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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

OCTOBER 1, 2017

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LIST OF ARTICLES

1. **Enteroaggregative E. coli Subclinical Infection and co-Infections and Impaired Child Growth in the MAL-ED Cohort Study.** {Abstract & UW comment} {Full article}
    - Study investigating the impact of enteroaggregative Escherichia coli infection on child growth, when either alone or in combination with other pathogens.

2. **Host-microbiota interactions and adaptive immunity.** {Abstract & UW comment} {Full article}
    - One review in a special series of reviews on the Microbiome-Immune System Interplay.

3. **Randomized controlled trial on the impact of early-life intervention with bifidobacteria on the healthy infant fecal microbiota and metabolome.** {Abstract & UW comment} {Full article}
    - Infants receiving a formula supplemented with commensal bacteria are compared with placebo and breastfed controls in this RCT to investigate changes in infant microbiome.

4. **Probiotics and the Gut Immune System: Indirect Regulation.** {Abstract & UW comment} {Full article}
    - Review of the interplays between bacteria and host immunity with a focus on probiotics.

5. **Initial Gut Microbial Composition as a Key Factor Driving Host Response to Antibiotic Treatment, as Exemplified by the Presence or Absence of Commensal Escherichia coli.** {Abstract & UW comment} {Full article}
    - Mouse model study investigating the ways in which the pre-existing microbial composition can modulate antibiotic treatment response.

6. **Deep Metaproteomics Approach for the Study of Human Microbiomes.** {Abstract & UW comment} {Full article}
    - Analysis of the human microbiome from stool, combining high-resolution mass spectrometry and deep metaproteomics.

7. **Transmission of the gut microbiota: spreading of health.** {Abstract & UW comment} {Full article}
    - Review of the transmission of human intestinal microbiota and its therapeutic potential.

8. **Protein energy malnutrition alters mucosal IgA responses and reduces mucosal vaccine efficacy in mice.** {Abstract & UW comment} {Full article}
    - Mouse model study investigating impact of protein energy malnutrition on immunity and vaccine efficacy.

9. **Early Life Inflammation and Neurodevelopmental Outcome in Bangladeshi Infants Growing Up in Adversity.** {Abstract & UW comment} {Full article}
    - Prospective cohort study of the relationship between systemic inflammation and poor neurodevelopment in children growing up in adversity.

10. **A randomized synbiotic trial to prevent sepsis among infants in rural India**. {Abstract & UW comment} {Full article}
    - An RCT in India to test the effect of synbiotic treatment (probiotic and prebiotic combination) on the incidence of neonatal sepsis in term infants.

DETAILS OF ARTICLES

1. Enteroaggregative E. coli Subclinical Infection and co-Infections and Impaired Child Growth in the MAL-ED Cohort Study.
   Limo A, Soares A, Filho J, Havt A, Lima I, Lima N, et al.
   Journal of Pediatric Gastroenterology. 2017 Sep 12 [Epub ahead of print].

ABSTRACT
OBJECTIVE: We evaluated the impact of subclinical enteroaggregative Escherichia coli (EAEC) infection alone and in combination with other pathogens in the first six months of life on child growth.
METHODS: Non-diarrheal samples from 1,684 children across eight Multisite Birth Cohort Study, Malnutrition and Enteric Diseases (MAL-ED) sites in Asia, Africa, and Latin America were tested monthly; over 90% of children were followed-up twice weekly for the first six months of life.
RESULTS: Children with subclinical EAEC infection did not show altered growth between enrollment and six months. Conversely, EAEC co-infection with any other pathogen was negatively associated with delta weight-for-length (WLZ) ($p < 0.05$) and weight-for-age (WAZ) ($p > 0.05$) z-scores between 0 and 6 months. The presence of two or more pathogens without EAEC was not significantly associated with delta WLZ and WAZ. The most frequent EAEC co-infections included Campylobacter spp. heat-labile toxin-producing enterotoxigenic E. coli, Cryptosporidium spp., and atypical enteropathogenic E. coli. Myeloperoxidase levels were increased with EAEC co-infection ($p < 0.05$). EAEC pathogen co-detection was associated with lower neopterin levels compared to those of no-pathogen control children ($p < 0.05$). Mothers of children with EAEC co-infections had lower levels of education, poorer hygiene and sanitation, lower socioeconomic status, and lower breastfeeding rates compared to mothers of children in whom no pathogen was detected ($p < 0.05$).
CONCLUSIONS: These data emphasize the public health importance of subclinical EAEC infection in early infancy in association with other pathogens and the need for improved maternal and child care, hygiene, sanitation, and socioeconomic factors.

