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GUT HEALTH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER

REPORT TO THE BILL & MELINDA GATES FOUNDATION

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1. Small Intestine Microbiota Regulate Host Digestive and Absorptive Adaptive Responses to Dietary Lipids.
   Martinez-Guryn K, Hubert N, Frazier K, Urlass S, Musch MW, Ojeda P, *et al.*
   Cell Host and Microbe. 23(4). 2018 April 11.
   PubMed ID: 29649441

ABSTRACT:
The gut microbiota play important roles in lipid metabolism and absorption. However, the contribution of the small bowel microbiota of mammals to these diet-microbe interactions remains unclear. We determine that germ-free (GF) mice are resistant to diet-induced obesity and malabsorb fat with specifically impaired lipid digestion and absorption within the small intestine. Small bowel microbes are essential for host adaptation to dietary lipid changes by regulating gut epithelial processes involved in their digestion and absorption. In addition, GF mice conventionalized with high-fat diet-induced jejunal microbiota exhibit increased lipid absorption even when fed a low-fat diet. Conditioned media from specific bacterial strains directly upregulate lipid absorption genes in murine proximal small intestinal epithelial organoids. These findings indicate that proximal gut microbiota play key roles in host adaptability to dietary lipid variations through mechanisms involving both the digestive and absorptive phases and that these functions may contribute to conditions of over- and undernutrition.

DOI: https://doi.org/10.1016/j.chom.2018.03.011
IMPACT FACTOR: 14.946
CITED HALF-LIFE: 4.3

START COMMENTARY: The authors note that this is one of the first studies to look at the microbial composition of the small bowel and the role of the microbiota in nutrient digestion and absorption. The authors compared lipid absorption between specific-pathogen free (SPF) mice and germ-free (GF) mice fed purified high fat (HF) or low fat (LF) diets. Initial experiments showed the GF mice had impaired lipid absorption compared to SPF mice, as shown in Figure 2. Specifically, SPF mice fed HF diets showed significantly greater lipid absorption than SPF LF mice and GF HF and LF mice. To further explore the possible mechanisms driving this difference in lipid absorption, the authors used 16s rRNA sequencing to look at the microbiota composition of the small intestine of SPF mice fed a HF or LF diet for 4 weeks. Figure 4B shows that mice fed a HF diet had greater relative abundance of Clostridiaceae and lower abundance of Bifidobacteriaceae and Bacteroidaceae compared to mice fed a LF diet. Next, the authors took GF mice and fed them either a HF or LF diet for 1 week, and then conventionalized them with either HF or LF jejunal microbiota from the SPF mice, followed by a 3-week maintenance diet that either retained their original assignment, or switched from HF to LF or vice versa. The authors found that while the gene abundance did not differ between the groups at any point, both groups of mice who received HF microbes during conventionalization showed increased lipid absorption compared to mice who received LF microbes, independent of their original or maintenance diet. The authors hypothesized that perhaps the HF microbes differentially reprogram the small intestine of the GF mouse. The results of this study suggest that interventions that target the small bowel microbiota and help increase lipid absorption may be important to promote nutrient digestion and uptake in individuals with impaired nutrient absorption (e.g., environmental enteric dysfunction).

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2. Markers of Environmental Enteric Dysfunction Are Associated With Neurodevelopmental Outcomes in Tanzanian Children.
Etheredge AJ, Manji K, Kellogg M, Tran H, Liu E, McDonald CM, *et al.*
Journal of Pediatric Gastroenterology and Nutrition. 2018 April 02. [Epub ahead of print]
PubMed ID: 29613921

