START CENTER
STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

GUT HEALTH DIGEST

UNIVERSITY OF WASHINGTON STRATEGIC ANALYSIS, RESEARCH & TRAINING (START) CENTER
REPORT TO THE BILL & MELINDA GATES FOUNDATION

MARCH 29, 2017

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LIST OF ARTICLES

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3. **Biomarkers of Environmental Enteric Dysfunction Among Children in Rural Bangladesh** {abstract & UW comment} {full article}
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5. **Pili-like proteins of Akkermansia muciniphila modulate host immune responses and gut barrier function.** {abstract & UW comment} {full article}
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6. **An Intestinal Organ Culture System Uncovers a Role for the Nervous System in Microbe-Immune Crosstalk.** {abstract & UW comment} {full article}
    - A novel 3D microfluidic organ culture system for modelling immune-microbe interactions.

7. **Optimization of metabolomics of defined in vitro gut microbial ecosystems.** {abstract & UW comment} {full article}
    - Review of bioreactor systems and metabololomics platforms for *ex vivo* modeling of human gut microbiota.

8. **The Role of the Immune System in Metabolic Health and Disease.** {abstract & UW comment} {full article}
    - Perspective on principles of immune-metabolic interactions and molecular interactions among diet, host, microbiome, and immune response.

9. **Dysbiosis and the immune system.** {abstract & UW comment} {full article}
    - Review of the causes and consequences of dysbiosis, role in common diseases, and potential therapeutics.

10. **Faecal microbiota transplantation—A clinical view** {abstract & UW comment} {full article}
    - Review of FMT in *Clostridium difficile* colitis and IBD and potential therapeutic use for metabolic, autoimmune, and behavioral conditions.

DETAILS OF ARTICLES

1. Application of penalized linear regression methods to the selection of environmental enteropathy biomarkers.
   Lu M, Zhou J, Naylor C, Kirkpatrick BD, Haque R, Petri WA Jr, Ma JZ.
   Biomark Res. 2017 Mar 9;5:9. doi: 10.1186/s40364-017-0089-4. eCollection 2017.

ABSTRACT

Background: Environmental Enteropathy (EE) is a subclinical condition caused by constant fecal-oral contamination and resulting in blunting of intestinal villi and intestinal inflammation. Of primary interest in the clinical research is to evaluate the association between non-invasive EE biomarkers and malnutrition in a cohort of Bangladeshi children. The challenges are that the number of biomarkers/covariates is relatively large, and some of them are highly correlated.

Methods: Many variable selection methods are available in the literature, but which are most appropriate for EE biomarker selection remains unclear. In this study, different variable selection approaches were applied and the performance of these methods was assessed numerically through simulation studies, assuming the correlations among covariates were similar to those in the Bangladesh cohort. The suggested methods from simulations were applied to the Bangladesh cohort to select the most relevant biomarkers for the growth response, and bootstrapping methods were used to evaluate the consistency of selection results.

Methods: Through simulation studies, SCAD (Smoothly Clipped Absolute Deviation), Adaptive LASSO (Least Absolute Shrinkage and Selection Operator) and MCP (Minimax Concave Penalty) are the suggested variable selection methods, compared to traditional stepwise regression method. In the Bangladesh data, predictors such as mother weight, height-for-age z-score (HAZ) at week 18, and inflammation markers (Myeloperoxidase (MPO) at week 12 and soluable CD14 at week 18) are informative biomarkers associated with children's growth.

Conclusions: Penalized linear regression methods are plausible alternatives to traditional variable selection methods, and the suggested methods are applicable to other biomedical studies. The selected early-stage biomarkers offer a potential explanation for the burden of malnutrition problems in low-income countries, allow early identification of infants at risk, and suggest pathways for intervention.

WEB: 10.1186/s40364-017-0089-4
IMPACT FACTOR: n/a
CITED HALF-LIFE: n/a

UW EDITORIAL COMMENT: Authors used samples from the PROVIDE cohort (infants in Mirpur urban slum in Dhaka, Bangladesh) to identify biomarkers significantly associated with height-for-age z-score (HAZ) of a one-year old. Four regression models were simulated using training and validation datasets: LASSO, SCAD, Minimax Concave Penalty (MCP), and Adaptive LASSO. SCAD, MCP and Adaptive LASSO were selected based on model simulations with low Type I error rates. All three models suggested similar sets of biomarkers for the data analysis: HAZ and weight-for-height z-score (WHZ) at week 8 and mother's weight were positively associated with HAZ at one-year and mannitol at week 12 was negatively associated. The authors provide an applicable methodology for using penalized regression methods to analyze high-dimensional and correlated data such as potential EED biomarkers.

