Clostridium difficile infection in pediatric patients (Review)

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Abstract. *Clostridium difficile (C. difficile)* infection (CDI) is the most common cause of healthcare-associated diarrhea and among adults, the worldwide incidence rate of the infection is increasing. There is a small amount of data in the literature for pediatric patients, but most indicate an increasing trend. *C. difficile* is a constituent of the normal microbiota; however, under specific conditions that cause a disruption of the normal bacterial flora, colonization of *C. difficile* and the released toxins that cause inflammation and mucosal damage occurs. Risk factors for CDI at any age include hospitalization, exposure to antibiotics, administration of proton pump inhibitors, invasive mechanical ventilation, immunosuppression and presence of associated comorbidities. Clinical manifestations range from asymptomatic colonization to fulminant disease characterized by toxic megacolon, intestinal perforation and, rarely, death. The aim of the present review was to outline the features of CDI in pediatric patients.

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1. Introduction

Clostridium difficile (*C. difficile)* is a Gram-positive, anaerobic, toxin-producing germ first isolated from the stool of healthy newborns in 1935 (1). It is the most common cause of antimicrobial therapy-associated diarrhea and is a common healthcare-associated pathogen (2). In recent years, there has been an increase in the incidence of community-acquired infection in subjects without known risk factors (3,4), such as previous exposure to antibiotics, patients with chronic gastrointestinal pathology or inflammatory bowel disease (IBD).

C. difficile may be considered a constituent of the normal microbiota, but under specific conditions that disrupt the normal intestinal microbiota, it colonizes the large intestine causing, through the action of its toxins, varying degrees of colonic damage, ranging from mild diarrhea to toxic megacolon (5).

In recent years, there have been substantial changes in its diagnostic and therapeutic management (6). However, there is a lack of research on *C. difficile* infection (CDI) in children, with much of the data being extrapolated from studies of adult patients (7).

The aim of the present review was to provide the pediatrician with up-to-date information and recommendations on CDI in pediatric patients.

2. Materials and methods

The Cochrane (https://www.cochrane.org/), MEDLINE (https://www.nlm.nih.gov/) and EMBASE (https://www.embase.com/) databases were explored from January 2000 to September 2023, using the terms '*Clostridium difficile* neonates', 'Child, pediatric, *Clostridium difficile*'; a total of 112 studies containing relevant data were selected and checked. Studies were excluded if they were not published in English or French, if the pediatric population was not treated separately from the adult population or if the study did not contain original data (Fig. 1). Studies that included adult groups were also selected for the pathogenesis and epidemiology chapter.

3. Epidemiology

C. difficile is a Gram-positive anaerobic bacterium that can exist in both toxigenic and non-toxigenic form (8). It is widespread in the natural environment, in human and animal feces and is part of the normal intestinal flora with the mode of transmission being fecal-oral or by direct contact (9).

The epidemiology of *C. difficile* in children is relatively unknown due to limited surveillance. Zilberberg *et al* (10) reported that the annual rate of pediatric hospitalization with CDI in the United States increased from 7.24 to 12.8/10,000 hospitalizations between 1997 and 2006. Another multicenter study of 22 pediatric hospitals in the United States found that the annual incidence of *C. difficile*-associated disease in hospitalized children nearly doubled over a five-year period (from 26 to 40 per 10,000 hospitalizations between 2001 and 2006) (11).

A study conducted between 2003 and 2012 revealed an increase from 24 to 58 per 10,000 discharges per year in all age groups, with the largest increases observed in patients >15 years of age (12). Most importantly, an increase in the incidence of CDI is observed in generally healthy children with no risk factors, such as recent exposure to antimicrobial drugs or repeated hospitalizations (1,13).

In Italy, a 5-year study (2014-2018) showed an increase from 0.75 to 9.80 per 1,000 hospitalizations of patients with community-acquired CDI (2).

A recent study including 23,052 children with *C. difficile* in the United States identified a decrease in hospitalized children, from 7.09 cases per 10,000 patients in 2013 to 4.89 cases per 10,000 patients in 2019. This decreasing trend is secondary to a decrease in antibiotic prescribing in both community and hospital settings, effective sterilization protocols, disease prevention policies, decreased specific testing for *C. difficile*, changing diagnostic algorithms over the past 10 years and increased recognition of *C. difficile* colonization, especially in children <1 year of age (14).

