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Chronic consequences on human health induced by microbial pathogens: Growth faltering among children in developing countries

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ABSTRACT

Enteric infections continue to cause approximately 500,000 childhood deaths annually worldwide. In addition to the burden of diarrhea, there is emerging evidence that exposure to enteric pathogens may induce physiologic abnormalities that lead to linear growth faltering. This enteric disease, known as environmental enteric dysfunction (EED) remains cryptic with regard to its causes and features. In this workshop, experts in the field addressed the contribution of enteric pathogens to growth faltering in the absence of clinical diarrhea. Also addressed were the role of the intestinal microbiota in normal childhood growth among children in developing countries. The impact of pathogen exposure could represent direct epithelial injury or could be mediated by perturbations in the normal microbiota or combinations of both.

1. Introduction

Enteric diseases afflicting children in developing countries include acute and chronic diarrheal diseases, enteric fever, and the recently appreciated, and still obscure disorder known as environmental enteric dysfunction (EED). This workshop was charged with examining the chronic consequences of enteric disease, with a particular focus on the impact of enteric diseases on childhood growth in impoverished settings. The workshop invited three speakers who were each experts on the microbial causes of growth faltering among children in developing countries. Dr. Guerrant was asked to address the role of subclinical infection with known enteric pathogens in growth faltering and other potential chronic consequences. It has been shown in multiple studies that children in developing settings commonly harbor known enteric pathogens in the absence of overt diarrhea; some of these carrier states have been linked to growth faltering. Doctors Joseph Planer (Washington University in St. Louis) and Dr. Colin Stine (University of Maryland School of Medicine) each examined the role of the commensal microbiota in childhood growth. Dr. Planer addressed patterns and characteristics of the microbiota as they relate to childhood growth, and Dr. Stine focused on particular bacterial species that may contribute to normal growth. Dr. Nataro opened the workshop by identifying key research gaps and posing questions about possible mechanisms by which microbes could trigger stunting and other potential consequences, even without overt diarrhea (i.e. 'subclinical' infection). These questions were revisited during the discussion period.

2. The burden of enteric infection is not limited to diarrhea

A major limitation in our assessment of the potential value of vaccines that could help control common enteric infections is an overly narrow interpretation of benefit as mainly the prevention of deaths from diarrhea. Even though the global diarrhea mortality remains unacceptably high (at some 500,000/yr for children <5 yo), it is likely that the far greater human and economic costs of enteric infections (with or without overt diarrhea) are on healthy child growth and development, and perhaps long-term cognitive and metabolic consequences. These costs are still not counted in official assessments of DALYs (Disability Adjusted Life Years combine mortality or years of life lost with morbidity or years lost to estimated disability, for an overall assessment of the "burden" of any "disease") or economic costs [1-9] largely because, unlike "diarrhea," these growth, cognitive and even metabolic consequences have not been formally categorized as disease entities. However they are totally analogous, in that each has multiple potential and often complex causes and measureable effects on human health and productivity. "Diarrhea" is actually a somewhat strange cultural notion, describing the physical consistency and frequency of physiologic evacuations from one end of a long multifunctional tube (the GI tract), that can be affected by eating an excess of polyols

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(e.g. sorbitol) or other intentional osmotic laxatives, or by a wide range of functional (irritable bowel syndrome), immunologic (inflammatory bowel disease), or pathogenic microbial infections (cholera, et al.). Hence, the most important step in advancing research and control of enteric infections could well be to recognize disorders and capture them by name, as we do "infectious diarrhea". Hence we suggest for growth decrements "*HAZdrop*", representing statistically significant reduction in the height-for-age Z score (HAZ) during the critical growth period that is also most likely affected by common multiple enteropathogen exposures, (from 4 to 24 months of age). For cognitive impairment we suggest "*COG-hit*" to represent the significant cognitive growth impairment that may occur in association with repeated or multiple enteric infections and intestinal and systemic inflammation, again in the critical window when most brain synaptogenesis occurs in humans (over the first 2 years of life after birth). For later metabolic consequences we offer "*MET-hit*" to signify the metabolic derangement that may predispose to obesity, diabetes and cardiovascular diseases later in life following early childhood infections, inflammation or undernutrition, as occurs with repeated and multiple enteric infections in early life. Field and bench research focused on these disorders could help define the magnitude, causes and costs (in terms of DALYs) of HAZdrop and COG-hit as well as the overt 'squirts' we call diarrhea. This workshop addresses these long-term impacts, their potential causes, mechanisms and magnitude.