WEB: 10.1097/MPG.0000000000001717
IMPACT FACTOR: 1.48
CITED HALF-LIFE: 7.00

START EDITORIAL COMMENT: Investigators categorized the children into seven groups depending on presence of enteric pathogens: no pathogens detected, any EAEC detected, EAEC and one other pathogen, EAEC and two other pathogens, EAEC and three or more pathogens, one or two pathogens other than EAEC, three or more pathogens other than EAEC. By using this categorization, investigators were able to investigate the true impact of EAEC alone versus a possible synergistic effect of multiple pathogens. Figure 4 provides WAZ, WLZ, and LAZ z-scores for all seven groups, showing that EAEC infection was only associated with impaired child growth in the case of co-infection with another pathogen. The EAEC and coinfection with 2-3 pathogens group was associated with higher fecal Myeloperoxidase concentrations, which may suggest synergy between EAEC and other pathogens on elicitation of neutrophil-mediated immune responses.

2. Host-microbiota interactions and adaptive immunity.
   McCoy K, Ronchi F, Geuking M.
   Immunological Reviews. 279:63–69. 2017 September.

ABSTRACT

The mammalian intestine is densely populated by non-pathogenic (commensal) microbes, which reach a density of 1012 CFU/g of colonic luminal content. The commensal microbiota is of crucial im- portance for the host as it plays a role in shaping the immune system, inducing protective immune responses, providing the host with essen- tial nutrients and vitamins, aiding in the digestion of indigestible food components, and competing with pathogens for the same niches.1 The mucosal epithelium mounts multiple innate immune mecha- nisms that function at mucosal sites to promote barrier function and maintain host-microbial homeostasis.2 The resident intestinal micro- biota also induces robust adaptive immunity that includes induction and differentiation of CD4+ T cells, intestinal epithelial lymphocytes (IEL), and B cells.3 In this review, we will discuss recent developments in the interplay between the intestinal microbiota and the adaptive immune system, with particular focus on the induction of systemic anti-microbial IgG responses, the function of microbial-induced maternal antibodies, and microbial-specific T-cell immunity.

WEB: 10.1111/imr.12575
IMPACT FACTOR: 15.33
CITED HALF-LIFE: 6.20

START EDITORIAL COMMENT: This month, Immunological Reviews published a special issue on Microbiome-Immune System Interplay**.** The issue includes several reviews relevant to this digest—while all cannot be included here due to limited space and diversity of articles, it might be worth reviewing for those interested in how the microbiome influences host immunity. This review covers mouse models of the role mucosal microbiota play in the induction of dominant IgA and IgG antibodies such as commensal bacteria-specific responses, maternal-infant transfer of antibodies (i.e. secretory IgA) and prevention of translocation into the mesenteric lymph nodes, CD4+ T-cell interplay, and the inhibition of IgE overexpression.

3. Randomized controlled trial on the impact of early-life intervention with bifidobacteria on the healthy infant fecal microbiota and metabolome.
   Bazanella M, Maier TV, Clavel T, Lagkouvardos I, Lucio M, Maldonado-Gomez MX, et al.
   Am J Clin Nutr. 2017 Sep 6 [Epub ahead of print].

ABSTRACT
BACKGROUND: Early-life colonization of the intestinal tract is a dynamic process influenced by numerous factors. The impact of probiotic-supplemented infant formula on the composition and function of the infant gut microbiota is not well defined.
OBJECTIVE: We sought to determine the effects of a bifidobacteria-containing formula on the healthy human intestinal microbiome during the first year of life.
DESIGN: A double-blind, randomized, placebo-controlled study of newborn infants assigned to a standard whey-based formula containing a total of 10^8 colony-forming units (CFU)/g of *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium longum*, *B. longum* subspecies *infantis* (intervention), or to a control formula without bifidobacteria (placebo). Breastfed controls were included. Diversity and composition of fecal microbiota were determined by 16S ribosomal RNA gene amplicon sequencing, and metabolite profiles were analyzed by ultrahigh-performance liquid chromatography-mass spectrometry over a period of 2 y.
RESULTS: Infants (*n* = 106) were randomly assigned to either the interventional (*n* = 48) or placebo (*n* = 49) group; 9 infants were exclusively breastfed throughout the entire intervention period of 12 mo. Infants exposed to bifidobacteria-supplemented formula showed decreased occurrence of *Bacteroides* and *Blautia* spp. associated with changes in lipids and unknown metabolites at month 1.

