Technical Meeting on EED,* the Microbiome and Undernutrition

*Environmental Enteric Dysfunction

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Key messages

- Stunting affects 161 million children under 5 years of age in low- and middle-income countries.[1]
- Evidence-based nutrition interventions, at 90% coverage, amount to only one-third reduction in stunting.
- Environmental insults acting through damaged gut function (a phenomenon referred to as environmental enteric dysfunction [EED]), are hypothesized to be responsible for a large part of intrauterine growth restriction and postnatal stunting, but the mechanisms remain largely unknown.
- Combating EED and stunting needs an integrated approach to improve the following: maternal health and pre-conception nutrition, infant and young child feeding (IYCF) practices, access to health care, and access to safe water and sanitation.
- A tool to assess EED is urgently needed to facilitate evaluation of interventions.
- Application of cutting-edge innovations such as the *omics* technologies and stable isotope techniques offer unprecedented opportunities to diagnose and characterize EED.
- Since EED depicts multiple causal pathways, striking the right mix of evidence-based interventions is a key prerequisite for success. Synergies across disciplines and sectors are needed.

Some 50 experts participated in a technical meeting on environmental enteric dysfunction organized and hosted by the International Atomic Energy Agency (IAEA) in Vienna, Austria on October 28–30, 2015. The meeting aimed to discuss current research, developments and experiences in diagnosing and evaluating EED, and the potential role of stable isotope techniques in EED diagnosis.

What is known about EED

Stunting develops as a result of sustained inadequate nutrition and recurrent infection.[2] Environmental insults affect linear growth through mechanisms that are yet to be fully understood.[3] Environmental enteropathy is a combination of infection-undernutrition induced failure of the mucosal barrier of the gut and has recently been referred to as environmental enteric dysfunction to reflect the numerous gut function deficits associated with it. EED affects approximately 50–95% of children under the age of 5 years in resource-poor settings. There is compelling evidence to support the association of EED with: **1)** gut permeability/leakiness; **2)** nutrient malabsorption; **3)** microbial translocation; **4)** alterations in gut microbiota diversity; **5)** gut and systemic inflammation; **6)** linear growth faltering; **7)** reduced effect of vaccines and; **8)** severe acute malnutrition (SAM).[4]

