The Intestinal Pathobiome: Its Reality and Consequences Among Infants and Young Children in Resource-Limited Settings

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(See the major article by Taniuchi et al on pages 1794–802.)

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The work by Taniuchi and colleagues at the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh and the University of Virginia, Charlottesville, presented in this issue of The Journal [1], is both significant and thought provoking. It complements the work of the Global Enterics Multi-Center Study (GEMS), an international consortium of sites using cutting-edge and traditional molecular and microbiological techniques to assess the burden and causative agents of intestinal infections among impoverished children in a number of locations around the world. Both the GEMS and Taniuchi et al have found a stark reality: it is “normal” to be able to detect a range of enteropathogens in the intestines of infants and young children in resource-limited settings, including those under surveillance with no evident diarrhea. This has advanced the concept of “enteropathogen excess” to ascribe etiology to specific episodes of diarrhea in these children.

The work by Taniuchi et al advances this concept. Their team used a molecular diagnostic, quantitative polymerase chain reaction, multiplex approach targeting 32 potential enteropathogen gene targets. They performed this analysis at a community level, in an informal settlement area of Dhaka, Bangladesh, enrolling 147 infants in a birth cohort and following them up through 1 year of life, collecting surveillance as well as diarrhea-related stool samples.

The results were striking. On average, these infants had approximately 4.7 episodes of diarrhea in their first year of life, or an episode of clinically apparent diarrhea approximately every 2.5 months. The mean duration of the episodes was 5.5 days, indicating that these infants had diarrhea for approximately 1 of their first 12 months of life. Detecting multiple pathogens in diarrheal stool samples was the norm, with a mean of 5.6 pathogens identified in each diarrheal sample. But perhaps the most striking finding, one that matches that seen by GEMS, was the detection of a mean of 4.3 enteropathogens in the surveillance stool samples collected from asymptomatic infants without diarrhea.

Taniuchi et al found that this enteropathogenic burden was present and detectable within the first month of life and persisted throughout the year of observation of the birth cohort, necessitating the use of a “pathogen excess approach” to attempt to ascribe causative agents to a specific episode of diarrhea. They not only incorporated a concept of pathogen excess, but they also determined whether the pathogen was detected in the recent surveillance stool samples from the infant in question. Using this approach, they were able to whittle down the list of potential causative agents from >5 to approximately 3 for specific episodes of diarrhea.

Looking at all diarrheal episodes, enteroaggregative Escherichia coli, Campylobacter, enteropathogenic E. coli, rotavirus, and Entamoeba histolytica were the most commonly identified probable contributors to diarrhea. When the authors considered only episodes of diarrhea that were moderate to severe, rotavirus, E. histolytica, and Cryptosporidium spp. rose to the top of the list. The team also performed a sobering comparison, performing a similar analysis on stool samples from of well infants in a Virginia daycare center, as well as in infants with diarrhea in Virginia. The norm in the United States was to be able to identify <1 enteropathogen in stool samples, including during diarrheal episodes.

These results suggest that we need to revise how we conceptualize the enteropathogenic burden of infants in resource-limited areas of the world. Depressingly, it seems “normal” to be able to detect many pathogens in the intestines of...
infants in resource-limited areas, beginning within the first month of life, even in the absence of overt diarrhea. These results have some very important implications and raise some very interesting questions. First, what is the tipping point for an infant to have an episode of diarrhea in light of this ever-present polymicrobial mix? Pathogen “excess” is a reasonable starting point; however, this approach is undoubtedly overly simplistic. Do certain pathogen combinations in some specific order affect the outcome? What about the host modifiers that may play very important roles?

Second, these results suggest that approaches to control or address single pathogens may have limited utility in such populations. Rotavirus was perhaps the easiest pathogen to go after, because it is a near-universal infection in the first year of life. Interestingly, the results in this current report may partially explain the decreased efficacy of rotavirus vaccine in resource-limited settings.

Third, the results also have diagnostic implications. How does one best configure surveillance systems to ascertain the “true” burden of a specific enteropathogen with regard to morbidity and/or mortality as one rolls out control programs in such resource-limited areas, and how does one ascribe a specific episode of diarrhea to a specific pathogen? It seems that the more you look, the more you find.

Finally, what is the relationship of this resource-limited intestinal microbiome, perhaps better conceptualized as an intestinal “pathobiome,” and the development of environmental enteropathy (previously referred to as tropical enteropathy or tropical gut)? It seems that for infants in resource-limited areas, the norm is a chronic state of intestinal inflammation with villous blunting and intestinal leakage and malabsorption, a condition that plays into a cycle of malnutrition, micronutrient deficiencies, and growth impairment and results in cognitive delay, poor take of intestinal vaccines, and poor absorption of nutrients and critical medications. As death rates from diarrhea continue to fall globally, we must more fully recognize the repercussions and longitudinal morbidity associated with the polyopathogen mix in the intestines of surviving infants and children, especially its relationship with environmental enteropathy.

The ultimate and optimal solution to all of these issues is safe water and adequate sanitation for all; however, with 0.8 billion individuals currently lacking safe water, and >2 billion currently lacking adequate sanitation, it will unfortunately take decades to reach such elusive goals of global equity. In the meantime, we as a global health community will have to ascertain more fully and then deal with the negative consequences of allowing a pathobiome to become the “normobiome” for so many infants and young children around the world.

Note

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