

Gut bacteria of malnourished children benefit from key elements in therapeutic food, study shows

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A clinical trial reported in 2021 and conducted by a team of researchers from Washington University School of Medicine in St. Louis and the International Center for Diarrhoeal Disease Research in Dhaka,

Bangladesh, showed that a newly designed therapeutic food aimed at repairing malnourished children's underdeveloped gut microbiomes was superior to a widely used standard therapeutic food.

Now, another study from the same research team at Washington University School of Medicine has identified key, naturally occurring biochemical components of this new therapeutic [food](#) and the important bacterial strains that process these components.

The study suggests that identifying these components and the key growth-promoting gut bacterial strains that function as their therapeutic targets can help guide treatment with the current food formulation and could enable creation of new, more effective formulations in the future.

The study, led by Jeffrey I. Gordon, MD, the Dr. Robert J. Glaser Distinguished University Professor at Washington University, was [published](#) Dec. 13 in *Nature*.

"We have identified bioactive elements of a microbiome-directed food," said Gordon, who is also director of the Edison Family Center for Genome Sciences & Systems Biology at the School of Medicine.

"These are naturally-occurring carbohydrate structures that could, in theory, be recovered in large quantities from the byproduct streams of food manufacturing and be used to produce prebiotics. We also have identified the microbes that process these food components, and in theory, there is potential for the organisms themselves to be part of a therapeutic intervention in children completely lacking these beneficial gut microbes."

Building on this work, the World Health Organization together with the Bill & Melinda Gates Foundation is supporting a large, multi-site clinical trial investigating this new therapeutic food—called MDCF-2, or

microbiome-directed complementary food. The trial, which is in its early stages, aims to enroll about 6,500 malnourished children, ages six months to two years, living in Africa and Southeast Asia.

Malnutrition is a leading cause of death in children under age five, and nearly 150 million children under this age suffer from stunted growth, according to the World Health Organization and the United Nations Children's Fund. Treatment with traditional therapeutic foods reduces deaths, but it does not substantially improve other long-term effects of malnutrition, including problems with metabolism, bone growth, immune function and [brain development](#).

"Our work has demonstrated that a healthy microbial community in the gut is necessary for healthy growth," Gordon said.

"Development of the gut microbial community in the first two years of life needs to be in sync with the development of the rest of the body, the other organ systems. When this microbial community is incompletely formed, simply giving more calories won't repair it. We are seeking specific food components that nurture healthy gut microbial communities in hopes of repairing the gut microbial community that has become dysfunctional in children with malnutrition."

The researchers, including co-first authors Matthew C. Hibberd, Ph.D., an assistant professor of pathology & immunology, and Daniel M. Webber, MD, Ph.D., an instructor in pathology & immunology, found that strains of the bacteria *Prevotella copri* were positively associated with increased growth in the children.

These organisms showed increases in the activities of metabolic pathways that use beneficial bioactive carbohydrate structures present in the MDCF-2 therapeutic food. Compared with children receiving the traditional therapeutic food, those receiving MDCF-2 showed higher

blood levels of certain proteins that support musculoskeletal growth and neurodevelopment as well as lower levels of proteins involved with inflammation—indicating that the effects of microbiome repair extend well beyond the walls of the gut.

"We performed extensive genomic analyses of fecal samples from these children," Hibberd said. "We know the identities of the bacteria that are responding to these food components, and the metabolic capabilities these bacteria have and express in response to treatment. It turns out that many of the bacteria strongly associated with growth in the children are enriched in pathways for carbohydrate metabolism."

[In the 2021 clinical trial](#), the MDCF-2 therapeutic food was given as a dietary supplement to provide about 20% of the children's daily energy requirements.

Ingredients of MDCF-2 include chickpea flour, soybean flour, peanut paste and mashed green banana pulp; the traditional, higher calorie, ready-to-use supplementary food includes rice, lentils and milk powder. Detailed analysis of the carbohydrates in these foods revealed that MDCF-2 contains more polysaccharides known as galactans and mannans, while the traditional therapeutic food contains more starch and cellulose.

The children receiving MDCF-2 showed increased growth compared with those receiving the traditional supplementary food, even though the caloric density of MDCF-2 was 15% lower than in the higher calorie food. The increased growth associated with MDCF-2 treatment was correlated with increased expression of metabolic pathways present in certain strains of *Prevotella copri* in children's microbiomes—pathways that are involved in the organism's utilization of polysaccharides present in MDCF-2.

"Information from food frequency questionnaires suggests that the children who had the greatest response to MDCF-2 were also consuming more nuts and legumes as part of their regular diets," Webber said.

"These nuts and legumes possess some of the same polysaccharides as MDCF-2. This suggests that there may be opportunities to adjust the composition and dose of MDCF-2 to further enhance its therapeutic effect."

Gordon added, "The upcoming clinical trials of MDCF-2 in East and West Africa and in South Asia will test the generalizability of its effectiveness in [malnourished children](#) from six months to 24 months of age with varying degrees of severity of malnutrition."

"The results from these and other studies should help advance our understanding of how our microbes collaborate with our [human cells](#) and organs to influence developmental biology, refine our approaches for the development of microbiome-directed therapeutics, and help us develop new approaches for feeding our [children](#) in order to ensure formation of healthy microbiomes during the first several years of postnatal life."

More information: Matthew C. Hibberd et al, Bioactive glycans in a microbiome-directed food for children with malnutrition, *Nature* (2023). [DOI: 10.1038/s41586-023-06838-3](https://doi.org/10.1038/s41586-023-06838-3)

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