ABSTRACT:
BACKGROUND: Chronic exposure to enteropathogens may result in environmental enteric dysfunction (EED), a subclinical condition associated with poor child growth. Growth faltering is strongly associated with poor neurodevelopment, and occurs during sensitive periods of postnatal brain development. We investigated the role of novel EED biomarkers, systemic inflammation, and micronutrient status on neurodevelopment in Tanzanian children.
METHODS: Non-stunted subjects with 6-week and 6-month blood samples and neurodevelopmental measures (n = 107) were included in this study. Samples were tested for biomarkers of gastrointestinal function (citrulline, antibodies to lipopolysaccharide, and flagellin), micronutrient status (iron, retinol binding protein [RBP], and vitamin D), systemic inflammation (C-reactive protein [CRP] and alpha-1-acid glycoprotein), and growth (insulin-like growth factor and insulin-like growth factor binding protein 3).
RESULTS: Cognitive scores at 15 months were associated with higher concentrations of 6-month anti-lipopolysaccharide IgG (β = 1.95, P = 0.02), anti-flagellin IgA (β = 2.41, P = 0.04), and IgG (β = 2.99, P = 0.009). Higher receptive language scores were positively associated with anti-flagellin IgG (β = 0.95, P = 0.05), and receptive language and gross motor scores were positively associated with citrulline at 6 months (β = 0.09, P = 0.02; β = 0.10, P = 0.03, respectively). Gross motor scores were positively associated with RBP at 6 months (β = 1.70, P = 0.03). Markers of systemic inflammation were not significantly associated with neurodevelopment.
CONCLUSIONS: Plasma citrulline, a marker of gastrointestinal mucosal surface area, and vitamin A status were associated with higher gross motor development scores. Novel markers for EED, but not inflammation, were positively associated with cognitive scores, suggesting a possible mechanistic pathway involving immune response and neuroprotection.

DOI: 10.1097/MPG.0000000000001978
IMPACT FACTOR: 2.799
CITED HALF-LIFE: 7.3

START COMMENTARY: Children included in this study were a subset of those in a larger randomized controlled trial examining a possible association between daily multivitamins and/or zinc and growth faltering. Children received either a daily supplement or placebo from 6 weeks to 18 months of age. Blood samples were drawn at enrollment, 6 and 12 months of age. The subset of children selected for this study (n=107) were non-stunted at enrollment, had blood samples available, and had at least one anthropometric measurement after enrollment recorded. The Bayley Scales of Infant and Toddler Development- third edition (BSID-III) was administered to the selected children at 15 months of age. Blood samples from all three time points were tested for biomarkers associated with EED. Contrary to their initial hypothesis, increased levels of both anti-LPS IgG and IgA and flagellin IgA and IgG, markers of EED, were associated with better neurodevelopment. The authors hypothesized that this finding suggests that cognitive development is positively associated with a more robust immune response to systemic exposure to gut bacteria, and that toll-like receptors may be involved given their presence on microglial cells and other cells within the central nervous system. The study was exploratory in nature and had several limitations, including the exclusion of stunted children from the study population, multiple testing for associations, and the inability to distinguish between maternal or infant derived

flagellin and LPS antibodies. This study suggests interesting and complex associations between EED biomarkers, vitamin A status, and cognitive development that should be further explored.

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3. Nutritional preferences of human gut bacteria reveal their metabolic idiosyncrasies.
Tramontano M, Andrejev S, Pruteanu M, Klünemann M, Kuhn M, Galardini M, *et al.*
Nature Microbiology. 3(4). 2018 April.
PubMed ID: 29556107

ABSTRACT:
Bacterial metabolism plays a fundamental role in gut microbiota ecology and host–microbiome interactions. Yet the metabolic capabilities of most gut bacteria have remained unknown. Here we report growth characteristics of 96 phylogenetically diverse gut bacterial strains across 4 rich and 15 defined media. The vast majority of strains (76) grow in at least one defined medium, enabling accurate assessment of their biosynthetic capabilities. These do not necessarily match phylogenetic similarity, thus indicating a complex evolution of nutritional preferences. We identify mucin utilizers and species inhibited by amino acids and short-chain fatty acids. Our analysis also uncovers media for in vitro studies wherein growth capacity correlates well with in vivo abundance. Further value of the underlying resource is demonstrated by correcting pathway gaps in available genome-scale metabolic models of gut microorganisms. Together, the media resource and the extracted knowledge on growth abilities widen experimental and computational access to the gut microbiota.

