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Clostridioides difficile Infection in Children—An Update

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Clostridioides difficile infection (CDI) remains a relevant healthcare-associated infectious disease that poses a significant burden on both pediatric and adult patients, especially in those with underlying comorbidities. In recent years, the evolution of insights into the disease led to substantial modifications in its diagnostic and therapeutic management. The latest elaborated consensus guidelines addressing specific pediatric aspects were released in 2018 by the American Academy of Pediatrics, the Infectious Disease Society of America, and the Society for Healthcare Epidemiology of America.[1] In the 2021 updates for adult patients, recommendations both in the United States and Europe received relevant revisions.[2,3] For children, however, the necessary reassessment is still pending with specific pediatric research lacking and many suggestions being extrapolated from studies in adult patients.[1] The following article summarizes up to date information and provides a practical approach for managing pediatric *C. difficile* infection (pCDI).

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EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Infections with the anaerobic, toxin-producing bacterium *C. difficile* are responsible for most cases of antibiotic-associated diarrhea.[4] In children, community acquired (CA-CDI) and hospital-acquired CDI (HA-CDI) have been delineated as quite distinct entities in recent years with different courses and outcomes.[5] Especially the incidence of CA-CDI in general is increasing whereas the severity of pCDI has remained fairly stable. The hypervirulent ribotype 027 (BI/NAP1) has not been demonstrated to be significant in children yet.[6] As an immunological peculiarity, infants are far more frequently colonized with both toxigenic and nontoxigenic *C. difficile* than older children and adults. The published colonization rates range from up to 80% in newborns to 40% to 60% under 1 month of age, 30% in children under 6 months, and 14% between 6 and 12 months of age.[7,8] The underlying mechanisms for this phenomenon are still poorly understood. A recent prospective case-control study demonstrated that colonization with *C. difficile* in infants is associated with a humoral immune response against toxins A and B, whereas another common theory explains asymptomatic cases lacking specific toxin receptors.[9,10]

DIAGNOSIS—WHEN, WHO AND HOW TO TEST?

The current Infectious Disease Society of America guideline for adults recommends testing in cases of new or not otherwise explained diarrhea occurring more than 3 times in 24 hours, an approach that can reasonably be adapted for pediatric patients as well.[1] With the high prevalence of asymptomatic *C. difficile* colonization in infants up to 2 years and the minimal probability of a clinically active pCDI in mind, testing of patients younger than 12 months should be reserved for cases with relevant intestinal comorbidity, mainly a colitis of other origin such as very early onset inflammatory bowel disease (VEO-IBD), Hirschsprung-associated enterocolitis, cow's milk protein induced colitis, or primary immunodeficiency.[1] Children between 1 and 2 years should primarily be screened for more likely differential diagnoses, intestinal comorbidity, and other relevant risk factors before being tested for *C. difficile*. All such cases should be discussed with a pediatric gastroenterologist and infectious disease specialist.

For children older than 2 years, *C. difficile* testing is recommended for patients with prolonged or worsening

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TABLE 1. Suggested therapeutic algorithm

	First-line treatment	Alternative option
First diagnosis of nonsevere pCDI	Vancomycin p.o.	Metronidazole p.o.
First diagnosis of severe pCDI	Vancomycin p.o.	Fidaxomicin p.o.
Recurrent pCDI	Vancomycin p.o. (prolonged and tapered) OR Fidaxomicin p.o.	+ Metronidazole i.v., FMT, consult specialist + pediatric surgeon

FMT indicates fecal microbiota transplantation; pCDI, pediatric *C. difficile* infection.

diarrhea, especially if combined with risk factors or relevant exposures.[1] Given the high rate of asymptomatic carriage and a high probability of diarrhea due to other infectious agents in children, laboratory testing should primarily be focused on other gastrointestinal pathogens.[11] As the detection of toxigenic *C. difficile* may simply reflect colonization rather than infection, all fecal samples positive in the screening should subsequently be tested for *C. difficile* free toxins A and B being more indicative of a present infection.[11] The current practice guidelines suggest a multistep algorithm for laboratory testing consisting of an initial enzyme immunoassay screening for glutamate dehydrogenase, followed by an enzyme-linked immunoassay for toxins A and B if positive. If these tests are discordant, an additional nucleic acid amplification test is recommended.[1] A diagnostic algorithm for pCDI is illustrated in Figure 1.

RISK FACTORS

Although antibiotic exposure is known to be the most important risk factor for CDI a recent large study of 1331 children with CA-CDI and 3993 controls demonstrated that preceding antibiotic exposure was absent in more than 40% of the patients.[12]

Regarding the exposure to proton pump inhibitors (PPI), a recent meta-analysis identified four studies that reported an increased risk of pCDI associated with the use of PPI.[13] Apart from being a risk factor for the development of pCDI *per se*, the use of PPI was also associated with a more severe course of the disease.[14] As the odds of developing CA-CDI were found to be similar for antibiotics and PPI,[12] a judicious use of both antibiotics and PPI in pediatric patients seems to be prudent. In particular, the application of multiple antibiotics should be viewed with caution, as the development of severe pCDI is associated with exposure to three different classes of antibiotics within 30 days prior to infection.[15]

A further risk factor for pCDI is predisposing comorbidity. In a study investigating the risk factors for pCDI in young children aged 1 to 5 years, a significantly higher number of cases than controls had underlying chronic comorbidities (33.3% vs. 12.1%) such as solid organ transplant, malignancy, neurological illness, or other gastrointestinal diseases.[16]