2. Environmental enteropathy is associated with cardiometabolic risk factors in Peruvian children. Lee G, Olortegui MP, Salas MS, Yori PP, Trigoso DR, Kosek P, Mispireta ML, Oberhelman R, Caulfield LE, Kosek MN.
J Dev Orig Health Dis. 2017 Mar 7:1-12. doi: 10.1017/S2040174417000071. [Epub ahead of print]

ABSTRACT
Environmental enteropathy (EE) is a syndrome of altered small intestine structure and function hypothesized to be common among individuals lacking access to improved water and sanitation. There are plausible biological mechanisms, both inflammatory and non-inflammatory, by which EE may alter the cardiometabolic profile. Here, we test the hypothesis that EE is associated with the cardiometabolic profile among young children living in an environment of intense enteropathogen exposure. In total, 156 children participating in the Peruvian cohort of a multicenter study on childhood infectious diseases, growth and development were contacted at 3-5 years of age. The urinary lactulose:mannitol ratio, and plasma antibody to endotoxin core were determined in order to assess intestinal permeability and bacterial translocation. Blood pressure, anthropometry, fasting plasma glucose, insulin, and cholesterol and apolipoprotein profiles were also assessed. Extant cohort data were also used to relate biomarkers of EE during the first 18 months of life to early child cardiometabolic profile. Lower intestinal surface area, as assessed by percent mannitol excretion, was associated with lower apolipoprotein-AI and lower high-density lipoprotein concentrations. Lower intestinal surface area was also associated with greater blood pressure. Inflammation at 7 months of age was associated with higher blood pressure in later childhood. This study supports the potential for a relationship between EE and the cardiometabolic profile.

WEB: 10.1017/S2040174417000071
IMPACT FACTOR: 2.16
CITED HALF-LIFE: 3.2

UW EDITORIAL COMMENT: Using the MAL-ED study (300 Peruvian infants), the authors investigate whether gut alterations are also associated with cardiometabolic conditions. One major limitation of the study is that metabolic syndrome cannot be defined in children 3-5 yeas old so biomarkers were used as intermediate outcome measures. Figure 1 illustrates the conceptual framework for linking the relationship between environmental enteropathy and stunting to the relationship between infection and chronic disease. The authors did not find evidence that chronic bacterial translocation was related to cardiometabolic factors, nor that WHZ acts as a mediator between environmental enteropathy and cardiometabolic biomarkers so the mechanism by which intestinal permeability is associated with a child's cardiometabolic profile remains unknown. Additionally, although high blood pressure was associated with greater intestinal permeability, the authors express caution in their interpretation due to the difficulty in measuring blood pressure in children.

3. Biomarkers of Environmental Enteric Dysfunction Among Children in Rural Bangladesh. Campbell RK, Schulze K, Shaikh S, Mehra S, Ali H, Wu L, Raqib R, Baker S, Labrique A, West KP Jr, Christian P.
J Pediatr Gastroenterol Nutr. 2017 Mar 8. doi: 10.1097/MPG.0000000000001557. [Epub ahead of print]

ABSTRACT
Objectives: Environmental enteric dysfunction (EED) may inhibit growth and development in low- and middle-income countries, but available assessment methodologies limit its study. In rural Bangladesh,

we measured EED using the widely-used lactulose mannitol ratio (L:M) test and a panel of intestinal and systemic health biomarkers to evaluate convergence among biomarkers and describe risk factors for EED.
Methods: In 539 18-month-old children finishing participation in a randomized food supplementation trial, serum, stool and urine collected after lactulose and mannitol dosing were analyzed for biomarkers of intestinal absorption, inflammation, permeability and repair, and systemic inflammation. EED scores for each participant were developed using principal component analysis (PCA) and partial least squares regression (PLS). Associations between scores and L:M and with child sociodemographic and health characteristics were evaluated using regression analysis.
Results: EED prevalence (L:M>0.07) was 39.0%; 60% had elevated acute phase proteins (CRP>5 mg/L or AGP>100 mg/dL). Correlations between intestinal biomarkers were low, with the highest between myeloperoxidase and α-1 antitrypsin ($r = 0.33$, $p < 0.01$), and biomarker values did not differ by supplementation history. A one-factor PLS model with L:M as the dependent variable explained only 8.6% of L:M variability. In adjusted models, L:M was associated with child sex and SES index, while systemic inflammation was predicted mainly by recent illness, not EED.
Conclusions: Impaired intestinal health is widespread in this setting of prevalent stunting, but a panel of serum and stool biomarkers demonstrated poor agreement with L:M. Etiologies of intestinal and systemic inflammation are likely numerous and complex in resource-poor settings, underscoring the need for a better case definition with corresponding diagnostic methods to further the study of EED.

