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Recent Advances in Understanding the Long-term Sequelae of Childhood Infectious Diarrhea

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Abstract

Worldwide, early childhood infectious diarrhea continues to be a significant concern. Diarrheal illness affects the world's youngest and most vulnerable citizens disproportionately. Estimates are that over 70% of the deaths from diarrhea occur in people younger than 24 months of age. Diarrhea and environmental enteropathy have been associated with growth failure and stunting. In addition, the burden of enteric disease also leads to cognitive and academic losses, thus resulting in loss of human capital and economic productivity. While considerable progress has been made on preventing and treating childhood diarrheal illness, the mortality and morbidity still remain unacceptably high. This paper seeks to review the recent (mainly from 2013) publications surrounding the global burden of childhood diarrhea and the implications for long-term sequelae.

Keywords

Enteric disease; early childhood infectious diarrhea; long-term sequelae; malnutrition; environmental enteropathy; cognitive development; early childhood development; pediatric infectious disease; environmental enteric dysfunction

Introduction

Worldwide, early childhood diarrheal illness continues to be a significant concern. The World Health Organization defines diarrhea as the "passage or 3 or more loose or liquid stools per day, or more frequently than is normal for the individual". (http://www.who.int/topics/diarrhoea/en/) Diarrhea is the second most common cause of death in children younger than 5 years and is preventable and treatable. Diarrheal illness kills about 760,000 young children per year and is a significant cause of malnutrition. (http://www.who.int/mediacentre/factsheets/fs330/en/index.html) While oral rehydration therapy has led to significant reductions in mortality, morbidity remains an important concern globally. When enteric infections disrupt the intestinal absorption and barriers, growth and health are hindered. The resulting malnutrition, inflammation, and illness may also lead to a decrease

Compliance with Ethics Guidelines
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in cognitive, academic and productivity outcomes as well as poorer health status. This paper seeks to review the recent (mainly from 2013) publications surrounding the global burden of childhood diarrhea and the implications for long-term sequelae.

Paper: Headings and Subheadings to break up the text

Global Burden of Childhood Diarrhea[1,2]

Unfortunately, childhood diarrheal illness continues to be a significant concern worldwide. A series published in 2013 in the Lancet entitled “Childhood Pneumonia and Diarrhoea” reviewed the epidemiology of childhood diarrhea from 2010-2011 around the world.[1] The authors estimate that in 2010 there were 1.731 billion episodes of diarrhea (36 million became severe episodes) in children less than 60 months. In 2011, an estimated 700,000 episodes of diarrhea led to death. 72% of diarrhea-related deaths occur during the first two years of life. Risk factors such as undernutrition, suboptimal breastfeeding and zinc deficiency contribute to morbidity and mortality of diarrhea. Rotavirus was the most common cause of vaccine-preventable diarrhea. While both deaths and poor outcomes are decreasing, the authors call for global action to more rapidly reduce the effects of diarrheal illness.

The global burden of childhood diarrhea is further being studied in two landmark studies funded by the Bill and Melinda Gates Foundation. The “*Global Enterics Multi-Center Study*” (GEMS) is the largest and most extensive study undertaken to examine childhood diarrhea in developing nations and initial findings were published in the Lancet in 2013[2]. (http://medschool.umaryland.edu/GEMS/). GEMS studied more than 22,000 children in Africa and Asia (study sites in Mali, the Gambia, Kenya, Mozambique, Bangladesh, India and Pakistan). Children (0-59 months) were enrolled over 3 years and followed for 60 days after diarrheal episode (and 60 days for controls). To be defined as a case, the diarrheal episode was new (previously had ≥7 days diarrhea free), and acute (onset in last 7 days) and meet at least one of the following: sunken eyes, loss of skin turgor, IV hydration prescribed, dysentery (blood in stools), or hospital admission. Four pathogens were responsible of the majority of moderate to severe diarrheal episodes: Rotavirus, Cryptosporidium, Shigella and Enterotoxigenic *E. coli*. Infants (0-11 months) had the highest risk of diarrhea and children who had an episode of moderate to severe diarrhea grew less and had a nearly 8.5 times increased risk of death in the following 60 days.

The “Interactions of Malnutrition & Enteric Infections: Consequences for Child Health and Development” (MAL-ED) study is collecting data on 200 children in each of 8 sites around the world (Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa and Tanzania) (http://mal-ed.fnih.org/). Children are followed from birth to 2 or 3 years of age, and comprehensive growth, diarrhea, nutrition, and developmental information is obtained. In addition, case-control studies are being done in Brazil and Bangladesh, as closely followed cohorts can have reduced diarrhea and improved growth over time due to close observation and contact with study personnel.[3] These case-control studies are collecting information on 500 children with moderate to severe malnutrition (weight-for-age [WAZ] Z-scores <-2) and 500 matched controls (WAZ >-1). As the MAL-ED study comes to completion, we wait with eager anticipation for the important information it will provide about diarrheal patterns,

growth, nutrition and cognitive outcomes of early childhood illness. Articles on MAL-ED methodology and initial findings should be forthcoming in the next year.

