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

MAY 29, 2017

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8. **The association of serum choline with linear growth failure in young children from rural Malawi.** {abstract & UW comment} {full article}
    - Cross-sectional study of the essential nutrient choline and linear growth.

9. **Starved Guts: Morphologic and Functional Intestinal Changes in Malnutrition.** {abstract & UW comment} {full article}
    - Review of limited data available from pre-clinical models of malnutrition.

10. **Transient activation of mucosal effector immune responses by resident intestinal bacteria in normal hosts is regulated by interleukin-10 signalling.** {abstract & UW comment} {full article}
    - Basic science of regulatory cytokine involved in gut inflammation maintenance

DETAILS OF ARTICLES

1. 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.
   Kosek MN, Lee GO, Guerrant RL, Haque R, Kang G, Ahmed T, Bessong P, Ali A, Mduma E, Yori PP, Faubion WA, Lima AAM, Olortegui MP, Mason C, Babji S, Singh R, Qureshi S, Kosek PS, Samie A, Pascal J, Shrestha S, McCormick BJJ, Seidman JC, Lang DR, Zaidi A, Caulfield LE, Gottlieb M; MAL-ED Network.
   J Pediatr Gastroenterol Nutr. 2017 May 3. [Epub ahead of print]

ABSTRACT
OBJECTIVES: To describe changes in intestinal permeability in early childhood in diverse epidemiologic settings.
METHODS: In a birth cohort study the lactulose:mannitol (LM) test was administered to 1,980 children at four time points in the first 24 months of life in eight countries. Data from the Brazil site with an incidence of diarrhea similar to that seen in the U.S. and no growth faltering was used as an internal study reference to derive age- and sex-specific Z-scores for mannitol and lactulose recoveries and the lactulose mannitol ratio.
RESULTS: 6,602 tests demonstrated mannitol recovery, lactulose recovery, and the L:M ratio were associated with country, sex, and age. There was heterogeneity in the recovery of both probes between sites with mean mannitol recovery ranging for 1.34%-to 5.88%, lactulose recovery of 0.19%-0.58%, and L:M ratios 0.10-0.17 in boys of 3 months of age across different sites. We observed strong sex-specific differences in both mannitol and lactulose recovery, with boys having higher recovery of both probes. Alterations in intestinal barrier function increased in most sites from 3-9 months of age and plateaued or diminished from 9-15 months of age.
CONCLUSIONS: Alterations in recovery of the probes differ markedly in different epidemiologic contexts in children living in the developing world. The rate of change in the L:M-Z ratio was most rapid and consistently disparate from the reference standard in the period between 6 and 9 months of age suggesting that this is a critical period of physiologic impact of enteropathy in these populations.

WEB: http://insights.ovid.com/crossref?an=00005176-900000000-97169
IMPACT FACTOR: 1.48
CITED HALF-LIFE: 7.00

UW EDITORIAL COMMENT: The MAL-ED consortium takes advantage of its detailed sample collection and diverse trial settings to provide a robust comparison of intestinal permeability measurements from different geographical and epidemiologic settings. While samples were processed in different laboratories, the authors made an effort to standardize findings across platforms with values measured in a reference laboratory. The variation observed in mannitol permeability measurements, even after adjustment for age, suggest that the risk of malabsorption is heterogenous in different populations with high risk and high prevalence of environmental enteropathy. The authors also note a wide range of permeability measures depending on the probe of interest and thus recommend that L:M studies describe the recovery rate of each probe separately, as well as the L:M ratio.

2. Infant Nutritional Status and Markers of Environmental Enteric Dysfunction are Associated with Midchildhood Anthropometry and Blood Pressure in Tanzania.
   Locks LM, Mwiru RS, Mtisi E, Manji KP, McDonald CM, Liu E, Kupka R, Kisenge R, Aboud S, Gosselin K, Gillman M, Gewirtz AT, Fawzi WW, Duggan CP.

J Pediatr. 2017 May 9. pii: S0022-3476(17)30488-2. [Epub ahead of print]

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: 5.20
CITED HALF-LIFE: 8.6

UW EDITORIAL COMMENT: This study has several limitations, which the authors acknowledge. Significantly, the participants in this study were recruited from two previous randomized control trials and fit criteria related to ease of contact. Despite their careful selection of eligible participants, the authors were only able to recruit less than a third of those they attempted to contact. Additionally, the authors only have biomarkers of EED at 6 weeks and 6 months of age, which misses a critical growth periods in which EED has a potential impact on child growth and devleopment.

