The changing epidemiology and challenges of paediatric *Clostridium difficile* infections

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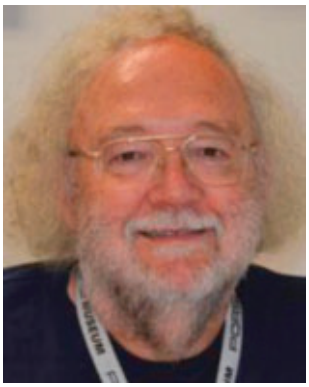

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Clostridium difficile **(recently also named *Clostridioides difficile*)[1] is an anaerobic spore-forming Gram-positive rod, the leading cause of hospital-acquired diarrhoea in high-income countries and a significant cause of community-acquired diarrhoea[2]. Since the first isolation of *C. difficile* as a commensal organism in healthy infants in 1935[3], this ubiquitous pathogen has led a chequered life as a pathogen of children. Despite high rates of *C. difficile* carriage in infants, they rarely develop clinical symptoms of disease. The reasons for this are not fully understood but may be due to a lack of toxin receptors in the gut. Nonetheless, increasing rates of *C. difficile* infection (CDI) in children have been observed in many parts of the world, especially in children without traditional risk factors, as well as a rising incidence of community-acquired CDI (CA-CDI)[4] – this is of concern. This complicated situation is compounded by diagnostic testing issues. Molecular detection methods have been widely implemented in Australia and North America and are more sensitive than toxin enzyme immunoassays (EIAs) or culture[5]. They are often used routinely in paediatric populations with a high prevalence of *C. difficile* such as children with malignancies[5]. Differentiating children who require treatment from those colonised with toxigenic strains remains a challenge for health care providers.**

Antimicrobials with activity against bowel flora including clindamycin, penicillins, cephalosporins and fluoroquinolones are most often associated with CDI[2]. *C. difficile* spores are most frequently acquired through faecal-oral transmission resulting in either asymptomatic colonisation or a spectrum of clinical manifestations (ranging from mild diarrhoea to pseudomembranous colitis, toxic megacolon and death)[2]. Most of the recent changes in the epidemiology of CDI outside Australia have been attributed to the appearance of an epidemic strain of *C. difficile*, RT 027 (which produces toxins A, B and binary toxin), in the early 2000s[5]. National surveillance for CDI in Australia was first introduced in 2010 and, since then, the rates of CDI have increased significantly[4].

Rising rates of *Clostridium difficile* infection in children

As with adults, recent antimicrobial exposure is the most significant risk factor for acquiring CDI in children along with the presence of comorbid conditions that alter the intestinal microbiota, placement of feeding tubes and frequent exposure to health care institutions[6]. Children were not considered to be a population at high risk of CDI, however, increasing hospitalisations for CDI and more severe disease has been observed in this cohort[7], including in the USA in children with haematological malignancies (HM) and inflammatory bowel diseases (IBD)[7]. The rate of CDI varies greatly based on the type of malignancy, and CDI is reported nearly 2.5 times more in patients with HM than those with solid organ tumours[8]. There are many gaps in knowledge of CDI epidemiology among children with HM and haematopoietic stem cell transplantation (HSCT), even though there are numerous studies in adults[9]. The work that has been done in children confirms CDI as an important disease in this particular group of patients[10]. Moreover, outbreaks of CDI in paediatric HM wards have been documented[11]. In Western

Australia more specifically, a case of severe CDI with binary toxin-positive *C. difficile* in a paediatric patient with newly diagnosed IBD was detected several years ago[12]. Recurrences of CDI have been observed in approximately 10–25% of paediatric patients[13], similar to adults. A 5-year retrospective study from Italy reported a substantial increase from 0.75/1000 hospitalisations to 9.8/1000 hospitalisations in the incidence of CA-CDI among children presenting with diarrhoea[14]. A case control study conducted in US reported an increased risk of CA-CDI in children within the first 30 days of antimicrobial exposure (cephalosporins specifically)[15], while a more recent US case control study identified an association of recent exposure to a household member with diarrhoeal illness with paediatric CA-CDI, hinting at the possibility of household contamination playing a role in transmitting *C. difficile* spores[16]. High gastric pH levels have also been hypothesised to influence CDI risk by allowing bacterial colonisation of the upper gastrointestinal tract[6]. Worldwide, there is limited information about the antimicrobial susceptibility patterns of *C. difficile* in children; however, a single-centre study found that *C. difficile* strains from children are less resistant compared to strains from adults, with most paediatric isolates being susceptible to vancomycin, metronidazole and rifaximin[17]. This study also reported a lack of difference in susceptibility between the first and subsequent isolates in paediatric CDI[17].

