

Environmental Enteric Dysfunction and Growth Failure/Stunting in Global Child Health

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Approximately 25% of the world's children aged <5 years have stunted growth, which is associated with increased mortality, cognitive dysfunction, and loss of productivity. Reducing by 40% the number of stunted children is a global target for 2030. The pathogenesis of stunting is poorly understood. Prenatal and postnatal nutritional deficits and enteric and systemic infections clearly contribute, but recent findings implicate a central role for environmental enteric dysfunction (EED), a generalized disturbance of small intestinal structure and function found at a high prevalence in children living under unsanitary conditions. Mechanisms contributing to growth failure in EED include intestinal leakiness and heightened permeability, gut inflammation, dysbiosis and bacterial translocation, systemic inflammation, and nutrient malabsorption. Because EED has multiple causal pathways, approaches to manage it need to be multifaceted. Potential interventions to tackle EED include: (1) reduction of exposure to feces and contact with animals through programs such as improved water, sanitation, and hygiene; (2) breastfeeding and enhanced dietary diversity; (3) probiotics and prebiotics; (4) nutrient supplements, including zinc, polyunsaturated fatty acids, and amino acids; (5) antiinflammatory agents such as 5-aminosalicylic acid; and (6) antibiotics in the context of acute malnutrition and infection. Better understanding of the underlying causes of EED and development of noninvasive, practical, simple, and affordable point-of-care diagnostic tools remain key gaps. "Omics" technologies (genomics, epigenomics, transcriptomics, proteomics, and metabolomics) and stable isotope techniques (eg, ¹³C breath tests) targeted at children and their intestinal microbiota will enhance our ability to successfully identify, manage, and prevent this disorder.

Malnutrition in young children increases the risks of death from diarrhea, pneumonia, and other infectious diseases and is associated with growth failure, cognitive delay, and loss of productivity.¹⁻⁴ Malnutrition manifests as "wasting," with loss of tissue mass and marked reductions (>2 SDs below the mean) in weight-for-height z scores, and "stunting," a chronic condition associated with height-for-age

z scores less than -2. The pathogenesis of stunting, which is more prevalent than wasting, is poorly understood. Prenatal and postnatal nutritional deficits and enteric and systemic infections clearly contribute, but recent findings implicate a central role for environmental enteric dysfunction (EED), a generalized disturbance of small intestinal structure and function with blunting or atrophy of intestinal villi, inflammatory cell infiltrates,

abstract

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TABLE 1 Determinants and Complications of EED

Determinants	Mechanisms, Consequences, and Treatment
Socioeconomic	Gross domestic product
Environmental	Water, sanitation, and hygiene Exposure to animal feces Crowding Seasonality
Early life exposures	Helminthic and parasitic infections Maternal microbiome and EED Mode of birth (vaginal versus cesarean) Infant and young child feeding practices
Gut microbiota	Microbiome diversity Functions of specific members of the microbiota Microbial translocation Prebiotics and probiotics Dietary diversity
Nutrients	Nutrient deficiencies (eg, zinc deficiency) Increased nutrient requirements Proinflammatory nutrients (eg, iron) Nutrient malabsorption
Immunity	Vaccine responses
Growth failure/undernutrition	Stunting Severe acute malnutrition
Inflammation	Gut inflammation Systemic inflammation Antiinflammatory agents

and hyperplasia of small intestinal crypts (Fig 1). EED is found at a high prevalence in stunted children living under unsanitary conditions and is pandemic in developing countries with limited resources (Table 1). Major gaps in our understanding of the pathogenesis of EED and its relationship to stunting limit our ability to diagnose and effectively prevent and treat this condition.

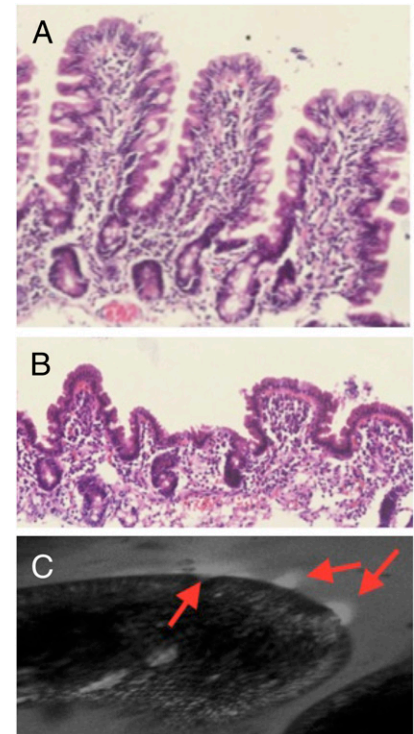
The present state-of-the-art consensus statement summarizes a 3-day meeting organized by the International Atomic Energy Agency, which focused on EED and the prospects for its reduction or amelioration in children living in the developing world.

PATHOBIOLOGY OF EED

EED may be defined as a global disturbance of intestinal structure and function that has its origin in environmental factors. The condition occurs with high frequency in developing areas with poor sanitation and limited public health resources, in association with microbial and parasitic contamination of food

and water. It is unlikely that any 1 pathogen explains the pathology of EED and more likely that it represents frequent, low-inoculum exposure to a range of pathogens,^{5,6} which could be regarded as a form of dysbiosis.