Asymptomatic *C. difficile* colonization is frequent in early childhood; the carrier rate is reported to be 1 to 84% in healthy newborns and infants (15), but it decreases to less than 5% by 8 years of age (6). The most likely source in infants is environmental contamination rather than maternal-fetal contamination (vaginal birth, premature rupture of membranes and prior administration of antimicrobial agents) and is favored by artificial feeding, gut immaturity and lack of protective gut microbiota (1,9). The gut of the newborn is sterile, but by 12 months of age, the gut of the infant has a flora similar to that of an adult (16).

Although infants have high carrier rates, they rarely develop clinical infection due to immunoglobulin fractions in breast milk that inhibit the binding of toxin A to its intestinal receptor, the absence in the newborn intestine of the intestinal receptor that binds to toxin A of *C. difficile* because of the immaturity of the intestinal mucosa and the nature and composition of the infant gut microflora that protects against *C. difficile* overgrowth (6,17).

Although infant testing is not recommended, recent data revealed that 26% of children hospitalized with CDI were infants younger than 1-year-old and 5% were newborns. What cannot be determined from this data is whether hospitalization rates for CDI represent true disease or asymptomatic carriers (18).

According to most studies, the incidence of CDI in children is increasing even in the community setting, similar to adult cases, but the severity of cases has not increased (6,19). This is due to a low percentage of cases with virulent North American pulsed field type 1 (NAP1) strains in children, 19.4% compared with >50% of cases in adults (20). This strain is characterized by deletions of the *tcdC* gene, resistance to fluoroquinolones, production of *C. difficile* transferase (CDT) or binary toxin, intensive spore production and increased production of toxins A and B (1,21). The detection of the NAP1 strain of *C. difficile* is not possible in most laboratories and, in most situations, it would not influence the clinical care of a patient (16). Further studies are needed to determine the role of the NAP1 strain in severe forms of *C. difficile* infection in the pediatric population.

4. Risk factors

Recognized risk factors for older children that acquire *C. difficile* have included the use of antibiotics and proton pump inhibitors (PPIs) for prolonged periods, immunosuppressive treatments, repeated enemas, the use of diapers, prolonged nasogastric tube insertion, gastrointestinal tract surgery, renal failure, the presence of IBD and impaired humoral immunity (1,6,22).

A previous study of pediatric *C. difficile* cases reported as risk factors the antibiotic treatment in 92% of children, the immunosuppressive treatment in 60%, a malignancy or organ transplant in 39%, while 13% had IBD (23). Among the antibiotics, the most commonly associated with increased risk of *C. difficile* infection are the combinations of antibiotics, cephalosporins, fluoroquinolones, penicillins, carbapenems and cotrimoxazole (14).

While a study conducted in 2020 found that clindamycin is associated with higher odds of community-acquired CDI in pediatrics [odds ratio (OR), 14.9; 95% confidence interval (CI), 5.2-42.3], followed by amoxicillin-clavulanate (OR, 2.2; 95% CI, 1.2-3.9) and cephalosporin (OR, 2; 95% CI, 1.1-3.6) (22), a different study reported an association between community-acquired CDI and cephalosporins (OR, 1.95; 95% CI, 0.68-4.95; P=0.16), exposure to clindamycin (OR, 2.70; 95% CI, 0.70-10.39; P=0.15) and the presence of a gastrointestinal feeding device (OR, 2.27; 95% CI, 0.92-5.60; P=0.08) (24), while a study conducted by Adams *et al* (25) reported an association between community-acquired CDI and clindamycin (OR, 73.00; 95% CI, 13.85-384.68) and third-generation cephalosporins (OR, 16.32; 95% CI, 9.11-29.26).

Chemotherapy is associated with an increased risk of CDI, possibly due to the antimicrobial properties of chemotherapeutic agents, the effects of immunosuppression and neutropenia, and changes in intestinal mucosa (26). Hypogammaglobulinemia is also associated with an increased risk of CDI.

While a number of studies suggest that drugs that suppress gastric acidity, particularly PPIs (27), cause the alteration of the gut microbiota, allowing pathogens including *C. difficile* to increase, in a previous pediatric study the H2 receptor antagonists have actually been associated with decreased colonization by *C. difficile* (28).

