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Department of Global Health | University of Washington

# GUT HEALTH DIGEST

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

REPORT TO THE BILL & MELINDA GATES FOUNDATION

AUGUST 31, 2017

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## LIST OF ARTICLES

1. **The Burden of Enteropathy and "Subclinical" Infections.** {Abstract & UW comment} {Full article}
    - Review of the definitions, diagnostics, and burden of environmental enteropathy.
2. **Impaired Barrier Function and Autoantibody Generation in Malnutrition Enteropathy in Zambia.** {Abstract & UW comment} {Full article}
    - A study of the associations between malnutrition enteropathy and both intestinal barrier failure and immune dysregulation through comparisons of individuals with SAM and healthy controls.
3. **Infant Nutritional Status and Markers of Environmental Enteric Dysfunction are Associated with Midchildhood Anthropometry and Blood Pressure in Tanzania.** {Abstract & UW comment} {Full article}
    - Investigation into whether markers of environmental enteric dysfuntion are associated with a variety of child health outcomes.
4. **The regulation of gut mucosal IgA B-cell responses: recent developments.** {Abstract & UW comment} {Full article}
    - Review of functions of the mucosal immune system, with a particular focus on the production of secretory IgA antibodies.
5. **A benign helminth alters the host immune system and the gut microbiota in a rat model system.** {Abstract & UW comment} {Full article}
    - Rat model study of the impact of helminth infection on gut microbial composition and the potential for helminth therapy.
6. **The Microbiome Activates CD4 T-cell-mediated Immunity to Compensate for Increased Intestinal Permeability.** {Abstract & UW comment} {Full article}
    - Mouse model investigating mucosal immune activation in those with increased intestinal permeability.
7. **Antigen-specific regulatory T-cell responses to intestinal microbiota.** {Abstract & UW comment} {Full article}
    - Review of the role of intestinal bacteria and antigen-specificity in the induction of IgA.
8. **Cross-modulation of pathogen-specific pathways enhances malnutrition during enteric co-infection with *Giardia lamblia* and enteroaggregative *Escherichia coli*.** {Abstract & UW comment} {Full article}
    - This study explores the ways in which common enteropathogens in children impact malnutrition using a model of protein deficient mice.
9. **Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: a randomised controlled study in Kenyan infants.** {Abstract & UW comment} {Full article}
    - Randomized trial investigating the efficacy of a new micronutrient powder on anemia and the gut microbiome.

10. **Epidemiology of enteroaggregative Escherichia coli infections and associated outcomes in the MAL-ED birth cohort.** {Abstract & UW comment} {Full article}
    - Study of the association between enteroaggregative Escherichia coli infection and both growth disorders and environmental enteropathy in children.

## DETAILS OF ARTICLES

1. The Burden of Enteropathy and "Subclinical" Infections.
   Rogawski E, Guerrant R.
   Pediatric Clinics of North America. 64(4):815-836. 2017 Aug.

**ABSTRACT**
Environmental enteropathy is a chronic condition of the small intestine associated with increased intestinal permeability, mucosal inflammation, malabsorption, and systemic inflammation. It is commonly accompanied by enteric infections and is misleadingly considered a subclinical disease. Potential effects of enteric infections and enteropathy on vaccine responses, child growth, cognitive development, and even later life obesity, diabetes, and metabolic syndrome are increasingly being recognized. Herein, we review the evolving challenges to defining environmental enteropathy and enteric infections, current evidence for the magnitude and determinants of its burden, new assessment tools, and relevant interventions.

**WEB:** 10.1016/j.pcl.2017.03.003
**IMPACT FACTOR:** 0.88
**CITED HALF-LIFE:** 9.00

**UW EDITORIAL COMMENT:** Authors review the history, definitions, and diagnostic approaches for environmental enteropathy (EE), and discuss the difficulty of determining its magnitude of burden. Authors note the challenge of determining causality between EE and a variety of outcomes due to an array of confounders and mediators that each play a role in the causal pathway – Figure 1 diagrams this relationship, with a useful example of the association between EE and impaired cognition. Additionally, authors highlight the array of diagnostic difficulties, like the inability to perform intestinal biopsy in most research studies despite it being the gold standard, and provide a table (Table 1) of potential biomarkers and their functions, which are used as alternatives to the gold standard.

2. Impaired Barrier Function and Autoantibody Generation in Malnutrition Enteropathy in Zambia.
   Amadi B, Besa E, Zyambo K, Kaonga P, Louis-Auguste J, Chandwe K, et al.
   EBioMedicine. 22:191-199. 2017 Aug.

**ABSTRACT**
Intestinal damage in malnutrition constitutes a threat to the survival of many thousands of children globally. We studied children in Lusaka, Zambia, with severe acute malnutrition (SAM) and persistent diarrhea using endoscopy, biopsy and analysis of markers and protective proteins in blood and intestinal secretions. We carried out parallel investigations in apparently healthy adults, and analyzed biomarkers only in apparently healthy children. Villus height and crypt depth did not differ in children with SAM and adult controls, but epithelial surface was reduced in children with SAM (median 445, interquartile range (IQR) 388, 562µm per 100µm muscularis mucosae) compared to adults (578, IQR 465,709; P=0.004). Histological lesions and disruptions of claudin-4 and E-cadherin were most pronounced in children with SAM. Circulating lipopolysaccharide, a marker of bacterial translocation, was higher in malnourished

children (251, IQR 110,460EU/ml) than in healthy children (51, IQR 0,111; P=0.0001). Other translocation markers showed similar patterns. Anti-Deamidated Gliadin Peptide IgG concentrations, although within the normal range, were higher in children with SAM (median 2.7U/ml, IQR 1.5-8.6) than in adults (1.6, 1.4-2.1; P=0.005), and were inversely correlated with villus height (ρ=-0.79, n=13, P=0.001). Malnutrition enteropathy is associated with intestinal barrier failure and immune dysregulation.

