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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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PRODUCED BY: MUNI, KM; ABRAMSON, R; BABIGUMIRA J.

LIST OF ARTICLES

1. **Plasma Tryptophan and the Kynurenine-Tryptophan Ratio are Associated with the Acquisition of Statural Growth Deficits and Oral Vaccine Underperformance in Populations with Environmental Enteropathy** {abstract & UW comment} {full article}
   Diagnostics/Gut Health
   - A prospective study of two birth cohorts with a high prevalence of stunting in Tanzania and Peru to examine the association between linear growth and levels of tryptophan, kynurenine, and the kynurenine-tryptophan ratio (KTR).

2. **Environmental Enteric Dysfunction is Associated with Poor Linear Growth and Can be Identified by Host Fecal mRNAs** {abstract & UW comment} {full article}
   Diagnostics/Gut Health
   - A cohort study that assessed the association between environmental enteric dysfunction (EED) and linear growth, the risk factors for EED, and the sensitivity and specificity of a host fecal mRNA test with the lactulose: mannitol test as the gold standard.

3. **Host-Protozoan Interactions Protect from Mucosal Infections through Activation of the Inflammasome** {abstract & UW comment} {full article}
   Infection/Inflammation
   - Identification of the protozoan *Tritrichomonas musculis* in a mouse-model microbiome and elucidation of its mutualistic interaction with the host epithelial inflammasomal.

4. **Protein malnutrition impairs intestinal epithelial turnover: a potential mechanism of increased cryptosporidiosis in a murine model** {abstract & UW comment} {full article}
   Gut/Nutrition/Infection
   - A murine model to explore the immune defense mechanisms underlying the interaction between malnutrition and cryptosporidiosis in gut epithelial tissue.

5. **Protein- and zinc-deficient diets modulate the murine microbiome and metabolic phenotype** {abstract & UW comment} {full article}
   Gut/Nutrition
   - A murine model experiment with nutrient deficient diets to observe changes in gut microbiota and metabolic consequences.

6. **Stable Engraftment of Bifidobacterium longum AH1206 in the Human Gut Depends on Individualized Features of the Resident Microbiome** {abstract & UW comment} {full article}
   Therapeutics
   - A double-blind, placebo-controlled trial examining the establishment and persistence of a human gut probiotic *Bifidobacterium longum* AH1206 in healthy adults.

7. **Fetal Microbiota-based Therapeutics for Recurrent Clostridium difficile Infection, Ulcerative Colitis and Obesity** {abstract & UW comment} {full article}
   Therapeutics
   - This review paper discusses gut microbial dysbiosis associated with three health conditions (*C. difficile* infection, ulcerative colitis, and obesity) and stool-based therapies to address this microbiome imbalance.

8. **Overcoming the limited availability of human milk oligosaccharides: challenges and opportunities for research and application** {abstract & UW comment} {full article}
   Therapeutics
   - A review of several approaches used to generate human milk oligosaccharides and the prospects of large commercial production of these compounds.

9. **Malnutrition Is Associated with Protection from Rotavirus Diarrhea: Evidence from a Longitudinal Birth Cohort Study in Bangladesh** {abstract & UW comment} {full article}
   Gut/Nutrition
   - A prospective cohort study among 626 slum-dwelling infants (3 years or younger) examining the association between nutritional status and susceptibility to rotavirus infection in early life.

10. **Giardia: a pathogen or commensal for children in high-prevalence settings?** {abstract & UW comment} {full article}
    Infection
    - A review of *Giardia lamblia* infection focusing on its effects on diarrhea and child growth.