THERAPY

In the first step of the pCDI treatment, the inciting agent is discontinued. Further treatment is initiated only in symptomatic infections after proper evaluation of the plausibility of *C. difficile* contribution.[1] In adults, the latest guideline updates changed the recommended antibiotic regime—oral metronidazole (p.o.) is no longer included in the therapeutic algorithm while vancomycin p.o. and fidaxomicin p.o. are recommended as first-line agents for the treatment of an initial episode of CDI. For children, though, metronidazole is still part of the recommended first-line treatment (although the strength of the 2018 recommendation is weak and the quality of evidence is low). We assume that the guidelines for children may change in the near future. Recent publications have demonstrated good therapeutic outcomes and only a few side effects for fidaxomicin in children[17,18] as well as significantly less treatment failures of vancomycin compared with metronidazole in pCDI.[19] For nonsevere cases of pCDI metronidazole might still be an option because the relatively high cost of vancomycin or antimicrobial resistance aspects may be a potential limitation for specific patients and healthcare systems.

So should it be fidaxomicin or vancomycin in the initial episode of pCDI? A phase 3 multicenter, randomized, single-blind study (SUNSHINE) addressed this aspect in 142 pediatric patients. The authors demonstrated that fidaxomicin was well tolerated and led to significantly higher global cure rates compared with vancomycin (68.4% vs. 50.0%).[18] Another multicenter clinical trial including 40 children with gastrointestinal disorders or malignancy and CDI demonstrated that fidaxomicin was well tolerated and had a high clinical response rate as seen in adults.[17] Accordingly, fidaxomicin may replace the formerly used antibiotics for the treatment of symptomatic pCDI in the future. However, as the cost is considerably high, pediatric data are scarce and experience is still lacking, we pragmatically suggest using fidaxomicin in cases of recurrent CDI. (Table 1.)

Another alternative therapeutic option that should be reserved for the treatment of multiple recurrent pCDI is fecal microbiota

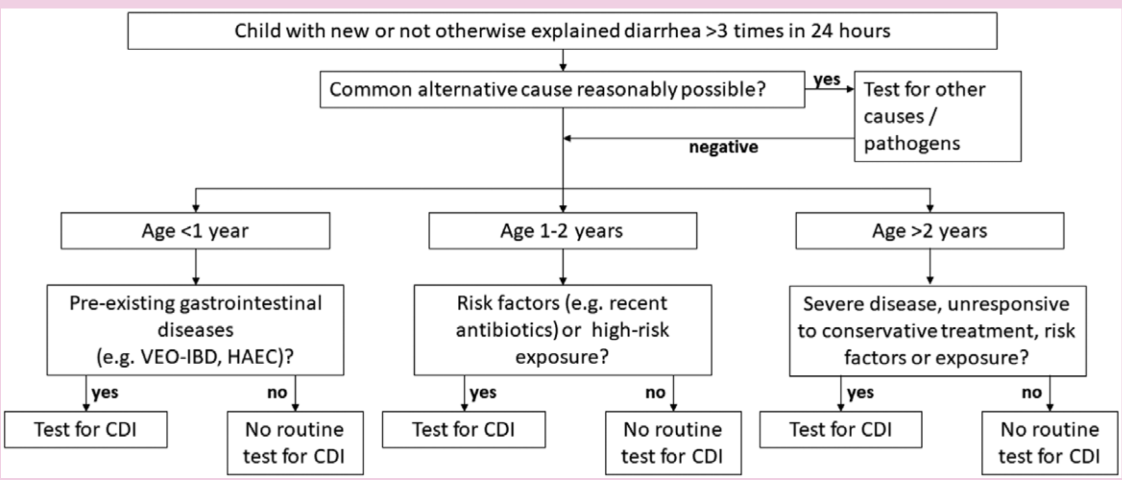

FIGURE 1. Diagnostic algorithm for pediatric CDI. No standard test for cure after treatment.

transplantation (FMT). A large retrospective multicenter study that included 335 children with recurrent CDI observed a cure rate of over 80% using a single FMT.[20] As the evidence for FMT in children is still exiguous, long-term outcomes after manipulation of the intestinal microbiome are not yet available, and safety alerts regarding FMT issued in the last years, the decision should be well balanced and the procedure ideally performed in specialized tertiary centers with multidisciplinary panels of experts involved. Other alternative therapeutic options for pCDI, such as toxin-binding agents, intravenous immunoglobulins, rifaximin, nitazoxanide, or probiotics, have not been sufficiently studied in detail in children. The same holds true for interesting new pharmacological options such as bezlotoxumab, a human monoclonal antibody neutralizing toxin B approved by the FDA for adult comedication and currently being tested in a phase 3 trial in children.[1,21]

CONCLUSION

Clostridioides difficile infections, especially those acquired in the community, are increasing in both children and adults and cause a high disease burden.

The diagnosis of CDI in children remains challenging because of the high rate of asymptomatic colonization, especially in toddlers, as well as the high incidence of coinfections. A systematic diagnostic approach, based on the age of the child as well as on risk factors and pre-existing diseases, should facilitate decision making on when, who, and how to test. Until now, vancomycin or metronidazole has remained the first-line medication in children because of scientific evidence, clinical experience, and costs, but it can be expected that guidelines for children will be adapted in the near future. Further studies focusing on pediatric patients are needed to define a standard medical treatment for children with CDI, as recent studies have confirmed the safety and efficacy of vancomycin and fidaxomicin in children. For multiple recurrent pCDI, FMT can be an effective alternative treatment option.

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