For malnourished children, new therapeutic food boosts gut microbes, healthy development

July 11 2019

Researchers at Washington University School of Medicine in St. Louis and the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh, are developing a new approach to address childhood malnutrition. They are designing therapeutic foods aimed at repairing the gut microbiomes of malnourished children. In a clinical trial of moderately malnourished children in Bangladesh, the team found that a type of therapeutic food they developed is

superior to standard therapy. Pictured is a Bangladeshi mother and child in the Nutritional Rehabilitation Unit of the International Centre for Diarrhoeal Disease Research Hospital in Dhaka. Credit: Rabiul Hasan

A new type of therapeutic food, specifically designed to repair the gut microbiomes of malnourished children, is superior to standard therapy in an initial clinical trial conducted in Bangladesh.

An interdisciplinary team of investigators from Washington University School of Medicine in St. Louis and the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh, have undertaken a new approach for addressing the pressing global health problem of childhood malnutrition. Their approach focuses on selectively boosting key growth-promoting gut microbes using ingredients present in affordable, culturally acceptable foods.

Their work supports the notion that healthy growth of infants and children is inexorably linked to healthy development of their gut communities following birth. The results of their research are described in two reports published July 12 in the journal *Science*.

"We found that children who are malnourished have incompletely formed gut microbial communities compared with their healthy counterparts" said senior author Jeffrey I. Gordon, MD, the Dr. Robert J. Glaser Distinguished University Professor and director of the Edison Family Center for Genome Sciences & Systems Biology at the School of Medicine. "Therefore, we set about to design therapeutic foods to repair this immaturity and to determine whether such repair would restore healthy growth."

The clinical trial, which was conducted by a team led by Tahmeed

Ahmed, Ph.D., the International Centre for Diarrhoeal Disease Research's director of Nutrition and Clinical Services, included 63 Bangladeshi children, 12-18 months of age, diagnosed with moderate acute malnutrition, meaning the children were ill but not close to death. The children were randomly assigned to one of four treatment groups. Children in three of the groups each received one of the three newly designed therapeutic foods, while those in the fourth group received a standard therapeutic food that was not designed based on a consideration of its effects on the gut microbiome.

All foods for the trial were locally produced at the International Centre for Diarrhoeal Disease Research. Children were brought twice daily to a nutritional rehabilitation center, where the therapeutic foods were administered by their mothers under the supervision of health-care workers. A set of measuring tools, developed through advances in genomic medicine, provided a new, much more comprehensive definition of molecular features associated with malnutrition, its underlying mechanisms, and the effectiveness of treatment.

One of the therapeutic foods stood out from the rest, even in this relatively short one-month trial. Measuring 1,300 blood proteins, including those intimately involved in directing bone growth, development of the brain, immune function, and metabolism in various tissues, revealed that this food prototype had produced a pronounced shift toward a healthy state compared with what was observed in the other three groups of children.

At the end of the study, the researchers also found that, unlike in the three other treatment groups, the gut microbial communities residing in the intestines of children receiving this lead therapeutic food had undergone a reconfiguration and more closely resembled microbial communities found in age-matched healthy children living in the same locale. This formulation contained, among other components, a mixture

of nutrients from chickpea, soy, bananas and peanuts.

Childhood malnutrition is a massive global health problem, affecting 150 million children under age 5 worldwide, according to the World Health Organization. Many studies have shown that malnutrition is the result of many factors, with reliable access to adequate amounts of affordable, nutritious food being one but not the only factor.

Existing therapeutic foods were developed to increase the amount of key nutrients children consume. Malnourished children who receive these foods are less likely to die, but other consequences of malnutrition have remained largely unresponsive to treatment, including stunted growth, impaired immunity and reduced cognitive function. Gordon noted that these foods were not designed based on a consideration of their effects on the development of the gut microbiome.

The new microbiome-directed therapeutic foods developed by the Washington University and International Centre for Diarrhoeal Disease Research team emanated from their earlier studies of gut microbial community development in healthy children living in Bangladesh. Several years ago, the team discovered that children with malnutrition had immature gut communities—ones that appeared younger than their age-matched healthy counterparts. Ahmed noted that several years ago they found that conventional therapeutic foods failed to repair this immaturity in the malnourished children they had treated.

Gordon's group went on to transplant immature communities from malnourished children, and normally maturing communities from healthy children, into mice that had been raised under sterile conditions. The results revealed that immature communities were associated with reduced weight gain, defective bone development plus abnormal metabolic and immune functions in the recipient animals. These findings provided early evidence that failure to form a normal microbial

community may be a cause rather than simply an effect of malnutrition.

