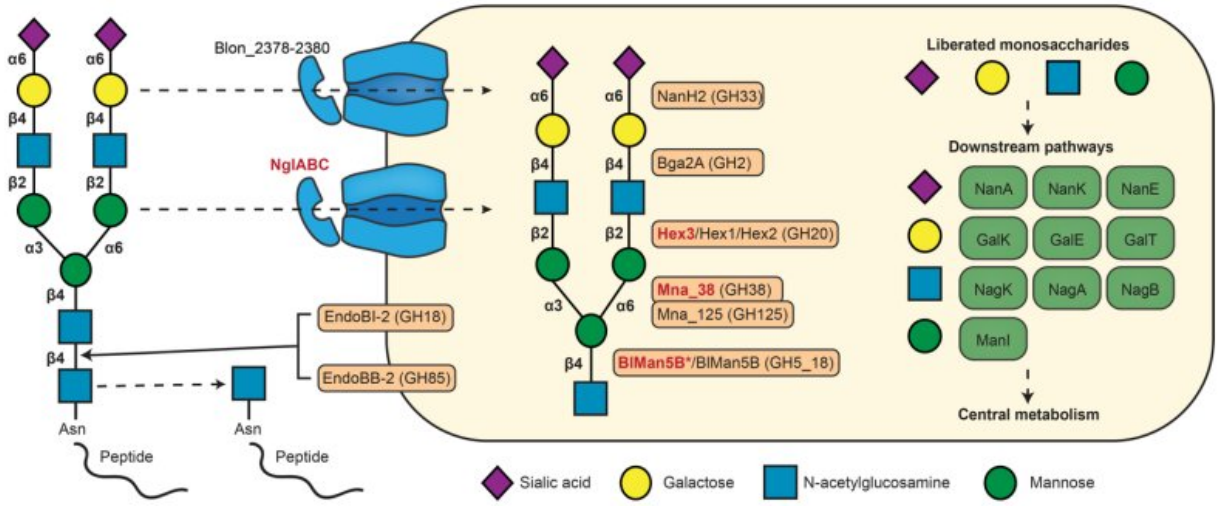
Gut bacterium supports growth in infants with severe acute malnutrition

April 15 2022, by Julia Evangelou Strait



Proposed scheme for *N*-glycan utilization by B. infantis Bg_2D9. Breakdown of glycosidic linkages by specific glycoside hydrolases (GHs) is indicated in orange boxes. Proteins encoded by genes in the *ngl* cluster are highlighted in red. Credit: *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.abk1107

About 18 million children under age five suffer from severe acute malnutrition, and more than 3 million children die from it each year. Treatment with high-calorie supplemental foods and antibiotics can prevent deaths, but these interventions often have limited impact on the long-term effects of severe acute malnutrition, such as persistent stunted growth, disrupted immune function and impaired brain development.

Even when treated with standard therapeutic foods, many children continue to have moderate forms of the disease and are at risk of falling back into severe acute malnutrition.

A new study, published April 13 in the journal *Science Translational Medicine*, from Washington University School of Medicine in St. Louis and the International Center for Diarrheal Disease Research in Dhaka, Bangladesh (icddr,b), shows that a standard milk-based therapy plus treatment with a specific strain of gut bacteria known as Bifidobacterium infantis (B. infantis) for four weeks promotes weight gain in infants with severe acute malnutrition, with accompanying reductions in gut inflammation. The clinical trial was conducted in Dhaka.

The B. infantis strain was chosen for the trial because it has been shown to be safe to give to infants as a probiotic and is known to thrive on specific carbohydrates present in human breast milk. The strain, which had been isolated from the gut microbes of a healthy infant in the U.S., is a commercially available probiotic that meets the Food and Drug Administration's good manufacturing practice guidelines and was provided by Evolve BioSystems.

Importantly, the investigators found that B. infantis was either undetectable or present in markedly reduced amounts in infants with severe acute malnutrition compared to those with healthy growth.

Although treatment with the U.S. strain of B. infantis produced significant improvements in growth in Bangladeshi infants with severe acute malnutrition, its level of colonization was still tenfold to a hundredfold lower than levels documented in healthy Bangladeshi infants. To identify strains that might colonize to a greater degree and potentially produce superior clinical responses, the research team cultured B. infantis strains from healthy children living in the same

community as those with severe acute malnutrition who were enrolled in the clinical trial.