The identification that there is a change in small intestinal structure and function in the tropics originated in the 1960s,¹ but it is only in the last ~2 decades that we have come to understand that it may have implications for nutrition and long-term health of children living in low-resource settings.²⁻⁴ In early reports, the focus was on structural derangements (shortened, blunted villi and increased crypt depth) and disturbances of permeability and absorption. More recently, additional derangements have been identified, including intestinal inflammation,⁷ systemic inflammation,⁸ and changes in the microbiome.⁹ The complexity of the EED syndrome is such that these derangements cannot be assumed to operate to the same degree in different children. For example, 1 child may have a very “leaky” gut with severe

**FIGURE 1**

Histologic sections from distal duodenal biopsy specimens from Zambian patients with EED. (A) Relatively normal mucosa has long, slender villi and short crypts, with only a slight increase in lamina propria lymphocytes; the villus height: crypt depth ratio approximates 3:1. (B) A biopsy specimen from a child with severe EED and moderate malnutrition showing villus shortening and reduction in villus height: crypt depth ratio to slightly more than 1:1. (C) Confocal laser endomicroscopy shows leakage of fluorescein (arrows) around a villus after an intravenous injection into the intestinal lumen.

microbial translocation (entry of gastrointestinal organisms into the systemic compartment) but not much malabsorption, whereas another child may have more significant malabsorption but only mild translocation. The meeting organized by the International Atomic Energy Agency identified several domains that may need to be individually measured to provide a full picture of gut dysfunction and to assess the impact of different interventions. These domains describe axes of measurement and aspects of pathophysiology: (1) gut leakiness/permeability¹⁰; (2) microbial translocation^{10,11}; (3) gut

inflammation⁷; (4) systemic inflammation⁸; (5) dysbiosis⁹; and (6) nutrient malabsorption.¹¹⁻¹³

As opposed to focal defects (as seen in Crohn's disease), EED predominantly affects the proximal small intestine in a global distribution. The condition is seasonal,⁵ reversible,¹⁴ and generally asymptomatic, as distinct from diarrheal disease. The anatomic and pathophysiologic basis of EED is reflected in the aforementioned domains. As with other enteropathies, EED is characterized by villus blunting, inflammation in the epithelium and lamina propria, and leakiness due to perturbation of tight junction integrity and microerosions (Fig 1). Evidence is also found of disturbances of mucus¹⁵ and antimicrobial peptides,¹⁶ which, together with tight junction failure and microerosions, could permit entry of microorganisms and their component parts into the systemic compartment from which, in health, they would be excluded. This translocation drives gut inflammation, further exacerbating gut dysfunction, and systemic inflammation,⁸ which can further perturb immune function and lead to anorexia. This positive feedback underlies the vicious cycle of malnutrition, infection, and immune failure described >5 decades ago in classic studies of malnutrition in Central America.⁴

Within the spectrum of EED, several disorders are recognized that look phenotypically similar and may have similar effects on childhood growth. Although these disorders have a common origin in unsanitary environments,^{4,6} they likely have distinct etiopathogeneses and therefore present different or overlapping targets for intervention. For example, the enteropathy of severe acute malnutrition comprises elements of acute and chronic infection, inflammation, and malabsorption. Seen in children with

weight-for-age z scores of -3 SDs or less, it has high (10%-20%) mortality when complicated by diarrhea, pneumonia, sepsis, hypoglycemia, and/or dehydration.^{17,18} EED may also include components of HIV-related enteropathy⁵ and aflatoxin-mediated enteropathy,¹⁹ conditions that we currently know very little about.¹ Zinc deficiency can cause enteropathy, but extensive experience with zinc supplementation suggests that it can ameliorate the effects of diarrhea and reduce gastrointestinal permeability but does not improve nutrient absorption.²⁰ Helminth infection, established for hookworm but not clearly shown for other helminths, may also contribute to EED.

It is self-evident from these observations that interventions for the various elements of EED are distinct and should be evaluated separately. A recent review proposed the inclusion of exposure to chemical toxicants such as pesticides and drugs as potential causes of EED.²¹ Put simply, EED does not have a single cause, and it is unlikely to be resolved by a single intervention.

GROWTH FAILURE AND STUNTING IN MALNUTRITION AND EED

The term "stunted" is applied to infants and children whose lengths (or heights) are >2 SDs below the median for age as determined by using World Health Organization growth standards. Stunting in the developing world results most commonly from chronic nutrient deficiencies, recurrent infection(s), and/or chronic inflammation (including EED). Nevertheless, large cohorts of "stunted" subjects may also include infants and children with hormonal or metabolic disorders causing postnatal growth failure; children with genetic or familial forms of short stature; and premature and/or small for

gestational age infants who fail to achieve adequate catch-up growth.

Indeed, in 20% to 25% of infants and children considered "stunted," the growth failure begins in utero: prematurity and intrauterine growth restriction, particularly in combination, increase the risk of postnatal stunting²²⁻²⁵ by twofold to sevenfold. This explains, in part, the high rates of stunting in developing countries, where mean length-for-age z scores at birth approximate -0.5, and low birth weight (LBW) is 6 times more common than in the developed world.^{23,25}

The health, maturity, and economic and social status of the mother play central roles in the pathogenesis of LBW and the growth of the child after birth. Factors predisposing to LBW and childhood stunting include: a history of moderate or severe maternal malnutrition, stunting, or early age at pregnancy; suboptimal pregnancy weight gain; maternal smoking; and inadequate infant feeding practices.²²⁻²⁵ The advent of EED in infancy or early childhood likely amplifies growth deficits sustained during the intrauterine and perinatal periods, resulting in stunting. Length-for-age z scores of stunted children typically decline from birth to a nadir between 18 and 24 months of age, presumably because rapidly growing infants and toddlers are particularly vulnerable to nutritional, infectious, and toxic environmental insults. In concert with nutritional deficits incurred during fetal, perinatal, and early postnatal life, the imposition of EED may limit nutrient delivery and utilization and thereby impair the maturation and proliferation of small intestinal epithelial cells, renal nephrons, pancreatic β cells, and skeletal myocytes and growth plate chondrocytes.^{26,27}