**WEB:** 10.1016/j.ebiom.2017.07.017
**IMPACT FACTOR:** 1.37
**CITED HALF-LIFE:** N/A

**UW EDITORIAL COMMENT:** HIV status, which has a dramatic impact on gut integrity, was known in children hospitalized with SAM, but not those sampled from the community. Interestingly, only villus surface area:volume ratio was different between HIV+ and HIV- children with SAM, otherwise markers of inflammation and gut microbial translocation were similar. Endoscopy/biopsy was not performed in children sampled from the community, due to ethical concerns around invasive sampling from apparently healthy children. This is a universal difficulty in studying apparently healthy children and those with presumed EED; the authors provide comparisons with historic data in the supplemental materials. Several biomarkers (16srDNA, LPS, LBP, FABP) do not have known reference ranges, limiting their interpretation.

3. Infant Nutritional Status and Markers of Environmental Enteric Dysfunction are Associated with Midchildhood Anthropometry and Blood Pressure in Tanzania.
   Locks L, Mwiru R, Mtisi E, Manji K, McDonald C, Liu E, et al.
   Journal of Pediatrics. 187: 225–233. 2017 Aug.

**ABSTRACT**
OBJECTIVE: To assess whether growth and biomarkers of environmental enteric dysfunction in infancy are related to health outcomes in midchildhood in Tanzania.
STUDY DESIGN: Children who participated in 2 randomized trials of micronutrient supplements in infancy were followed up in midchildhood (4.6-9.8 years of age). Anthropometry was measured at age 6 and 52 weeks in both trials, and blood samples were available from children at 6 weeks and 6 months from 1 trial. Linear regression was used for height-for-age z-score, body mass index-for-age z-score, and weight for age z-score, and blood pressure analyses; log-binomial models were used to estimate risk of overweight, obesity, and stunting in midchildhood.
RESULTS: One hundred thirteen children were followed-up. Length-for-age z-score at 6 weeks and delta length-for-age z-score from 6 to 52 weeks were associated independently and positively with height-for-age z-score and inversely associated with stunting in midchildhood. Delta weight-for-length and weight-for-age z-score were also positively associated with midchildhood height-for-age z-score. The 6-week and delta weight-for-length z-scores were associated independently and positively with midchildhood body mass index-for-age z-score and overweight, as was the 6-week and delta weight-for-age z-score. Delta length-for-age z-score was also associated with an increased risk of overweight in midchildhood. Body mass index-for-age z-score in midchildhood was associated positively with systolic blood pressure. Serum anti-flagellin IgA concentration at 6 weeks was also associated with increased blood pressure in midchildhood.
CONCLUSIONS: Anthropometry at 6 weeks and growth in infancy independently predict size in midchildhood, while anti-flagellin IgA, a biomarker of environmental enteric dysfunction, in early infancy

is associated with increased blood pressure in midchildhood. Interventions in early life should focus on optimizing linear growth while minimizing excess weight gain and environmental enteric dysfunction.

**WEB:** 10.1016/j.jpeds.2017.04.005
**IMPACT FACTOR:** 1.49
**CITED HALF-LIFE:** N/A

**UW EDITORIAL COMMENT:** A strong association between anti-flagellan IgA and high blood pressure concluded from this study contributes to the growing hypothesis that infant EED plays a role in long term cardiometabolic outcomes. Table III shows associations between blood pressure and a variety of baseline measurements, where small p-values can be seen for anti-flagellan IgA measurements. Interestingly, none of the anthropometric indicators were strongly associated with change in blood pressure.

4. The regulation of gut mucosal IgA B-cell responses: recent developments.
   Lycke NY, Bemark M.
   Mucosal Immunol. Volume/Issue. 2017 Jul 26. [Epub ahead of print]

**ABSTRACT**
The majority of activated B cells differentiate into IgA plasma cells, with the gut being the largest producer of immunoglobulin in the body. Secretory IgA antibodies have numerous critical functions of which protection against infections and the role for establishing a healthy microbiota appear most important. Expanding our knowledge of the regulation of IgA B-cell responses and how effective mucosal vaccines can be designed are of critical importance. Here we discuss recent developments in the field that shed light on the uniqueness and complexity of mucosal IgA responses and the control of protective IgA responses in the gut, specifically.

**WEB:** 10.1038/mi.2017.62
**IMPACT FACTOR:** 5.21
**CITED HALF-LIFE:** 3.10

**UW EDITORIAL COMMENT:** This publication, containing nearly 200 referenced studies, reviews the functions of the mucosal immune system, particularly its role in the production of secretory IgA antibodies. Specific topics discussed include antigen uptake and induction of IgA B-cell responses, IgA promoting factors, and synchronizing gut IgA responses. Of particular interest, authors discuss the interplay between gut microbiota diversity and IgA production, and highlight the complexity of this interrelationship.

5. A benign helminth alters the host immune system and the gut microbiota in a rat model system.
   Wegener Parfrey L, Jirků M, Šima R, Jalovecká M, Sak B, Grigore K, et al.
   PLoS One. 12(8):e0182205. 2017 Aug 3.

