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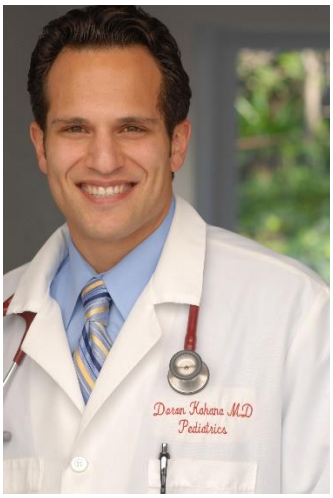

Clostridium difficile in Children

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Clostridium difficile (C. diff) was first described as a component of normal neonatal flora in 1935.[i] A spectrum of disease has since been characterized, from asymptomatic carriage, to diarrhea, colitis, and toxic megacolon with shock; C. diff infection (CDI) is strongly associated with antibiotic therapy and is currently a leading nosocomial burden in adults, carrying a significant mortality rate and financial cost. Hospitalizations in children for CDI have also increased, with rates more than doubling from 1997 to 2006.[ii]

C. diff is an anaerobic, Gram-positive, spore-forming bacillus that is found in the environment as well as the intestinal tract of animals and humans. The pathogenicity of C. diff is attributed to production of two protein toxins: A (enterotoxin) and B (cytotoxin). The toxins enter the cytoplasm of colonocytes by binding to receptors on the luminal side and then inactivate several proteins involved in cytoskeleton organization, triggering apoptosis and resulting in colitis and diarrhea. Average colonization rate in neonates (<1 month of age) is 37% (range 0-61%); between 1-6 months of age colonization rates remain high at 30% but then drop to 10% by the end of the first year of life. By 3 years of age, carriage rates drop further to 0-3%, similar to that found in adults. The exact mechanism of protection in infants remains unclear, theories include the lack of surface toxin receptors, protective factors in breast milk, and the defense provided by the neonatal flora. Breast-fed infants have lower rates of colonization with C. diff than formula-fed infants; although this difference does not appear to carry over beyond weaning.[iii]

Detection of C. diff in infants may be non-contributory to diarrheal illness; however, cases of C. diff-associated disease and mortality in this age group have been reported.[iv] In hospitalized children, the rise of CDI rates is associated with known risk factors, such as non-judicial antibiotic use, immunosuppression, bowel dysfunction (e.g. inflammatory bowel disease, IBD), gastric acid suppression, underlying malignancy or hematologic condition, and cardiovascular disease.[v] In patients with IBD, rates of CDI have increased 2- to 4-fold in the past decade, resulting in greater patient morbidity and higher mortality.[vi] Community-acquired illness is also increasing, but many of the patients tested were likely to have had a concurrent viral infection.[vii]

The American Academy of Pediatrics (AAP) 2013 guidelines recommend testing for CDI in children with diarrhea (3 or more loose stools in a 24-hour period); however, testing in children less than 1 year of age is discouraged unless there are specific gut motility disorders, such as Hirschsprung's disease, or in the setting of an outbreak. For children between 1 and 3 years of age, testing can be considered if alternative causes, such as viral infections, have been explored first. Positive findings in children between 2 and 3 years of age do not obviate an alternative etiology, which should be pursued. Children 3 years of age and older with a positive result should be treated as probable CDI. Repeat testing is discouraged before 4 weeks after the initial positive test result, even with recurrence of symptoms.[viii]

A specific testing methodology is not clearly endorsed by the AAP; however, Nucleic acid amplification test (NAAT) is the most sensitive method for the detection of the organism. A direct cell cytotoxicity assay (CCTA) carries a sensitivity of 75-85% and may be negative if the concentration of the toxin in the sample is too low or has been degraded; it also has a relatively long turnaround time. Enzyme immunoassays (EIA) can detect either the presence of toxins A and B or the presence of the metabolic enzyme glutamate dehydrogenase (GDH); however, EIA displays variable sensitivity and specificity, with high rates of false-positives, and therefore is not recommended as a standalone test for the diagnosis of CDI. GDH assays have a high sensitivity as a screening test (87.6-100%) and a negative predictive value of >97%, plus they are low cost and easy to perform, making them an attractive screening method with EIA or NAAT for confirmation. Nonetheless, positive C. diff results need to be interpreted with caution and in correlation with the clinical picture, given the high rate of asymptomatic carriage in young children.[ix]

Treatment in children with CDI should begin with discontinuation of existing antibiotics and correction of fluid and electrolyte imbalance. Opiates increase the risk of ileus and toxic megacolon; antimotility agents, such as loperamide, should be avoided. Marked leukocytosis, azotemia, fever, severe abdominal pain, and >6 stools/day indicate severe colitis. Signs of shock, such as hypotension and cardiovascular collapse, characterize fulminant colitis. In mild-to-moderate disease, metronidazole 30 mg/kg/day in 4 divided doses for 10-14 days is most commonly recommended due to its low cost. Nitazoxanide has been found to be at least as effective as metronidazole, carries a safer profile, and tastes better as a suspension (personal experience); however, it is moderately costly. In moderate-to-severe disease, oral vancomycin 40 mg/kg/day in 4 divided doses for 10-14 days is recommended; adjuvant therapy with metronidazole IV as well as vancomycin retention enemas may be considered. Fidaxomicin, a narrow-spectrum macrolide, showed initial response rates higher than vancomycin, and is currently the only other drug FDA-approved for the treatment of CDI; however, it is extremely costly. Fecal transplantation has proven to be very effective in adult patients.[x]

Probiotics have been evaluated as adjunct therapy in CDI and are strongly encouraged by the author; however, most reviews and meta-analyses are equivocal. Contrary to common belief, probiotics do not recolonize the intestines but largely work indirectly, via activation of Pattern Recognition Receptors (PRR), such as Toll-Like Receptors (TLR), which are part of the innate immune system; activation of TLR triggers an intracellular cascade that results in gene expression and cellular differentiation. Other proposed mechanisms of action include competitive exclusion (i.e. colonization resistance), metabolic activity (e.g. byproducts), induction of adaptive immunity, quorum sensing, and horizontal gene transfer. The microbiome is also vulnerable to its own diseases, such as infections with bacteriophages, which are viruses that attack bacteria.[xi]

Saccharomyces boulardii, a yeast probiotic, has the strongest evidence in CDI and is believed to work indirectly through immunomodulation as well as directly by inhibiting C. diff toxin-A receptor binding. This results in decreased transcription factor activation and thereby less inflammation, colonocyte apoptosis, and fluid secretion/diarrhea.[xii]

In conclusion, C. diff is commonly a normal colonizer in infancy and laboratory testing should be minimized in the first year of life. CDI is an increasing burden on society and related to antibiotic use and gastric acid suppression. Confirmation stool tests are

available, new antibiotics are effective but expensive, and probiotics appear to have a role as adjunct therapy.

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