DOI: 10.1038/s41564-018-0123-9
IMPACT FACTOR: *NA*
CITED HALF-LIFE: *NA*

START COMMENTARY: The innovative screening and growth process developed by the authors of this study allowed for the investigation of several mechanistic and functional evaluations of gut bacterial species that have not previously been able to be explored. The 96 gut bacterial strains were chosen by identifying species with a relative abundance of 1% or more and prevalence of more than 10% in metagenomics data provided from 4 different studies comprised of 364 human subjects from 4 countries (Denmark, Spain, China, USA). The heat map in Figure 2a highlights the diversity of the growth media preferences of the bacterial strains in the study. While some strains grew well in almost all the media, others only grew in one or two. Interestingly, *Akkermansia muciniphila* and *Ruminococcus torques* displayed similar growth patterns in the screen; both species grew almost exclusively in two defined media that contained mucin. The authors noted that the two species have previously been observed competing for a similar ecological niche in the mucus layer. As seen in Figure 3b, 11 species grew better in defined media than in rich media, and that authors hypothesized that the robustness of these species would aid survival in low-nutrient environments. After initial growth experiments, the investigators ran a series of screens in which they added or altered the level of different nutrients in the media. Figure 4a shows the results of screens in which the amino acid and/or small chain fatty acids (SCFA) concentrations of growth media were altered. Additional SCFAs only boosted the growth of *Lactobacillus vaginalis*, while inhibiting the growth of the other species tested. The exclusion of aromatic amino acids decreased the growth of several species tested. This study systematically tested the growth of a wide range of common gut bacterial species, identifying the best media for use in future experiments and challenging the current dogma that most bacteria have complex metabolic requirements.

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4. Environmental Enteropathy, Micronutrient Adequacy and Length Velocity in Nepalese Children - the Mal-Ed Birth Cohort Study.
   Morseth MS, Henjum S, Schwinger C, Strand TA, Shrestha SK, Shrestha B, *et al*.
   Journal of Pediatric Gastroenterology and Nutrition. 2018 April 03. [Epub ahead of print]
   PubMed ID: 29620600

ABSTRACT:
OBJECTIVES: Environmental enteropathy (EE) is likely associated with growth retardation in children, but the association between EE and length velocity z-score (LVZ) has not been investigated. The objective of the study was to assess associations between fecal markers for intestinal inflammation and LVZ and whether these associations were influenced by micronutrient adequacy among 9-24 months old children in Bhaktapur, Nepal.
METHODS: Data was divided into 5 time slots (9-12, 12-15, 15-18, 18-21 and 21-24 months). Anthropometric measurement and dietary assessment (by 24 h recall) were performed monthly. Mean nutrient density adequacy (MNDA) was calculated based on nutrient density adequacy (NDA) of ten micronutrients (thiamin, riboflavin, niacin, vitamin B6, folate, vitamin C, vitamin A, calcium, iron and zinc). Anti-1-antitrypsin (AAT), myeloperoxidase (MPO) and neopterin (NEO) were measured in stool samples collected at the beginning of each time slot. An environmental enteropathy (EE) score was calculated based on all three fecal markers. Associations between AAT, MPO, NEO and EE-score and LVZ were assessed by multiple linear regression analyses and Generalized estimating equations (GEE) models.
RESULTS: Associations between fecal markers and EE-score and LVZ were generally weak. EE-score and MPO for 3-month- and MPO for 6-month growth periods were significantly associated with LVZ from 9-24 months. These associations were slightly modified by MNDA.
CONCLUSIONS: EE-score and MPO were significantly associated with LVZ in 9-24 months old Nepali children. Further studies to establish the usefulness of AAT, MPO and NEO in assessing EE and growth retardation are warranted.