Participants of the technical meeting come from diverse professional fields

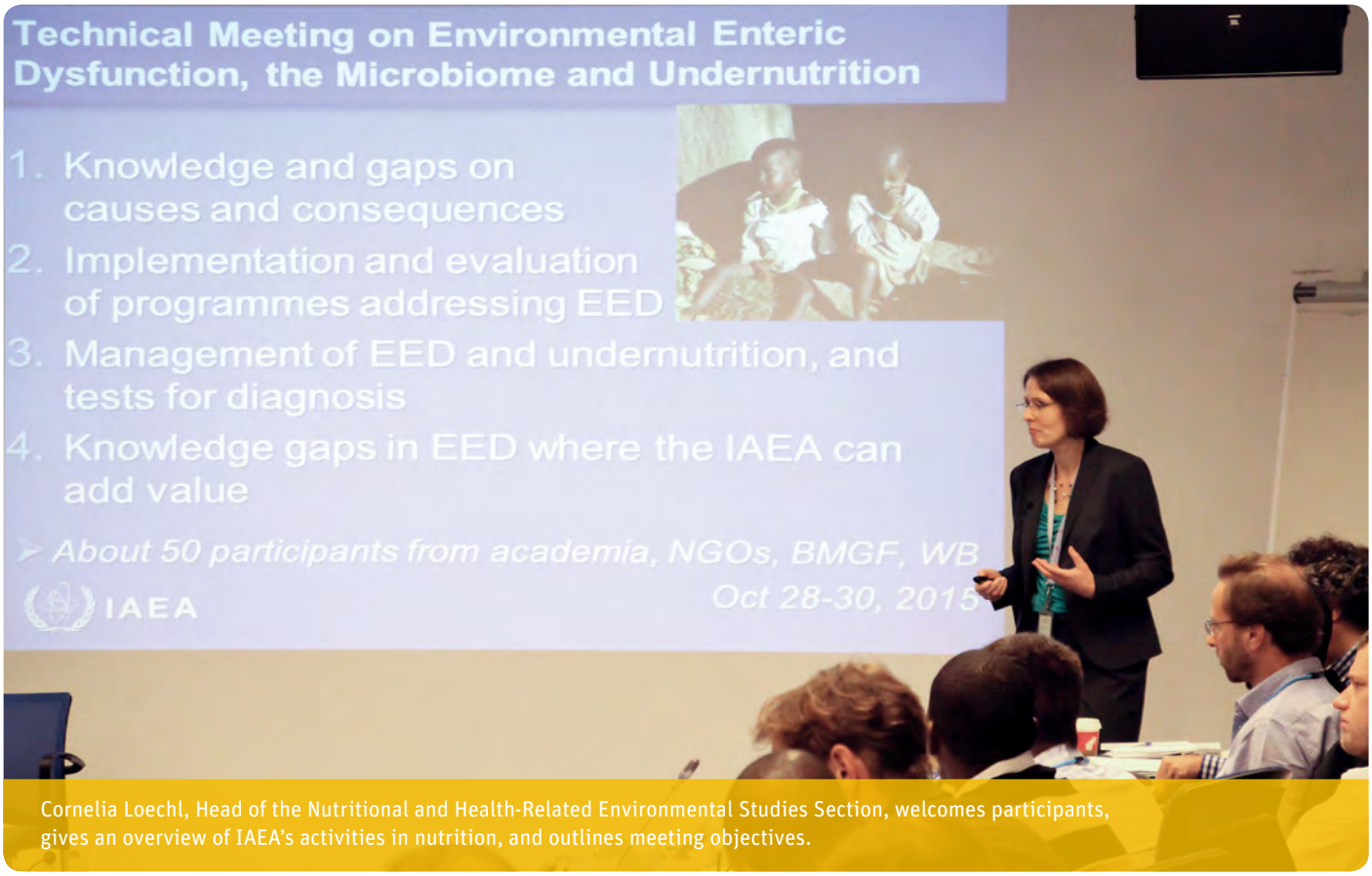
1. Gut microbiome and EED

The gut microbiota is largely acquired at birth and develops quickly in the first year of life toward an adult-like pattern. It influences host development, immunity, metabolism and gut motility[5] and is in turn influenced by factors including mode of delivery, breastfeeding practices, dietary diversity, genotype, pathobiology, physiology, age, the environment, immune system and host lifestyle.[6]

Unfavorable nutritional conditions can influence the microbial community composition, most often resulting in sub-optimal microbiota maturity, which is in turn correlated with host weight loss. Although there are no studies to date of the gut microbiome in the specific context of EED, there is evidence that some gut intestinal pathogens have specific mechanisms of action (such as mucin degradation) that make a link with EED biologically plausible.[7]

2. How does EED limit growth?

Insulin growth factor (IGF-I) regulates growth and other functions in the body during pregnancy. Inflammation of the small intestine in EED is associated with high C-reactive protein and may be accompanied by release of cytokines such as interleukin 6 (IL-6) that reduce appetite and food intake and impair production and action of chondrocyte growth factors. Stress-induced activation of the hypothalamic-pituitary-adrenal axis stimulates a rise in cortisol and insulin-like growth-factor-binding protein-1 (IGFBP-1), which inhibit IGF-1 action and induce chondrocyte apoptosis. A reduction in hepatic growth hormone (GH) receptor expression and inhibition of GH signaling by fibroblast growth



Cornelia Loechl, Head of the Nutritional and Health-Related Environmental Studies Section, welcomes participants, gives an overview of IAEA's activities in nutrition, and outlines meeting objectives.