**ABSTRACT**
Helminths and bacteria are major players in the mammalian gut ecosystem and each influences the host immune system and health. Declines in helminth prevalence and bacterial diversity appear to play a role in the dramatic rise of immune mediated inflammatory diseases (IMIDs) in western populations. Helminths are potent modulators of immune system and their reintroduction is a promising therapeutic avenue for IMIDs. However, the introduction of helminths represents a disturbance for the host and it is

important to understand the impact of helminth reintroduction on the host, including the immune system and gut microbiome. We tested the impact of a benign tapeworm, Hymenolepis diminuta, in a rat model system. We find that H. diminuta infection results in increased interleukin 10 gene expression in the beginning of the prepatent period, consistent with induction of a type 2 immune response. We also find induction of humoral immunity during the patent period, shown here by increased IgA in feces. Further, we see an immuno-modulatory effect in the small intestine and spleen in patent period, as measured by reductions in tissue immune cells. We observed shifts in microbiota community composition during the patent period (beta-diversity) in response to H. diminuta infection. However, these compositional changes appear to be minor; they occur within families and genera common to both treatment groups. There was no change in alpha diversity. Hymenolepis diminuta is a promising model for helminth therapy because it establishes long-term, stable colonization in rats and modulates the immune system without causing bacterial dysbiosis. These results suggest that the goal of engineering a therapeutic helminth that can safely manipulate the mammalian immune system without disrupting the rest of the gut ecosystem is in reach.

**WEB:** 10.1371/journal.pone.0182205
**IMPACT FACTOR:** 3.54
**CITED HALF-LIFE:** 2.70

**UW EDITORIAL COMMENT:** Authors acknowledge the divergent conclusions that have been made in regards to the changes in microbiota as a result of helminth infection, with various studies concluding with both beneficial and harmful effects of helminths on microbial composition. However, in this study, while alpha diversity remains stable, results show both a gradual change in gut microbiota and an induction of type 2 immune response, warranting further investigation of the potential for helminth therapy.

6. The Microbiome Activates CD4 T-cell-mediated Immunity to Compensate for Increased Intestinal Permeability.
   Edelblum KL, Sharon G, Singh G, Odenwald MA, Sailer A, Cao S, et al.
   Cell Mol Gastroenterol Hepatol. 4(2):285-297. 2017 Jun 10.

**ABSTRACT**
BACKGROUND & AIMS: Despite a prominent association, chronic intestinal barrier loss is insufficient to induce disease in human subjects or experimental animals. We hypothesized that compensatory mucosal immune activation might protect individuals with increased intestinal permeability from disease. We used a model in which intestinal barrier loss is triggered by intestinal epithelial-specific expression of constitutively active myosin light chain kinase (CA-MLCK). Here we asked whether constitutive tight junction barrier loss impacts susceptibility to enteric pathogens.
METHODS: Acute or chronic *Toxoplasma gondii* or *Salmonella typhimurium* infection was assessed in CA-MLCK transgenic or wild-type mice. Germ-free mice or those lacking specific immune cell populations were used to investigate the effect of microbial-activated immunity on pathogen translocation in the context of increased intestinal permeability.
RESULTS: Acute *T gondii* and *S typhimurium* translocation across the epithelial barrier was reduced in CA-MLCK mice. This protection was due to enhanced mucosal immune activation that required $CD4^+$ T cells and interleukin 17A but not immunoglobulin A. The protective mucosal immune activation in CA-MLCK mice depended on segmented filamentous bacteria (SFB), because protection against early *S typhimurium* invasion was lost in germ-free CA-MLCK mice but could be restored by conventionalization with SFB-containing, not SFB-deficient, microbiota. In contrast, chronic *S*

*typhimurium* infection was more severe in CA-MLCK mice, suggesting that despite activation of protective mucosal immunity, barrier defects ultimately result in enhanced disease progression. CONCLUSIONS: Increased epithelial tight junction permeability synergizes with commensal bacteria to promote intestinal $CD4^+$ T-cell expansion and interleukin 17A production that limits enteric pathogen invasion.

**WEB:** 10.1016/j.jcmgh.2017.06.001
**IMPACT FACTOR:** N/A
**CITED HALF-LIFE:** N/A

**UW EDITORIAL COMMENT:** This article demonstrates the paradox that increased intestinal permeability may limit enteric pathogen invasion in some cases, including protozoan and bacterial. Authors assert that commensal bacteria are necessary for this protection, in that they play a role in driving the CD4+ T-cell expansion that is responsible for the protection. Using a mouse model, investigators shed light on this immune response and the extent to which this activation of immunity can compensate for intestinal barrier dysfunction.

7. Antigen-specific regulatory T-cell responses to intestinal microbiota.
   Russler-Germain EV, Rengarajan S, Hsieh CS.
   Mucosal Immunol. 2017 Aug 2. [Epub ahead of print]

**ABSTRACT**
The mammalian gastrointestinal tract can harbor both beneficial commensal bacteria important for host health, but also pathogenic bacteria capable of intestinal damage. It is therefore important that the host immune system mount the appropriate immune response to these divergent groups of bacteria-promoting tolerance in response to commensal bacteria and sterilizing immunity in response to pathogenic bacteria. Failure to induce tolerance to commensal bacteria may underlie immune-mediated diseases such as human inflammatory bowel disease. At homeostasis, regulatory T (Treg) cells are a key component of the tolerogenic response by adaptive immunity. This review examines the mechanisms by which intestinal bacteria influence colonic T-cells and B-cell immunoglobulin A (IgA) induction, with an emphasis on Treg cells and the role of antigen-specificity in these processes. In addition to discussing key primary literature, this review highlights current controversies and important future directions.