DOI: 10.1097/MPG.0000000000001990
IMPACT FACTOR: 2.799
CITED HALF-LIFE: 7.3

START COMMENTARY: 240 infants/children who participated in the MAL-ED birth cohort in Bahktapur, Nepal were included in this study. Under the MAL-ED protocol, anthropometric measures were taken monthly throughout the study, and stool samples were collected monthly for children <12 months, and quarterly up to 36 months of age. For this analysis, data was only used from 9 months onward, because data collection methodology changed at this age and included the available information for calculating micronutrient adequacy. A unique method used by this study was the choice of 3-month and 6-month length-velocity z-score, rather than length-for-age z-score (LAZ) or change in LAZ as the outcome of interest. Investigators observed that overall, concentrations of fecal markers decreased slowly over the period of the study. However, only MPO was found to be significantly associated with linear growth over a 6-month period. Similar studies have been done with children from other countries in the MAL-ED study, and the results have been mixed. Findings from the Bangladesh and Brazil MAL-ED studies (cohort and case-control, respectively) observed similar associations for MPO with 3-month delta LAZ, however the study in Brazil also observed an association between AAT and 3-month delta LAZ. Similar associations between MPO and linear growth over 6 month periods have also been observed in children in Brazil, but were not significant in the Bangladesh cohort. The authors suggested that the differences are due to the high intra-individual variability of the fecal markers used in this study, higher values

observed versus other settings, and the multiple immunological processes (particularly in acute vs. chronic infections) in which they are involved. Additional biomarkers, which are perhaps less variable, or that provide additional supportive data, should be considered in future studies.

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5. Metabolic phenotyping of malnutrition during the first 1000 days of life.
Mayneris-Perxachs J, and Swann JR.
European Journal of Nutrition. 2018 April 11. [Epub ahead of print]
PubMed ID: 29644395

ABSTRACT:
Nutritional restrictions during the first 1000 days of life can impair or delay the physical and cognitive development of the individual and have long-term consequences for their health. Metabolic phenotyping (metabolomics/metabonomics) simultaneously measures a diverse range of low molecular weight metabolites in a sample providing a comprehensive assessment of the individual's biochemical status. There are a growing number of studies applying such approaches to characterize the metabolic derangements induced by various forms of early-life malnutrition. This includes acute and chronic undernutrition and specific micronutrient deficiencies. Collectively, these studies highlight the diverse and dynamic metabolic disruptions resulting from various forms of nutritional deficiencies. Perturbations were observed in many pathways including those involved in energy, amino acid, and bile acid metabolism, the metabolic interactions between the gut microbiota and the host, and changes in metabolites associated with gut health. The information gleaned from such studies provides novel insights into the mechanisms linking malnutrition with developmental impairments and assists in the elucidation of candidate biomarkers to identify individuals at risk of developmental shortfalls. As the metabolic profile represents a snapshot of the biochemical status of an individual at a given time, there is great potential to use this information to tailor interventional strategies specifically to the metabolic needs of the individual.

DOI: 10.1007/s00394-018-1679-0
IMPACT FACTOR: 4.370
CITED HALF-LIFE: 4.2

START COMMENTARY: This review article discusses the techniques used for metabolic phenotyping and the current findings from the literature on metabolic phenotypes during the first two years of a child's life. The article summarizes several consistent findings on nutritional deficiencies throughout each of the different stages of newborn development. Table 1 summarizes the studies discussed in the paper and the main findings in neonates. Both large for gestational age (LGA) and Inter-uterine growth restriction (IUGR) children have been shown to have increased levels of myo-inositol, sarcosine, creatine, and creatinine in their urine compared to appropriate-for-gestational age (AGA) babies. The authors suggest that the changes in the metabolic profile of these children result from adaptations that occur in response to intrauterine hyperglycemia. Table 2 summarizes metabolomic human studies during the post-natal development phase. Of note, during the first 6 months of a child's life, the authors summarize studies that have looked at the metabolic profile of breast milk and the impact on child health. Notably, several studies demonstrated that several human milk oligosaccharides (HMOs) decrease in breast milk during the first month of a child's life. As HMOs are known to be important prebiotics for commensal bacteria, this finding may suggest that prebiotic supplementation may be a warranted intervention even in children who are exclusively breastfed. During postnatal development between 6 months and 12 months of age, the authors summarize several studies that have looked at the metabolic phenotype in severely undernourished children. Several studies showed that undernourished children had decreased levels of amino acid, that then increased after nutritional interventions; it is hypothesized that this is due to the greater availability of dietary protein made available after the nutritional intervention, which results in greater oxidation of amino acids and a reduction in the oxidation of fatty-acids. The review

also summarizes the metabolic and microbiome differences observed in states of acute and chronic malnutrition, as well as micronutrient deficiencies and environmental enteric dysfunction.