3. Biomarkers to Stratify Risk Groups among Children with Malnutrition in Resource-Limited Settings and to Monitor Response to Intervention
   McGrath C.J.; Arndt M.B.; Walson J.L.
   Horm Res Paediatr. 2017 May 9. [Epub ahead of print]

ABSTRACT
Despite global efforts to reduce childhood undernutrition, current interventions have had little impact on stunting and wasting, and the mechanisms underlying growth faltering are poorly understood. There is a clear need to distinguish populations of children most likely to benefit from any given intervention and to develop tools to monitor response to therapy prior to the development of morbid sequelae. In resource-limited settings, environmental enteric dysfunction (EED) is common among children,

contributing to malnutrition and increasing childhood morbidity and mortality risk. In addition to EED, early alterations in the gut microbiota can adversely affect growth through nutrient malabsorption, altered metabolism, gut inflammation, and dysregulation of the growth hormone axis. We examined the evidence linking EED and the gut microbiome to growth faltering and explored novel biomarkers to identify subgroups of children at risk of malnutrition due to underlying pathology. These and other biomarkers could be used to identify specific groups of children at risk of malnutrition and monitor response to targeted interventions.

WEB: 10.1159/000471875
IMPACT FACTOR: 1.66
CITED HALF-LIFE: 3.8

UW EDITORIAL COMMENT: Figure 1 compares biomarkers used to identify and screen for EED, microbial dysfunction, systematic inflammation, and growth hormone resistance. This article provides a succinct overview of relevant EED, inflammatory, and metabolic biomarkers that may, in combination, be useful to predict children at highest risk of stunting.

4. Chronic consequences on human health induced by microbial pathogens: Growth faltering among children in developing countries.
   Nataro, J.P. and Guerrant, R.L.
   Vaccine. 2017 May 23. pii: S0264-410X(17)30659-X. [Epub ahead of print]

ABSTRACT
Enteric infections continue to cause approximately 500,000 childhood deaths annually worldwide. In addition to the burden of diarrhea, there is emerging evidence that exposure to enteric pathogens may induce physiologic abnormalities that lead to linear growth faltering. This enteric disease, known as environmental enteric dysfunction (EED) remains cryptic with regard to its causes and features. In this workshop, experts in the field addressed the contribution of enteric pathogens to growth faltering in the absence of clinical diarrhea. Also addressed were the role of the intestinal microbiota in normal childhood growth among children in developing countries. The impact of pathogen exposure could represent direct epithelial injury or could be mediated by perturbations in the normal microbiota or combinations of both.

WEB: 10.1016/j.vaccine.2017.05.035
IMPACT FACTOR: 3.41
CITED HALF-LIFE: 5.9

UW EDITORIAL COMMENT: The authors suggest that a major limitation in assessing the potential value of an enteric disease vaccine is the underestimation of the burden of enteric disease as only deaths from diarrhea. Instead of this narrow definition, the effects of diarrhea may be accounted for by dissecting the disorder into three separate effects: growth decrements, cognitive impairment, and metabolic derangement. The authors also describe biomarkers and animal models used in the study of EED, and the role of the human gut microbiota in child health and growth.

5. The effects of micronutrient deficiencies on bacterial species from the human gut microbiota.
   Hibberd, M.C., Wu, M., Rodionov, D.A, Li, X., Cheng, J., Griffin, N.W., Baratt, M.J., Giannone, R.J., Hettich, R.L., Osterman, A.L., Gordon, J. I.

Science Translational Medicine. 17 May 2017: Vol. 9, Issue 390, eaal4069.