Economic costs are high[4-6]

The economic costs of childhood infectious diarrhea remain high and troubling, as discussed in three recent publications in 2013[4-6]. One study from Emory University in Atlanta, Georgia and Universidad Mayor San Andres in La Paz, Bolivia, found that 45% of patients' families paid greater than 1% of the household income for that year in caring for one diarrheal episode in a child younger than 5 years (n-1,107)[4]. Indirect costs and loss of income were also high. In the Pediatric Hospital of Cairo University in Egypt, the mean cost per diarrheal episode consumed 29.5% of the mean monthly income for a family and this burden was great for the families.[6] A study from the Hospital for Sick Children in Toronto examined quality of life outcomes associated with acute gastroenteritis in parents and children 3 months to 5 years.[5] They explored the psychometric properties of a quality of life questionnaire to measure physical symptoms and socio-emotional function. The authors propose that trials of interventions for childhood gastroenteritis could use quality of life as an important measure.

Growth Outcomes

Early childhood diarrheal illness has been associated with growth shortfalls in cohorts around the world in past studies.[7-10] During the past year, there have been 4 significant papers that examine these growth outcomes.[11-14] One analysis of 7 cohort studies from Peru, Brazil, Guinea-Bissau, and Bangladesh examined 1,007 children with 597,638 child-days of diarrhea surveillance. The association between mean diarrhea burden and length at 2 years was −0.38 cm (95% CI: −0.59, −0.17).[11] Another paper in 2013 proposed the term "environmental enteric dysfunction" to describe the changes in small bowel function associated with altered mucosal architecture, reduced enterocyte mass and evidence of immune activation and inflammation in the mucosa.[12] This alteration in architecture and gut dysfunction is likely the result of factors in the environment to which children are exposed, and results in the decreases in growth and stunting seen in children in developing settings. The paper calls for more research into environmental enteric dysfunction, its relationship to growth and ways to improve enteric dysfunction in children in low-income countries. Another study examined data from 112 districts in India to examine relationships between open defecation and stunting.[14] Districts with higher rates of open defecation had more stunting (R^2 34.5%). A 10% increase in open defecation was associated with a 0.7 percent increase in the number of children with stunting on an ecological analysis. On a population level, this paper found an association between poor sanitation practices and human growth. Finally, using data from the MAL-ED study described above, the association between intestinal inflammation (measured by neopterin, alpha-anti-trypsin, and myeloperoxidase in the stool) and growth failure was examined.[13] Higher composite stool inflammatory scores were associated with 1.08 cm less growth in height 6 months after the test. While some of these children did not exhibit overt diarrheal symptoms, subclinical enteropathy without overt diarrhea is likely to affect far more children than is outwardly evident by diarrhea rates. These four papers contribute to the field by further clarifying relationships and

continuing the discussing of mechanisms for the relationships between enteric disease and growth.

Stunted growth is concerning because of its association with poorer human capital outcomes.[15-18] An important analysis of growth during the early years as a predictor of adult health, height and schooling was recently published in the Lancet.[19] This study used data from five birth cohort studies (Brazil, Guatemala, India, the Philippines, and South Africa- more information on these cohorts can be found at www.cohortsgroup.org). The findings in these analyses support the importance of adequate health and nutrition during pregnancy and in the early days. Children with greater birth weights and growth in the first two years of life had higher adult height and more years of schooling attained. This supports the significance of interventions in the first 1000 days of life.