The scientists found one strain that contained genes that allow it to utilize complex carbohydrates present in the local diet more efficiently than the strain investigated in the clinical trial. They went on to study germ-free mice colonized with gut microbial communities—called the microbiota—obtained from an infant with severe acute malnutrition before treatment to show that this Bangladeshi strain was a more efficient colonizer than the U.S. B. infantis strain. These findings set the stage for future clinical studies to test the effects of this newly discovered strain on restoring growth in children with severe acute malnutrition.

"Bacterial strain selection is a critical element in designing future therapies for repairing dysfunctional gut microbial communities that lead to malnutrition," said co-senior author Jeffrey I. Gordon, MD, the Dr. Robert J. Glaser Distinguished University Professor and director of the Edison Family Center for Genome Sciences and Systems Biology at Washington University School of Medicine. "This pilot study not only shows promising results in treating children with severe acute malnutrition but also underscores how proper development of the gut microbiota is linked to healthy growth of infants."

The clinical trial was led by co-senior author Tahmeed Ahmed, MBBS, Ph.D., executive director of the icddr,b, and Sharika Nuzhat, MBBS, a pediatrician in the Nutrition and Clinical Services Division of icddr,b. The trial involved 60 infants ages two months to six months with severe acute malnutrition, meaning their weight-for-height growth curves were at least three standard deviations below the average for healthy children.

All of the infants initially received standard care, including a course of antibiotics and a milk-based formula recommended by the World Health

Organization. One group was randomly assigned to receive additional treatment with the commercial strain of B. infantis alone for 28 days; a second group received the B. infantis strain plus a complex "prebiotic" sugar from human breast milk; and a third control group received lactose as a placebo. The investigators quantified the types of bacterial strains present in fecal samples from infants with severe acute malnutrition collected at baseline before the therapy began, at day 28, and four weeks after the interventions had stopped.

"At the start of the trial, B. infantis—this very important early colonizer of the infant gut—was either completely absent or present at only very low levels in infants with severe acute malnutrition," said first author Michael J. Barratt, Ph.D., an associate professor of pathology & immunology and executive director of the Center for Gut Microbiome and Nutrition Research at Washington University. "While the interventions increased the representation of B. infantis, the levels observed were still well below those we see in healthy breastfed infants of the same age in this Bangladeshi community. The results are very encouraging but left a question in our mind: Can we do even better?"

The team analyzed the gut bacteria of healthy infants from the same Dhaka community and found a strain of B. infantis that possessed additional genes devoted to metabolizing plant-based carbohydrates commonly found in the local diet, as well as other types of carbohydrates, including those from human breast milk. In experiments performed by Kazi Ahsan, MBBS, a senior scientist in the Gordon lab, and Barratt, both B. infantis strains were transplanted into germ-free mice that had been colonized with a microbiota recovered prior to treatment from an infant with severe acute malnutrition who had been enrolled in the clinical trial. Mice were fed a diet representative of the foods eaten by Bangladeshi children, including rice, lentils and milk.

The investigators found that the Bangladeshi B. infantis strain reached

higher levels in the guts of the mice than the U.S.-derived strain—potentially through its superior adaptation to the local diet. They also found that compared to mice that received the microbiota from severely malnourished infants alone, mice that received the same impaired microbiota and also were colonized with B. infantis gained more weight and had markedly reduced levels of potentially harmful bacteria present in their microbiota.

"Given the unique genomic features of the Bangladeshi B. infantis strain that confer superior fitness in our preclinical models, we now plan to repeat the human study using this strain," Barratt said. "This will allow us to determine whether the results translate to infants with severe acute malnutrition in Bangladesh through improved growth and more durable recovery from severe malnutrition."

More information: Michael J. Barratt et al, Bifidobacterium infantis treatment promotes weight gain in Bangladeshi infants with severe acute malnutrition, *Science Translational Medicine* (2022). DOI: 10.1126/scitranslmed.abk1107

Provided by Washington University School of Medicine in St. Louis