The specific mechanisms by which EED causes growth failure and postnatal stunting are poorly understood, although inadequate or

inconsistent energy intake, recurrent infection, and local and systemic inflammation likely play important roles. Factors contributing to growth failure may include immaturity of the gut microbiome²⁸ and deficiencies of certain gut microbes and/or breast milk constituents such as sialylated oligosaccharides that promote gut barrier integrity, nutrient utilization, and tissue anabolism.^{29–31} Even in the absence of diarrhea, the permeability of the small bowel toward carbohydrates and α_1 -antitrypsin is increased,^{7,32} suggesting a role for macronutrient malabsorption. Many children with EED also have deficiencies in micronutrients absorbed by the small bowel such as iron and zinc, which, if depleted, can reduce appetite, villous surface area, and gastrointestinal absorptive capacity.^{33,34}

Inflammation of the small intestine in EED is associated with high C-reactive protein levels and may be accompanied by release of cytokines that reduce appetite and food intake³⁵ and impede production and action of chondrocyte growth factors. Recent studies^{36,37} found that stunted, malnourished Ugandan infants and children (age 6 months–5 years) had high levels of interleukin 6 (IL-6), which blocks growth hormone induction of insulin-like growth factor 1 (IGF-1) production and inhibits IGF action at the growth plate.^{38,39} Likewise, IL-6 levels were elevated soon after delivery in a subset of Zimbabwean infants with LBW.⁸ Interestingly, IL-6 levels are high in children and adults with inflammatory bowel disease and correlate inversely with childhood growth rates and IGF-1 levels.⁴⁰ Thus, the rise in IL-6 (and other cytokines) in association with small bowel inflammation may limit food intake, IGF-1 production, and linear growth in children with EED. Inadequate intake and malabsorption of zinc in EED may also reduce IGF-1

production and action⁴¹ and thereby attenuate linear growth.

Growth failure in EED may be exacerbated by the development of acute malnutrition, most commonly a consequence of gastrointestinal and pulmonary infections and sepsis.⁴² Endocrinologic studies^{36,37} provide insight into the pathogenesis of growth failure in malnourished children. Nutrient deprivation provokes a striking increase in growth hormone and fall in insulin, which in concert promote lipolysis and deplete white adipose fat stores and thereby reduce levels of the adipocyte hormone leptin. Hypoleptinemia downregulates the hypothalamic-pituitary-thyroid axis and inhibits conversion of T4 to its more active form, T3.⁴³ The fall in T3 impairs chondrocyte maturation and growth. The stress of acute malnutrition and concurrent infection activates the hypothalamic-pituitary-adrenal axis and stimulates a rise in cortisol^{36,37} and IGF binding protein 1, which in combination inhibit IGF-1 action and induce chondrocyte apoptosis.^{44,45} A reduction in hepatic growth hormone receptor expression⁴⁶ and inhibition of growth hormone signaling⁴⁷ by fibroblast growth factor 21 limit IGF-1 production and thereby contribute to growth failure in patients with EED.

Therapeutic measures in EED, including nutritional supplements and antibiotics, may fail to restore growth in children stunted before the age of 2 years.²⁴ In some cases, this outcome may simply reflect a genetic or familial tendency to short stature. Alternatively, failure of catch-up growth in children with prenatal or early postnatal growth failure might be explained by: (1) inadequate reserve, or epigenetic changes,^{48,49} in cells critical for growth, including myocytes and chondrocytes; (2) long-term defects in small intestinal maturation and growth⁵⁰; and/or (3) recurrent bouts

of nutrient deprivation, infection, and cytokine excess associated with small bowel inflammation. The SHINE (Sanitation Hygiene Infant Nutrition Efficacy) trial is currently investigating the hypothesis that EED has adverse consequences in addition to postnatal growth failure, including reduced oral vaccine efficacy, anemia, impaired neurocognitive development, and fetal growth restriction and prematurity resulting from maternal EED.⁵¹ EED has recently been linked to reduced efficacy of oral polio and rotavirus vaccines in Bangladeshi infants.⁵²

EED BIOMARKERS AND DIAGNOSTIC TESTS

Difficulties in identifying the multiple etiologies of EED and in distinguishing EED from other types of intestinal dysfunctions impose considerable challenges for diagnosis and hamper development of specific diagnostic tests. Endoscopic and histopathologic evaluation of small intestinal biopsy specimens, with continuous measures of mucosal architecture (villus height in micrometers rather than ordinal scales of blunting),⁵ allow for direct observation of aberrant epithelial structures and inflammation status. However, noninvasive or less-invasive diagnostic assays are preferred for logistic reasons (ie, use in nonclinical settings and because they are better accepted by patients). Depending on the aspect of gut function or dysfunction of interest, biomarkers of EED may fall under 1 of 5 categories,⁵³ namely: (1) intestinal absorption and mucosal permeability; (2) enterocyte mass and function; (3) inflammation; (4) microbial translocation and immune activation; and (5) intestinal injury and repair.