"There is uncertainty about what foods are best to administer during the period of complementary feeding—when children transition from exclusive milk feeding to solid foods," Gordon said. "Our studies were inspired by the notion that these commonly used, affordable, culturally acceptable complementary foods could contain ingredients coveted by key microbes that are underrepresented and underperforming in the gut microbiomes of malnourished children. These microbes were our therapeutic targets."

This study provides the first evidence that a therapeutic food, developed specifically to support growth and expansion of gut microbes linked to healthy microbiome development, has beneficial effects outside the gut related to many aspects of healthy growth. These effects involve key mediators of metabolism, and of bone, brain and immune system development—organ systems that have been very difficult to repair in malnourished children by supplementing their diet with traditional therapeutic foods.

In first of the two papers—co-first authors Jeanette L. Gehrig, Ph.D., Siddarth Venkatesh, Ph.D., and Hao-Wei Chang, all members of the Gordon lab—describe how they first used germ-free mice, and then germ-free piglets, colonized with gut microbial community members from Bangladeshi children to screen a series of diets comprised of complementary food ingredients used in Bangladesh. They formulated Microbiome-Directed Complementary Food prototypes that could repair immature microbial communities from malnourished Bangladeshi children in both these animal models and improve the health of the animals. These prototypes then were tested in the double-blind controlled feeding study described above.

In the second paper, first author Arjun S. Raman, MD, Ph.D., from the

Gordon lab, describes development of new computational methods, based on methods originally developed by the field of econophysics to analyze how fluctuations in the economy affect features of complex, dynamic financial markets. The approach provided new, generally applicable ways of characterizing the organization of human gut communities—their normal development, how they are perturbed in disease states such as malnutrition, and how they respond to therapeutic interventions designed to repair them.

"The goal of human microbiome research is not simply to describe the component parts of a microbial community but rather to characterize how the components interact with one another to shape community functions," Gordon said. "Complicating matters, the number of possible interactions between the components in a gut community is literally astronomical."

According to Raman, the researchers wanted to be able to focus their attention, finding ways to reduce the number of components or features of the microbiome to a minimum number that could portray in an informative way the organizational properties of healthy and diseased gut communities.

Studying the microbiomes of healthy Bangladeshi children sampled monthly from birth through five years, and using the new computational method, they identified a network of 15 gut bacterial community members that consistently interacted with one another. They named this network an ecogroup. The components of the ecogroup provided an accurate way of describing normal gut development of infants and children living in Bangladesh as well as several other low-income countries. It further served as a sensitive and accurate way of determining how severely disrupted microbial communities are in children with moderate and severe malnutrition, and the degree to which they are repaired with various treatments.

"A longer and larger clinical trial is currently underway at two sites in Bangladesh to see if the new Microbiome-Directed Complementary Food has sustained benefits," Ahmed said. "This trial includes children with moderate malnutrition as well as children with severe malnutrition treated with conventional therapy but left with incompletely repaired microbiomes, stunting and various other growth impairments."

Added Michael J. Barratt, Ph.D., an assistant professor of pathology and immunology and executive director of the Center for Gut Microbiome and Nutrition Research at Washington University: "It is possible that some children may have gut microbial communities so damaged that a food-based intervention alone won't be sufficient. So our Washington University and International Centre for Diarrhoeal Disease Research team is interested in studying the possibility of giving the specific beneficial organisms—or even the beneficial products those microbes make, as we become more knowledgeable about what those are—in combination with a Microbiome-Directed Complementary Food. That could be a second line of defense. Our studies also present the possibility of monitoring development of gut microbial communities and catching deviations from normal development earlier in life, giving us opportunities for prevention."

Gordon emphasized that their efforts designed to repair the perturbed microbial communities of malnourished children hold the promise of revealing more informed guidelines for feeding children in the first several years of life so that they can develop healthy microbiomes.

"We need to be effective stewards of the precious microbial resources of our children," he said. "If we are, the effects may be long-lived and herald a new dimension to preventive medicine—one that starts with their developing microbiomes."

More information: J.L. Gehrig el al., "Effects of microbiota-directed

foods in gnotobiotic animals and undernourished children," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aau4732

A.S. Raman el al., "A sparse covarying unit that describes healthy and impaired human gut microbiota development," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aau4735