**WEB:** 10.1038/mi.2017.65
**IMPACT FACTOR:** 5.21
**CITED HALF-LIFE:** 3.10

**UW EDITORIAL COMMENT:** Authors highlight the antigen-specificity of IgA responses in the gut and its complexities, in that IgA can be induced by both pathogenic bacteria and unharmful intestinal bacteria. Much remains to be investigated in regards to IgA responses to gut microbiota and authors discuss some of the conflicting data, particularly around the role of Treg cells in IgA production.

8. Cross-modulation of pathogen-specific pathways enhances malnutrition during enteric co-infection with Giardia lamblia and enteroaggregative Escherichia coli.
   Bartelt L, Bolick D, Mayneris-Perxachs J, Kolling GL, Medlock G, Zaenker E, et al.
   PLoS Pathog. 13(7): e1006471. 2017 Jul 27.

**ABSTRACT**
Diverse enteropathogen exposures associate with childhood malnutrition. To elucidate mechanistic pathways whereby enteric microbes interact during malnutrition, we used protein deficiency in mice to develop a new model of co-enteropathogen enteropathy. Focusing on common enteropathogens in malnourished children, *Giardia lamblia* and enteroaggregative *Escherichia coli* (EAEC), we provide new insights into intersecting pathogen-specific mechanisms that enhance malnutrition. We show for the first time that during protein malnutrition, the intestinal microbiota permits persistent *Giardia* colonization and simultaneously contributes to growth impairment. Despite signals of intestinal injury, such as IL1α, *Giardia*-infected mice lack pro-inflammatory intestinal responses, similar to endemic pediatric *Giardia*infections. Rather, *Giardia* perturbs microbial host co-metabolites of proteolysis during growth impairment, whereas host nicotinamide utilization adaptations that correspond with growth recovery increase. EAEC promotes intestinal inflammation and markers of myeloid cell activation. During co-infection, intestinal inflammatory signaling and cellular recruitment responses to EAEC are preserved together with a *Giardia*-mediated diminishment in myeloid cell activation. Conversely, EAEC extinguishes markers of host energy expenditure regulatory responses to *Giardia*, as host metabolic adaptations appear exhausted. Integrating immunologic and metabolic profiles during co-pathogen infection and malnutrition, we develop a working mechanistic model of how cumulative diet-induced and pathogen-triggered microbial perturbations result in an increasingly wasted host.

**WEB:** 10.1371/journal.ppat.1006471
**IMPACT FACTOR:** 7.64
**CITED HALF-LIFE:** 3.80

**UW EDITORIAL COMMENT:** This novel mouse model demonstrates ways in which sequential enteric infections may interact to progressively degrade host mucosal integrity in a protein-deficient host. Both pathogen-specific and synergistic immune and metabolic responses are described. Figure 5 presents a model of metabolic alterations as a result of microbial co-infection in the setting of protein deficiency. It includes a diagram of the loss of host-mediated nicotinamide-pathway energy regulation.

9. Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: a randomised controlled study in Kenyan infants.
   Paganini D, Uyoga MA, Kortman GAM, Cercamondi CI, Moretti D, Barth-Jaeggi T, et al.
   Gut. 2017 Aug 3. [Epub ahead of print].

**ABSTRACT**
OBJECTIVE: Iron-containing micronutrient powders (MNPs) reduce anaemia in African infants, but the current high iron dose (12.5 mg/day) may decrease gut *Bifidobacteriaceae* and *Lactobacillaceae*, and increase enteropathogens, diarrhoea and respiratory tract infections (RTIs). We evaluated the efficacy and safety of a new MNP formula with prebiotic galacto-oligosaccharides (GOS) combined with a low dose (5 mg/day) of highly bioavailable iron.
DESIGN: In a 4-month, controlled, double-blind trial, we randomised Kenyan infants aged 6.5-9.5 months (n=155) to receive daily (1) a MNP without iron (control); (2) the identical MNP but with 5 mg iron (2.5 mg as sodium iron ethylenediaminetetraacetate and 2.5 mg as ferrous fumarate) (Fe group); or (3) the identical MNP as the Fe group but with 7.5 g GOS (FeGOS group).
RESULTS: Anaemia decreased by ≈50% in the Fe and FeGOS groups ($p<0.001$). Compared with the control or FeGOS group, in the Fe group there were (1) lower abundances of *Bifidobacterium* and *Lactobacillus* and higher abundances of *Clostridiales* ($p<0.01$); (2) higher

abundances of virulence and toxin genes (VTGs) of pathogens ($p<0.01$); (3) higher plasma intestinal fatty acid-binding protein (a biomarker of enterocyte damage) ($p<0.05$); and (4) a higher incidence of treated RTIs ($p<0.05$). In contrast, there were no significant differences in these variables comparing the control and FeGOS groups, with the exception that the abundance of VTGs of all pathogens was significantly lower in the FeGOS group compared with the control and Fe groups ($p<0.01$).
CONCLUSION: A MNP containing a low dose of highly bioavailable iron reduces anaemia, and the addition of GOS mitigates most of the adverse effects of iron on the gut microbiome and morbidity in African infants.