Microbiota and metabolite profiles of intervention and placebo groups converged during the study period, and long-term colonization (24 mo) of the supplemented *Bifidobacterium* strains was not detected. Significant differences in microbiota and metabolites were detected between infants fed breast milk and those fed formula ($P < 0.005$) and between infants birthed vaginally and those birthed by cesarean delivery ($P < 0.005$). No significant differences were observed between infant feeding groups regarding growth, antibiotic uptake, or other health variables ($P > 0.05$).
CONCLUSION: The supplementation of bifidobacteria to infant diet can modulate the occurrence of specific bacteria and metabolites during early life with no detectable long-term effects.

WEB: 10.3945/ajcn.117.157529
IMPACT FACTOR: 4.56
CITED HALF-LIFE: 9.60

START EDITORIAL COMMENT: Over the 12 months of the study, differences in the sequence abundance of major bacterial phyla converged in the 3 groups. By 24 months, none of the 4 strains included in the bifido-supplemented formula were detected in any of the arms. This suggests transient differences between bifido-supplemented infants and non-supplemented infants. Also, infants with formula with and without bifido supplements were more similar in terms of the richness and diversity of their microbiome than those in breastfed group, and their metabolic profiles were more similar as well (figure 5D). Figure 3 presents visual representations of microbiota changes throughout the first year of life in each of the three study arms. Panel C of Figure 3 presents relative abundances of *Actinobacteria, Firmicutes, Bacteroidetes, and Proteobactera.* It can be seen in this panel that the relative abundances among the different study arms differ greatly for each bacteria – for example, the relative abundance of *Actinobacteria* is much higher in breastfed infants, while the relative of *Firmicutes* is much lower in breastfed infants. One limitation is that the breastfed group was much smaller than the other two formula-fed groups.

4. Probiotics and the Gut Immune System: Indirect Regulation.
   La Fata G, Weber P, Mohajeri M.
   Probiotics Antimicrob Proteins. 2017 Aug 31.

ABSTRACT
The gastrointestinal tract (GIT) represents the largest interface between the human organism and the external environment. In the lumen and upper part of the mucus layer, this organ hosts an enormous number of microorganisms whose composition affects the functions of the epithelial barrier and the gut immune system. Consequentially, the microorganisms in the GIT influence the health status of the organism. Probiotics are living microorganisms which, in specific conditions, confer a health benefit to the host. Among others, probiotics have immunomodulatory properties that usually act directly by (a) increasing the activity of macrophages or natural killer cells, (b) modulating the secretion of immunoglobulins or cytokines, or indirectly by (c) enhancing the gut epithelial barrier, (d) altering the mucus secretion, and (e) competitive exclusion of other (pathogenic) bacteria. This review focuses on specific bacteria strains with indirect immunomodulatory properties. Particularly, we describe here the mechanisms through which specific probiotics enhance the gut epithelial barrier and modulate mucus production. Moreover, we describe the antimicrobial properties of specific bacteria strains. Recent data suggest that multiple pathologies are associated with an unbalanced gut microflora (dysbiosis). Although the cause-effect relationship between pathology and gut microflora is not yet well established, consumption of specific probiotics may represent a powerful tool to reestablish gut homeostasis and promote gut health.