ABSTRACT
Vitamin and mineral (micronutrient) deficiencies afflict 2 billion people. Although the impact of these imbalances on host biology has been studied extensively, much less is known about their effects on the gut microbiota of developing or adult humans. Therefore, we established a community of cultured, sequenced human gut–derived bacterial species in gnotobiotic mice and fed the animals a defined micronutrient-sufficient diet, followed by a derivative diet devoid of vitamin A, folate, iron, or zinc, followed by return to the sufficient diet. Acute vitamin A deficiency had the largest effect on bacterial community structure and metatranscriptome, with *Bacteroides vulgatus,* a prominent responder, increasing its abundance in the absence of vitamin A. Applying retinol selection to a library of 30,300 *B. vulgatus* transposon mutants revealed that disruption of *acrR* abrogated retinol sensitivity. Genetic complementation studies, microbial RNA sequencing, and transcription factor–binding assays disclosed that AcrR is a repressor of an adjacent AcrAB-TolC efflux system. Retinol efflux measurements in wild-type and *acrR*-mutant strains plus treatment with a pharmacologic inhibitor of the efflux system revealed that AcrAB-TolC is a determinant of retinol and bile acid sensitivity in *B. vulgatus*. Acute vitamin A deficiency was associated with altered bile acid metabolism in vivo, raising the possibility that retinol, bile acid metabolites, and AcrAB-TolC interact to influence the fitness of *B. vulgatus* and perhaps other microbiota members. This type of preclinical model can help to develop mechanistic insights about the effects of, and more effective treatment strategies for micronutrient deficiencies.

WEB: 10.1126/scitranslmed.aal4069
IMPACT FACTOR: 16.26
CITED HALF-LIFE: 3.2

UW EDITORIAL COMMENT: Acute nutrient deficiency was modeled using mouse fed a micronutrient insufficient diet for a 21-day period in between two 14-day periods with a micronutrient sufficient diet. Figure 1C presents changes in the percent relative abundance of bacterial species in each of five micronutrient deficient diets conditions. The control group (micronutrient sufficient) also experienced relatively large changes in relative abundance between sampling periods, despite no change in diet, which suggests that variation in relative abundance of *B. dorei* may be unrelated to nutrient deficiencies. *B. vulgatus* had smaller differences in abundance, but the overall scale of changes in relative abundance suggests that relative abundance should be interpreted cautiously as an effect of micronutrient deficiency. Furthermore, there is no evidence that *B. vulgatus* is associated with host growth so the association of its abundance with vitamin A deficiency has no conclusive interpretation.

6. Chemical and pathogen-induced inflammation disrupt the murine intestinal microbiome.
Borton MA, Sabag-Daigle A, Wu J, Solden LM, O'Banion BS, Daly RA, Wolfe RA, Gonzalez JF, Wysocki VH, Ahmer BMM, Wrighton KC.
Microbiome. 2017 April 27; 5(1):47.

ABSTRACT
Background: Salmonella is one of the most significant food-borne pathogens to affect humans and agriculture. While it is well documented that Salmonella infection triggers host inflammation, the impacts on the gut environment are largely unknown. A CBA/J mouse model was used to evaluate intestinal responses to Salmonella-induced inflammation. In parallel, we evaluated chemically induced inflammation by dextran sodium sulfate (DSS) and a non-inflammation control. We profiled gut microbial diversity by sequencing 16S ribosomal ribonucleic acid (rRNA) genes from fecal and cecal

samples. These data were correlated to the inflammation marker lipocalin-2 and short-chain fatty acid concentrations.
RESULTS: We demonstrated that inflammation, chemically or biologically induced, restructures the chemical and microbial environment of the gut over a 16-day period. We observed that the ten mice within the Salmonella treatment group had a variable Salmonella relative abundance, with three high responding mice dominated by >46% Salmonella at later time points and the remaining seven mice denoted as low responders. These low- and high-responding Salmonella groups, along with the chemical DSS treatment, established an inflammation gradient with chemical and low levels of Salmonella having at least 3 log-fold lower lipocalin-2 concentration than the high-responding Salmonella mice. Total short-chain fatty acid and individual butyrate concentrations each negatively correlated with inflammation levels. Microbial communities were also structured along this inflammation gradient. Low levels of inflammation, regardless of chemical or biological induction, enriched for Akkermansia spp. in the Verrucomicrobiaceae and members of the Bacteroidetes family S24-7. Relative to the control or low inflammation groups, high levels of Salmonella drastically decreased the overall microbial diversity, specifically driven by the reduction of Alistipes and Lachnospiraceae in the Bacteroidetes and Firmicutes phyla, respectively. Conversely, members of the Enterobacteriaceae and Lactobacillus were positively correlated to high levels of Salmonella-induced inflammation.
CONCLUSIONS: Our results show that enteropathogenic infection and intestinal inflammation are interrelated factors modulating gut homeostasis. These findings may prove informative with regard to prophylactic or therapeutic strategies to prevent disruption of microbial communities, or promote their restoration.