WEB: 10.1097/MPG.0000000000001557
IMPACT FACTOR: 2.4
CITED HALF-LIFE: 7.0

UW EDITORIAL COMMENT: The authors add to a growing body of evidence about the limitations of the lactulose:mannitol ratio test to indicate EED. This study was nested in a community-based randomized trial of complementary food supplements in northwest Bangladesh. Biomarkers of intestinal and systemic health did not improve in children receiving the intervention food supplementation.

4. Environmental Enteric Dysfunction is Associated with Carnitine Deficiency and Altered Fatty Acid Oxidation.
   Richard D. Semba, Indi Trehan, Ximin Li, Ruin Moaddel, M. Isabel Ordiz, Kenneth M. Maleta, Klaus Kraemer, Michelle Shardell, Luigi Ferrucci, Mark Manary
   EBioMedicine. Volume 17, March 2017, Pages 9-10.

ABSTRACT
Background: Environmental enteric dysfunction (EED), a condition characterized by small intestine inflammation and abnormal gut permeability, is widespread in children in developing countries and a major cause of growth failure. The pathophysiology of EED remains poorly understood.
Methods: We measured serum metabolites using liquid chromatography-tandem mass spectrometry in 400 children, aged 12–59 months, from rural Malawi. Gut permeability was assessed by the dual-sugar absorption test.
Findings: 80.7% of children had EED. Of 677 serum metabolites measured, 21 were negatively associated and 56 were positively associated with gut permeability, using a false discovery rate approach ($q < 0.05$, $p < 0.0095$). Increased gut permeability was associated with elevated acylcarnitines, deoxycarnitine, fatty acid β-oxidation intermediates, fatty acid ω-oxidation products, odd-chain fatty acids, trimethylamine-N-oxide, cystathionine, and homocitrulline, and with lower citrulline, ornithine, polyphenol metabolites, hippurate, tryptophan, and indolelactate.

Interpretation: EED is a syndrome characterized by secondary carnitine deficiency, abnormal fatty acid oxidation, alterations in polyphenol and amino acid metabolites, and metabolic dysregulation of sulfur amino acids, tryptophan, and the urea cycle. Future studies are needed to corroborate the presence of secondary carnitine deficiency among children with EED and to understand how these metabolic derangements may negatively affect the growth and development of young children.

WEB: 10.1016/j.ebiom.2017.01.026
IMPACT FACTOR: 1.37
CITED HALF-LIFE: n/a

UW EDITORIAL COMMENT: This cross-sectional study used a lactulose:mannitol (L:M) test to identify children with EED and then measured their serum metabolites to determine whether specific metabolites are biomarkers for EED. In light of limitations associated with the L:M test, the findings would be more informative if the data were normalized to body weight, indexed to height-for-age z-score, and presented with other gut dysfunction markers. The authors acknowledge that their metabolomics platform was unable to validate previously published findings that indicated a positive association between serum glutamate and gut permeability, as well as other metabolites that previous studies had identified as significant. This study highlights the limitations of metabolomics in assessing EED due to procedural differences between platforms and the influence of statistical methods on which set of specific metabolites are identifiable.

5. Pili-like proteins of Akkermansia muciniphila modulate host immune responses and gut barrier function.
   Ottman N, Reunanen J, Meijerink M, Pietilä TE, Kainulainen V, Klievink J, Huuskonen L, Aalvink S, Skurnik M, Boeren S, Satokari R, Mercenier A, Palva A, Smidt H, de Vos WM, Belzer C.
   PLoS One. 2017 Mar 1;12(3):e0173004. eCollection 2017.