DETAILS OF ARTICLES

1. Plasma Tryptophan and the Kynurenine-Tryptophan Ratio are Associated with the Acquisition of Statural Growth Deficits and Oral Vaccine Underperformance in Populations with Environmental Enteropathy
   Kosek MN, Mduma E, Kosek PS, Lee GO, Svensen E, Pan WK, Olortegui MP, Bream JH, Patil C, Asayag CR, Sanchez GM, Caulfield LE, Gratz J, Yori PP.
   American Journal of Tropical Medicine and Hygiene. 2016 Oct 5;95(4):928-937.
   PMID: 27503512

ABSTRACT
Early childhood enteric infections have adverse impacts on child growth and can inhibit normal mucosal responses to oral vaccines, two critical components of environmental enteropathy. To evaluate the role of indoleamine 2,3-dioxygenase 1 (IDO1) activity and its relationship with these outcomes, we measured tryptophan and the kynurenine-tryptophan ratio (KTR) in two longitudinal birth cohorts with a high prevalence of stunting. Children in rural Peru and Tanzania (N = 494) contributed 1,251 plasma samples at 3, 7, 15, and 24 months of age and monthly anthropometrics from 0 to 36 months of age. Tryptophan concentrations were directly associated with linear growth from 1 to 8 months after biomarker assessment. A 1-SD increase in tryptophan concentration was associated with a gain in length-for-age Z-score (LAZ) of 0.17 over the next 6 months in Peru (95% confidence interval [CI] = 0.11-0.23, P < 0.001) and a gain in LAZ of 0.13 Z-scores in Tanzania (95% CI = 0.03-0.22, P = 0.009). Vaccine responsiveness data were available for Peru only. An increase in kynurenine by 1 μM was associated with a 1.63 (95% CI = 1.13-2.34) increase in the odds of failure to poliovirus type 1, but there was no association with tetanus vaccine response. A KTR of 52 was 76% sensitive and 50% specific in predicting failure of response to serotype 1 of the oral polio vaccine. KTR was associated with systemic markers of inflammation, but also interleukin-10, supporting the association between IDO1 activity and immunotolerance. These results strongly suggest that the activity of IDO1 is implicated in the pathophysiology of environmental enteropathy, and demonstrates the utility of tryptophan and kynurenine as biomarkers for this syndrome, particularly in identifying those at risk for hyporesponsivity to oral vaccines.

WEB: 10.4269/ajtmh.16-0037
IMPACT FACTOR: 2.45
CITED HALF-LIFE: 9.9

UW EDITORIAL COMMENT: The authors used IDO1 as a surrogate measure for environmental enteropathy dysfunction. IDO1 itself was not measured directly but indirectly through its enzymatic activity on tryptophan, which it converts to kynurenine. Low levels of tryptophan and high kynurenine and KTR are markers for increased IDO1 activity. The authors' main objective was therefore to assess whether tryptophan, kynurenine, and KTR were good biomarkers/predictors of the effects of environmental enteropathy on linear growth and oral polio vaccine response. Their findings seem to support this possibility (see figures 1 and 4 and table 4). There also seems to be correlation between various markers of inflammation and tryptophan, kynurenine, and KTR (Table 3). One interesting point to note about the article is that the authors reported that levels of kynurenine and tryptophan were not associated with lactulose permeability (a gold standard measure of EED). If these biomarkers are good predictors of an EED state, they should have a strong association with the L:M test.

2. Environmental Enteric Dysfunction is Associated with Poor Linear Growth and Can be Identified by Host Fecal mRNAs
   Ordiz MI, Shaikh N, Trehan I, Maleta K, Stauber J, Shulman R, Devaraj S, Tarr PI, Manary MJ.
   Journal of Pediatric Gastroenterology Nutri. 2016 Nov;63(5):453-459.
   PMID: 27347722

