EED as a cause of stunting

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FOR NORMAL GROWTH AND DEVELOPMENT
3 CONDITIONS MUST BE MET

No excess of symptomatic common infections such as malaria, diarrhea, or lower respiratory tract infections

Good growth and development

Good gut health

Diet provides adequate macro- and micronutrients in bioavailable forms
STUNTING

- Affects 25% of children globally, 35% in Africa, 38% in Ethiopia.

- Stunting is associated with:
  - Increased mortality from diarrhea, pneumonia, other infectious diseases.
  - Impaired cognitive development.
  - Reduced income (by up to 22%).
  - Reduced life expectancy by up to 17%.
  - A significant portion of stunting comes from EED which comes from marginal diet + microbial imbalance.

- Need for interventions to reduce this cause of morbidity and mortality.
STUNTING IN AFRICA HAS MANY CAUSES

• About 33% of stunting occurs in utero, evidence suggest this is mostly a result of maternal inflammation

• About 50% of stunting occurs from 6-12 mo of age, and this thought to be the result of inadequate diet

• About 15% of stunting occurs after 1 year of age and this is thought to be the result of poor gut health.
ENVIRONMENTAL ENTERIC DYSFUNCTION

- Develops in the first three years of a child in developing countries.
- It is characterized by a chronic inflammation of the small intestine, abnormal villous architecture and reduced intestinal mucosal surface area.
- Etiology of the disease is unknown, it is associated with unsanitary living conditions, colonization by intestinal pathogens and malnutrition.
CHILDREN WITH SEVERE EED IN LEGUME STUDY

% Severe EED children

Age (Months)

0 10 20 30 40 50

5-8 8-11 11-13 13-16 16-19 19-23 23-26 >26
DIAGNOSIS OF EED

- Because the collection of routine biopsy specimens is impractical and unethical, enteropathy is most commonly identified using site specific sugar absorption test.
- This test involves the ingestion of sugars that are not metabolized, some fraction of the monosaccharides are absorbed and then excreted in the urine, disaccharides are absorbed in lessor. Most common is

Lactulose:Mannitol test
INTERPRETATION OF DUAL SUGAR ABSORPTION TEST
INTERPRETATION OF DUAL SUGAR ABSORPTION TEST

- Simplistic interpretation is that lactulose enters the body through damaged pathways, and more lactulose represents more damage.
- Mannitol is normalizing factor for transit time and bowel length, and also more mannitol is absorbed from healthy guts.
- Test result is expressed as a ratio L:M
- But Mannitol is **not** absorbed transcellularly, wherever lactulose can enter so can and does mannitol. In reality mannitol is a composite measure of normal and damaged epithelial surfaces, which reduces its utility as a normalizing factor.
- It is better just to use lactulose absorption alone to determine amount of gut damage and extend the urine collection time to reduce variations in gut transit time.
BIOLOGICAL PERTURBATIONS IN EED

Low circulating
- Phosphatidylcholines
- Sphingomyelins
- Tryptophan
- Ornithine
- Citrulline
- Carnitine

High circulating
- Glutamate
- Taurine
- Serotonin

Low abundance
- Succinivibrio
- Klebsiella
- Clostridium_XI

High abundance
- Megasphaera
- Mitsuokella
- Suterella

KEGG Signalling Pathways
- NF-kappa B signaling pathway
- Toll-like receptor signaling pathway
- NOD-like receptor signaling pathway
- Chemokine signaling pathway
- TNF signaling pathway
- Osteoclast differentiation
- B-cell receptor signalling pathway
- FC gamma R-mediated phagocytosis
- NK cell mediated cytotoxicity
- T-cell receptor signaling pathway

GeneGO Canonical Pathways
- Inegrin inside-out signalling in neutrophils
- Inhibition of neutrophil migration by proresolving lipid mediators in COPD
- Transcription regulation of granulocyte development
- Lipoxin inhibitory action on fMLF induced neutrophil chemotaxis
- G-CSF induced myeloid differentiation
- Chemokines and adhesion

Transcripts
- ARRB2
- CXCR2
- LYN, CLEC7A
- NCF2, FCGR2A
- FGFR3B, BCL2A1
- SOCS3, IFITM1
- FCR16, PIK3AP1

Host Response
- Recruitment of diverse immunologically active cells
- Enhanced anti-viral defenses
- Chronic inflammation
- Compromised Mucus layer
- Compromised cell adhesion and increased permeability
- Apoptosis
Recurrent infection progressively disables host protection against intestinal inflammation
(Based on *Salmonella* study in mice, 2017)
STUNTING IS PREDICTED BY THE LACTULOSE:MANNNITOL TEST

L:M is correlated with change in HAZ. Pearson's correlation coefficient = -0.27 (P<0.001). Spearman's correlation coefficient = -0.32 (P<0.001).