ABSTRACT
Gut barrier function is key in maintaining a balanced response between the host and its microbiome. The microbiota can modulate changes in gut barrier as well as metabolic and inflammatory responses. This highly complex system involves numerous microbiota-derived factors. The gut symbiont Akkermansia muciniphila is positively correlated with a lean phenotype, reduced body weight gain, amelioration of metabolic responses and restoration of gut barrier function by modulation of mucus layer thickness. However, the molecular mechanisms behind its metabolic and immunological regulatory properties are unexplored. Herein, we identify a highly abundant outer membrane pili-like protein of A. muciniphila MucT that is directly involved in immune regulation and enhancement of trans-epithelial resistance. The purified Amuc_1100 protein and enrichments containing all its associated proteins induced production of specific cytokines through activation of Toll-like receptor (TLR) 2 and TLR4. This mainly leads to high levels of IL-10 similar to those induced by the other beneficial immune suppressive microorganisms such as Faecalibacterium prausnitzii A2-165 and Lactobacillus plantarum WCFS1. Together these results indicate that outer membrane protein composition and particularly the newly identified highly abundant pili-like protein Amuc_1100 of A. muciniphila are involved in host immunological homeostasis at the gut mucosa, and improvement of gut barrier function.

WEB: 10.1371/journal.pone.0173004
IMPACT FACTOR: 3.1
CITED HALF-LIFE: 3.1

UW EDITORIAL COMMENT:
Table 1 & Figure 2 contrast the effects of different bacteria and bacterial fractions on cytokine production. *A. muciniphila* induced IL-8, IL-6, IL-1β, IL-10 and TNF-α, which suggests the bacteria may hold both anti- and pro- inflammatory roles, and thus may have a more complex role in preserving the balance of the gut ecosystem. Immunolabeling also suggests there may be different numbers of MucT pili per cell, which play a role in the mechanism by which *A. muciniphila* induces cytokine production.

6. An Intestinal Organ Culture System Uncovers a Role for the Nervous System in Microbe-Immune Crosstalks.
   Nissan Yissachar, Yan Zhou, Lloyd Ung, Nicole Y. Lai, James F. Mohan, Allen Ehrlicher, David A. Weitz, Dennis L. Kasper, Isaac M. Chiu, Diane Mathis, Christophe Benoist
   Cell. Volume 168, Issue 6, 9 March 2017, Pages 1135–1148. e12.

ABSTRACT
Investigation of host-environment interactions in the gut would benefit from a culture system that maintained tissue architecture yet allowed tight experimental control. We devised a microfabricated organ culture system that viably preserves the normal multicellular composition of the mouse intestine, with luminal flow to control perturbations (e.g., microbes, drugs). It enables studying short-term responses of diverse gut components (immune, neuronal, etc.). We focused on the early response to bacteria that induce either Th17 or RORg$^+$ T-regulatory (Treg) cells in vivo. Transcriptional responses partially reproduced in vivo signatures, but these microbes elicited diametrically opposite changes in expression of a neuronal-specific gene set, notably nociceptive neuropeptides. We demonstrated activation of sensory neurons by microbes, correlating with RORg$^+$ Treg induction. Colonic RORg$^+$ Treg frequencies increased in mice lacking TAC1 neuropeptide precursor and decreased in capsaicin-diet fed mice. Thus, differential engagement of the enteric nervous system may partake in bifurcating pro- or anti-inflammatory responses to microbes.

WEB: /10.1016/j.cell.2017.02.009
IMPACT FACTOR: 28.7
CITED HALF-LIFE: 9

UW EDITORIAL COMMENT: The authors developed a novel system to culture mouse intestine *ex vivo* by connecting excised intestinal segments to mechanical ports through which delivery of molecules and microorganisms could be controlled. Their experiments confirmed the preservation of critical intestinal functions of interest including epithelial barrier integrity and enteric nervous system structure. The authors then used this model to study the host transcriptional response to introduced gut microbiota and identified the activation of neuron-related genes.

7. Optimization of metabolomics of defined in vitro gut microbial ecosystems.
   Dirk K. Wissenbacha, Kaitlyn Oliphantb, Ulrike Rolle-Kampczyka, Sandi Yenb, Henrike Hökea, Sven Baumanna, Sven B. Haangea, Elena F. Verdud, Emma Allen-Vercoe.
   International Journal of Medical Microbiology, Volume 306, Issue 5, Aug. 2016, Pages 280-289.