The most commonly applied noninvasive assay to assess EED is a dual sugar test, the lactulose:mannitol test, which is based

on oral dosing and subsequent urinary measurement of lactulose and mannitol to evaluate both epithelial absorptive capacity and permeability in the small intestine (aforementioned domains 1 and 7).^{54,55} In addition, recent research has identified various serum and fecal biomarkers of intestinal inflammation in the context of EED.^{3,56} Serum biomarkers include lipopolysaccharide, soluble CD 14, IGF-1, ferritin, IL-6, IL-1 β , C-reactive protein, zonulin, and endogenous endotoxin-core antibody (EndoCab, Hycult Biotech, Uden, the Netherlands). Fecal biomarkers include regenerating islet-derived 1 beta, calprotectin, myeloperoxidase, neopterin, α_1 -antitrypsin, and lactoferrin. Although these biomarkers permit assessment of intestinal/systemic inflammation and/or intestinal epithelial barrier dysfunction, the main limitation to their use is that they are not specific for EED because they correlate with prevalence, activity, and/or severity of various other gastrointestinal diseases. One of the downstream consequences of EED is vaccine failure,^{28,57} but it has not been generally accepted as a diagnostic measure of EED. Cutting edge innovations such as -omics and nuclear technologies (stable isotope techniques) may provide a much-needed capability to diagnose and better understand EED.

APPLICATION OF -OMICS TECHNOLOGY

Much has been learned about the biology of health and disease states through application of -omics technologies: genomics, epigenomics, transcriptomics, proteomics, and metabolomics.⁵⁸ The essence of -omics is an agnostic survey across the total spectrum of a given type of molecule or analyte class. As a pathologic condition, EED is an excellent candidate for -omics surveys because so little is known

about the mechanisms through which it exerts its deleterious effects.

A large transcriptomic study of rural African children using a novel method to assess host transcripts in feces found diverse activation of many of the immunologic responses seen in the gut epithelium.⁵⁹ Twelve transcripts were associated with the severity of EED, including chemokines that stimulate T-cell proliferation, Fc fragments of multiple immunoglobulin families, interferon-induced proteins, activators of neutrophils and B cells, and mediators that dampen cellular responses to hormones. EED-associated transcripts were mapped to pathways related to cell adhesion and responses to a broad spectrum of viruses, bacteria, and parasites. Several mucins, regulatory factors, and protein kinases associated with maintenance of the mucous layer were expressed at lower levels in children with EED than in normal children. The pattern of expression was compatible with an assault by multiple microorganisms from diverse phyla. In addition, antiviral transcripts were detected. This rich data set offers clues for those seeking pharmacologic intervention against EED as well as novel fecal biomarkers for the condition.

Epigenomics and proteomics have not been applied to EED as far as we know. Metabolomic analysis has been undertaken, but major findings have not been released.⁶⁰ Although the complex effects of prenatal and postnatal environmental factors clearly complicate the analysis of children with EED, we anticipate future research using genomic and metabolomic approaches to dissect the pathobiology of EED.

DIAGNOSTIC POTENTIAL OF STABLE ISOTOPE ASSAYS

Beyond the use of the lactulose: mannitol test and various serum and fecal biomarkers,^{11,56} nonradioactive,

stable isotope techniques are emerging as promising noninvasive/less invasive, safe tools for measuring gastrointestinal function and determining EED. The foundation of these methods is oral administration of an isotopically labeled compound and subsequent monitoring of the appearance of the compound or its catabolic products in breath, feces, urine, and/or blood.⁶¹ Depending on the type of labeled compound, stable isotope assays can assess epithelial function in several domains (ie, absorption, permeability, metabolism) and can be used to characterize a particular microorganism or group of microorganisms that catabolize the ingested compound. This latter feature is especially useful for probing microbial activities in the upper gastrointestinal tract in EED; analysis of fecal microbiota⁹ provides an inadequate proxy for the composition and function of microbiota in the stomach, the duodenum, or the small bowel.

Characterizing microbial activity, particularly in the upper gastrointestinal tract, is important for 2 reasons. First, EED is associated with infections by pathogens (eg, *Helicobacter pylori*) and microbial overgrowth and general dysbiosis in the small intestine in humans. Second, exposure to a defined mixture of commensal bacterial isolates, including *Escherichia coli* and members of the *Bacteroidales*, triggered a phenotype in moderately malnourished mice that resembled human EED.⁶² This finding provides strong evidence for the role played by microorganisms in the pathogenesis of EED.

Available noninvasive, stable isotope breath tests for potential use in EED include, but are not limited to, a highly sensitive and specific ¹³C-urease assay for *H pylori*⁶³ and application of various ¹³C-sugars (eg, sucrose, xylose, glucose, lactose)^{64,65} or ¹³C-labeled glycosyl ureides^{66,67} to

measure epithelial barrier function, absorptive capacity, and intestinal transit time, and to identify small intestinal bacterial overgrowth and dysbiosis. In addition, intestinal absorption and bioavailability of specific micronutrients, in particular iron and zinc, from diets can be measured after oral ingestion of isotopically labeled iron (^{54}Fe , ^{57}Fe , and ^{58}Fe)⁶⁸ and zinc (^{67}Zn , ^{68}Zn , and ^{70}Zn)^{12,69} compounds. Although the use of different stable isotope compounds in a single composite assay for simultaneous assessment of multiple intestine-associated clinical end points has not yet been fully exploited, the available and established stable isotope assays have great potential for application in EED diagnostics and research.

EMERGING APPROACHES FOR THE PREVENTION AND TREATMENT OF EED

The treatment of EED is fraught with difficulties. First, in the absence of robust point-of-care biomarkers, the identification of EED in the individual child is problematic. Moreover, there is no robust evidence from clinical trials that specific interventions can cure or ameliorate the signs and symptoms of EED.