Linear regression modeling of change in HAZ over subsequent 3 months identified the following predictive factors:
EED IS ASSOCIATED WITH STUNTING

![Panel A: Scatter plot showing the relationship between Ln. lactulose:mannitol ratio and length growth (cm/month). The correlation coefficient (r) is -0.532.]

![Panel B: Bar chart showing the change in HAZ z scores for different percent lactulose excretion categories: < 0.13, 0.13 - 0.25, 0.25 - 0.37, > 0.37. The bars are followed by asterisks (*) indicating statistical significance.]

- Better growth →
- Worse EED / gut health →
PREVIOUS INTERVENTIONS ATTEMPTED TO HEAL EED AND REDUCE STUNTING

- Probiotic: Lactobacillus GG
- Antibiotic intervention: rifaximin
- Deworming with albendazole
- High-dose zinc.
- Prebiotic intervention: dietary resistant starch type 2.
- Poly-unsaturated fatty acid supplementation.
- Complementary feeding with legumes: common bean and cowpea.
- Lactoferrin and Lysozyme supplementation.
WASH BENEFIT STUDY

- Focus on: Water quality, sanitation, hand washing and nutritional intervention during the first years of life.
- Rural Bangladesh and Kenya – cluster-randomized controlled trials
- >6400 newborns per country
- Measure primary outcomes after two years of intervention:
  1. Length for age Z scores (LAZ) and caregiver report diarrhea
  2. Stunting prevalence, markers EED and child development scores (verbal, motor and personal/social)
WASH BENEFIT STUDIES IN KENYA - FINDINGS

- None of the interventions reduced diarrhea prevalence compared with the active control.
- The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.
- Among the children receiving nutrition intervention (feeding counseling + lipid nutrient supplements) LAZ was about 0.15 z-scores greater.
Sanitation, handwashing and nutrition interventions (or combinations) reduced diarrhea prevalence by 40%.

The individual water, sanitation, and handwashing groups, and combined water, sanitation, and handwashing group had no effect on linear growth.

Among the children receiving nutrition intervention (feeding counseling + lipid nutrient supplements) LAZ was about 0.19 z-scores greater.
SHINE study

- Focus on: Effect of improved water, sanitation and hygiene and/or improved infant feeding on child stunting and anemia at 18 months age.
- Rural Zimbabwe - randomized control trial
- 5280 participants
- Measure primary outcomes after two years of intervention:
  1. Length and hemoglobin at 18 months.
  2. Infant EED, anthropometric measurements, program impact pathways, breastfeeding, maternal/infant HIV effect, diarrhea prevalence, child neurodevelopment, mycotoxin exposure, maternal and child microbiota, rotavirus an polio vaccination and adverse birth outcomes.
Legumes and growth

- Randomized, double-blind controlled clinical complementary feeding trial were conducted in Malawi with common bean and cowpea.

- Local legumes were chosen for their nutrient and fiber content; nutrients to provide protein and indigestible carbohydrate to nurture the microbiota, provided about 40% of complementary food requirement.

- Goal to improve gut health & reduce stunting.
Change in LAZ and WHZ in 6-12 mo old

Change length for age Z-score
-0.6
-0.4
-0.2
0.0
Cowpea
Common bean
Control

Weight for length Z-score
-0.4
-0.2
0.0
0.2
0.4
0.6
Cowpea
Common bean
Control
EED and microbiota signature - Species

Aggregated "mean" Rank: Species

- s
- s_dispar
- s_prausnitzii
- s_gnavus
- s_reuteri
- s_neonatale
- s_mucilaginosa
- s_obeum

Relative abundance
Thank you