Cognitive Outcomes

Previous studies have examined cognitive and academic outcomes of early childhood infectious diarrhea[20-26] One study showed that, in addition to stunting being associated with low cognitive function, the academic benefits of schooling were also reduced by 30% if children were stunted.[27] Further research continues to be needed into the timing, specific indicators, and modifiable mechanisms of loss of human capital so preventative measures can be implemented more effectively. Recently, a trial was completed by our group in a Brazil shantytown to examine effect of zinc, vitamin A, and glutamine, alone or in combination, on cognitive outcomes in children with low median height-for-age z-scores. These children lived in an area with poor sanitary conditions. The trial found that girls receiving a combination of glutamine, zinc and vitamin A had higher verbal learning scores than girls receiving placebo.[28] Other recent studies also demonstrate the continued importance of clean water, hand-washing and sanitation in ameliorating the effects of enteric disease. In a study from 2 peri-urban areas in South Africa that examined sources of drinking water, households with children under 5 years who used open-topped storage containers had the poorest water quality (taking into account heterotrophic bacteria, total coliforms, E. coli, conductivity, turbidity, pH, and total and residual chlorine).[29] This study found that households that practiced open defecation had higher levels of E. coli in their drinking water and higher rates of adverse health outcomes. In an important study in Karachi, Pakistan, a neighborhood hand-washing intervention (free soap and weekly hand-washing promotion for 9 months) was instituted for 9 months. In a study examining outcomes 5 years later, children who lived in the neighborhoods with the handwashing intervention in their first 30 months of life had higher global developmental quotients on the Battelle Developmental Inventory II at 5 to 7 years of age compared with controls, with implications for the effects of bacterial illnesses on cognitive outcomes.[30] This group also found that 5 years after handwashing education, neighborhoods that received the intervention were more likely to have soap at handwashing, and to know the key times to wash hands (after toileting, before cooking, before meals), and the group purchased more soap than controls.[31] These findings suggest longer-term (5 year) behavioral change after intervention, which is promising.

A recent analysis of data from 4 study sites in low and middle-income countries (the Philippines, Brazil, Peru and Guatemala) assessed cognitive outcomes of early childhood diarrheal burdens.[32] They found that most of this relationship was mediated through stunting. However, the authors note that many of the complex relationships are multi-factorial, as childhood diarrheal status is likely related to nutrition, poverty, caregiving and developmental stimulation, and all are likely important in developmental outcomes. Further research continues to be needed.

In addition to the important tasks of examining the outcomes of diarrheal illness and bacterial infections, this year a call for more research into the associations between protozoal infections and human outcomes was published. More information is needed on the effects of the "Neglected Enteric Protozoa" on child development and future potential, though basic science studies provide support for causative associations.[33]

Metabolic Outcomes

In addition to the contribution of enteric infections to undernutrition and growth shortfalls during childhood, recent hypotheses have explored the associations between early childhood enteric enteropathy/malnutrition and later obesity and metabolic outcomes.[34] These hypotheses extend a line of research related to fetal origins of disease, following extensive findings that individuals born small for gestational age (SGA) are more likely as adults to develop obesity, diabetes and cardiovascular disease.[35-37] Currently, the early origins of adult disease program postulates that during fetal development and early childhood, individuals respond to caloric insufficiency and other stresses by inducing epigenetic changes that alter metabolic programming to prepare the individual for future nutrient scarcity.[38] During 2013 these connections were highlighted in a review as a potential long-term burden of childhood diarrhea, citing prior studies that demonstrated that in countries with a high prevalence of enteric infections, poor early childhood growth was associated with findings related to metabolic syndrome (MetS) and pre-diabetes.[39] In addition, the first study linking diarrhea specifically to long-term MetS risk was published in 2013. This study by our group evaluated 389 Guatemalan participants of the Institute of Nutrition of Central America and Panama (INCAP) long term study, with detailed data regarding diarrhea episodes during the first 2 years of life and adult data regarding waist circumference, blood pressure, serum triglycerides, HDL-cholesterol and fasting glucose—all components of MetS.[40] Following adjustment for adult body mass index (BMI, a significant cause of metabolic syndrome itself), individuals with a higher diarrhea burden in the first 6 months of life were more likely to exhibit MetS as adults—suggesting that childhood diarrhea could be in the causative pathway of risk for MetS. Additional publications in 2013 served as reminders of the high rates in LMIC of children born small for gestational age (27% of all births) and early childhood stunting (26% of children in LMIC), serving as a reminder of the need for improved maternal and child nutrition.[41,42] Together these risk factors for later metabolic disease may be important contributors to the global burgeoning of obesity.[43,44]

New Topics in Treatment to Prevent Long-Term Outcomes

Treatment in Developed Countries—A recent overview of Cochrane reviews about treatments for acute gastroenteritis in children in developed nations found that children who

received intravenous therapy were at increased risk of phlebitis. In addition, paralytic ileus was more common in children receiving oral rehydration therapy.[45] Children who were treated with oral ondansetron (an anti-emetic) had fewer visits to the emergency department and lower rates of intravenous hydration than those who received placebo. When children hospitalized for gastroenteritis received certain probiotics, their hospital stay was decreased by 1.12 days.