**WEB:** 10.1136/gutjnl-2017-314418
**IMPACT FACTOR:** 5.78
**CITED HALF-LIFE:** 8.60

**UW EDITORIAL COMMENT:** Figures 3 and 4 provide visuals of the group differences in gut microbial composition at 3 weeks and 4 months, respectively, and parts D through F of both figures give simplified versions of the primary taxa of interest. It can be seen that, when comparing the MNP without-iron arm with the MNP with iron and prebiotic galacto-oligosaccharides arm, there are no statistically significant differences in the primary taxa of interest, indicating that it is the high dose of iron that plays a role in the development of an unfavorable gut microbiome.

10. Epidemiology of enteroaggregative Escherichia coli infections and associated outcomes in the MAL-ED birth cohort.
    Rogawski ET, Guerrant RL, Havt A, Lima IFN, Medeiros PHQS, Seidman J, et al.
    PLoS Negl Trop Dis. 11(7):e0005798. 2017 Jul 24.

**ABSTRACT**
BACKGROUND: Enteroaggregative E. coli (EAEC) have been associated with mildly inflammatory diarrhea in outbreaks and in travelers and have been increasingly recognized as enteric pathogens in young children with and without overt diarrhea. We examined the risk factors for EAEC infections and their associations with environmental enteropathy biomarkers and growth outcomes over the first two years of life in eight low-resource settings of the MAL-ED study.
METHODS: EAEC infections were detected by PCR gene probes for aatA and aaiC virulence traits in 27,094 non-diarrheal surveillance stools and 7,692 diarrheal stools from 2,092 children in the MAL-ED birth cohort. We identified risk factors for EAEC and estimated the associations of EAEC with diarrhea, enteropathy biomarker concentrations, and both short-term (one to three months) and long-term (to two years of age) growth.
RESULTS: Overall, 9,581 samples (27.5%) were positive for EAEC, and almost all children had at least one detection (94.8%) by two years of age. Exclusive breastfeeding, higher enrollment weight, and macrolide use within the preceding 15 days were protective. Although not associated with diarrhea, EAEC infections were weakly associated with biomarkers of intestinal inflammation and more strongly with reduced length at two years of age (LAZ difference associated with high frequency of EAEC detections: -0.30, 95% CI: -0.44, -0.16).
CONCLUSIONS: Asymptomatic EAEC infections were common early in life and were associated with linear growth shortfalls. Associations with intestinal inflammation were small in magnitude, but suggest a pathway for the growth impact. Increasing the duration of exclusive breastfeeding may help prevent these potentially inflammatory infections and reduce the long-term impact of early exposure to EAEC.

**WEB:** 10.1371/journal.pntd.0005798

**IMPACT FACTOR:** 4.45
**CITED HALF-LIFE:** 3.2

**UW EDITORIAL COMMENT:** This article supports the evidence base for the association between poor child health development outcomes and EAEC presence, regardless of whether symptomatic diarrhea is present. Authors examined a variety of markers of environmental enteropathy— they suggest that intestinal inflammation may be a viable pathway towards these poor health outcomes of children, despite somewhat weak associations, due to a statistically significant association between high contemporary concentrations of myeloperoxidase (MPO) and EAEC. However, EAEC was not associated with markers of systematic inflammation or intestinal permeability. The full list of markers can be found in Table 2.

## ADDITIONAL ARTICLES OF INTEREST

Changes in the intestinal microbiota following the administration of azithromycin in a randomised placebo-controlled trial among infants in south India.

Tissue is the Issue: Duodenal Biopsies to Elucidate Gut Structure and Function Among Undernourished Children in Low-Resource Settings

Identification of Subsets of Enteroaggregative Escherichia coli Associated with Diarrheal Disease among Under 5-Year-Old Children from Rural Gambia.

Intestinal colonisation patterns in breastfed and formula-fed infants during the first 12 weeks of life reveal sequential microbiota signatures.

Early gut mycobiota and mother-offspring transfer.

Human milk oligosaccharide categories define the microbiota composition in human colostrum.

## ARTICLE ARCHIVE (JAN 2016-PRESENT)

**EED Biology & Review Articles**
Introducing the sporobiota and sporobiome.

Patterns of Early-Life Gut Microbial Colonization during Human Immune Development: An Ecological Perspective

Parasitic protozoa and interactions with the host intestinal microbiota.

Gastrointestinal inflammation by gut microbiota disturbance induces memory impairment in mice.

New insights into environmental enteric dysfunction.

Tropical Enteropathies.

Age and Sex Normalization of Intestinal Permeability Measures for the Improved Assessment of Enteropathy in Infancy and Early Childhood: Results from the MAL-ED Study.

Infant Nutritional Status and Markers of Environmental Enteric Dysfunction are Associated with Midchildhood Anthropometry and Blood Pressure in Tanzania.

Biomarkers to Stratify Risk Groups among Children with Malnutrition in Resource-Limited Settings and to Monitor Response to Intervention

Association between Enteropathogens and Malnutrition in Children Aged 6-23 mo in Bangladesh: a Case-Control Study.

Causal Pathways from Enteropathogens to Environmental Enteropathy: Findings from the MAL-ED Birth Cohort Study.

Biomarkers of Environmental Enteric Dysfunction: The good, the bad and the ugly.

Application of penalized linear regression methods to the selection of environmental enteropathy biomarkers.

Environmental enteropathy is associated with cardiometabolic risk factors in Peruvian children.