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6. Lactobacillus paracasei CNCM I-3689 reduces vancomycin-resistant Enterococcus persistence and promotes Bacteroidetes resilience in the gut following antibiotic challenge.
Crouzet L, Derrien M, Cherbuy C, Plancade S, Foulon M, Chalin B, *et al.*
Scientific Reports. 8(1). 2018 March 23.
PubMed ID: 29572473

ABSTRACT:
Enterococci, in particular vancomycin-resistant enterococci (VRE), are a leading cause of hospital-acquired infections. Promoting intestinal resistance against enterococci could reduce the risk of VRE infections. We investigated the effects of two *Lactobacillus* strains to prevent intestinal VRE. We used an intestinal colonisation mouse model based on an antibiotic-induced microbiota dysbiosis to mimic enterococci overgrowth and VRE persistence. Each *Lactobacillus* spp. was administered daily to mice starting one week before antibiotic treatment until two weeks after antibiotic and VRE inoculation. Of the two strains, *Lactobacillus paracasei* CNCM I-3689 decreased significantly VRE numbers in the feces demonstrating an improvement of the reduction of VRE. Longitudinal microbiota analysis showed that supplementation with *L. paracasei* CNCM I-3689 was associated with a better recovery of members of the phylum Bacteroidetes. Bile salt analysis and expression analysis of selected host genes revealed increased level of lithocholate and of ileal expression of camp (human LL-37) upon *L. paracasei* CNCM I-3689 supplementation. Although a direct effect of *L. paracasei* CNCM I-3689 on the VRE reduction was not ruled out, our data provide clues to possible anti-VRE mechanisms supporting an indirect anti-VRE effect through the gut microbiota. This work sustains non-antibiotic strategies against opportunistic enterococci after antibiotic-induced dysbiosis.

DOI: 10.1038/s41598-018-23437-9
IMPACT FACTOR: 4.259
CITED HALF-LIFE: 2.0

START COMMENTARY: This study used mouse models to explore the possible effects of probiotics in controlling the expansion of VRE in the intestine. Figure 1 shows the mean log VRE concentrations found at day 14, 18, and 21 in clindamycin-pretreated mice who received *L. paracasei ssp.*, *L. rhamnosus ssp.*, or control prior to the introduction of *E. faecalis*. Because differences in VRE were pronounced in mice that received *L. paracasei,* additional trials were run to evaluate the possible effect of *L. paracasei* supplementation on the gut microbiota. The results can be seen in Figure 3. Trials 4 and 5 omitted the inoculation of *E. faecalis* V583 at day 11. In trial 3, microbiota were only analyzed at baseline and 11 days after *E. faecalis* inoculation. Trials 1 and 2 used the standard protocol; trial 2 had one less control mouse than trial 1. Additional details about the relative abundance of gut microbiota phylum and alpha diversity at different points in the study between the control and *L. paracasei* mice can be found in the Supplemental Tables S2 and S3. These results suggest that *L. paracasei* contributes to a significant reduction in the amount of persisting VRE, likely by increasing the amount of the genera Bacteroidetes present. However, the results were not seen in all supplemented mice, suggesting there are important sources of inter-individual variation in mice that warrant further exploration.

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7. Environmental Enteropathy in Undernourished Pakistani Children: Clinical and Histomorphometric Analyses.
   Syed S, Yeruva S, Herrmann J, Sailer A, Sadiq K, Iqbal N, *et al.*
   The American Journal of Tropical Medicine and Hygiene. 2018 April 02. [Epub ahead of print]
   PubMed ID: 29611507