WEB: 10.1007/s12602-017-9322-6
IMPACT FACTOR: 1.76
CITED HALF-LIFE: N/A

START EDITORIAL COMMENT: After broadly introducing microbiota and probiotics, the article reviews three main interplays between bacteria and host immunity: probiotics' effect on the gut epithelial barrier, mucus secretion and modulation, and various antimicrobial properties of beneficial and pathogenic bacteria. Authors also provide a detailed description of the makeup and function of the gut intestinal barrier in order to better inform the above three sections. Figure 1 is a visual representation of the intestinal barrier, which shows the location and function of various cell types and gut bacteria, in addition to displaying several interactions between bacteria and intestinal barrier. Tables 1, 2, 3 describe evidence supporting probiotic strains' improvement of intestinal epithelial function, regulation of the mucous layer, and antimicrobial properties, respectively.

5. Initial Gut Microbial Composition as a Key Factor Driving Host Response to Antibiotic Treatment, as Exemplified by the Presence or Absence of Commensal Escherichia coli.
   Ju T, Shoblak Y, Gao Y, Yang K, Fouhse J, Finlay BB, et al.
   Appl Environ Microbiol. 83(17). 2017 August.

ABSTRACT
Antibiotics are important for treating bacterial infection; however, efficacies and side effects of antibiotics vary in medicine and experimental models. A few studies have correlated microbiota composition variations with health outcomes in response to antibiotics; however, no study has demonstrated causality. We had noted variation in colonic expression of C-type lectins, regenerating islet-derived protein 3β (Reg3β) and Reg3γ, after metronidazole treatment in a mouse model. To investigate the effects of specific variations in the preexisting microbiome on host response to antibiotics, mice harboring a normal microbiota were allocated to 4 treatments in a 2-by-2 factorial arrangement with or without commensal *Escherichia coli* and with or without metronidazole in drinking water. *E. coli* colonized readily without causing a notable shift in the microbiota or host response. Metronidazole administration reduced microbiota biodiversity, indicated by decreased Chao1 and Shannon index values, and altered microbiota composition. However, the presence of *E. coli* strongly affected metronidazole-induced microbiota shifts. Remarkably, this single commensal bacterium in the context of a complex population led to variations in host responses to metronidazole treatment, including increased expression of antimicrobial peptides Reg3β and Reg3γ and intestinal inflammation indicated by tumor necrosis factor alpha levels. Similar results were obtained from 2-week antibiotic exposure and with additional *E. coli* isolates. The results of this proof-of-concept study indicate that even minor variations in initial commensal microbiota can drive shifts in microbial composition and host response after antibiotic administration. As well as providing an explanation for variability in animal models using antibiotics, the findings encourage the development of personalized medication in antibiotic therapies.
IMPORTANCE: This work provides an understanding of variability in studies where antibiotics are used to alter the gut microbiota to generate a host response. Furthermore, although providing evidence only for the one antibiotic, the study demonstrated that initial gut microbial composition is a key factor driving host response to antibiotic administration, creating a compelling argument for considering personalized medication based on individual variations in gut microbiota.

WEB: 10.1128/AEM.01107-17

IMPACT FACTOR: 4.31
CITED HALF-LIFE: 0.00

START EDITORIAL COMMENT: Treatment of mice with a commensal E. *coli* strain altered the relationship between administration of metronidazole and expression of antimicrobial peptides and inflammation. This may have ramifications for treatment in humans, so further research is needed. While this study provides important insight into initial microbial composition as a determinant of antibiotic response, it uses only one specific broad-spectrum antibiotic to do so. Additionally, this particular antibiotic, metronidazole, may have other indirect effects on the microbiome in light of its anti-parasitic activity.

6. Deep Metaproteomics Approach for the Study of Human Microbiomes.
   Zhang X, Chen W, Ning Z, Mayne J, Mack D, Stintzi A.
   Analytical Chemistry. 89(17):9407−9415. 2017 September 5.

ABSTRACT
Host−microbiome interactions have been shown to play important roles in human health and diseases. Most of the current studies of the microbiome have been performed by genomic approaches through next-generation sequencing. Technologies, such as metaproteomics, for functional analysis of the microbiome are needed to better understand the intricate host−microbiome interactions. However, significant efforts to improve the depth and resolution of gut metaproteomics are still required. In this study, we combined an efficient sample preparation technique, high resolution mass spectrometry, and metaproteomic bioinformatics tools to perform ultradeep metaproteomic analysis of human gut microbiome from stool. We reported the deepest analysis of the microbiome to date with an average of 20558 protein groups identified per sample analysis. Moreover, strain resolution taxonomic and pathway analysis using deep metaproteomics revealed strain level variations, in particular for Faecalibacterium prausnitzii, in the microbiome from the different individuals. We also reported that the human proteins identified in stool samples are functionally enriched in extracellular region pathways and in particular those proteins involved in defense response against microbial organisms. Deep metaproteomics is a promising approach to perform in-depth microbiome analysis and simultaneously reveals both human and microbial changes that are not readily apparent using the standard genomic approaches.