WEB: 10.1186/s40168-017-0264-8
IMPACT FACTOR: 9.00
CITED HALF-LIFE: 2.0

UW EDITORIAL COMMENT: These authors found that *Salmonella* colonization was highly variable among infected mice. With only a sample size of ten infected mice, however, their interpretation is limited in its generalizability. Mice were classified into “high” (n=3) and “low” responders (n=7) and the authors suggest that other studies may have found similar variability but that it is usually obscured in the literature because other authors report an average relative abundance.

7. Gut microbiota interactions with the immunomodulatory role of vitamin D in normal individuals
Renata V. Lutholda, Gabriel R. Fernandesb, Ana Carolina Franco-de-Moraesc, Luciana G.D. Folchettia, Sandra Roberta G. Ferreirac.
Metabolism. 2017 Apr;69:76-86. doi: 10.1016/j.metabol.2017.01.007. Epub 2017 Jan 13.

ABSTRACT
Due to immunomodulatory properties, vitamin D status has been implicated in several diseases beyond the skeletal disorders. There is evidence that its deficiency deteriorates the gut barrier favoring translocation of endotoxins into the circulation and systemic inflammation. Few studies investigated whether the relationship between vitamin D status and metabolic disorders would be mediated by the gut microbiota composition.
OBJECTIVE: We examined the association between vitamin D intake and circulating levels of 25(OH)D with gut microbiota composition, inflammatory markers and biochemical profile in healthy individuals.
METHODS: In this cross-sectional analysis, 150 young healthy adults were stratified into tertiles of intake and concentrations of vitamin D and their clinical and inflammatory profiles were compared. The DESeq2 was used for comparisons of microbiota composition and the log2 fold changes (log2FC)

represented the comparison against the reference level. The association between 25(OH)D and fecal microbiota (16S rRNA sequencing, V4 region) was tested by multiple linear regression.
RESULTS: Vitamin D intake was associated with its concentration (r=0.220, p=0.008). There were no significant differences in clinical and inflammatory variables across tertiles of intake. However, lipopolysaccharides increased with the reduction of 25(OH)D (p-trend <0.05). Prevotella was more abundant (log2FC 1.67, p<0.01), while Haemophilus and Veillonella were less abundant (log2FC -2.92 and -1.46, p<0.01, respectively) in the subset with the highest vitamin D intake (reference) than that observed in the other subset (first plus second tertiles). PCR (r=-0.170, p=0.039), E-selectin (r=-0.220, p=0.007) and abundances of Coprococcus (r=-0.215, p=0.008) and Bifdobacterium (r=-0.269, p=0.001) were inversely correlated with 25(OH)D. After adjusting for age, sex, season and BMI, 25(OH)D maintained inversely associated with Coprococcus (β=-9.414, p=0.045) and Bifdobacterium (β=-1.881, p=0.051), but significance disappeared following the addition of inflammatory markers in the regression models.
CONCLUSION: The role of vitamin D in the maintenance of immune homeostasis seems to occur in part by interacting with the gut microbiota. The attenuation of association of bacterial genera by inflammatory markers suggests that inflammation participate in part in the relationship between the gut microbiota and vitamin D concentration. Studies with appropriate design are necessary to address hypothesis raised in the current study.

WEB: 10.1016/j.metabol.2017.01.007
IMPACT FACTOR: 4.38
CITED HALF-LIFE: 9.3

UW EDITORIAL COMMENT: Participants were recruited from nutrition college programs and were overwhelmingly young healthy adult females with a low intake of vitamin D. There was limited variability in their dietary habits, which may have depressed the sensitivity of this study to detect associations. Furthermore, as a cross-sectional study, correlations among vitamin D, species abundance, and inflammation markers should be interpreted cautiously. The abundance of *Akkermansia* was correlated with 25(OH)D (a vitamin D marker), though this was not statistically significant.

8. The association of serum choline with linear growth failure in young children from rural Malawi.
Semba RD, Zhang P, Gonzalez-Freire M, Moaddel R, Trehan I, Maleta KM, Ordiz MI, Ferrucci L, Manary MJ.
Am J Clin Nutr. 2016 Jul;104(1):191-7. Epub 2016 Jun 8.