ABSTRACT:
Despite nutrition interventions, stunting thought to be secondary to underlying environmental enteropathy (EE) remains pervasive among infants residing in resource-poor countries and remains poorly characterized. From a birth cohort of 380 children, 65 malnourished infants received 12 weeks of nutritional supplementation with ready-to-use therapeutic food (RUTF). Eleven children with insufficient response to RUTF underwent upper endoscopy with duodenal biopsies, which were compared with U.S., age-matched specimens for healthy, celiac disease, non-celiac villous atrophy, non-celiac intraepithelial lymphocytosis, and graft-versus-host disease patients. Of the 11 children biopsied, EE was found in 10 (91%) with one subject with celiac disease. Morphometry demonstrated decreased villus-to-crypt (V:C) ratios in EE relative to healthy and non-celiac lymphocytosis patients. Environmental enteropathy villus volumes were significantly decreased relative to healthy controls. In EE, average CD3+ cells per 100 epithelial cells and per 1,000 µm2 of lamina propria and the number of lamina propria CD20+ B-cell aggregates were increased relative to all other groups. Our results indicate that V:C ratios are reduced in EE but are less severe than in celiac disease. Environmental enteropathy intraepithelial and lamina propria T lymphocytosis is of greater magnitude than that in celiac disease. The increases in lamina propria B and T lymphocytes suggest that non-cytolytic lymphocytic activation may be a more prominent feature of EE relative to celiac disease. These results provide new insights into shared yet distinct histological and immunological features of EE and celiac disease in children.

DOI: 10.4269/ajtmh.17-0306
IMPACT FACTOR: 2.549
CITED HALF-LIFE: >10.0

START COMMENTARY: This study presents preliminary results from the larger birth cohort of children. For this analysis, children were selected for biopsy if they had WHZ score < -2 and clinical histories indicating malabsorption following the 12-week RUTF intervention. This study is novel because it was able to directly compare the histology and immunohistochemistry of the duodenal in children with EE with healthy and diseased controls (Figure 1). Contrary to what previous studies have assumed, this study showed that the presentation and composition of the villi in children with EE was significantly different than that of children with celiac disease. The villus-crypt ratio and villus volumes in children with EE were significantly lower than in healthy individuals, however these measurements were less extreme than those observed among patients with celiac disease. Interestingly, as shown in Figure 3, EE children showed higher levels of intraepithelial T lymphocytosis, despite having relatively preserved villi. This observation, along with the increased numbers of lamina propria B-cell aggregates suggests that children with EE launch a more intense lymphocytic recruitment compared to children with celiac disease. The authors suggested this contrasting response may be due to altered microbiota. However, the study is limited because they did not have stool samples from all subjects to compare the microbiota composition and metabolic activity.

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8. Selective maternal seeding and environment shape the human gut microbiome.
   Korpela K, Costea P, Coelho LP, Kandels-Lewis S, Willemsen G, Boomsma DI, *et al*.
   Genome Research. 28(4). 2018 April.
   PubMed ID: 29496731

ABSTRACT:
Vertical transmission of bacteria from mother to infant at birth is postulated to initiate a life-long host-microbe symbiosis, playing an important role in early infant development. However, only the tracking of strictly defined unique microbial strains can clarify where the intestinal bacteria come from, how long the initial colonizers persist, and whether colonization by other strains from the environment can replace existing ones. Using rare single nucleotide variants in fecal metagenomes of infants and their family members, we show strong evidence of selective and persistent transmission of maternal strain populations to the vaginally born infant and their occasional replacement by strains from the environment, including those from family members, in later childhood. Only strains from the classes Actinobacteria and Bacteroidia, which are essential components of the infant microbiome, are transmitted from the mother and persist for at least 1 yr. In contrast, maternal strains of Clostridia, a dominant class in the mother's gut microbiome, are not observed in the infant. Caesarean-born infants show a striking lack of maternal transmission at birth. After the first year, strain influx from the family environment occurs and continues even in adulthood. Fathers appear to be more frequently donors of novel strains to other family members than receivers. Thus, the infant gut is seeded by selected maternal bacteria, which expand to form a stable community, with a rare but stable continuing strain influx over time.