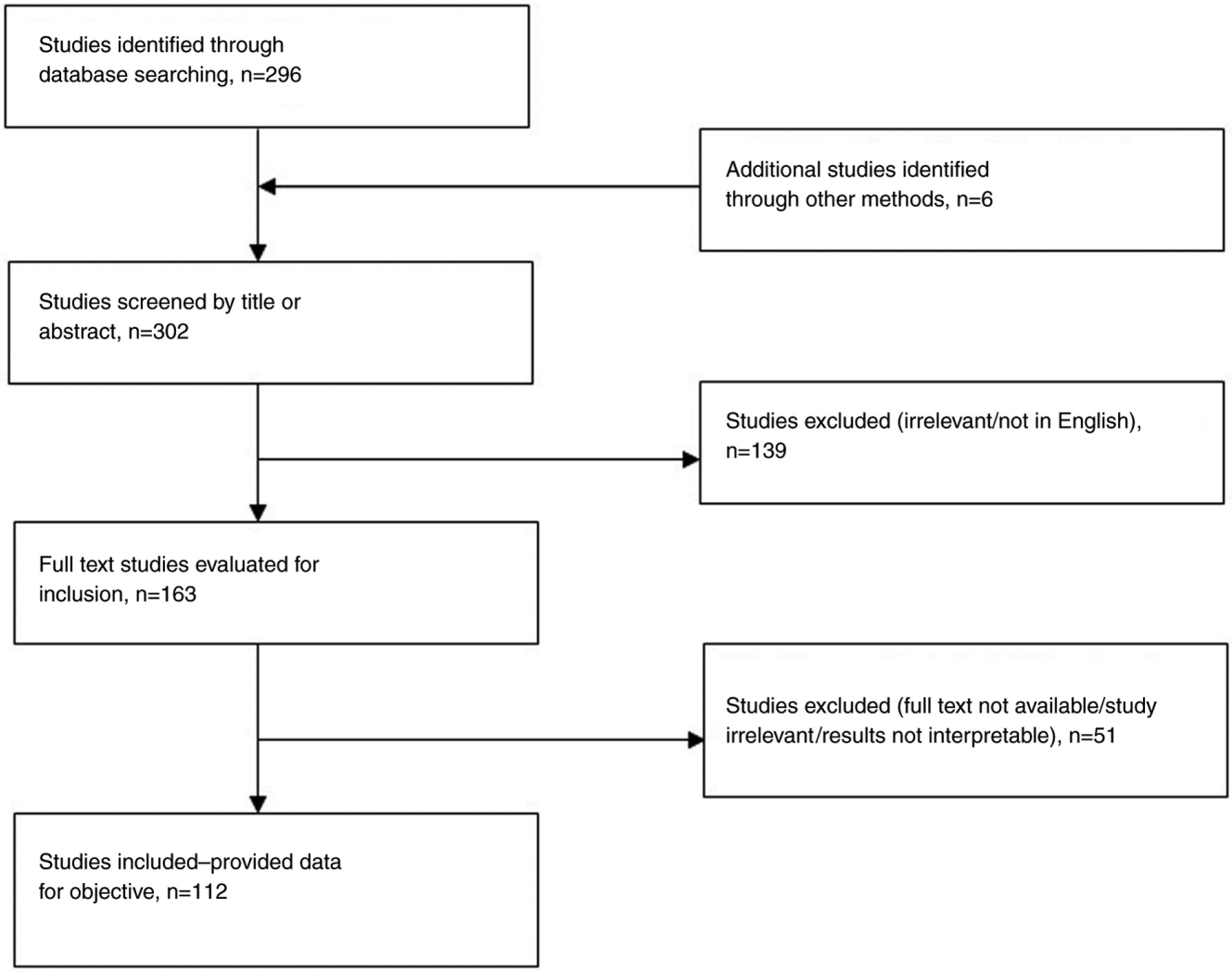

Figure 1. Study selection.

The presence of frequent and prolonged hospitalizations among children with *C. difficile* is highlighted by numerous studies; this is due to the exposure to an environmental reservoir of *C. difficile*, with the possible transmission of this pathogen, and is indirectly associated with other risk factors such as the use of antibiotics and PPIs (1).

Inflammation of the intestinal epithelium secondary to viral gastroenteritis (noroviruses and caliciviruses), may facilitate adhesion and colonization by *C. difficile* and the occurrence of infection (1).