Because EED has its roots in the environment, the mainstay of preventing the condition is to “clean” the environment. This approach is challenging because water scarcity still afflicts 40% of the world’s population, and 13% of the population still defecates in the open.⁷⁰ Furthermore, one-sixth of the world’s people lack access to safe drinking water. The provision of basic sanitation facilities, potable water, and improved hygiene practices cut the chain of transmission of pathogenic bacteria that can colonize the small intestine and cause EED. Indeed, a study in Bangladesh found that ensuring a clean environment increased population height-for-age 0.54 SD

compared with children living in default conditions.⁷¹ Moreover, stunting prevalence was reduced by 22%. More recently, a public sanitation program in Mali showed that enhanced access to toilets did not reduce the prevalence of diarrhea but increased childhood growth, particularly in those <2 years of age.⁷² A possible explanation could be reduced chronic exposure to pathogenic bacteria, resulting in reduced severity or prevalence of EED.

Ensuring hygiene at critical times is critical to preventing EED. A study conducted in slums and villages in Bangladesh revealed that 40% of complementary foods prepared by mothers were contaminated with *E coli*; this contamination resulted in higher rates of diarrhea and malnutrition.⁷³ It is now believed that zinc deficiency, rampant in developing countries, co-exists with EED and increases the severity of the condition.^{20,33,34} Given the inadequate dietary intake of zinc in children living in developing countries, the importance of its supplementation,⁷⁴ either long term or at least as part of treatment of diarrhea, cannot be overestimated. The claim that exclusive breastfeeding can reduce gut inflammation was recently validated in South African children.⁷⁵

In summary, emerging evidence suggests that the following factors, in combination, can reduce the incidence, prevalence, and severity of EED: (1) access to safe drinking water and improved hygiene practices in low-income countries; (2) provision of sanitary toilet facilities and changes in public behavior regarding their use; (3) exclusive breastfeeding for the first 6 months and continued breastfeeding thereafter; and (4) zinc supplementation.

Because stunting is a hallmark of EED, a major goal should be to prevent the condition as well as treat its complications. In the context of poor socioeconomic conditions,

preventive and therapeutic measures include increasing access of children to appropriate and adequate diets containing animal-source foods, supplementation with zinc, and adequate treatment of recurrent illnesses such as diarrhea and pneumonia. Population-wide prevention of EED will require adequate nutrition and health maintenance of all girls of reproductive age and women prior to, during, and after pregnancy.

Under conditions of extreme food insecurity, supplementation with nutritious ready-to-use food for children with severe or moderate acute malnutrition has been shown to enhance clinical recovery.^{76,77} Agents that can offset or reduce chronic inflammation at the gut mucosal level are currently being evaluated. These include 5-aminosalicylic acid, which in a recent study was not efficacious⁷⁸; the nasal steroid budesonide; and an immunomodulatory small molecule called ogulfanide disodium.³ Only well-designed, randomized controlled trials that assess efficacy and adverse effects in settings of high prevalence of stunting/EED can lead the way to effective and safe treatments.

SUMMARY AND FUTURE DIRECTIONS

Reducing by 40% the number of children aged <5 years who are stunted is a global target for 2030. Systematic reviews have revealed that optimal nutrition intervention packages for high-risk children may only partially reduce the prevalence and severity of stunting.^{79,80} We do not know if nutritional therapies fail because stunted children have altered intestinal microbiota, insufficient nutrient intake, nutrient malabsorption, or disordered partition of nutrients. It is also unclear if nutrient utilization/wastage is too high to permit adequate lean tissue accretion.

Finally, we don't know if insults inflicted before or soon after birth are fully reversible even with adequate postnatal nutrient repletion.

The complexity of the EED syndrome is such that gastrointestinal derangements cannot be assumed to operate to the same degree in different children. There may be considerable individual variation in gut "leakiness", bacterial translocation, malabsorption, and nutrient requirements. Given the burden of concurrent infection and inflammation, EED-afflicted children may require considerably higher nutrient intakes than healthy children in order to maintain normal weight gain.

Our understanding of EED is severely limited by its complex spectrum, absence of robust biomarkers, and noninvasive, simple point-of-care diagnostic tools. Several domains may need to be evaluated in each child to provide a full picture of gut dysfunction and to assess the impact of different interventions. These domains include: (1) gut leakiness/permeability; (2) microbial translocation; (3) gut inflammation; (4) systemic inflammation; (5) dysbiosis; and (6) nutrient malabsorption. Further investigation will be needed to characterize fully the effects of gut dysfunction on hormonal and metabolic status, childhood growth, and neurocognitive function.

Potential interventions to tackle EED should include: (1) increased access to clean water, and improved

sanitation and hygiene, including reduction of exposure to feces and contact with animals; (2) promotion of dietary diversity and breastfeeding; (3) adequate supplementation with micro- and macronutrients including zinc and amino acids; (4) antiinflammatory agents; and (5) antibiotics for children with severe acute malnutrition and infection. Some of these interventions (especially water, sanitation, and hygiene, infant feeding practices, and nutrient repletion) are being tested individually or combined in large randomized controlled studies in a number of countries. Information gained from these investigations may guide the development of novel therapies in the future.

The application of omics technologies (eg, genomics, epigenomics, transcriptomics, proteomics, metabolomics) and use of stable isotopes should allow us to better define the nature and extent of gastrointestinal damage and dysfunction in EED and can be used to characterize microbial activities in the upper gastrointestinal tract in affected children. Stable isotopes can also be employed to assess body composition as a proxy for dietary quality and nutritional status and as a determinant of childhood morbidity and mortality. While validation of the various diagnostic techniques is obligatory, these new approaches should ultimately enhance our ability to prevent and treat environmental enteropathy.