DOI: 10.1101/gr.233940.117
IMPACT FACTOR: 11.922
CITED HALF-LIFE: 7.3

START COMMENTARY: This is one of the largest studies performed to evaluate maternal and environmental microbiota seeding of the infant gut. The authors had stool samples from previous studies for 100 Swedish, 42 US and 5 Italian infant-mother pairs for analysis. Stool samples were taken from all mother and infants within the first week proceeding birth. Additional infant stool samples were collected at the age of 4 months and 12 months in the Swedish sample, 6 months in the US sample, and at 7 months and one year in the Italian sample. There were 25 infants delivered via Cesarean section (C-section). From these mother-infant paired samples, investigators used stringent criteria to look for specific shared bacterial strains between mother and infant. The investigators looked for rare single nucleotide variants (rmSNV), defined as those SNVs that were not shared with any non-family member (to reduce noise from common SNVs in the population), shared between two individuals to indicate evidence of transmission. To reduce the possibility that rmSNVs were similar by chance, investigators required >20% rmSNV sharing between samples to be categorized as strain sharing. Results showed that vaginally delivered infants had a high level of shared microbiota from the Actinobacteria and Bacteroidia family, but this was not seen in the infants delivered via C-section, suggesting that some maternal seeding may happen in the vaginal canal. However, in both vaginal and Cesarean delivered infants, the degree of shared maternal microbiota increased during the first year of life, as shown in Figure 1A. In addition to the infant-mother pairs, the authors also had metagenomic data from 8 German and 2 Dutch families, which had children across a wide age range. Investigators analyzed these data to look for similarities between infants and other family members, as well as children compared to other family members. As shown in Figure 3, the results suggest that maternal similarities decrease after the first year of life, while shared familial microbiota peaks between 2 to 10 years old. While the results are

interesting, they are highly limited by the small sample size and the cross-sectional nature of the data collection. Further studies should be conducted to analyze influences on the microbiota overtime and whether interventions to alter the gut microbiota of the mother could confer benefits to their infants.

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9. Intestinal pathogen clearance in children with severe acute malnutrition is unrelated to inpatient morbidity.
   Versloot CJ, Attia S, Bourdon C, Richardson SE, Potani I, Bandsma RHJ, and Voskuijl W.
   Clinical Nutrition ESPEN. 24. 2018 April.
   PubMed ID: 29576347

ABSTRACT:
BACKGROUND & AIMS: Children with Severe Acute Malnutrition (SAM) often suffer from diarrhea, which is associated with increased mortality. The contribution of intestinal bacteria, parasites and viruses to morbidity such as diarrhea in SAM remains poorly understood. To evaluate their association with clinical outcomes, we detected stool pathogens in children with SAM at hospital admission and after clinical stabilization prior to discharge.
METHODS: 15 intestinal pathogens, fecal calprotectin and C-reactive protein (CRP) were determined at admission and after clinical stabilization in children aged 8-59 months (n = 47) hospitalized in Malawi for complicated SAM. Differences in fecal pathogens, intestinal and systemic inflammation, and clinical outcomes between time points were evaluated using the Wilcoxon Signed-Rank test or Wilcoxon rank-sum test.
RESULTS: On admission pathogens were present in nearly all children and after clinical stabilization many were cleared with only 55% of children still harboring a pathogen (89% vs. 55%, p = 0.001). Nosocomial infections were infrequent. The pathogens Giardia lamblia and Shigella spp. were most likely to persist. After clinical stabilization, fecal calprotectin was higher in children harboring a pathogen (median (IQR): 383 mg/kg (903-149 mg/kg) vs 140 mg/kg (300-71 mg/kg), p = 0.03). CRP did not correlate with fecal calprotectin levels nor was it associated with pathogen detection. Presence of stool pathogens was not associated with clinical outcomes such as diarrhea.
CONCLUSIONS: Fecal pathogens were very common and cleared in most children with complicated SAM treated with antibiotics. The presence of stool pathogens after stabilization was associated with increased intestinal inflammation but not with clinical outcomes.

DOI: 10.1016/j.clnesp.2018.01.004
IMPACT FACTOR: 3.057
CITED HALF-LIFE: 9.5

START COMMENTARY: The 47 children analyzed in this study were taking part in separate randomized controlled trial evaluating the impact of different nutritional rehabilitation formulations in children with SAM. As part of that study, stool samples were collected from children on study entry (hospital admittance for SAM) as well as after clinical stabilization had been achieved. The investigators found no association between diarrheal episodes and the presence of pathogens in children's stool. Additionally, presence of pathogens did not significantly increase duration of hospital stay or intestinal inflammation. The authors noted that the study was limited by the lack of a control group of healthy children due to difficulty with getting parents of healthy children to agree to allow for samples to be taken. In addition, the study was not able to look at the impact of second-line antibiotic (100% were on cotrimoxazole) use on pathogen clearance because 8 different second-line antibiotics were administered for varying lengths of time and were initiated at different times. As both SAM and antibiotic use have shown associations with altered microbiota, the findings of the study could be enhanced if investigators are able to analyze the changes in the microbiota in children who cleared their pathogens and those who did not. The null findings in this study with respect to pathogen persistence and clinical outcomes in children with SAM highlight the complexities of asymptomatic infections, as well as the difficulty of studying these infections in the field.

