bowel disease,³¹ celiac disease,³² and psychiatric disorders.³³ While (FMT) is an extremely effective way to break the cycle of rCDI in adult populations,³⁴ the long-term effects are unknown, particularly for pediatric patients. Early studies suggest good efficacy for FMT in pediatric rCDI.³⁵ Despite this, many questions about the long-term effects of FMT in pediatric populations remain unknown and there continues to be a need for safe and effective antibiotics for pediatric CDI.

Our structured review highlights the data for use of fidaxomicin in pediatric CDI. Mechanistically, its narrow spectrum leads to less post antibiotic dysbiosis.⁸ This is appealing given the potential concerns of dysbiosis in pediatric populations.³⁶ High-quality evidence from the SUNSHINE indicate that fidaxomicin efficacy parallels the adult population.¹⁶ Specifically, similar cure rates, but lower recurrence rates with fidaxomicin compared to vancomycin. Importantly, the safety profile of fidaxomicin in a pediatric population was favorable. Given the narrow spectrum, minimal absorption, safety profile, and efficacy, fidaxomicin is an extremely appealing option for pediatric CDI.

The main limitation of widespread fidaxomicin use is similar to that in adults: cost and subsequent insurance coverage. The antibiotic is only useful if it is attainable in real-time for a patient with active CDI. While expensive, in the adult population, early fidaxomicin use is cost-effective.³⁷ For non-severe CDI, fidaxomicin is the cost-effective option for index CDI, when combined in a strategy with early FMT use to manage CDI.³⁷⁻⁴¹ Fidaxomicin incurs a higher initial cost for CDI, but the decreased rates of rCDI (and subsequent morbidity and mortality) offset those costs. It is reasonable to assume these trade-offs would be similar, if not greater, in pediatric populations.

No antibiotic is without tradeoffs, and there are limitations to fidaxomicin use. First, as noted, is the cost. No resource is unlimited, and cost does need to be considered in the use for pediatric CDI. Rather than be a universal first-line agent,

it may best be suited to those with a severe CDI, an increased risk of recurrence, or those who might experience significant morbidity with recurrence.³⁰ Regarding severe CDI, there is a knowledge gap with the optimal treatment. In adults, the 2018 ISDA/SHEA guidelines favor vancomycin for severe CDI,²⁴ although the IDSA/SHEA 2021 focused update notes that severe CDI is a risk factor for rCDI and thus fidaxomicin may have a benefit in preventing recurrence.¹⁴ Although pediatric patients with severe CDI were included in a phase 2a trial with fidaxomicin, efficacy based on severity was not reported.^{15,30} Ultimately, prospective randomized trials are needed in specific subpopulations to guide treatment decisions. Additionally, specific pediatric cost-effectiveness models would be useful to balance the cost-benefit trade-offs for initial and subsequent CDI therapy.

As fidaxomicin is minimally absorbed, its safety profile is overall excellent. However, all medications have side effects and allergic reactions or drug-induced liver injury can occur. While fidaxomicin is narrow spectrum, it does lead to some alterations of the intestinal microbiota and decreased diversity. Newer antibiotics selective only for *C difficile* may have no effect on the commensal microbiota and eventually supplant fidaxomicin. In the adult population, there are clinical trials of extended fidaxomicin regimens. While there are no controlled pediatric data on this practice, it likely would have a similar effect to adults. However, this again brings into consideration costs of care. For those with multiple rCDI, the pros and cons of extended fidaxomicin courses need to be balanced with FMT and other newer therapies such as bezlotoxumab, which has completed recruitment for a pediatric specific CDI clinical trial (NCT03182907).

Conclusion

Fidaxomicin is safe and effective for pediatric CDI. From a purely mechanistic point of view, its minimal absorption and preservation of commensal microbiota make it an ideal first-line candidate for treating pediatric CDI. In practice, however, cost limits its use. In pediatric patient with a low risk of recurrence, the cost of fidaxomicin may not outweigh a small decrease in subsequent CDI episodes. Currently, there is one randomized controlled study for fidaxomicin in pediatric CDI. Ideally, other controlled studies, or decision-based models, could help determine specific populations that may preferentially benefit from fidaxomicin use earlier on. However, the overall theme of pediatric fidaxomicin is similar to adults, similar cure rates to oral vancomycin, with lower rCDI rates. Fidaxomicin should be considered for all pediatric CDI, with providers individualizing the benefit of lower recurrence against the higher initial cost.

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