Panelists from different sectors deliberate how interventions can best be packaged to address EED and stunting.

factor 21 and possibly zinc deficiency, further limit IGF-1 production and thereby contribute to growth failure.[8,9]

3. Energy and nutrient requirements in EED

Nutrient deprivation is associated with a decrease in epithelial barrier function and elevated detection of indicators for bacterial translocation. Vitamin A, zinc and some amino acids such as glutamine, threonine, leucine and cysteine are potentially involved in improving gut barrier function and absorptive capacity. Zinc, probiotics, flavonoids and n-3 polyunsaturated fatty acids (PUFA) have been associated with reduced inflammation.[4] In contrast, inorganic iron potentially shifts the microbiome towards a more pathogenic profile and increases gut inflammation. Inflammation and reduced absorption, both of which are evident in EED, may result in increased energy and nutrient requirements in children with EED. In children with EED, energy and zinc requirements are increased by up to 15% and 50%, respectively.

4. Use of stable isotopes in evaluating gut dysfunction

Stable isotopes have been used to assess gut dysfunction (small intestine bacteria overgrowth [SIBO], celiac disease and chemotherapy-induced small-intestinal damage in rats) with different substrates (starch and other carbohydrates, mixed triglycerides, fatty acids, proteins, etc.). An example of a diagnostic ^{13}C breath test is the ^{13}C-urea breath test used to diagnose and monitor *Helicobacter pylori* infection in the stomach. The high specificity and sensitivity associated with the test makes it the ideal non-invasive diagnostic technique.[10] The ^{13}C-sucrose breath test is a promising future technique to assess gut function and has been used in Australia to measure the absorptive capacity of the small intestine.[11] The glucose hydrogen breath test is currently the most accurate non-invasive test to diagnose SIBO. Combined ^{13}C and H_2 breath tests could also be used to assess fermentation and SIBO with higher specificity by correcting for gastric emptying rate.

5. Biomarkers of EED

While malabsorption, gut barrier dysfunction and gut inflammation are overlapping components of EED, it is difficult to identify specific markers of each that could be used solely for EED diagnosis. An ideal EED biomarker should be highly associated with stunting, age- and population-specific, and classified according to the underlying causes of EED, namely: **1)** intestinal permeability and nutrient absorption (e.g., ^{13}C sucrose breath test, lactulose-mannitol intestinal permeability test), **2)** bacterial translocation (e.g., lipopolysaccharides), **3)** intestinal inflammation (e.g., myeloperoxidase), **4)** systemic inflammation (e.g., C-reactive protein), **5)** functional enterocyte mass (e.g., citrulline), **6)** intestinal repair (e.g., promoter glucagon-like

peptide-2 [GLP-2]), 7) mucosal immune underachievement (e.g., kynurenine/tryptophan ratio)[12] and 8) alterations in microbiota diversity.

6. Ongoing interventions to address EED

Interventions to address EED include: a) water, sanitation and hygiene (WASH), b) reduction of exposure to feces and contact with domestic animals; c) provision of probiotics and prebiotics; d) improvement of dietary diversity and breastfeeding practices; e) supplementation with nutrients such as zinc, PUFA and amino acids and; f) treatment with anti-inflammatory agents and antibiotics in the context of SAM and infection. Some of these aspects are already being tested individually or combined in large randomized controlled studies in a number of countries. Determining the right mix of evidence-based interventions to maximize effectiveness against EED remains a major gap.

7. The way forward

Several gaps in knowledge requiring attention include the classification and better understanding of the underlying causes of EED. Developing practical, simple, and affordable tools to diagnose and characterize EED to allow better targeting of interventions in vulnerable populations is overdue. Stable isotopes can be used to assess absorptive capacity/permeability of the gut, bacterial translocation and body composition as a proxy indicator of dietary quality and morbidity. Since EED depicts multiple causal pathways, striking the right mix of evidence-based interventions is a key prerequisite for success. Synergies across disciplines and sectors are needed.

> "There is a need to develop tools to diagnose and characterize EED in order to allow better targeting of interventions in vulnerable populations"

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