Comorbidities (especially chronic gastrointestinal and neurological diseases) are associated with CDI, due to the numerous associated risk factors that trigger disturbances of the gut microbiota such as: i) Prolonged hospitalization, ii) the use of antibiotics or PPIs and iii) immunosuppression (1,29). Thus, according to studies, IBD (OR, 3.72; 95% CI, 1.52-9.12), renal failure (OR, 2.64; 95% CI, 1.23-5.68), hematologic cancer (OR, 1.75; 95% CI, 1.02-5.68) and diabetes mellitus (OR, 1.15; 95% CI, 1.05-1.27) were associated with CDI (30). A study conducted in 2018 demonstrated that other conditions identified as risk factors for CDI included coagulopathy (OR, 3.07; 95% CI, 1.34-7.06), pneumonia (OR, 2.37; 95% CI, 1.73-3.25), female pelvic infection (OR, 2.01; 95% CI 1.21-3.37), IBD (OR, 1.96; 95% CI, 1.36-2.81), irritable bowel syndrome (OR, 1.66; 95% CI, 1.23-2.24), iron deficiency anemia (OR, 1.55; 95% CI, 1.02-2.33), viral infections (OR, 1.51; 95% CI, 1.06-2.15), depression (OR, 1.45; 95% CI, 1.06-1.98) and stroke (OR 1.43, 95% CI 1.00-2.03) (31).

5. Pathogenesis

The incubation period from exposure to onset of symptomatic CDI (CSI) is two to three days. The reservoir for *C. difficile* spores is represented by toilets, furniture in the clinic, telephones and medical devices (thermometers, stethoscopes).

Important pathophysiological characteristics of *C. difficile* include the resistance to heat of the spore (which allows its persistence in the environment for several months), the resistance to acids, antibiotics and the production of toxins (28).

Once in the gut, bile acids play an important role in inducing the germination of *C. difficile* spores (1). Colonization does not necessarily mean symptomatic infection, only 25-30% of asymptomatic colonized patients develop diarrhea (32).

The microbial intestinal ecosystem, rich in the anaerobic *Bacteroides* and *Firmicutes* species, plays an important role

in the regulation of host physiology, especially in the defense against pathogens, in the stimulation of angiogenesis or in the nutrition process (1).

C. difficile begins to dominate and colonize the large intestine when the balance of intestinal microorganisms is disturbed, which is the first step of infection.

C. difficile is not invasive, virulence is due mainly to enzymes such as collagenase, hyaluronidase, chondroitin sulfatase, as well as toxins A and B, which damage the cytoskeleton of epithelial cells, leading to disruption of tight junctions and loss of mucosal functionality (32). Toxin A (enterotoxin) can disrupt neuronal function and cause aberrant calcium release (33). Toxin B (cytotoxin) exerts its effect on white blood cells by altering neutrophil chemotaxis and activating mast cells and macrophages, which leads to the release of inflammatory mediators (26,33). There is also a third toxin, CDT, a binary toxin that is produced by certain *C. difficile* strains, including the PCR027 ribotypes, which theoretically could have clinical impact, however its role is unclear. The end result of toxin activity in the gut is fluid secretion, mucosal damage and interstitial inflammation (1).

In more severe forms, microulcerations covered with pseudo-membranes (composed of destroyed intestinal cells, neutrophils and fibrin) begin to appear on the surface of the intestinal mucosa (32).

6. Clinical picture

A case definition of CDI includes the presence of symptoms (usually watery diarrhea) and either one stool test result that is positive for *C. difficile* toxin or colonoscopy findings demonstrating pseudomembranous colitis.

The clinical picture of CDI is very heterogeneous and ranges from asymptomatic carrier state, mild or moderate diarrhea, to fulminant life-threatening colitis (34). Although the incubation period is not precisely defined, recent studies revealed that it is longer than 3 days and is highly dependent on the individual.

The symptomatic illness can be mild, moderate or severe. The mild and moderate form is usually characterized by watery diarrhea (<4 stools/day in the mild form and more in the moderate form), low-grade fever and mild abdominal pain, without phenomena of systemic toxicity. Other clinical manifestations include nausea, weakness and loss of appetite. Fecal occult blood testing is often positive, although active bleeding is rarely present (32). The severe form involves high fever, intense abdominal pain, abdominal distension, vomiting food, numerous watery stools with mucus and blood leading to significant dehydration, hypoalbuminemia with peripheral edema and subsequent circulatory shock (32).