3. The triple burden of enteric infection

Shown in Fig. 1 [adapted from Ref. [3]] are the range of potential health consequences from enteric infections. These include overt diarrhea as well as a range of potentially long-term effects such as growth failure (henceforth "HAZdrop"), cognitive impairment (henceforth "COG-hit") and later life metabolic syndrome (henceforth "MET-hit") that may follow 'asymptomatic' (meaning without overt diarrhea) or symptomatic enteric infections. Although much more information is needed to better understand the magnitude and mechanisms of each disorder (and hence optimal and innovative interventions), references supporting each of these arrows are shown. Numerous studies document lasting stunting, cognitive and metabolic consequences of diarrheal or asymptomatic enteric infections, sometimes independently of other consequences [3–30]. In addition to the potential association of diarrhea with impaired cognition independently of also significant effects on growth reported from studies in Northeast Brazil by Pinkerton et al. [12], Kvestad et al. have also described associations of diarrhea with impaired cognition independently of growth in children in North India as well [31].

Several specific enteric protozoan and bacterial pathogens have been incriminated in growth and even later cognitive effects. These include enteroaggregative *E. coli*, *Cryptosporidium, Campylobacter* and *Giardia* [32–36]. Furthermore, the cognitive deficit that has been reported as being most impaired is higher executive function and semantic fluency [11,37], effects also noted in Alzheimer's Disease; hence the report of ApoE4 allele risks that, somewhat surprisingly, appear to be protective of these cognitive effects only in those children with heavy diarrhea burdens in early childhood [38,39]. Additional data are emerging in the laboratory of Dr. J. Kipnis suggesting associations between serum interferon-gamma levels and social dysfunction, suggesting a link with this key anti-pathogen immune response [40].

Further studies of the association of impaired growth with early childhood enteric and other infections suggest that the mechanisms involved may include reduced production of growth signaling (e.g. IGFBP-3 and IGF-1) [41]. Recent work by Kosek and

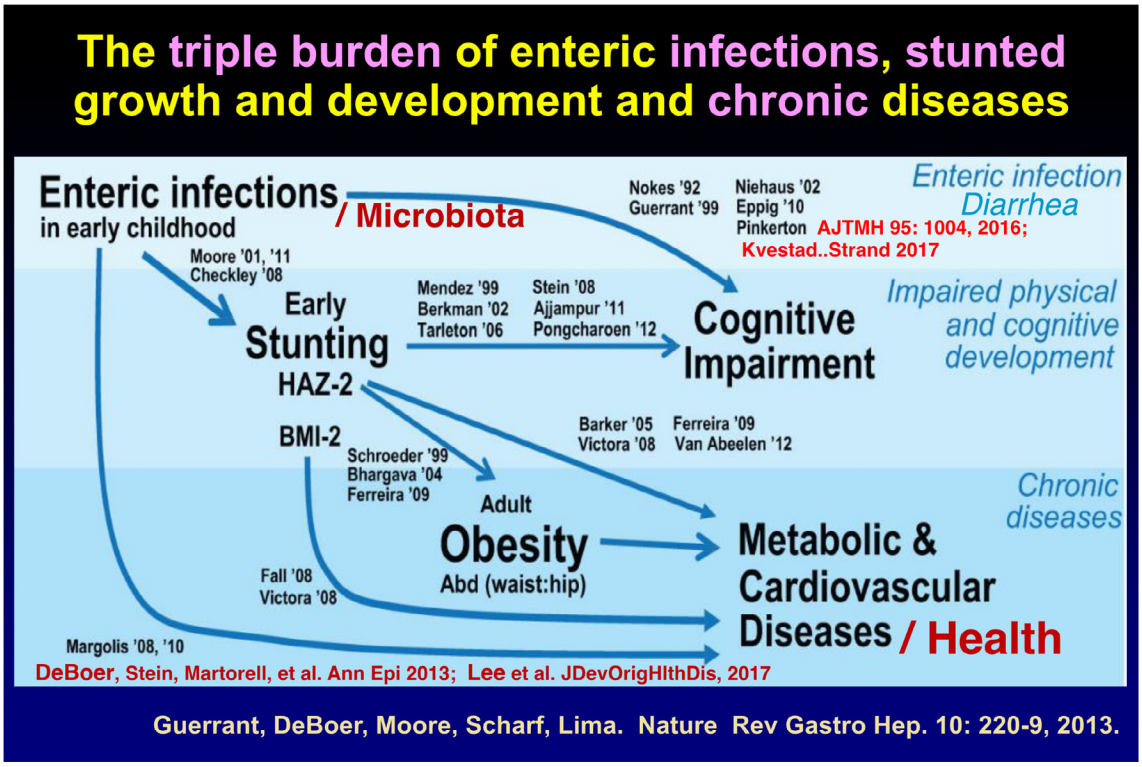

Fig. 1. The triple burden of enteric infections, stunted growth and development of chronic diseases. Recurrent and chronic enteric infections lead to linear growth faltering ("stunting" refers to height-for-age two or more Z score units below the international median). Infections may exert their effects directly and/or via perturbations of the intestinal microbiome. Linear growth faltering is associated directly or indirectly with cognitive impairment, and with later life disorders, including obesity and metabolic syndrome (adapted from Ref. [3]).

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