WEB: 10.1021/acs.analchem.7b02224
IMPACT FACTOR: 6.42
CITED HALF-LIFE: 7.70

START EDITORIAL COMMENT: Figure 3 gives a visual representation of the potential of deep metaproteomics by presenting the taxonomic analysis described in the article's abstract above. This includes strain-level analysis of abundant species of microbiota among the entire data set, strain-level distributions, and relative abundance, of three of the most abundant species: F. *prausnitzii*, B. *thetaiotaomicron,* and E. *rectale.* Authors note that one particular benefit of this approach is that deep metaproteomics allows analysis of human proteins in addition to microbiota proteins, which might provide a way to further study host-microbe interactions. Table 1 gives a breakdown of 35 of the most abundant human proteins that were analyzed for association with the microbiome, of which nearly all were significantly associated. Limitations include a small number of children in the study (n=4) and no description of their ages; however, the study accomplishes its primary goal of being a proof of concept for the application of this new technology.

7. Transmission of the gut microbiota: spreading of health.
   Browne HP, Neville BA, Forster SC, Lawley TD.
   Nat Rev Microbiol. 15(9):531-543. 2017 September.

ABSTRACT
Transmission of commensal intestinal bacteria between humans could promote health by establishing, maintaining and replenishing microbial diversity in the microbiota of an individual. Unlike pathogens, the routes of transmission for commensal bacteria remain unappreciated and poorly understood, despite the likely commonalities between both. Consequently, broad infection control measures that are designed to prevent pathogen transmission and infection, such as over sanitation and the overuse of antibiotics, may inadvertently affect human health by altering normal commensal transmission. In this Review, we discuss the mechanisms and factors that influence host-to-host transmission of the intestinal microbiota and examine how a better understanding of these processes will identify new approaches to nurture and restore transmission routes that are used by beneficial bacteria.

WEB: 10.1038/nrmicro.2017.50
IMPACT FACTOR: 9.76
CITED HALF-LIFE: 5.80

START EDITORIAL COMMENT: This review takes a comprehensive and holistic approach in discussing the transmission of human intestinal microbiota. Topics discussed include the various shared and distinguished transmission routes between commensal and pathogenic bacteria, host selection of commensal bacteria, microbiota survival in the environment, common reservoirs of commensal bacteria, and finally microbiota perturbation and restoration. Of particular interest is the last section, in which authors discuss the various ways in which microbiota diversity can be negatively impacted— including poor diet and overuse of antibiotics— and discuss recent developments in interventions to counter these impairments. Pre-incubated neonatal swabs, faecal microbiota transplantation (FMT), and probiotics are among the interventions discussed. FMT is highlighted as a very successful method for treatment of recurrent C. *difficile* infection recently and authors hypothesize that biotherapeutics will soon offer treatments for other similar disorders. Figure 4 highlights donor suitability for commensal microbiota donation based upon signature species, microbiota features, and bacterial profile. Authors emphasize the importance of building the evidence base for the health benefits of individual members of commensal bacterial communities.

8. Protein energy malnutrition alters mucosal IgA responses and reduces mucosal vaccine efficacy in mice.
   Rho S, Kim H, Shim SH, Lee SY, Kim MJ, Yang BG, et al.
   Immuno Lett. 190:247-256. 2017 August 30.