Colonisation of *C. difficile* in the neonatal and paediatric gut

The role of *C. difficile* in the paediatric gut remains controversial, and it is still unclear whether it is a primary pathogen capable of causing disease or a harmless bystander, often in diseases caused by other pathogens such as rotavirus[18]. Asymptomatic gut colonisation with *C. difficile* can occur at higher rates (up to 90%) in infants aged less than 1 year old, compared to adults[19]. Neonates and infants who harbour high numbers of toxigenic strains often do not display any signs or symptoms of CDI[18]. The reason for this is not fully understood although it has been implied that this could be due to the lack (or minimal expression) of mature toxin receptors[18,19]. Additionally, the gestational age at birth, infant feeding mode, maternal diet, family lifestyle, geographical location and host genetics shape the initial microbiota[20,21]. There is still uncertainty regarding the source of infant gut colonisation and there are many theories[21]. Some studies show the possibility of transmission from the mother's urogenital tract (via vaginal delivery); however, this idea has been challenged[22]. Other plausible theories suggest the colonisation of *C. difficile* in the sterile neonatal gut immediately after birth comes from various environmental sources[23]. This high colonisation rate drops rapidly between ages 1–3 years to approximately 5–15% as the gut microflora starts to resemble that of an adult[19]. Postnatal factors such as breastfeeding practices further configure the microbiota in early life as breastfed infants tend to have significantly lower rates of *C. difficile* colonisation compared to formula fed[20]. Again, conflicting findings of higher colonisation rates (of toxigenic *C. difficile*) in children (non-infant age group) in developed countries and lower rates in low-income countries make it more difficult to diagnose CDI[20]. It is likely that wide variations of enteric pathogens exist between low- and high-income countries, possibly explaining the reasons for these differing findings. Interestingly, a recent study by Kociolek and colleagues supports the hypothesis that colonisation of toxigenic *C. difficile* is linked to humoral immune response against toxins A and B in infants, as opposed to the trans-placental transfer of maternal antibodies[24].

Challenges in diagnosing CDI in children

Many controversies still surround the testing methodologies for paediatric CDI[5,25,26]. The classification of paediatric age groups differs across countries, leading to variations in surveillance of *C. difficile*[5]. Surveillance guidelines for CDI in Australia (developed by the Australian Commission on Safety and Quality in Healthcare) exclude testing children under 2 years of age due to the high carriage rates and, as a result, most laboratories in Australia do not test this group of children[26]. This creates a gap in knowledge about understanding the extent of *C. difficile* colonisation in infants and the impact this can have in CDI. Distinguishing colonisation from symptomatic infection is also a challenge and the available laboratory tests (including molecular detection methods) are not helpful in making that distinction[5,19]. Identifying clinical predictors of severe CDI in children is difficult mainly because diarrheal illnesses are frequently encountered in children commonly associated with viral agents[5]. This places significant pressure on the importance of obtaining a full clinical history, and searching for other possible causes of diarrhoea. Also, there still exists a lack of validated clinical criteria across different countries, leading to discrepancies in defining clinically significant diarrhoea in infants and incontinent children. As a result, deciding which children presenting with diarrhoea in an ambulatory setting should be tested for *C. difficile* is also difficult. The IDSA (Infectious Diseases Society of America)/SHEA (Society for Healthcare Epidemiology of America) guidelines recommends specific tests such as EIAs and NAATs (Figure 1), either as a multi-step or single test (depending on whether the institutions have pre-set criteria for testing samples)[25]. In an Australian study, molecular methods were recommended over other testing methodologies such as a GDH algorithm or culture[26].