Other severe complications of CDI include toxic megacolon, intestinal paralysis, small bowel infiltration, colonic perforation, reactive arthritis, renal failure, systemic inflammatory response syndrome, sepsis and death (35).

Complications are more likely to occur among children with hematological malignancies or those treated with hematopoietic stem cell transplantation, infants with Hirschsprung's disease or patients with IBD (1).

The mortality rate due directly to CDI is estimated at 5%, while mortality associated with complications reaches 15-25% and up to 34% in intensive care units (32).

7. Diagnostic tests

The diagnosis of CDI is based on the association between medical history, clinical presence of >3 semi-consistent stools/24 h or bloody stools and laboratory tests (9). Because of the slow turnaround time, isolation of the organism from stool is not a clinically useful diagnostic test, nor is stool testing of asymptomatic patients.

Cell culture cytotoxicity neutralization assay (CCCA) has been replaced by more sensitive diagnostics, the most common test method used today for *C. difficile* toxins is the enzyme immunoassay (EIA), which detects toxins A and/or B. It is preferred due to the rapid turnaround time, the ease of testing and the high specificity (1).

Detection of glutamine dehydrogenase, an antigen present on *C. difficile*, although very sensitive, only indicates the presence of the pathogen. It should only be used as part of a 2-step algorithm, with confirmation of positive results using either an EIA for toxin A/B or a CCCA.

Molecular tests using nucleic acid amplification tests (NAATs) are now preferred by numerous laboratories because they have high sensitivity and specificity, comparable turnaround times to EIA and do not need to be part of a 2- or 3-step algorithm (14). In a previous study, the sensitivities of PCR tests with high sensitivity and specificity for toxins A and B compared with the EIA test were higher (95 vs. 35%, respectively), and the specificity was equal to 100% (36). Using PCR tests, positivity rates for stool samples doubled, from 7.9 to 8.3% with EIA and from 14.9 to 18.1% with PCR (9).

Stool testing in newborns and infants <1 year of age is not recommended except in the presence of risk factors such as Hirschsprung-associated enterocolitis or primary immunodeficiency, surgery on the gastrointestinal tract or the presence of an infectious outbreak; the presence of *C. difficile* is considered colonization (1). In children aged 1 to 2 years presenting with diarrhea, testing for *C. difficile* may be considered after testing for other causes of diarrhea, especially viral infection. In children >2 years of age, testing is similar to adult testing and is recommended for patients with prolonged or worsening diarrhea, especially if combined with relevant risk factors or exposures.

The presence of pseudo-membranes and hyperemic, friable rectal mucosa on colonoscopy suggests pseudomembranous colitis and establishes the diagnosis of CDI, regardless of the age of the child (1,14).

Since C. difficile toxin excretion lasts up to 4 weeks after healing, it is recommended that testing for possible relapse has to be conducted later than 4 weeks after therapy, using the more sensitive NAAT test (9).

8. Treatment

The treatment of CDI in children is based on clinical data from adults and is determined by the number and severity of episodes (37). The therapeutic recommendations in CDI are

Table I. Summary of therapies for children with *Clostridium difficile* infection.

Initial episode	
Mild to moderate infection	Oral metronidazole (7,5 mg/kg per dose-up to 500 mg qid) for 10 to 14 days Or Oral vancomycin (10 mg/kg per dose-up to 125 mg qid) for 10 days
Severe infection	Oral vancomycin (10 mg/kg per dose-up to 500 mg qid) for 10 days ± Iv metronidazole (10 mg/kg per dose-up to 500 mg tid) for 10 days (if ileus, toxic megacolon, shock is present)
Recurrence	
First recurrence	Oral metronidazole (7,5 mg/kg per dose-up to 500 mg qid) for 10 to 14 days Or Oral vancomycin (10 mg/kg per dose-up to 125 mg qid) for 10 days
Second recurrence	Oral vancomycin (10 mg/kg per dose-up to 125 mg qid) for 10 days (if not used previously) Or Tapered or pulsed regimens of vancomycin: Vancomycin 10 mg/kg per dose qid (max 125 mg) for 10 days, followed by vancomycin 10 mg/kg per dose bid (max 125 mg) for 7 days followed by vancomycin 10 mg/kg per dose once daily (max 125 mg) for 7 days followed by vancomycin 10 mg/kg per dose every 2 to 3 days (max 125 mg) for 2 to 8 weeks
Other options for recurrent infection (more than 2 recurrences)	Oral fidaxomicin (16 mg/kg per dose-up to 400 mg bid) for 10 days Fecal microbiota transplantation
Progressive or fulminant colitis	Surgery-colectomy should be considered in such patients

Qid, four times a day; iv, intravenous; tid, three times a day; bid, twice a day.

the following: i) General principles, ii) etiological treatment, iii) surgery, iv) supportive treatment, v) fecal microbiota transplantation, vi) upcoming treatment and vii) prevention.