ABSTRACT
OBJECTIVE:
Environmental enteric dysfunction (EED) can be assessed by the lactulose:mannitol (L:M) test. Our objective was to determine if selected host fecal transcripts were correlated with EED, and whether transcripts and clinical characteristics could be used to predict EED in rural African children.
METHODS:
Demographic and sanitation characteristics, along with L:M testing and host fecal transcript analyses from 798 asymptomatic Malawian children aged 12 to 61 months were compared with linear growth over the subsequent 3 months. Fecal host mRNA analysis included quantification of expression of 18 transcripts associated with L:M. Permeability was categorized as normal (L:M ≤ 0.15), moderate (0.15<L:M<0.45) and severe (L:M ≥ 0.45), and random forest predictive models were created.
RESULTS:
L:M was inversely correlated with linear growth over the subsequent 3 months ($r = -0.32$, $P < 0.001$) and severe EED was associated with stunting ($P < 0.0001$). Age younger than 24 months, weight-for-height z score <0, domesticated animals in the child's sleep environment, lack of a pit latrine combined with a potentially contaminated water source, and a recent history of diarrhea were associated with severe EED. A random forest model using CD53, HLA-DRA, MUC12, and TNF was 84% sensitive for severe EED and 83% sensitive for no EED.
CONCLUSIONS:
Selected host fecal transcripts can be used in a random forest model as a noninvasive biomarker for categories of EED in rural African children.

WEB: 10.1097/MPG.0000000000001315
IMPACT FACTOR: 2.4
CITED HALF-LIFE: 7.0

UW EDITORIAL COMMENT: This was a prospective cohort study among 798 children aged 12 to 61 months drawn from participants in three EED studies in Malawi. The study had three objectives: assess the association between EED and linear growth (measured as change in HAZ) over a three-month period; validate a new test for EED (using host fecal mRNA transcripts to predict EED through random forest modeling) with the L:M test as the gold standard; and assess risk factors for EED. The authors' main finding is that using host fecal mRNA transcripts can be used as an alternative test for diagnosing EED in rural Africa (sensitivity of 84% and specificity of 83% for severe EED). EED was also found to be a strong predictor of growth faltering and associated with several clinical and environment al factors (Table 1). The study's main limitations include: reliance on only one L:M measure, assumption of L:M test as a good gold standard, and use of different laboratories to measure the L:M and the mRNAs. The authors discuss some of the limitations in their discussion section.

3. Host-Protozoan Interactions Protect from Mucosal Infections through Activation of the Inflammasome
   Aleksey Chudnovskiy, Arthur Mortha, Veronika Kana, Andrea Kennard, Juan David Ramirez, Adeeb Rahman, Romain Remark, Ilaria Mogno, Ruby Ng, Sasha Gnjatic, El-ad David Amir, Alexander Solovyov, Benjamin Greenbaum, Jose Clemente, Jeremiah Faith, Yasmine Belkaid, Michael E. Grigg, Miriam Merad
   Cell. Volume 167, Issue 2, p444–456.e14, 6 October 2016
   PMID: 27716507

ABSTRACT
While conventional pathogenic protists have been extensively studied, there is an underappreciated constitutive protist microbiota that is an integral part of the vertebrate microbiome. The impact of these species on the host and their potential contributions to mucosalimmune homeostasis remain poorly studied. Here, we show that the protozoan Tritrichomonas musculis activates the host epithelialinflammasome to induce IL-18 release. Epithelial-derived IL-18 promotes dendritic cell-driven Th1 and Th17 immunity and confers dramatic protection from mucosal bacterial infections. Along with its role as a "protistic" antibiotic, colonization with T. musculis exacerbates the development of T-cell-driven colitis and sporadic colorectal tumors. Our findings demonstrate a novel mutualistic host-protozoan interaction that increases mucosal host defenses at the cost of an increased risk of inflammatory disease

WEB: http://dx.doi.org/10.1016/j.cell.2016.08.076
IMPACT FACTOR: 28.71
CITED HALF-LIFE: 9.0

UW EDITORIAL COMMENT
The findings of this study are limited to a murine model system and vulnerable to their environment in an animal housing facility. However, the observed effects of the protozoan on colonic immune response are notable in that the accumulation of IFN-γ-producing CD4+ T_H1 and IL-17-producing CD4+ T_H17 cells to promote anti-bacterial defenses occurs without mucosal injury. Additionally, the authors determined *T. mu*'s closest human ortholog *Dientamoeba fragilis* to be prevalent in healthy human fecal samples (N=188) and identified a widespread distribution of *D. fragilis* in humans. The immunology of flagellate protozoans is poorly described in the literature and therefore *T. mu* may be a valuable model for understanding the pathogenic or protective effects of these organisms on mucosal surfaces in future studies.