CONCLUSIONS

EED does not have a single cause or even a single causal pathway, and it is unlikely to be resolved by a single intervention. The identification of EED is fraught with difficulties due to the absence of robust point-of-care biomarkers. Better understanding of the underlying causes and pathogenesis of EED, development of noninvasive, practical, simple, and affordable point-of-care diagnostic tools, and longitudinal studies designed to treat or ameliorate signs and symptoms of EED remain key gaps. Cutting-edge innovations using the field of -omics and stable isotope techniques may provide a much-needed capability to better understand, prevent, and treat EED.

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ABBREVIATIONS

EED: environmental enteric dysfunction
IGF: insulin-like growth factor
IL-6: interleukin 6
LBW: low birth weight

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REFERENCES

- Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. *Am J Trop Med Hyg.* 2012;86(5):756–763
- Keusch GT, Denno DM, Black RE, et al. Environmental enteric dysfunction: pathogenesis, diagnosis, and clinical consequences. *Clin Infect Dis.* 2014;59(suppl 4):S207–S212
- Petri WA Jr, Naylor C, Haque R. Environmental enteropathy and malnutrition: do we know enough to intervene? *BMC Med.* 2014;12:187
- Guerrant RL, DeBoer MD, Moore SR, Scharf RJ, Lima AA. The impoverished gut—a triple burden of diarrhoea, stunting and chronic disease. *Nat Rev Gastroenterol Hepatol.* 2013;10(4):220–229
- Kelly P, Menzies I, Crane R, et al. Responses of small intestinal architecture and function over time to environmental factors in a tropical population. *Am J Trop Med Hyg.* 2004;70(4):412–419
- Humphrey JH. Child undernutrition, tropical enteropathy, toilets, and handwashing. *Lancet.* 2009;374(9694):1032–1035
- Kosek M, Haque R, Lima A, et al; MAL-ED Network. Fecal markers of intestinal inflammation and permeability associated with the subsequent acquisition of linear growth deficits in infants. *Am J Trop Med Hyg.* 2013;88(2):390–396
- Prendergast AJ, Rukobo S, Chasekwa B, et al. Stunting is characterized by chronic inflammation in Zimbabwean infants. *PLoS One.* 2014;9(2):e86928
- Smith MI, Yatsunenکو T, Manary MJ, et al. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science.* 2013;339(6119):548–554
- Kelly P, Besa E, Zyambo K, et al. Endomicroscopic and transcriptomic analysis of impaired barrier function and malabsorption in environmental enteropathy. *PLoS Negl Trop Dis.* 2016;10(4):e0004600
- Korpe PS, Petri WA Jr. Environmental enteropathy: critical implications of a poorly understood condition. *Trends Mol Med.* 2012;18(6):328–336
- Krebs NF, Miller LV, Hambidge KM. Zinc deficiency in infants and children: a review of its complex and synergistic interactions. *Paediatr Int Child Health.* 2014;34(4):279–288
- Denno DM, VanBuskirk K, Nelson ZC, Musser CA, Hay Burgess DC, Tarr PI. Use of the lactulose to mannitol ratio to evaluate childhood environmental enteric dysfunction: a systematic review. *Clin Infect Dis.* 2014;59(suppl 4):S213–S219
- Lindenbaum J, Harmon JW, Gerson CD. Subclinical malabsorption in developing countries. *Am J Clin Nutr.* 1972;25(10):1056–1061
- Amadi B, Fagbemi AO, Kelly P, et al. Reduced production of sulfated glycosaminoglycans occurs in Zambian children with kwashiorkor but not marasmus. *Am J Clin Nutr.* 2009;89(2):592–600
- Dhaliwal W, Bajaj-Elliott M, Kelly P. Intestinal defensin gene expression in human populations. *Mol Immunol.* 2003;40(7):469–475
- Amadi B, Kelly P, Mwiya M, et al. Intestinal and systemic infection, HIV, and mortality in Zambian children with persistent diarrhea and malnutrition. *J Pediatr Gastroenterol Nutr.* 2001;32(5):550–554
- Kerac M, Bunn J, Chagaluka G, et al. Follow-up of post-discharge growth and mortality after treatment for severe acute malnutrition (FuSAM study): a prospective cohort study. *PLoS One.* 2014;9(6):e96030
- Smith LE, Stoltzfus RJ, Prendergast A. Food chain mycotoxin exposure, gut health, and impaired growth: a conceptual framework. *Adv Nutr.* 2012;3(4):526–531
- Lindenmayer GW, Stoltzfus RJ, Prendergast AJ. Interactions between zinc deficiency and environmental enteropathy in developing countries. *Adv Nutr.* 2014;5(1):1–6
- Mapesa JO, Maxwell AL, Ryan EP. An exposome perspective to environmental enteric dysfunction. *Environ Health Perspect.* 2016;124(8):1121–1126
- Tiwari R, Ausman LM, Agho KE. Determinants of stunting and severe stunting among under-fives: evidence from the 2011 Nepal Demographic and Health Survey. *BMC Pediatr.* 2014;14:239
- Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. *Paediatr Int Child Health.* 2014;34(4):250–265
- Sania A, Spiegelman D, Rich-Edwards J, et al. The contribution of preterm birth and intrauterine growth restriction to childhood undernutrition in Tanzania. *Matern Child Nutr.* 2015;11(4):618–630
- Christian P, Lee SE, Donahue Angel M, et al. Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries. *Int J Epidemiol.* 2013;42(5):1340–1355
- Thorn SR, Rozance PJ, Brown LD, Hay WW Jr. The intrauterine growth restriction phenotype: fetal adaptations and potential implications for later life insulin resistance and diabetes. *Semin Reprod Med.* 2011;29(3):225–236
- Zohdi V, Sutherland MR, Lim K, Gubhaju L, Zimanyi MA, Black MJ. Low birth weight due to intrauterine growth restriction and/or preterm birth: effects on nephron number and long-term renal health. *Int J Nephrol.* 2012;2012:136942
- Subramanian S, Huq S, Yatsunenکو T, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature.* 2014;510(7505):417–421
- Schwarzer M, Makki K, Storelli G, et al. Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition. *Science.* 2016;351(6275):854–857
- Blanton LV, Charbonneau MR, Salih T, et al. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. *Science.* 2016;351(6275):19
- Charbonneau MR, O'Donnell D, Blanton LV, et al. Sialylated milk oligosaccharides promote microbiota-dependent growth in