General principles. It is very important to: Eliminate favoring factors whenever possible (interruption of antibiotics and gastric anti-secretory drugs); eliminate aggravating factors (no administration of antiperistalsis drugs); initiate etiological therapy and adopt measures in order to limit human transmission as quickly as possible after the diagnostic suspicion has been made.

Etiological treatment of the first episode. For children with their first episode of mild to moderate CDI, metronidazole and vancomycin are recommended, while oral vancomycin is preferred over metronidazole for children with a first episode of severe CDI (Table I) (38).

Metronidazole should be administered in a dose of 7,5 mg/kg three times a day orally; indicative duration: 10 days (should not be extended to >14 days because of the increased risk of neurotoxicity) (39); it is no longer effective if the colonic inflammation has improved, therefore it is not administered more than 3-4 days after the remission of symptoms.

Vancomycin should be administered in a dose of 10 mg/kg every 6 h orally, for 10-14 days. In special situations such as toxic megacolon or ileus, it is recommended to increase the doses and administer simultaneously by several routes: Vancomycin 10 mg/kg every 6 h orally, to which vancomycin 10 mg/kg every 6-12 h by therapeutic enema (in 100-500 ml saline) should be added and intravenous metronidazole 10 mg/kg every 8 h for 10 days.

In adults, based on the improved clinical cure rates and lower recurrence risk, fidaxomicin and vancomycin are now recommended as preferred first line therapies (40).

In children, there have recently been studies that indicated an increase in the use of vancomycin to the detriment of metronidazole (41). A study published in 2020, which followed 192 patients with moderate CDI, treated with oral metronidazole or oral vancomycin, concluded that patients treated with vancomycin had a faster resolution of symptoms, while recurrence at 12 weeks was similar in both groups (42).

Fidaxomicin is a registered macrocyclic antibiotic in clinical practice for the treatment of CDI, which achieves very high fecal concentrations with minimal systemic absorption; a previous study revealed that the efficacy of fidaxomicin is similar to vancomycin and it is more active *in vitro* against *C. difficile* strains including NAP1/BI/027 (43). Moreover, it is effective at achieving clinical cure and preventing recurrent infections and it is well tolerated in pediatric patients (44). A multicenter Phase III SUNSHINE study, which investigated the efficacy of fidaxomicin therapy in pediatric patients with CDI, compared with oral vancomycin, concluded that

fidaxomicin is well tolerated and has an improved sustained response rate than vancomycin at 30 days from the end of the treatment (45).

Fidaxomicin is a newly United States FDA approved option for treatment in children >6 months of age and who weigh >4 kg; the weight-based dosing is 16 mg/kg per dose (max 200 mg per dose), orally, twice daily for 10 days, available as tablets and liquid formulations (46). There is no proper treatment for the fulminant forms of *Clostridium* infection, therefore additional studies are needed to improve the prognosis in these forms (47).

Etiological treatment of relapses. For the first relapse, the guidelines recommend the same options and doses as for the initial episode, oral metronidazole or oral vancomycin in children.

Starting with the second relapse, patients may benefit from tapering and pulsed oral vancomycin: 10 mg/kg every 6 h (max 125 mg) for 10 days; subsequently 10 mg/kg every 12 h (max 125 mg) for 7 days; then 10 mg/kg once daily (max 125 mg) for 7 days and finally 10 mg/kg every 2-3 days for 14-56 days (47).

Secondary prophylaxis with oral vancomycin in pediatric patients with a history of CDI, while receiving systemic antibiotics, may reduce the risk of recurrences (48).

Surgery. The criteria for surgical treatment are: Colon perforations; a worsening of the condition of the patient despite adequate drug therapy; toxic megacolon or severe ileus; the occurrence of shock and CDI in the recovery period after a colonic intervention.