4. Protein malnutrition impairs intestinal epithelial turnover: a potential mechanism of increased cryptosporidiosis in a murine model
   J Liu, D. T. Bolicka, G. L. Kollinga, Z Fua, and R. L. Guerranta
   Infection and Immunity. November 2016, Volume 84, Issue 11
   PMID: 27736783

ABSTRACT
Malnutrition and cryptosporidiosis form a vicious cycle and lead to acute and long-term growth impairment in children from developing countries. Insights into mechanisms underlying the vicious cycle will help to design rational therapies to mitigate this infection. We test the effect of short term protein malnutrition on C. parvum infection in a murine model by examining stool shedding, tissue

burden and histologic change, and explore the mechanism underlying the interaction between malnutrition and Cryptosporidiosis through immunostaining and immunoblotting. Protein malnutrition increased stool shedding and intestine-associated C. parvum organisms, accompanied by significant suppression of C. parvum-induced caspase 3 activity, expression of PCNA and Ki67, but an activation of the AKT survival pathway in intestinal epithelial cells. We find that even very brief periods of protein malnutrition may enhance (or intensify) cryptosporidiosis by suppressing C. parvum-induced cell turnover and caspase-dependent apoptosis of intestinal epithelial cells. This implicates a potential strategy to attenuate C. parvum effects by modulating apoptosis and promoting regeneration in the intestinal epithelium.

WEB: 10.1128/IAI.00705-16
IMPACT FACTOR: 3.603
CITED HALF-LIFE: >10.0

UW EDITORIAL COMMENT
The authors highlight epithelial turnover rate as a major defense response to infection, enabling the shedding of infected cells while strengthening the gut barrier. They hypothesize that malnutrition, specifically insufficient protein, weakens this defense mechanism. However, there is no direct evidence that epithelial shedding is suppressed by protein malnutrition and the authors plan to investigate this in future work. Figure 4B and 4C show greater density of cleaved caspase 3 positive cells (a marker for apoptosis and indication of cell shedding) in nourished infected group than malnourished infected group.

5. Protein- and zinc-deficient diets modulate the murine microbiome and metabolic phenotype
   Jordi Mayneris-Perxachs, David T Bolick, Joy Leng, Greg L Medlock, Glynis L Kolling, Jason A Papin, Jonathan R Swann, and Richard L Guerrant
   American Journal of Clinical Nutrition. October 2016, 104 (4)
   PMID: 27733402

ABSTRACT
Background: Environmental enteropathy, which is linked to undernutrition and chronic infections, affects the physical and mental growth of children in developing areas worldwide. Key to understanding how these factors combine to shape developmental outcomes is to first understand the effects of nutritional deficiencies on the mammalian system including the effect on the gut microbiota.
Objective: We dissected the nutritional components of environmental enteropathy by analyzing the specific metabolic and gut-microbiota changes that occur in weaned-mouse models of zinc or protein deficiency compared with well-nourished controls.
Design: With the use of a ^{1}H nuclear magnetic resonance spectroscopy–based metabolic profiling approach with matching 16S microbiota analyses, the metabolic consequences and specific effects on the fecal microbiota of protein and zinc deficiency were probed independently in a murine model.
Results: We showed considerable shifts within the intestinal microbiota 14–24 d post weaning in mice that were maintained on a normal diet (including increases in Proteobacteria and striking decreases in Bacterioidetes). Although the zinc-deficient microbiota were comparable to the age-matched, well-nourished profile, the protein-restricted microbiota remained closer in composition to the weaned enterotype with retention of Bacteroidetes. Striking increases in Verrucomicrobia (predominantly *Akkermansia muciniphila*) were observed in both well-nourished and protein-deficient mice 14 d post weaning. We showed that protein malnutrition impaired growth and had major

metabolic consequences (much more than with zinc deficiency) that included altered energy, polyamine, and purine and pyrimidine metabolism. Consistent with major changes in the gut microbiota, reductions in microbial proteolysis and increases in microbial dietary choline processing were observed. **Conclusions:** These findings are consistent with metabolic alterations that we previously observed in malnourished children. The results show that we can model the metabolic consequences of malnutrition in the mouse to help dissect relevant pathways involved in the effects of undernutrition and their contribution to environmental enteric dysfunction.