Biomarkers of Environmental Enteric Dysfunction Among Children in Rural Bangladesh.

Environmental Enteric Dysfunction is Associated with Carnitine Deficiency and Altered Fatty Acid Oxidation.

Determinant Variables, Enteric Pathogen Burden, Gut Function, and Immune-Related Inflammatory Biomarkers Associated with Childhood Malnutrition: A Prospective Case-Control Study in Northeastern Brazil.

The Association Between Fecal Biomarkers of Environmental Enteropathy and Rotavirus Vaccine Response in Nicaraguan Infants.

Systemic inflammation, growth factors, and linear growth in the setting of infection and malnutrition

Environmental Enteric Dysfunction and the Fecal Microbiota in Malawian Children

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

Biomarkers of Environmental Enteropathy, Inflammation, Stunting, and Impaired Growth in Children in Northeast Brazil.

Environmental enteropathy.

Environmental Enteropathy: Elusive but Significant Subclinical Abnormalities in Developing Countries.

Endomicroscopic and Transcriptomic Analysis of Impaired Barrier Function and Malabsorption in Environmental

Environmental Enteric Dysfunction in Children.

Environmental Enteric Dysfunction Includes a Broad Spectrum of Inflammatory Responses and Epithelial Repair Processes.

The Impact of Environmental Enteropathy and Systemic Inflammation on Infant Growth Failure

Small Intestine Bacterial Overgrowth and Environmental Enteropathy in Bangladeshi Children.

Decoding Hidden Messages: Can Fecal Host Transcriptomics Open Pathways to Understanding Environmental Enteropathy?

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

Malnutrition Is Associated with Protection from Rotavirus Diarrhea: Evidence from a Longitudinal Birth Cohort Study in Bangladesh

**Nutrition/metabolism**

Formula diet driven microbiota shifts tryptophan metabolism from serotonin to tryptamine in neonatal porcine colon.

Detrimental Impact of Microbiota-Accessible Carbohydrate-Deprived Diet on Gut and Immune Homeostasis: An Overview

Chronic consequences on human health induced by microbial pathogens: Growth faltering among children in developing countries.

The effects of micronutrient deficiencies on bacterial species from the human gut microbiota.

Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals.

The association of serum choline with linear growth failure in young children from rural Malawi.

Starved Guts: Morphologic and Functional Intestinal Changes in Malnutrition.

Which dietary components modulate longitudinal growth?

Influence of diet on the gut microbiome and implications for human health.

Nopal feeding reduces adiposity, intestinal inflammation and shifts the cecal microbiota and metabolism in high-fat fed rats

Western diets, gut dysbiosis, and metabolic diseases: Are they linked?

Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children

Microbiome, Growth Retardation, and Metabolism: Are they related?

Linking Dietary Patterns with Gut Microbial Composition and Function.

Impacts of resistant starch and wheat bran consumption on enteric inflammation in relation to colonic bacterial community structures and short-chain fatty acid concentrations in mice.

Diet-Microbiota Interactions Mediate Global Epigenetic Programming in Multiple Host Tissues

Systemic inflammation, growth factors, and linear growth in the setting of infection and malnutrition.

Environmental Enteric Dysfunction is Associated with Altered Bile Acid Metabolism

Metabolic alterations in children with environmental enteric dysfunction.

Genetic and Metabolic Signals during Acute Enteric Bacterial Infection Alter the Microbiota and Drive Progression to Chronic Inflammatory Disease

Interactions between intestinal pathogens, enteropathy and malnutrition in developing countries.

Child Stunting is Associated with Low Circulating Essential Amino Acids.

Diet–microbiota interactions as moderators of human metabolism

Protein malnutrition impairs intestinal epithelial turnover: a potential mechanism of increased cryptosporidiosis in a murine model

A Comparison of Diarrheal Severity Scores in the MAL-ED Multisite Community-Based Cohort Study.

Metabolomic Changes in Serum of Children with Different Clinical Diagnoses of Malnutrition.

Mortality in children with complicated severe acute malnutrition is related to intestinal and systemic inflammation: an observational cohort study.

Steroid Administration and Growth Impairment in Children with Crohn's Disease.

Effects of a gut pathobiont in a gnotobiotic mouse model of childhood undernutrition

A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility

**Microbiome Therapies**

Lactobacillus acidophilus/Bifidobacterium infantis probiotics are associated with increased growth of VLBWI among those exposed to antibiotics

Early antibiotic exposure in low-resource settings is associated with increased weight in the first two years of life.

The path towards microbiome-based metabolite treatment.

Next-generation probiotics: the spectrum from probiotics to live biotherapeutics

Severity of pancreatitis- associated intestinal mucosal barrier injury is reduced following treatment with the NADPH oxidase inhibitor apocynin.

Targeting the gut microbiota with inulin-type fructans: preclinical demonstration of a novel approach in the management of endothelial dysfunction.

Interleukin-23 Increases Intestinal Epithelial Cell Permeability In Vitro

Pili-like proteins of Akkermansia muciniphila modulate host immune responses and gut barrier function.

The anti-inflammatory drug mesalamine targets bacterial polyphosphate accumulation

*Akkermansia muciniphila i*mproves metabolic profiles by reducing inflammation in chow diet-fed mice

Longitudinal change of selected human milk oligosaccharides and association to infants' growth, an observatory, single center, longitudinal cohort study

Abrupt suspension of probiotics administration may increase host pathogen susceptibility by inducing gut dysbiosis

Toward a Personalized Approach in Prebiotics Research

Dietary Fiber and Prebiotics and the Gastrointestinal Microbiota.