- models of infant undernutrition. *Cell*. 2016;164(5):859–871
32. Gilmartin AA, Petri WA Jr. Exploring the role of environmental enteropathy in malnutrition, infant development and oral vaccine response. *Philos Trans R Soc Lond B Biol Sci*. 2015;19;370(1671). pii: 20140143
 33. Southon S, Gee JM, Bayliss CE, Wyatt GM, Horn N, Johnson IT. Intestinal microflora, morphology and enzyme activity in zinc-deficient and Zn-supplemented rats. *Br J Nutr*. 1986;55(3):603–611
 34. Prasad AS. Clinical manifestations of zinc deficiency. *Annu Rev Nutr*. 1985;5:341–363
 35. Braun TP, Marks DL. Pathophysiology and treatment of inflammatory anorexia in chronic disease. *J Cachexia Sarcopenia Muscle*. 2010;1(2):135–145
 36. Bartz S, Mody A, Hornik C, et al. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. *J Clin Endocrinol Metab*. 2014;99(6):2128–2137
 37. Mody A, Bartz S, Hornik CP, et al. Effects of HIV infection on the metabolic and hormonal status of children with severe acute malnutrition. *PLoS One*. 2014;9(7):e102233
 38. De Benedetti F, Alonzi T, Moretta A, et al. Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. *J Clin Invest*. 1997;99(4):643–650
 39. Sederquist B, Fernandez-Vojvodich P, Zaman F, Säwendahl L. Recent research on the growth plate: impact of inflammatory cytokines on longitudinal bone growth. *J Mol Endocrinol*. 2014;53(1):T35–T44
 40. Sanderson IR. Growth problems in children with IBD. *Nat Rev Gastroenterol Hepatol*. 2014;11(10):601–610
 41. Cesur Y, Yordaman N, Doğan M. Serum insulin-like growth factor-I and insulin-like growth factor binding protein-3 levels in children with zinc deficiency and the effect of zinc supplementation on these parameters. *J Pediatr Endocrinol Metab*. 2009;22(12):1137–1143
 42. Jones KD, Thitiri J, Ngari M, Berkley JA. Childhood malnutrition: toward an understanding of infections, inflammation, and antimicrobials. *Food Nutr Bull*. 2014;35(suppl 2):S64–S70
 43. Araujo RL, Andrade BM, da Silva ML, Ferreira AC, Carvalho DP. Tissue-specific deiodinase regulation during food restriction and low replacement dose of leptin in rats. *Am J Physiol Endocrinol Metab*. 2009;296(5):E1157–E1163
 44. Säwendahl L. The effect of acute and chronic stress on growth. *Sci Signal*. 2012;5(247):pt9
 45. Lee PD, Giudice LC, Conover CA, Powell DR. Insulin-like growth factor binding protein-1: recent findings and new directions. *Proc Soc Exp Biol Med*. 1997;216(3):319–357
 46. Maes M, Maiter D, Thissen JP, Underwood LE, Ketelslegers JM. Contributions of growth hormone receptor and postreceptor defects to growth hormone resistance in malnutrition. *Trends Endocrinol Metab*. 1991;2(3):92–97
 47. Fazeli PK, Klibanski A. Determinants of GH resistance in malnutrition. *J Endocrinol*. 2014;220(3):R57–R65
 48. Gat-Yablonski G, Phillip M. Nutritionally-induced catch-up growth. *Nutrients*. 2015;7(1):517–551
 49. Quilter CR, Cooper WN, Cliffe KM, et al. Impact on offspring methylation patterns of maternal gestational diabetes mellitus and intrauterine growth restraint suggest common genes and pathways linked to subsequent type 2 diabetes risk. *FASEB J*. 2014;28(11):4868–4879
 50. Mickiewicz M, Zabielski R, Grenier B, et al. Structural and functional development of small intestine in intrauterine growth retarded porcine offspring born to gilts fed diets with differing protein ratios throughout pregnancy. *J Physiol Pharmacol*. 2012;63(3):225–239
 51. Prendergast AJ, Humphrey JH, Mutasa K, et al; Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial Team. Assessment of environmental enteric dysfunction in the SHINE trial: methods and challenges. *Clin Infect Dis*. 2015;61(suppl 7):S726–S732
 52. Naylor C, Lu M, Haque R, et al; PROVIDE Study Teams. Environmental enteropathy, oral vaccine failure and growth faltering in infants in Bangladesh. *EBioMedicine*. 2015;2(11):1759–1766
 53. Syed S, Ali A, Duggan C. Environmental enteric dysfunction in children: a review. *J Pediatr Gastroenterol Nutr*. 2016;63(1):6–14
 54. Lee GO, Kosek P, Lima AA, et al. Lactulose: mannitol diagnostic test by HPLC and LC-MSMS platforms: considerations for field studies of intestinal barrier function and environmental enteropathy. *J Pediatr Gastroenterol Nutr*. 2014;59(4):544–550
 55. Menzies I. Absorption of intact oligosaccharide in health and disease. *Biochem Soc Trans*. 1974;2(5):1042–1047
 56. Crane RJ, Jones KD, Berkley JA. Environmental enteric dysfunction: an overview. *Food Nutr Bull*. 2015;36(suppl 1):S76–S87
 57. Levine MM. Immunogenicity and efficacy of oral vaccines in developing countries: lessons from a live cholera vaccine. *BMC Biol*. 2010;8:129
 58. Chu Y, Corey DR. RNA sequencing: platform selection, experimental design, and data interpretation. *Nucleic Acid Ther*. 2012;22(4):271–274
 59. Yu J, Ordiz MI, Stauber J, et al. Environmental enteric dysfunction includes a broad spectrum of inflammatory responses and epithelial repair processes. *Cell Mol Gastroenterol Hepatol*. 2015;2(2):158–174.e1
 60. Preidis GA, Hotez PJ. The newest “omics”—metagenomics and metabolomics—enter the battle against the neglected tropical diseases. *PLoS Negl Trop Dis*. 2015;9(2):e0003382
 61. Romagnuolo J, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. *Am J Gastroenterol*. 2002;97(5):1113–1126