ABSTRACT
The metabolic functionality of a microbial community is a key to the understanding of its inherent ecological processes and the interaction with the host. However, the study of the human gut microbiota is hindered by the complexity of this ecosystem. One way to resolve this issue is to derive defined communities that may be cultured ex vivo in bioreactor systems and used to approximate the native

ecosystem. Doing so has the advantage of experimental reproducibility and ease of sampling, and furthermore, in-depth analysis of metabolic processes becomes highly accessible.

Here, we review the use of bioreactor systems for ex vivo modelling of the human gut microbiota with respect to analysis of the metabolic output of the microbial ecosystem, and discuss the possibility of mechanistic insights using these combined techniques. We summarize the different platforms currently used for metabolomics and suitable for analysis of gut microbiota samples from a bioreactor system. With the help of representative datasets obtained from a series of bioreactor runs, we compare the outputs of both NMR and mass spectrometry based approaches in terms of their coverage, sensitivity and quantification. We also discuss the use of untargeted and targeted analyses in mass spectroscopy and how these techniques can be combined for optimal biological interpretation. Potential solutions for linking metabolomic and phylogenetic datasets with regards to active, key species within the ecosystem will be presented.

WEB: 10.1016/j.ijmm.2016.03.007
IMPACT FACTOR: 3.9
CITED HALF-LIFE: 5.8

UW EDITORIAL COMMENT: There are three criteria of relevance for evaluating model systems: relevance for human health, mechanistic insights, and feasibility. Human subjects are ideal but have ethical and cost limitations. Animal models (especially gnotobiotic mice colonized with human microbiota) have cost and technical constraints and *ex vivo* culturing in bioreactors limits what interpretations that can be drawn about host-microbiome interactions. The authors also highlight the importance of metabolomics (a combination of NMR and mass spectrometry) for obtaining broad biological information about microbiome pathways.

8. The Role of the Immune System in Metabolic Health and Disease
   Zmora N, Bashiardes S, Levy M, Elinav E.
   Cell Metab. 2017 Mar 7;25(3):506-521.

ABSTRACT
In addition to the immune system's traditional roles of conferring anti-infectious and anti-neoplastic protection, it has been recently implicated in the regulation of systemic metabolic homeostasis. This cross-talk between the immune and the metabolic systems is pivotal in promoting "metabolic health" throughout the life of an organism and plays fundamental roles in its adaptation to ever-changing environmental makeups and nutritional availability. Perturbations in this intricate immune-metabolic cross-talk contribute to the tendency to develop altered metabolic states that may culminate in metabolic disorders such as malnutrition, obesity, type 2 diabetes mellitus (T2DM), and other features of the metabolic syndrome. Regulators of immune-metabolic interactions include host genetics, nutritional status, and the intestinal microbiome. In this Perspective, we highlight current understanding of immune-metabolism interactions, illustrate differences among individuals and between populations in this respect, and point toward future avenues of research possibly enabling immune harnessing as means of personalized treatment for common metabolic disorders.

WEB: 10.1016/j.cmet.2017.02.006
IMPACT FACTOR: 17.3
CITED HALF-LIFE: 4.6

UW EDITORIAL COMMENT: This perspective piece provides simple and clear graphics detailing the cytokines and human cell types involved in immune-metabolic interactions throughout the human lifespan (Figure 1), between nutrients and the immune system (Figure 2), and between the microbiome and immune system (Figure 3).

9. Dysbiosis and the immune system.
   Levy M1, Kolodziejczyk AA1, Thaiss CA1, Elinav E1.
   Nat Rev Immunol. 2017 Mar 6. [Epub ahead of print]

ABSTRACT
Throughout the past century, we have seen the emergence of a large number of multifactorial diseases, including inflammatory, autoimmune, metabolic, neoplastic and neurodegenerative diseases, many of which have been recently associated with intestinal dysbiosis - that is, compositional and functional alterations of the gut microbiome. In linking the pathogenesis of common diseases to dysbiosis, the microbiome field is challenged to decipher the mechanisms involved in the de novo generation and the persistence of dysbiotic microbiome configurations, and to differentiate causal host-microbiome associations from secondary microbial changes that accompany disease course. In this Review, we categorize dysbiosis in conceptual terms and provide an overview of immunological associations; the causes and consequences of bacterial dysbiosis, and their involvement in the molecular aetiology of common diseases; and implications for the rational design of new therapeutic approaches. A molecular-level understanding of the origins of dysbiosis, its endogenous and environmental regulatory processes, and its downstream effects may enable us to develop microbiome-targeting therapies for a multitude of common immune-mediated diseases.