WEB: 10.3945/ajcn.116.131797
IMPACT FACTOR: 6.703
CITED HALF-LIFE: >10.0

UW EDITORIAL COMMENT
Murine models were used to elucidate biochemical mechanisms of nutrient deficiencies, representing two major nutritional deficiencies common in children from impoverished areas: protein- and zinc-deficiencies. In this study, a protein-deficient diet contained 2% protein (~20% is normal) and the zinc-deficient diet was devoid of zinc. The greatest microbial diversity was observed at the point of weaning, with this diversity mostly maintained in the protein-deficient mice. The authors hypothesize that insufficient protein locked microbiota into its pre-malnourished microbial state. The authors were not able to determine whether intestinal inflammation after protein deficiency had an impact on the bacterial composition. The authors suggest that the limited perturbations observed in the zinc-deficient mouse models may have resulted from microbiota obtaining residual zinc from the host (further depleting the host but starving off bacterial compositional changes during the study period). Alternatively, zinc-associated bacterial alterations may occur at a lower taxonomic level than measured in this study.

6. Stable Engraftment of Bifidobacterium longum AH1206 in the Human Gut Depends on Individualized Features of the Resident Microbiome
María X. Maldonado-Gómez, Inés Martínez, Francesca Bottacini, Amy O'Callaghan, Marco Ventura, Douwe van Sinderen, Benjamin Hillmann, Pajau Vangay, Dan Knights, Robert W. Hutkins, Jens Walter
Cell. Volume 20, Issue 4, p515–526, 12 October 2016
PMID: 27693307

ABSTRACT
Live bacteria (such as probiotics) have long been used to modulate gut microbiota and human physiology, but their colonization is mostly transient. Conceptual understanding of the ecological principles as they apply to exogenously introduced microbes in gut ecosystems is lacking. We find that, when orally administered to humans, *Bifidobacterium longum* AH1206 stably persists in the gut of 30% of individuals for at least 6 months without causing gastrointestinal symptoms or impacting the composition of the resident gut microbiota. AH1206 engraftment was associated with low abundance of resident *B. longum* and underrepresentation of specific carbohydrate utilization genes in the pre-treatment microbiome. Thus, phylogenetic limiting and resource availability are two factors that control the niche opportunity for AH1206 colonization. These findings suggest that bacterial species and functional genes absent in the gut microbiome of individual humans can be reestablished, providing opportunities for precise and personalized microbiome reconstitution

WEB: http://dx.doi.org/10.1016/j.chom.2016.09.001
IMPACT FACTOR: 28.71
CITED HALF-LIFE: 9.0

UW EDITORIAL COMMENT
This human trial was a double-blind, placebo-controlled, crossover study with two testing periods (placebo & probiotic, plus a 14-day exposure and 28-day follow-up for persistence of probiotic in fecal samples). Additional samples were collected 11 and 20 weeks after completion of study to test long-term persistence. The authors used three methods for assessment of the probiotic's persistence: quantitative real-time PCR of fecal strains, sequencing of 16S rRNA gene tags and whole metagenome sequencing, and species typing of selectively cultured fecal bifidobacterial. Substantial inter-personal variability was noted in levels of persistence of the probiotic in human guts, though these differences could not be explained by differences in species richness, evenness, or community stability.