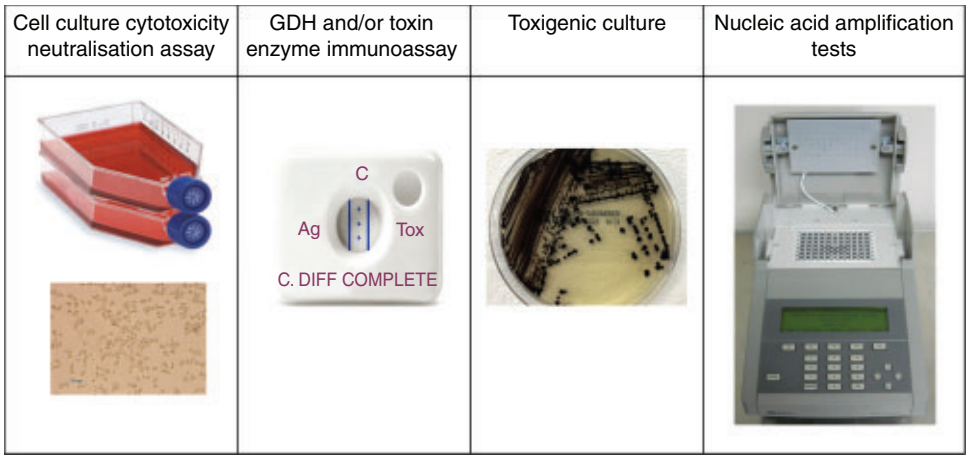

Figure 1. Key laboratory methods for *Clostridium difficile* detection. The cell cytotoxicity neutralisation assay (CCNA), historically considered a gold standard, is performed by inoculating stool sample filtrates into cultured cells. A characteristic cytopathic effect can be observed in the presence of toxins in the filtrate, following incubation. Despite being the gold standard for many years, CCNA is less sensitive than toxigenic culture methods. Toxigenic culture is used in some laboratories as another gold standard for *C. difficile* detection in faecal and environmental samples, as recommended by the SHEA/IDSA guidelines. Toxin enzyme immunoassays (EIAs) such as C. diff Quik Chek Complete rapidly detects both *C. difficile* glutamate dehydrogenase (GDH) and toxins A/B, and are often used to rule out *C. difficile* in laboratories that lack access to molecular testing. The use of nucleic acid amplification tests (NAATs) is now widespread in high-income countries although they are more expensive than the other testing methods. NAATs are also more sensitive in detecting toxigenic *C. difficile*, which may not necessarily be an advantage. A 2-step algorithm consisting of a sensitive screening test first, such as GDH or PCR, followed by a specific test such as detection of toxins is recommended.

Management of CDI in children

The IDSA and SHEA recommend either metronidazole or vancomycin for non-severe initial or first recurrence of CDI in children[25,27]. For moderate and severe CDI, oral vancomycin is given[25]. For a second or more episode of recurrent CDI, the best treatment option is yet to be determined. The current recommendations, of tapered regimens of either only vancomycin or vancomycin followed by rifaximin, stem from limited data[25,28]. Fidaxomicin has not been approved by the FDA for paediatric CDI, however, there was a good clinical response and tolerability in phase 2 trials[17]. Faecal microbiota transplantation (FMT) is regarded as the best treatment for recurrent CDI in adult patients[29] due to its ability to restore the microbiota back to its initial healthy form. The constantly evolving microbiome in children and its effect on the immune system has an impact on the success of FMT. A recent review on current data on FMT in paediatric CDI reported ~90% improvement of symptoms with a 4% recurrence rate and no severe complications[30]. Based on adult studies and the limited data on children, FMT might be considered for treatment in children with recurrent or severe CDI episodes[25,29,30]. Administration of probiotics achieved 60% reduction of CDI risk in children and adults, according to a recent systematic review, and was also safe[31].

Vaccines are considered the only type of intervention capable of providing long-term protection against CDI and, given the extensive testing of vaccines in clinical trials currently, a licensed *C. difficile* vaccine may become available within the next decade[32]. However, whether this vaccine (designed for adults) will be suitable for children is not known. Even if a paediatric *C. difficile* vaccine is developed, its use will depend on surveillance (which is not done for paediatric CDI in most parts of the world). Also, it is difficult to recognise which groups of children would benefit from vaccination and, in the context of CA-CDI, it is unclear whether it is worth vaccinating those in close contact with neonates/infants. Therefore, it is evident that there is limited data on the various treatment options for paediatric CDI, compared to the adult CDI. More important, complications and mortality in paediatric CDI are rare, making it difficult to compare data for the different treatments in children, but this may relate to a lack of surveillance.

How children play a role in the transmission of *C. difficile* in the context of CA-CDI is not fully understood, however, exposure to infants is a risk for getting CDI[33]. There are higher rates of CA-CDI in females than males possibly because women are the primary care givers for neonates and infants. There is high potential for asymptomatic carriers to shed *C. difficile* into the environment. Thus, young children are good examples of human reservoirs who could pose a threat to the elderly and immunocompromised in the community. Even though there are management plans in place to treat and prevent paediatric CDI in hospitals, controlling the shedding and transmission of *C. difficile* from paediatric carriers to other individuals still remains a challenge for health care providers.

Conclusion

The amount of research conducted on *C. difficile* among paediatric patients is limited and an understanding of the ability of healthy neonates and infants to tolerate high rates of toxigenic *C. difficile* is required. Studying the epidemiology of CDI among children and determining the main source of infection and risk factors will guide better public health responses and eventually aid in reducing the

burden of CDI on the local healthcare system. Future studies investigating the duration and extent of natural *C. difficile* immunisation, and the age at which this happens, will aid in understanding the possibility of vaccinating children and the public health value it could have. One stumbling block to learning more about diagnosing CDI in children is the lack of a standardised scoring system for paediatric infections, thus making it harder to study disease burden that inevitably leads to confusion in deciding who to treat. More work is required to address this problem.

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

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