ABSTRACT
Oral vaccine responsiveness is often lower in children from less developed countries. Childhood malnutrition may be associated with poor immune response to oral vaccines. The present study was designed to investigate whether protein energy malnutrition (PEM) impairs B cell immunity and ultimately reduces oral vaccine efficacy in a mouse model. Purified isocaloric diets containing low protein (1/10 the protein of the control diet) were used to determine the effect of PEM. PEM increased

both nonspecific total IgA and oral antigen-specific IgA in serum without alteration of gut permeability. However, PEM decreased oral antigen-specific IgA in feces, which is consistent with decreased expression of polymeric Immunoglobulin receptor (pIgR) in the small intestine. Of note, polymeric IgA was predominant in serum under PEM. In addition, PEM altered B cell development status in the bone marrow and increased the frequency of IgA-secreting B cells, as well as IgA secretion by long-lived plasma cells in the small intestinal lamina propria. Moreover, PEM reduced the protective efficacy of the mucosally administered cholera vaccine and recombinant attenuated Salmonella enterica serovar Typhimurium vaccine in a mouse model. Our results suggest that PEM can impair mucosal immunity where IgA plays an important role in host protection and may partly explain the reduced efficacy of oral vaccines in malnourished subjects.

WEB: 10.1016/j.imlet.2017.08.025
IMPACT FACTOR: 1.85
CITED HALF-LIFE: 7.70

START EDITORIAL COMMENT: Figure 1 provides five informative and intuitive visual representations of the results of this study, including an analysis of various immunoglobulin subgroups between study arms, a comparison of IgA and IgG between study arms stratified by serum vs. feces analysis, and an *in vivo* permeability analysis to assess intestinal barrier function. Interestingly, there were marked decreases in IgA but not IgG in protein energy malnourished (PEM) mice. Also, there was lower S. *typhimurium*-specific IgA in the feces of PEM mice, but higher IgA in serum of PEM mice, compared with mice receiving normal nutrition. One limitation of this study is the use of fecal biomarker concentrations as a proxy for the analysis of the local IgA levels in portions of the intestinal tract. While challenging or unfeasible in human populations living in low resource settings (especially in children), sacrifice and duodenal and ileal biopsy would have yielded richer data in these murine models. A second limitation is lack of survival analyses for *S. Typhimurium* and cholera vaccine challenge models, a missed opportunity for understanding the different survival experiences of the two groups.

9. Early Life Inflammation and Neurodevelopmental Outcome in Bangladeshi Infants Growing Up in Adversity.
   Jiang NM, Tofail F, Ma JZ, Haque R, Kirkpatrick B, Nelson CA, et al.
   Am J Trop Med Hyg. 2017 Jul 17 [Epub ahead of print].

ABSTRACT
Exposure to profound adversity can negatively affect the neurodevelopment of children, but biologic mechanisms that underlie this association remain unknown. We sought to determine whether elevated levels of the inflammatory markers C-reactive protein (CRP) and soluble CD14 (sCD14) are associated with neurodevelopmental outcomes in Bangladeshi children. A total of 422 infant-mother pairs from an urban slum in Dhaka, Bangladesh, were enrolled at birth and followed prospectively. Inflammation was measured with sCD14, interleukin (IL)-1β, and IL-6 at 18 weeks, and CRP at 6, 18, 40, and 53 weeks. Psychologists assessed cognitive, language, motor, and social emotional development using the Bayley Scales of Infant and Toddler Development at 78 and 104 weeks of age. We tested for the association of inflammatory markers with developmental outcomes, independent of previously identified associations such as malnutrition, family income, and maternal education. Every 10 pg/mL increase in sCD14 was associated with a 1.1-2.0 decrement in cognitive and motor scores at 78 weeks and in all domains at 104 weeks. The cumulative number of CRP elevations that a child experienced in the first year of life, as well as IL-1β and IL-6 at 18 weeks of age, were also negatively associated with Bayley Scales results. CRP,

sCD14, IL-1β, and IL-6 were associated with lower neurodevelopmental outcomes. Our findings implicate a role of inflammation in the neurodevelopment of children growing up in adversity.