ABSTRACT
BACKGROUND: Choline is an essential nutrient for cell structure, cell signaling, neurotransmission, lipid transport, and bone formation. Choline can be irreversibly converted to betaine, a major source of methyl groups. Trimethylene N-oxide (TMAO), a proatherogenic molecule, is produced from the metabolism of dietary choline by the gut microbiome. The relation between serum choline and its closely related metabolites with linear growth in children is unknown.
OBJECTIVE: The aim was to characterize the relation between serum choline and its closely related metabolites, betaine and TMAO, with linear growth and stunting in young children.
DESIGN: We measured serum choline, betaine, and TMAO concentrations by using liquid chromatography isotopic dilution tandem mass spectrometry in a cross-sectional study in 325 Malawian children, aged 12-59 mo, of whom 62% were stunted.
RESULTS: Median (25th, 75th percentile) serum choline, betaine, and TMAO concentrations were 6.4 (4.8, 8.3), 12.4 (9.1, 16.3), and 1.2 (0.7, 1.8) µmol/L, respectively. Spearman correlation coefficients of

age with serum choline, betaine, and TMAO were -0.57 (P < 0.0001), -0.26 (P < 0.0001), and -0.10 (P = 0.07), respectively. Correlation coefficients of height-for-age z score with serum choline, betaine-to-choline ratio, and TMAO-to-choline ratio were 0.31 (P < 0.0001), -0.24 (P < 0.0001), and -0.29 (P < 0.0001), respectively. Serum choline concentrations were strongly and significantly associated with stunting. Children with and without stunting had median (25th, 75th percentile) serum choline concentrations of 5.6 (4.4, 7.4) and 7.3 (5.9, 9.1) µmol/L (P < 0.0001).
CONCLUSIONS: Linear growth failure in young children is associated with low serum choline and elevated betaine-to-choline and TMAO-to-choline ratios. Further work is needed to understand whether low dietary choline intake explains low circulating choline among stunted children living in low-income countries and whether increasing choline intake may correct choline deficiency and improve growth and development.

WEB: 10.3945/ajcn.115.129684
IMPACT FACTOR: 6.70
CITED HALF-LIFE: >10.0

UW EDITORIAL COMMENT: There is no established definition of choline deficiency on the basis of serum choline concentrations and it is not well understood how underlying factors of individuals, especially genetics, might affect dietary requirements for choline. Furthermore, as a cross-sectional study, causality cannot be inferred and the positive association observed may be due to underlying nutritional differences between choline-rich and choline-poor foods.

9. Starved Guts: Morphologic and Functional Intestinal Changes in Malnutrition
Attia S, Feenstra M, Swain N, Cuesta M, Bandsma R.
J Pediatr Gastroenterol Nutr. 2017 May 9. [Epub ahead of print].

ABSTRACT
Malnutrition contributes significantly to death and illness worldwide and especially to the deaths of children less than five years of age. The relation between intestinal changes in malnutrition and morbidity and mortality has not been well characterized; however, recent research indicates that the functional and morphologic changes of the intestine secondary to malnutrition itself contribute significantly to these negative clinical outcomes and may be potent targets of intervention. The aim of this review was to summarize current knowledge of experimental and clinically observed changes in the intestine from malnutrition pre-clinical models and human studies. Limited clinical studies have shown villous blunting, intestinal inflammation and changes in the intestinal microbiome of malnourished children. In addition to these findings, experimental data using various animal models of malnutrition have found evidence of increased intestinal permeability, upregulated intestinal inflammation, and loss of goblet cells. More mechanistic studies are urgently needed to improve our understanding of malnutrition-related intestinal dysfunction and to identify potential novel targets for intervention.

WEB: 10.1097/MPG.0000000000001629
IMPACT FACTOR: 1.48
CITED HALF-LIFE: 7.00

UW EDITORIAL COMMENT: The authors note that there are morphological similarities between EED and malnutrition-related enteropathy. In addition, the two conditions generally share overlapping geographies, which can make distinguishing between them nearly impossible in many settings. The primary characteristics of malnutrition enteropathy also overlap with those associated with EED,

including lower diversity in the intestinal microbiome and impairment of intestinal epithelial barrier function and the mucin layer.