WEB: 10.1038/nri.2017.7
IMPACT FACTOR: 38.4
CITED HALF-LIFE: 6.9

UW EDITORIAL COMMENT: This review provides a synopsis of the types of dysbiosis (bloom of pathobionts, loss of commensals, and loss of diversity) and mechanisms by which dysbiosis can occur (infection & inflammation, diet & xenobiotics, genetics, familial transmission, and other causes). It also details the role of the immune system in regulating gut microbiota and link of dysbiosis to common immune-related disorders including IBD, celiac disease, rheumatoid arthritis, multiple sclerosis, and asthma. The authors' assert that comparing the microbiomes of patients with different diseases, rather than between healthy and diseased individuals, is more informative to understanding the role of microbiota in human health and disease. They also suggest that) dysbiosis be interpreted as a functional state rather than a taxonomic one, since the metabolic roles of microbes are highly dependent on community and environmental dynamics rather than species attributes of species taxonomy.

10. Faecal microbiota transplantation—A clinical view.
    J. Mattnerb, F. Schmidta, and B. Siegmund.
    International Journal of Medical Microbiology. Volume 306, Issue 5, Aug. 2016. Pages 310-315.

ABSTRACT
Faecal microbiota transplantation has gained increasing attention over the last decade as various phenotypes could be transferred from a donor to a recipient in different animal models. Clinically, however, the sole indication with evidence from a randomized placebo controlled trial is refractory

Clostridium difficile infection. Despite revealing successful clinical outcomes, questions concerning regulatory affairs, the identification of the best donor, the optimal mixture of the transplant as well as the preferred route of administration remain to be clarified even for this indication. Initiated by the idea that alterations in the composition of the intestinal microbiota are associated with intestinal inflammation in inflammatory bowel disease, several studies investigated whether faecal microbiota transplantation would be an equally suitable approach for these devastating disorders. Indeed, the available data indicate changes in the microbiota composition following faecal microbial transplantation depending on the degree of intestinal inflammation. Furthermore, first data even provide evidence that the transplantation of an "optimized" microbiota induces clinical remission in ulcerative colitis. However, despite these intriguing results it needs to be considered that not only "a cure of inflammation", but also risk factors and phenotypes including obesity can be transferred via faecal microbiota transplantation. Thus, a deeper understanding of the impact of a distinct microbiota composition is required before "designing" the optimal faecal microbiota transplant.

WEB: 10.1016/j.ijmm.2016.02.003
IMPACT FACTOR: 3.9
CITED HALF-LIFE: 5.8

UW EDITORIAL COMMENT: The authors review seminal research and clinical investigations involving fecal microbiota transplant (FMT) and highlight the relevant related considerations for clinical practice in the context of different diseases. There are major research gaps regarding clinical evidence for the therapeutic use of FMT in relation to metabolic and behavioral diseases, and well-designed prospective clinical trials are needed. The authors also note that there is evidence in the literature suggesting FMT can be potentially harmful to the host by transferring susceptibility to cancer, and thus caution is warranted.

ADDITIONAL ARTICLES OF INTEREST (MARCH PUBLICATIONS)

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

Dysbiosis in intestinal inflammation: Cause or consequence

The shape of the microbiome in early life

Leading microbiome-based therapeutic falters in Phase II trial

Optimization of metabolomics of defined in vitro gut microbial ecosystems

Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance.

EED Biology & Review Articles

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

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

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.

Impact of prebiotics on metabolic and behavioral alterations in a mouse model of metabolic syndrome.

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

Effects of bovine colostrum on recurrent respiratory tract infections and diarrhea in children.

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

Gut Health Diagnostics & Research

Droplet digital PCR quantifies host inflammatory transcripts in feces reliably and reproducibly.

Gut-Brain Cross-Talk in Metabolic Control

Dynamics of the human microbiome in inflammatory bowel disease

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

Dynamics and Trends in Fecal Biomarkers of Gut Function in Children from 1-24 Months in the MAL-ED Study.

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Gut check

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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

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Commendation for Exposing Key Advantage of Organ Chip Approach

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GEMS extend understanding of childhood diarrhoea

Infectious disease: something in the water

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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
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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

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