7. Fecal Microbiota-based Therapeutics for Recurrent Clostridium difficile Infection, Ulcerative Colitis and Obesity
   Christian Carlucci, Elaine O. Petrof, Emma Allen-Vercoe
   EBioMedicine. 2016 Oct 1. pii: S2352-3964(16)30450-9
   PMID: 27720396

ABSTRACT
The human gut microbiome is a complex ecosystem of fundamental importance to human health. Our increased understanding of gut microbial composition and functional interactions in health and disease states has spurred research efforts examining the gut microbiome as a valuable target for therapeutic intervention. This review provides updated insight into the state of the gut microbiome in recurrent *Clostridium difficile* infection (CDI), ulcerative colitis (UC), and obesity while addressing the rationale for the modulation of the gut microbiome using fecal microbiota transplant (FMT)-based therapies. Current microbiome-based therapeutics in pre-clinical or clinical development are discussed. We end by putting this within the context of the current regulatory framework surrounding FMT and related therapies.

WEB: http://dx.doi.org/10.1016/j.ebiom.2016.09.029
IMPACT FACTOR: not available
CITED HALF-LIFE: not available

UW EDITORIAL COMMENT: In their Table 1, the authors outlined the major changes to the gut microbiome associated with CDI, UC, and obesity. The information is based off findings from various studies that compared fecal samples from participants with the condition to those without it. The authors reported that while the evidence for the effectiveness of fecal microbiota transplantation (FMT) against CDI was strong, it is mixed for UC. The authors attributed this to UC's complex etiology. The use of FMT in obesity is still confined to animal models. One randomized clinical trial investigating the effect of FMT on metabolic syndrome in humans reported increased gut microbial diversity and insulin sensitivity 6 weeks after FMT. Stool-substitute therapies are also discussed very briefly in the article specifically in the context of treatment for CDI. The authors conclude that both FMT and stool-substitute therapies need further research to facilitate their wider use.

8. Overcoming the limited availability of human milk oligosaccharides: challenges and opportunities for research and application
Bode L, Contractor N, Barile D, Pohl N, Prudden AR, Boons GJ, Jin YS, Jennewein S.
Nutrition Reviews. 2016 Oct;74(10):635-44
PMID: 27634978

ABSTRACT
Human milk oligosaccharides (HMOs) are complex sugars highly abundant in human milk but currently not present in infant formula. Rapidly accumulating evidence from in vitro and in vivo studies, combined with epidemiological associations and correlations, suggests that HMOs benefit infants through multiple mechanisms and in a variety of clinical contexts. Until recently, however, research on HMOs has been limited by an insufficient availability of HMOs. Most HMOs are found uniquely in human milk, and thus far it has been prohibitively tedious and expensive to isolate and synthesize them. This article reviews new strategies to overcome this lack of availability by generating HMOs through chemoenzymatic synthesis, microbial metabolic engineering, and isolation from human donor milk or dairy streams. Each approach has its advantages and comes with its own challenges, but combining the different methods and acknowledging their limitations creates new opportunities for research and application with the goal of improving maternal and infant health

WEB: 10.1093/nutrit/nuw025
IMPACT FACTOR: 5.591
CITED HALF-LIFE: not available

UW EDITORIAL COMMENT: The paper highlights the benefits associated with HMOs including acting as a prebiotic that helps microbiota composition and block enteropathogens. The paper is however primarily a review of three major approaches to generating HMOs (isolation from human and bovine milk, chemoenzymatic synthesis, and bioengineering of microorganisms). Using microorganisms is discussed as the most promising of the three approaches as it may allow the production of HMOs in the human gut or in food if probiotic or food fermenting bacteria are engineered to produce HMOs. The authors conclude that two HMOs produced by chemical synthesis are currently approaching market approval (HMOs produced by Glycom A/S and Jennewein Biotechnologie GmbH).

9. Malnutrition Is Associated with Protection from Rotavirus Diarrhea: Evidence from a Longitudinal Birth Cohort Study in Bangladesh
Verkerke H, Sobuz S, Ma JZ, Petri SE, Reichman D, Qadri F, Rahman M, Haque R, Petri WA Jr.
Journal of Clinical Microbiology. 2016 Oct;54(10):2568-74
PMID: 27510830

ABSTRACT
Rotavirus is a leading cause of dehydrating diarrhea and death among infants and children globally, particularly in communities of the developing world. While numerous studies have described the complex relationships among infectious diarrhea, growth faltering, and poverty, the impact of nutritional status on susceptibility to rotavirus diarrhea is not well understood. In a longitudinal study conducted over the first 3 years of life among 626 slum-dwelling infants enrolled at birth in Dhaka, Bangladesh, we observed that common measures of healthy growth and development were positively associated with a risk of symptomatic rotavirus infection. This finding runs counter to the idea that improving childhood nutrition will implicitly decrease the incidence of symptomatic infection by enteric

pathogens. As childhood nutrition improves worldwide, rotavirus infection may remain a public health challenge, making universal vaccination of even greater importance.