10. Transient activation of mucosal effector immune responses by resident intestinal bacteria in normal hosts is regulated by interleukin-10 signaling.
Wu C, Sartor RB, Huang K, Tonkonogy SL.
Immunology. 2016 Jul;148(3):304-14.

ABSTRACT
Interleukin-10 (IL-10) is a key regulator of mucosal homeostasis. In the current study we investigated the early events after monoassociating germ-free (GF) wild-type (WT) mice with an Escherichia coli strain that we isolated previously from the caecal contents of a normal mouse housed under specific pathogen-free conditions. Our results show that interferon-γ (IFN-γ) secreted by mesenteric lymph node (MLN) cells from both IL-10 deficient mice and WT mice, stimulated ex vivo with E. coli lysate, was dramatically higher at day 4 after monoassociation compared with IFN-γ secreted by cells from GF mice without E. coli colonization. Production of IFN-γ rapidly and progressively declined after colonization of WT but not IL-10-deficient mice. The E. coli lysate-stimulated WT MLN cells also produced IL-10 that peaked at day 4 and subsequently declined, but not as precipitously as IFN-γ. WT cells that express CD4, CD8 and NKp46 produced IFN-γ; WT CD4-positive cells and B cells produced IL-10. Recombinant IL-10 added to E. coli-stimulated MLN cell cultures inhibited IFN-γ secretion in a dose-dependent fashion. MLN cells from WT mice treated in vivo with neutralizing anti-IL-10 receptor antibody produced more IFN-γ compared with MLN cells from isotype control antibody-treated mice. These findings show that a resident E. coli that induces chronic colitis in monoassociated IL-10-deficient mice rapidly but transiently activates the effector immune system in normal hosts, in parallel with induction of protective IL-10 produced by B cells and CD4(+) cells that subsequently suppresses this response to mediate mucosal homeostasis.

WEB: 10.1111/imm.12612
IMPACT FACTOR: 4.078
CITED HALF-LIFE: n/a

UW EDITORIAL COMMENT: Figure 6 neatly presents an exponential decay relationship between increased concentrations of recombinant IL-10 and the declining production of IFN-γ by mesenteric lymph nodes cells *in vitro*. This work confirms and builds heavily directly upon previous findings by El Aidy and colleagues:
- El Aidy et al. Temporal and spatial interplay of microbiota and intestinal mucosa drive establishment of immune homeostasis in conventionalized mice. Mucosal Immunol. 2012; 5:567-79.
El Aidy et al. Transient inflammatory-like state and microbial dysibiosis are pivotal in establishment of mucosal homeostasis during colonization of germ-free mice. Benef Microbes. 2014; 5:67-77.

ADDITIONAL ARTICLES OF INTEREST (MAY PUBLICATIONS)

Microbe Profile: Akkermansia muciniphila: a conserved intestinal symbiont that acts as the gatekeeper of our mucosa

Zinc Transporter SLC39A7/ZIP7 Promotes Intestinal Epithelial Self-Renewal by Resolving ER Stress.

ARTICLE ARCHIVE (JAN 2016-APRIL 2017)

EED Biology & Review Articles

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

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

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.

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

Engineering bacterial thiosulfate and tetrathionate sensors for detecting gut inflammation.

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

Optimization of metabolomics of defined in vitro gut microbial ecosystems.

An Intestinal Organ Culture System Uncovers a Role for the Nervous System in Microbe-Immune Crosstalks.

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.

Fecal Markers of Environmental Enteropathy and Subsequent Growth in Bangladeshi Children.

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

Co-culture of Living Microbiome with Microengineered Human Intestinal Villi in a Gut-on-a-Chip Microfluidic Device.

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

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.

Host cell attachment elicits posttranscriptional regulation in infecting enteropathogenic bacteria.

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

A prominent glycyl radical enzyme in human gut microbiomes metabolizes trans-4-hydroxy-l-proline.

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.

Changes in Intestinal Motility and Gut Microbiota Composition in a Rat Stress Model

Enteric Pathogens and Their Toxin-Induced Disruption of the Intestinal Barrier through Alteration of Tight Junctions in Chickens.

Intestinal commensal bacteria mediate lunch mucosal immunity and promote resistance of newborn mice to infection.

Statoviruses, A novel taxon of RNA viruses present in the gastrointestinal tracts of diverse mammals.

Campylobacter jejuni and associated immune mechanisms: short-term effects and long-term implications for infants in low-income countries.

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