WEB: 10.4269/ajtmh.17-0083
IMPACT FACTOR: 1.67
CITED HALF-LIFE: 9.80

START EDITORIAL COMMENT: Two main points are of note in this study of rural Bangladeshi infants enrolled in the cohort. First, plasma sCD14 concentrations at age 18 weeks, a marker of monocyte activation primarily attributable translocation of gram-negative (LPS-containing) bacterial species, was negatively associated with cognitive, socio-emotional, and motor scores at age 2 years. Because sCD14 has previously been associated with linear growth faltering and oral vaccine efficacy (Naylor et al. 2015 and Guerrant 2016), this association presents an important area for further research and this study helps to contribute to the growing body of knowledge for the mechanistic links between cognition and inflammation. Additionally, it presents an area for possible inflammation therapy through this pathway. Second, building upon prior observations of associations between child growth and levels of systemic inflammation marker CRP (Prendergast 2014- Zimbabwe, among others)- there was a dose-response relationship observed between CRP assessed at multiple time points and neurodevelopmental outcomes at age 2 years, with worse outcomes as the levels of CRP increased. Interestingly, because CRP is an acute-phase protein, the repeated assessment of this marker enabled the authors to treat each elevation in CRP as an inflammatory "hit", with hits accumulating over early life. While CRP is not a source-specific signal of systemic inflammation, microbial translocation represents one major source of such hits.

10. A randomized synbiotic trial to prevent sepsis among infants in rural India.
Panigrahi P, Parida S, Nanda NC, Satpathy R, Pradhan L, Chandel DS, et al.
Nature. 548(7668):407-412. 2017 August 24.

ABSTRACT
Sepsis in early infancy results in one million annual deaths worldwide, most of them in developing countries. No efficient means of prevention is currently available. Here we report on a randomized, double-blind, placebo-controlled trial of an oral synbiotic preparation (Lactobacillus plantarum plus fructooligosaccharide) in rural Indian newborns. We enrolled 4,556 infants that were at least 2,000 g at birth, at least 35 weeks of gestation, and with no signs of sepsis or other morbidity, and monitored them for 60 days. We show a significant reduction in the primary outcome (combination of sepsis and death) in the treatment arm (risk ratio 0.60, 95% confidence interval 0.48-0.74), with few deaths (4 placebo, 6 synbiotic). Significant reductions were also observed for culture-positive and culture-negative sepsis and lower respiratory tract infections. These findings suggest that a large proportion of neonatal sepsis in developing countries could be effectively prevented using a synbiotic containing L. plantarum ATCC-202195.

WEB: 10.1038/nature23480
IMPACT FACTOR: 11.57
CITED HALF-LIFE: N/A

START EDITORIAL COMMENT: This study contributes to the growing knowledge around the efficacy of synbiotic (probiotic + prebiotic) therapy for the prevention of a number of common diseases, which has had mixed results in prior studies. In this study, investigators saw a 40% reduction in the primary

outcome of sepsis and death in the treatment group of more than 2,000 infants, who received the synbiotic compared with the placebo group. Table 2 provides counts and relative risk measures for this primary outcome, in addition to secondary outcomes including the all-cause diarrhea (RR= 0.20), lower respiratory tract infections (RR= 0.66), and omphalitis (RR= 0.23) . Impressively, the number needed to treat for the primary outcome was only 27. As the therapy costs an estimated $1 per child, a $27 investment in the therapy would result in one less case of sepsis in this population. Authors stressed the importance of further research comparing the timing of intervention, the need to test therapy in preterm/underweight infants who are at increased risk for fatal sepsis, and the specific choice of probiotic used (as this may differ in other settings and/or high-risk groups).

ADDITIONAL ARTICLES OF INTEREST

The **intestinal microbiota**: Antibiotics, colonization resistance, and **enteric** pathogens.

Targeting the **gut microbiota** by dietary nutrients: a new avenue for human **health**.

Gut Protozoa: Friends or Foes of the Human Gut Microbiota?

Fecal Microbiota Transplantation: Beyond Clostridium difficile.

ARTICLE ARCHIVE (JAN 2016-PRESENT)

EED Biology & Review Articles

The regulation of gut mucosal IgA B-cell responses: recent developments.

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

The Burden of Enteropathy and "Subclinical" Infections.

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

Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: a randomised controlled study in Kenyan infants.

Cross-modulation of pathogen-specific pathways enhances malnutrition during enteric co-infection with Giardia lamblia and enteroaggregative Escherichia coli.

Impaired Barrier Function and Autoantibody Generation in Malnutrition Enteropathy in Zambia.

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?

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

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Limited diversity sparks inflammation at the mucosal border

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I'll have a turkey and cheese sandwich

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The microbiome and innate immunity

The microbiota in adaptive immune homeostasis and disease

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