62. Brown EM, Wlodarska M, Willing BP, et al. Diet and specific microbial exposure trigger features of environmental enteropathy in a novel murine model. *Nat Commun*. 2015;6:7806
63. Di Rienzo TA, D'Angelo G, Ojetti V, et al. ¹³C-urea breath test for the diagnosis of *Helicobacter pylori* infection. *Eur Rev Med Pharmacol Sci*. 2013;17(suppl 2):51–58
64. Dellert SF, Nowicki MJ, Farrell MK, Delente J, Heubi JE. The ¹³C-xylose breath test for the diagnosis of small bowel bacterial overgrowth in children. *J Pediatr Gastroenterol Nutr*. 1997;25(2):153–158
65. Ritchie BK, Brewster DR, Davidson GP, et al. ¹³C-sucrose breath test: novel use of a noninvasive biomarker of environmental gut health. *Pediatrics*. 2009;124(2):620–626
66. Ruemmele FM, Heine WE, Keller KM, Lentze MJ. Metabolism of glycosyl ureides by human intestinal brush border enzymes. *Biochim Biophys Acta*. 1997;1336(2):275–280
67. Berthold HK, Schober P, Scheurlen C, et al. Use of the lactose-[¹³C] ureide breath test for diagnosis of small bowel bacterial overgrowth: comparison to the glucose hydrogen breath test. *J Gastroenterol*. 2009;44(9):944–951
68. Troesch B, Egli I, Zeder C, Hurrell RF, Zimmermann MB. Fortification iron as ferrous sulfate plus ascorbic acid is more rapidly absorbed than as sodium iron EDTA but neither increases serum nontransferrin-bound iron in women. *J Nutr*. 2011;141(5):822–827
69. Sparacino G, Shames DM, Vicini P, King JC, Cobelli C. Double isotope tracer method for measuring fractional zinc absorption: theoretical analysis. *Am J Physiol Endocrinol Metab*. 2002;282(3):E679–E687
70. United Nations. *The Millennium Development Goals Report*. New York, NY: Department of Economic and Social Affairs of the United Nations Secretariat; 2015
71. Lin A, Arnold BF, Afreen S, et al. Household environmental conditions are associated with enteropathy and impaired growth in rural Bangladesh. *Am J Trop Med Hyg*. 2013;89(1):130–137
72. Pickering AJ, Djebbari H, Lopez C, Coulibaly M, Alzua ML. Effect of a community-led sanitation intervention on child diarrhoea and child growth in rural Mali: a cluster-randomised controlled trial. *Lancet Glob Health*. 2015;3(11):e701–e711
73. Islam MA, Ahmed T, Faruque ASG, et al. Microbiological quality of complementary foods and its association with diarrhoeal morbidity and nutritional status of Bangladeshi children. *Eur J Clin Nutr*. 2012;66(11):1242–1246
74. Chen P, Soares AM, Lima AA, et al. Association of vitamin A and zinc status with altered intestinal permeability: analyses of cohort data from northeastern Brazil. *J Health Popul Nutr*. 2003;21(4):309–315
75. Moodley-Govender E, Mulol H, Stauber J, Manary M, Coutosoudis A. Increased exclusivity of breastfeeding associated with reduced gut inflammation in infants. *Breastfeed Med*. 2015;10(10):488–492
76. Christian P, Shaikh S, Shamim AA, et al. Effect of fortified complementary food supplementation on child growth in rural Bangladesh: a cluster-randomized trial. *Int J Epidemiol*. 2015;44(6):1862–1876
77. Brewster DR, Manary MJ, Menzies IS, O'Loughlin EV, Henry RL. Intestinal permeability in kwashiorkor. *Arch Dis Child*. 1997;76(3):236–241
78. Jones KD, Hünten-Kirsch B, Laving AM, et al. Mesalazine in the initial management of severely acutely malnourished children with environmental enteric dysfunction: a pilot randomized controlled trial. *BMC Med*. 2014;12:133
79. Dewey KG, Adu-Afarwuah S. Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Matern Child Nutr*. 2008;4(suppl 1):24–85
80. Bhutta ZA, Ahmed T, Black RE, et al; Maternal and Child Undernutrition Study Group. What works? Interventions for maternal and child undernutrition and survival. *Lancet*. 2008;371(9610):417–440

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