The types of surgery are: Total or subtotal colectomy with terminal ileostomy-preferred choice; less aggressive interventions are rarer, in cases where total colectomy is not accepted.

Effectiveness of the interventions: Reducing the risk of death by 2-3 times, from 35-80 to 12-35%, if the intervention takes place early, especially before the colon is severely damaged; lactate <5 mmol/l and the number of white blood cells <50,000/mm^3 (49-50).

Supportive treatment must include hydro-electrolytic rebalancing; correction of hypoproteinemia; prevention of deep thrombosis and correction of organ dysfunctions.

Fecal microbiota transplantation (FMT). FMT is the process of implanting intestinal microbiota, using a special filtration method, from a healthy donor into the gastrointestinal tract of the patient, in order to restore the intestinal flora of the recipient and help to achieve an optimal function of the intestinal system. Delivery methods include gastrostomy, colonoscopy, nasogastric tube, nasoduodenal catheters, retention enema or capsule. FMT has demonstrated great efficacy in the treatment of severe and recurrent CDI in adults (51), but in pediatric patients, the implications of altering the microbiome at such an early age in development raises numerous question marks and requires further research.

In adults, after FMT there have been reports of infectious and non-infectious complications, including the development of flares of IBD, potential metabolic disorders or nutritional deficiencies (51,52).

A multicenter retrospective study that included 335 pediatric and young adult patients (ages ranging from 11 months to 23 years), demonstrated the very favorable efficacy of FMT in the treatment of CDI, with no episodes of recurrence in 81% of the patients (51). Among the independent predictors of FMT success, the use of fresh stool vs. frozen stool, the lack of a feeding tube, delivery by colonoscopy and a lower number of CDI episodes before FMT were identified. A total of 4.7% of the patients had a severe adverse event during the 3-month follow-up period: Aspiration pneumonia, vomiting and dehydration and inflammatory bowel syndrome flare.

FMT has been demonstrated to be relatively safe in immunocompromised adult patients and patients with IBD, but the long-term safety of FMT still needs to be established. Because of that, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, as well as the European Society for Gastroenterology, Hepatology and Nutrition recommend performing FMT in established centers, where long-term side effects can be monitored and which have rigorous donor screening (53).

Probiotics. No published guide recommends the use of probiotics for the prevention or treatment of CDI in children, because of the lack of the evidence (54).

Upcoming treatment. The Clinical Practice Guideline, issued by the Infectious Diseases Society of America, recommends the use of bezlotoxumab in addition to standard of care antibiotics for adult patients with a recurrence of CDI within the past 6 months (40). Bezlotoxumab is an IgG monoclonal antibody against *C. difficile* that binds to toxin B and neutralizes its effects on mammalian cells (55). It is not approved in patients under 18 years of age.

Recently, a multicenter, double-blind, placebo-controlled study (MODIFY III) of bezlotoxumab in 111 children (between 1 and <18 years of age) receiving antibacterial treatment for CDI, showed a safety profile similar to that observed in studies in adults and was generally well tolerated (56).

In adult patients with CDI, there are numerous ongoing studies that follow clinical efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of new molecules including a DNA polymerase inhibitor (ibezapolstat) (57), ridinilazole (58) and a novel topoisomerase inhibitor (59).

Prevention. The transmission of CDI occurs via the fecal-oral route, through contact with the patient or patients in the contaminated environment. Controlling the spread of *C. difficile* into the environment is essential in healthcare facilities.

Washing the hands with soap and water, the use of gloves in symptomatic patients and decontamination using chlorine-based products are measures that prevent the transmission of CDI.

People with *C. difficile*-associated diarrhea should be placed in isolation for the duration of treatment.

Given that exposure to antibiotics is the main risk factor for CDI, programs to reduce inappropriate use of antibiotics in children, especially in outpatient settings, need to be implemented (47).

9. Conclusions

Although the incidence of CDI is not really known, all data in the literature indicated an increase in community cases. Clinicians should be more responsible for recommending outpatient antibiotic therapy.

The diagnosis must take into account both the presence of risk factors and the presence of clinical signs and follow specific diagnostic testing algorithms. Further studies are needed to evaluate different treatment strategies for children with a poor response to classic treatment.

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Availability of data and materials

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Authors' contributions

DD, IRM, VP, DCC, RP, SAN and CEN contributed equally to the acquisition, analysis and systematization of the data, manuscript writing and critical revision for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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