A microbial protein that alleviates metabolic syndrome

Can probiotics modulate human disease by impacting intestinal barrier function?

Human Milk Oligosaccharides Influence Neonatal Mucosal and Systemic Immunity.

Oral Microbiota in Infants Fed a Formula Supplemented with Bovine Milk Fat Globule Membranes - A Randomized Controlled Trial.

Dietary Prebiotics and Bioactive Milk Fractions Improve NREM Sleep, Enhance REM Sleep Rebound and Attenuate the Stress-Induced Decrease in Diurnal Temperature and Gut Microbial Alpha Diversity.

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Starter formula enriched in prebiotics and probiotics ensures normal growth of infants and promotes gut health: a randomized clinical trial.

Diet-induced extinctions in the gut microbiota compound over generations

Microbiome: Eating for trillions

An important chapter in the infection-malnutrition story.

Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition

Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children

Sialylated Milk Oligosaccharides Promote Microbiota-Dependent Growth in Models of Infant Undernutrition

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Sialylated galacto-oligosaccharides and 2'-fucosyllactose reduce necrotising enterocolitis in neonatal rats

Rebooting the microbiome.

Fecal microbiota transplantation: in perspective.

Fecal Microbiota-based Therapeutics for Recurrent Clostridium difficile Infection, Ulcerative Colitis and Obesity

Microbial therapeutic interventions.

High-affinity monoclonal IgA regulates gut microbiota and prevents colitis in mice

Stable Engraftment of Bifidobacterium longum AH1206 in the Human Gut Depends on Individualized Features of the Resident Microbiome

Protein- and zinc-deficient diets modulate the murine microbiome and metabolic phenotype

Fecal Microbiota-based Therapeutics for Recurrent Clostridium difficile Infection, Ulcerative Colitis and Obesity

Overcoming the limited availability of human milk oligosaccharides: challenges and opportunities for research and application

Efficacy of Probiotics Versus Placebo in the Prevention of Necrotizing Enterocolitis in Preterm Very Low Birth Weight Infants: A Double-Blind Randomized Controlled Trial

Eosinophils, probiotics, and the microbiome.

A Combined Intervention of Zinc, Multiple Micronutrients, and Albendazole Does Not Ameliorate Environmental Enteric Dysfunction or Stunting in Rural Malawian Children in a Double-Blind Randomized Controlled Trial

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Genome-resolved metaproteomic characterization of preterm infant gut microbiota development reveals species-specific metabolic shifts and variabilities during early life.

More than just a gut feeling: constraint-based genome-scale metabolic models for predicting functions of human intestinal microbes.

Potential and active functions in the gut microbiota of a healthy human cohort.

Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43.

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Organs-on-chips with integrated electrodes for trans-epithelial electrical resistance (TEER) measurements of human epithelial barrier function.

A methodologic framework for modeling and assessing biomarkers of environmental enteropathy as predictors of growth in infants: an example from a Peruvian birth cohort.

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Engineered Regulatory Systems Modulate Gene Expression of Human Commensals in the Gut

MicrobiomeAnalyst: a web-based tool for comprehensive statistical, visual and meta-analysis of microbiome data.

Honeybee gut microbiota promotes host weight gain via bacterial metabolism and hormonal signaling.

Leading microbiome-based therapeutic falters in Phase II trial

Faecal microbiota transplantation—A clinical view.

Optimization of metabolomics of defined in vitro gut microbial ecosystems

Community dynamics drive punctuated engraftment of the fecal microbiome following transplantation using freeze-dried, encapsulated fecal microbiota.

Challenges of metabolomics in human gut microbiota research

The Role of the Immune System in Metabolic Health and Disease

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Gut-Brain Cross-Talk in Metabolic Control

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The human gut microbiome as source of innovation for health: Which physiological and therapeutic outcomes could we expect?

Tryptophan: A gut microbiota-derived metabolites regulating inflammation

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Etiology of Diarrhea, Nutritional Outcomes and Novel Intestinal Biomarkers in Tanzanian Infants: A Preliminary Study.

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MiniBioReactor Arrays (MBRAs) as a Tool for Studying C. difficile Physiology in the Presence of a Complex Community.

Reverse Engineering Human Pathophysiology with Organs-on-Chips.

Human Microbiota-Associated Mice: A Model with Challenges

Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip.

Optimization of Quantitative PCR Methods for Enteropathogen Detection

Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study

Diagnostics: Filling in the missing pieces

Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability

Gut check

Population-level analysis of gut microbiome variation

Childhood undernutrition, the gut microbiota, and microbiota-directed therapeutics

Environmental Enteric Dysfunction is Associated with Poor Linear Growth and Can be Identified by Host Fecal mRNAs

Commendation for Exposing Key Advantage of Organ Chip Approach

Biomarkers of Environmental Enteropathy are Positively Associated with Immune Responses to an Oral Cholera Vaccine in Bangladeshi Children

Shifts in *Lachnospira* and *Clostridium* sp. in the 3-month stool microbiome are associated with preschool age asthma

**Other Gut Infections/Health**

Longitudinal development of the gut microbiome and metabolome in preterm neonates with late onset sepsis and healthy controls.

(Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease.

Chemical and pathogen-induced inflammation disrupt the murine intestinal microbiome.

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Regulation of intestinal permeability: the role of proteases.

Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments

Bap180/Baf180 is required to maintain homeostasis of intestinal innate immune response in Drosophila and mice

Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction

Mice with infectious colitis exhibit linear growth failure and subsequent catch-up growth related to systemic inflammation and IGF-1.

Molecular insight into Evolution of Symbiosis between Breast-Fed Infants and a Member of the Human Gut Microbiome Bifidobacterium longum

An insider's perspective: Bacteroides as a window into the microbiome

Antibiotics, Pediatric Dysbiosis, and Disease

Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance.

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Microbial Respiration and Formate Oxidation as Metabolic Signatures of Inflammation-Associated Dysbiosis.

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The Bactericidal Lectin RegIIIβ Prolongs Gut Colonization and Enteropathy in the Streptomycin Mouse Model for Salmonella Diarrhea.

Mining the Human Gut Microbiota for Immunomodulatory Organisms.

Feedback control of AHR signalling regulates intestinal immunity

Reinforcement of intestinal epithelial barrier by arabinoxylans in overweight and obese subjects: A randomized controlled trial: Arabinoxylans in gut barrier.

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The Role of Fibronectin in the Adherence and Inflammatory Response Induced by Enteroaggregative Escherichia coli on Epithelial Cells.

Early-life enteric infections: relation between chronic systemic inflammation and poor cognition in children.

GEMS extend understanding of childhood diarrhoea

Infectious disease: something in the water

Genomic diversity of EPEC associated with clinical presentations of differing severity.
Gene-microbiota interactions contribute to the pathogenesis of inflammatory bowel disease

Taking it Personally: Personalized Utilization of the Human Microbiome in Health and Disease

Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome

Giardia: a pathogen or commensal for children in high-prevalence settings?

Tuft Cells: New Players in Colitis.

PGE2 is a direct and robust mediator of anion/fluid secretion by human intestinal epithelial cells

Dysbiosis is not an answer

Epidemiology and Impact of *Campylobacter* Infection in Children in 8 Low-Resource Settings: Results From the MAL-ED Study

The microbiota and immune response during *Clostridium difficile* infection

Enterocyte Purge and Rapid Recovery Is a Resilience Reaction of the Gut Epithelium to Pore-Forming Toxin Attack

**Microbiome & Infection**

The Gut Microbiome: Connecting Spatial Organization to Function

Intestinal, extra-intestinal and systemic sequelae of Toxoplasma gondii induced acute ileitis in mice harboring a human gut microbiota.

The shape of the microbiome in early life

Dysbiosis and the immune system.

Dysbiosis in intestinal inflammation: Cause or consequence

Discovery of Reactive Microbiota-Derived Metabolites that Inhibit Host Proteases

A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice

Microbiome-Modulated metabolites at the Interface of Host Immunity

Gastrointestinal Inflammation and Repair: Role of Microbiome, Infection, and Nutrition

Formation of propionate and butyrate by the human colonic microbiota.

Xenobiotic Receptor-Mediated Regulation of Intestinal Barrier Function and Innate Immunity.

Identifying species of symbiont bacteria from the human gut that, alone, can induce intestinal Th17 cells in mice

Microbiota Diurnal Rhythmicity Programs Host Transcriptome Oscillations

Persistent microbiome alterations modulate the rate of post-dieting weight regain

Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease

Influence of early life exposure, host genetics and diet on the mouse gut microbiome and metabolome

Impact of the gut microbiota on enhancer accessibility in gut intraepithelial lymphocytes.

Universality of human microbial dynamics

Reparative inflammation takes charge of tissue regeneration

Intrinsic Defense Mechanisms of the Intestinal Epithelium

Lipocalin 2 Protects from Inflammation and Tumorigenesis Associated with Gut Microbiota Alterations

Gut Microbial Metabolites Fuel Host Antibody Responses

IFN-γ Hinders Recovery from Mucosal Inflammation during Antibiotic Therapy for Salmonella Gut Infection

Limited diversity sparks inflammation at the mucosal border

Rhythm and bugs: circadian clocks, gut microbiota, and enteric infections.

I'll have a turkey and cheese sandwich

A microbial perspective of human developmental biology

The microbiome and innate immunity

The microbiota in adaptive immune homeostasis and disease

Interactions between the microbiota and pathogenic bacteria in the gut

Microbiome-wide association studies link dynamic microbial consortia to disease

Host-microbe interaction: Rules of the game for microbiota

The Host Shapes the Gut Microbiota via Fecal MicroRNA

Another Reason to Thank Mom: Gestational Effects of Microbiota Metabolites

Preterm infant gut microbiota affects intestinal epithelial development in a humanized microbiome gnotobiotic mouse model.

Development of the gut microbiota and mucosal IgA responses in twins and gnotobiotic mice

Host Selection of Microbiota via Differential Adhesion

Tummy Time: The Infant Microbiota–IgA Connection

Antibiotics, birth mode, and diet shape microbiome maturation during early life

Integrated multi-omics of the human gut microbiome in a case study of familial type 1 diabetes

Host-Protozoan Interactions Protect from Mucosal Infections through Activation of the Inflammasome

Adaptive immune response in symptomatic and asymptomatic enteric protozoal infection: evidence for a determining role of parasite genetic heterogeneity in host immunity to human giardiasis

The Liver at the Nexus of Host-Microbial Interactions

Modeling human enteric dysbiosis and rotavirus immunity in gnotobiotic pigs.

Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity

Culture of previously uncultured members of the human gut microbiota by culturomics