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10. Subclinical Enteric Parasitic Infections and Growth Faltering in Infants in São Tomé, Africa: A Birth Cohort Study.
Garzón M, Pereira-da-Silva L, Seixas J, Papoila AL, and Alves M.
International Journal of Environmental Research and Public Health. 15(4). 2018 April 05.
PubMed ID: 29621166

ABSTRACT:
The associations between enteric pathogenic parasites and growth in infants in São Tomé were explored using a refined anthropometric approach to recognize early growth faltering. A birth cohort study was conducted with follow-up to 24months of age. Microscopic examination for protozoa and soil-transmitted helminths was performed. Anthropometric assessments included: z-scores for weight-for-length (WLZ), length-for-age (LAZ), weight (WAVZ) and length velocities (LAVZ), length-for-age difference (LAD), and wasting and stunting risk (≤ - 1 SD). Generalized additive mixed effects regression models were used to explore the associations between anthropometric parameters and enteric parasitic infections and cofactors. A total of 475 infants were enrolled, and 282 completed the study. The great majority of infants were asymptomatic. *Giardia lamblia* was detected in 35.1% of infants in at least one stool sample, helminths in 30.4%, and *Cryptosporidium* spp. in 14.7%. *Giardia lamblia* and helminth infections were significantly associated with mean decreases of 0.10 in LAZ and 0.32 in LAD, and of 0.16 in LAZ and 0.48 in LAD, respectively. *Cryptosporidium* spp. infection was significantly associated with a mean decrease of 0.43 in WAVZ and 0.55 in LAVZ. The underestimated association between subclinical parasitic enteric infections and mild growth faltering in infants should be addressed in public health policies.

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CITED HALF-LIFE: 3.4

START COMMENTARY: The authors reported that this is the first birth cohort study conducted in São Tomé and Principe. Newborn infants were recruited from local hospitals in three districts in São Tomé. Anthropometric measurements were taken monthly during the first year of life, and bimonthly during the second year. Stool samples were collected from each child at during visits at 3, 6, 9, 12, 16, 18, and 24 months of age. The authors used two dynamic age measurements, and one absolute measurement, in addition to standard WLZ and LAZ measurements to investigate possible associations between enteric infections and growth. One unique growth measurement was the length-for-age-difference during the neonatal period (LAD= observed length $_{t= 24 \text{ months}}$ – population median length $_{t=24 \text{ months}}$). Two growth velocity measurements were also calculated by looking at two-month intervals for weight and length increments. The authors noted that the LAD method allowed for the identification of subtle deficits in growth that may be missed by solely relying on conventional measures. For example, while average WLZ and LAZ measurements during the study period were within one standard deviation of the mean by WHO standards, the observed LAD deficits of -1.52cm and -1.44cm in males at birth remained almost unchanged throughout the study period. One major limitation of the study is that due to the high attrition of study participants, there is a high potential for bias in the results. As shown in Figure 2, only the 282 infants presented at the month 24 visit were included in this analysis, and among those participants, the mean number of visits attended was 18. Stool samples were collected in 388 infants, but only 56.7% of those infants had at least four of the seven samples collected. The large amount of missing data may have impacted the results of the study, especially because infants who were not included in the analytic sample tended to have lower weight and length at birth, lived in districts with lower wealth indices, had poorer access to improved sanitation and water sources, and had younger,

less educated mothers (Supplementary Table S1). It would be interesting to know if adjustment for baseline LAD in the model would have altered model results (and reduced potential confounding, as low LAD at birth could be associated with both low LAD at the end of, and increased susceptibility to enteric parasite infection during the neonatal period).

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ADDITIONAL ARTICLES OF INTEREST

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