Treatment in Developing Nations—Several recent studies emphasize the importance of identification of children suffering from diarrhea in order to treat them.[46-49] Access to healthcare, knowledge of treatment options and cost remain significant factors. An important study published in Pediatrics in 2013 gave short course Zinc (20 mg by mouth daily for 2 weeks) to infants 6 to 11 months in a transitional urban community in Delhi, India, who were at risk of illness (N=134 treatment, 124 placebo).[50] During 5 months of follow-up, the treatment group had a 39% reduction in incidence of diarrheal episodes and 39% reduction in days of diarrhea.

An important topic discussed with emphasis recently involves **integrated interventions**: pairing nutrition, pneumonia, and child development interventions with diarrheal education and treatment.[51,52] In April of 2013, the New York Academy of Sciences hosted a conference entitled “Every Child’s Potential: Integrating Nutrition, Health, and Psychosocial Interventions to Promote Early Childhood Development.” According to the World Health Organization, 24% of children under 5 years do not meet their developmental potential due to undernutrition, lack of educational and developmental opportunities for learning and social and environmental instability. To address malnutrition, enteric disease, and lack of childhood stimulation, which can all lead to loss of academic achievement, economic productivity and well-being, integrated interventions will continue to be important. This group of experts from around the world sought to discuss interventions to promote early childhood development in health for the critical first 1000 days of life, when the human brain is developing rapidly. Ideas and key questions can be found in the meeting summary: (http://www.nyas.org/Publications/EBriefings/Detail.aspx?cid=3e02ea70-3585-4273-975b-32419b851368).

Research priorities

On-going research will continue to provide understanding of the sequelae of enteric infections and ways to both prevent diarrheal illness and prevent morbidity from the infection. A recent discussion of diarrheal illness notes that investment in diarrheal disease control has been disproportionately low compared with other illnesses.[53] A review by our group examined biomarkers and interventions to lessen the effects of the “triple burden” of diarrhea, malnutrition and chronic disease.[39] Specific biomarkers of enteropathy are important for understanding pathogenesis, predictors of sequelae and response to intervention and several known and potential biomarkers from urine, stool, and blood are listed in the paper.[39] More work is underway, particularly that funded by the Bill and Melinda Gates Foundation Biomarkers Grants: (http://www.grandchallenges.org/GCGHDocs/Gut_Function_Biomarkers_Rules_and_Guidelines.pdf). In addition, a systems biology approach to intervening based upon host and microbe genetics, nutrition status and

anthropometry, bowel architecture, inflammation and metabolomics will likely be helpful in tailoring interventions to a specific child's needs.[39] The "Child Health and Nutrition Research Initiative" (CHNRI) is a network supported by the Global Forum for Health Research that sets research priorities in child health, development and nutrition. The CHNRI process systematically and transparently gathers and evaluates research priorities. The context and priority of the problem are determined, experts generate and rank research questions, stakeholders weight the criteria, scores for the research questions are generated, and agreement between the experts is examined.[53] A recent CHNRI process gathered team leaders in 10 areas of focus within the topic of childhood diarrhea, and each of the 10 team leaders gathered a team of 20 experts in their fields to submit and rank research questions. From this process, the top 5 research questions identified all revolved around successful use of oral rehydration therapy and zinc in treating children with diarrhea. A follow-up workshop of 38 participants agreed with the research priorities determined and brought them to the attention of stakeholders who can help with implementation.[54] Of note, this group emphasized the "urgent need to determine the long-term effects of chronic and recurrent bouts of diarrhea on the physical and intellectual development of affected children." Next, a group of international experts in diarrheal treatment were convened to discuss which emerging interventions would be feasible, low-cost, efficacious, deliverable and sustainable.[55] The top 5 emerging interventions by overall research priority score were 1) household –or community level- water treatment, 2) sustainable, affordable latrine options, 3) antibiotic therapy of *Cryptosporidium* diarrhea, 4) oral or transcutaneous vaccine development, and 5) probiotics and prebiotics.

Conclusion

A review of the key papers published in 2013 reveals that early childhood infectious diarrhea continues to be a serious concern around the world, although mortality and morbidity are improving. Growth failure remains a significant adverse consequence and the discussion of environmental enteric dysfunction by Keusch, et al., provides expert insight into possible mechanisms. The influences of early childhood infectious diarrhea, as well as malnutrition, on health, development and human capital are continuing to be explored and we look forward to further information coming from the MAL-ED studies. Recent calls in the Lancet for improved early childhood health around the world[1] note the importance of focusing on the first 1000 days of life. "The 165 million children with stunted growth in 2011 have compromised cognitive development and physical capabilities, making yet another generation less productive than they would otherwise be."[56] With this knowledge, the important work of improving early childhood health and development so that children can learn and grow to their full potential remains.

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