Clostridium difficile in Children: Colonization and Consequences

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(See the Major Article by Sammons et al on pages 1–8.)

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The incidence of Clostridium difficile infection (CDI) has dramatically increased in the past decade. In some parts of the United States, CDI now surpasses methicillin-resistant Staphylococcus aureus as the most common healthcare-associated infection [1]. CDI also appears to be causing increasingly severe illnesses and more deaths, and exerting a growing burden on healthcare systems [2–6]. The preponderance of literature on this problem has been derived from adult clinical and epidemiologic studies.

Clostridium difficile was first described in the stools of neonates in 1935, and termed Bacillus difficile “because of the unusual difficulty . . . encountered in its isolation and study” [7]. Although Hall and O’toole found that strains from infant stools were virulent when inoculated into guinea pigs and rabbits [7], C. difficile was not generally considered to be a human pathogen until 4 decades later, when Bartlett et al linked these bacteria to antibiotic-associated pseudomembranous colitis [8]. Now, nearly 4 more decades after that seminal association, emerging data suggest we need to focus on the biology of C. difficile in children.

Sammons et al [9], in the current issue of Clinical Infectious Diseases, highlight the importance of C. difficile as a pediatric pathogen. They report a large multicenter retrospective analysis of morbidity and mortality associated with CDI in children. Children who develop symptomatic C. difficile diarrhea after admission to the hospital have a 6-fold greater risk of dying during that hospitalization than do controls with similar underlying disease and risk factors. In addition, children with CDI have significantly longer hospital stays and incur more costs than matched controls. These results are generalizable to the greater US population because the large dataset was obtained from children’s hospitals around the country.

The study by Sammons et al [9] has additional strengths: They performed rigorous propensity score matching that took into consideration not only demographic data but also risk factors that would impact disease severity. The authors therefore minimized the bias that is inherent to studies of C. difficile in pediatrics, because children with significant comorbidities are at higher risk of acquiring C. difficile, and it might be difficult to attribute causality to C. difficile in these settings. They complemented this thorough evaluation with a sensitivity analysis that fortified their results. Their study had several limitations (as they acknowledge), such as using the third day of hospitalization as a cutoff to distinguish community-onset from hospital-onset disease, and the potential inaccuracy of information obtained from an administrative dataset. Taken together, the data reported by Sammons et al compel us to end our complacency about childhood CDI.

It is understandable why we have discounted the importance of CDI in childhood. Multiple studies demonstrate that healthy infants often excrete C. difficile [10–24], so attribution of pathogenicity in childhood cannot be claimed with conviction when a child with diarrhea has a positive C. difficile assay. Indeed, in a recent Seattle study, the frequency of C. difficile carriage was higher in controls than cases in children younger than 2 years [25]. Nonetheless, multiple reports over the past decade serve as preludes for the article by Sammons et al: Hospital diagnoses of pediatric C. difficile infection are increasing [26–30], and C. difficile infections are very common in children with inflammatory bowel diseases [31] and cancer [32]. Nylund et al [30] refuted the contention that C. difficile infections in...
children are mild [28, 33] by demonstrating greater mortality, length of hospital stay, and hospitalization costs in children with CDI compared to controls. Some of the challenges encountered in pediatric CDI are the same as those encountered in adults. We still do not know how best to detect this pathogen in stool [34, 35]. We also need to provide better guidance for clinicians who diagnose and then must decide whether to treat C. difficile in children; that is, which positive tests are truly actionable? Despite our increasing respect for this pathogen, we doubt that most children whose stools contain C. difficile in hospital, even if they have diarrhea, warrant antibiotic therapy, and we are concerned about inappropriate overreaction to a positive test. Indeed, we have seen children infected with Escherichia coli O157:H7 who were treated with metronidazole soon after presentation because a rapid test suggested the presence of C. difficile, before culture results indicated the presence of E. coli. This is concerning because recent data suggest that metronidazole, like other antibiotics, appears to confer risk for the development of the hemolytic uremic syndrome in such patients [36, 37]. We do, however, need to be more alert to early severe CDI, and start appropriate treatments as quickly as possible. Unfortunately, there are no validated CDI clinical scores in children, and physicians have to rely on their clinical impressions to identify such patients. Recent data suggest that stratification of C. difficile severity might obligate combined microbiologic and host assessments, and potentially the attenuation of severe host response to infection [38].

Once we determine who should be treated, the choice of therapy is also not settled. We are hesitant to endorse metronidazole as the “drug of choice” [39] over vancomycin. If a child infected with C. difficile is ill enough to warrant treatment, we are concerned that nitroimidazoles are inferior to vancomycin [40]. We recognize concerns about selecting for vancomycin-resistant enterococci, but, interestingly, treatment with metronidazole has its own association with vancomycin-resistant enterococcal colonization and infection [41–44]. In view of current data, it seems appropriate for practitioners to raise their thresholds for starting antimicrobials for nonevere childhood C. difficile infections (although recognizing that we cannot accurately stage such illnesses in children), while lowering their thresholds for using vancomycin when they do choose to treat.

Pediatric C. difficile biology has one particularly important additional aspect: the large number of asymptomatic carriers in the community. It is plausible that many of the severely ill children identified by Sammons et al [9] were colonized prior to hospitalization, and that C. difficile acquired in the community “bloomed” in-hospital, because of either host biology or exogenous factors such as antibiotics. If such children at risk are identified on admission, strategies might be used to prevent severe C. difficile illness from ensuing. Also, in view of demonstrated intrahospital spread of C. difficile between adults [45] via contaminated healthcare workers [46, 47] and devices [46], we need to confirm that best practices are in place in children’s hospitals to prevent nosocomial spread, even from asymptomatic carriers. Such practices would include appropriate contact precautions and strict hand hygiene, which can reduce the incidence of CDI by as much as 80% [48, 49], and, of course, antimicrobial stewardship programs [50].

An additional reason to study asymptomatically colonized children is that they might pose risks to adults in their midst. Children, especially those younger than 1 year, are quite possibly the major worldwide reservoir of presumptively virulent (ie, toxigenic) C. difficile [25, 51]. Adults in their vicinities remain at much greater risk of serious disease than children, our new appreciation of the potential virulence of C. difficile in children notwithstanding [52, 53]. If the adult roommate of a hospitalized grandparent is found to be excreting C. difficile, current guidelines call for the infected patient to be transferred to a private room [54] to protect the grandparent. However, on discharge, that grandparent would generally not be given recommendations to avoid changing the diaper of a 1-year-old grandchild, an activity that might be just as hazardous as occupying a hospital bed across the room from a colonized patient. For influenza, we have learned that controlling childhood infection is an excellent way to prevent adult infections [55], and we need to determine the extent to which the enteric contents of children play a role in serious adult infections.

Clostridium difficile colonization of children is still an enigma. The role of C. difficile as a pathogen of children is now less enigmatic, thanks to the contribution of Sammons et al [9]. Investigators interested in, and clinicians who request tests for and must respond to, childhood CDI now have better-defined challenges and opportunities because of this work. Let us hope we will not have to wait another 4 decades before we meet these challenges.

Notes

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