WEB: 10.1128/JCM.00916-16
IMPACT FACTOR: 3.63
CITED HALF-LIFE: >10.0

UW EDITORIAL COMMENT: The study took place between 2008 and 2012 and was conducted among infants (under 3 years) who were not vaccinated against rotavirus in a slum with high prevalence of malnutrition in the Bangladeshi capital Dhaka. The study was motivated by previous studies that had shown a negative association between improved childhood nutrition and incidence of rotavirus diarrhea. The outcome (rotavirus positive diarrhea) was ascertained using ELISA. The exposure was calculated from infant anthropometric measures using the WHO Anthro software. A generalized mixed-effects model was used for the analysis. The key finding of the study is that malnutrition is negatively associated with rotavirus diarrhea in the first three years of life. This is shown in Figure 4 of the paper presented as three different panels of adjusted odds ratios with weight-for age, height-for age, and weight-for height Z scores in the x axis. In their exploration of possible explanation for their interesting findings, the authors postulated that malnourished children may have been a higher risk of environmental enteropathy, a condition associated with shortening of the enterocytic villi. This shortening of the villi may have inhibited entry and replication of the rotavirus. The authors also discussed the possible influence of malnutrition on the gut microbiome and how that may have affected rotavirus entry.

10. Giardia: a pathogen or commensal for children in high-prevalence settings?
    Bartelt LA, Platts-Mills JA.
    Current Opinion Infectious Diseases. 2016 Oct;29(5):502-7
    PMID: 27479025

ABSTRACT
PURPOSE OF REVIEW:
Giardia is a common intestinal parasite worldwide, and infection can be associated with clear and sometimes persistent symptomatology. However, in children in high-prevalence settings, it is not associated with or is perhaps even protective against acute diarrhea, and the association with long-term outcomes has been difficult to discern.
RECENT FINDINGS:
Recent studies have made progress in helping us disentangle this apparent paradox. First, prospective, well-characterized cohort studies have added to the data on the association between Giardia and diarrhea in these settings and have further characterized associations between Giardia infection and nutrition, gut function, and growth. Second, animal models have further characterized the host response to Giardia and helped elucidate mechanisms by which Giardia could impair child development. Finally, new work has shed light on the heterogeneity of human Giardia strains, which may both explain discrepant findings in the literature and help guide higher-resolution analyses of this pathogen in the future.
SUMMARY:
The true clinical impact of endemic pediatric giardiasis remains unclear, but recent prospective studies have confirmed a high prevalence of persistent, subclinical Giardia infections and associated growth shortfalls. Integrating how nutritional, microbial, metabolic, and pathogen-strain variables influence

these outcomes could sharpen delineations between pathogenic and potentially beneficial attributes of this enigmatic parasite.

WEB: 10.1097/QCO.0000000000000293
IMPACT FACTOR: 4.439
CITED HALF-LIFE: not available

UW EDITORIAL COMMENT: Key points discussed in the paper include the lack of evidence supporting a strong association between Giardia lamblia infection and diarrhea, possible protective effect of Giardia lamblia on diarrhea, and the effect of persistent Giardia lamblia infection on early childhood growth. The authors discussed possible mechanisms for this effect on child growth. These mechanisms include altered mucosal integrity and chronic inflammation. Giardia lamblia infection is associated with increased L:M ratio (indicative of gut permeability) and is presented as a possible cause of EED through its degradation of cytoskeletal and tight junction proteins. EED then leads to poor growth.