

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Kwashiorkor and the Gut Microbiota

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Malnutrition is a global health problem and a major contributor to childhood morbidity and mortality. Kwashiorkor and marasmus are two forms of severe undernutrition prevalent in regions confronting food insecurity and high burdens of infectious disease. The cause of kwashiorkor, a form of malnutrition notable for stunted growth, generalized edema, dermatologic manifestations, and hepatic steatosis, has remained elusive. Over the past 60 years, there have been many ideas about the pathogenesis of kwashiorkor, including inadequate dietary protein, the leaky gut syndrome (compromised gut epithelial barrier), and intestinal inflammation. Results of a study by Smith et al.¹ now implicate the gut microbiota, the vast collection of microbes that reside within the intestinal tract, as a central factor in the cause of kwashiorkor. A clinical trial recently reported in the *Journal* showed that giving oral antibiotic agents to children with severe acute malnutrition was associated with decreased mortality and an increased rate of recovery,² further strengthening the case for a direct association between the microbiota and malnutrition.

Using both human fecal surveys and mouse models, Smith et al. have begun to elucidate the contribution of the gut microbiota and diet to kwashiorkor (see Fig. 1 for a schematic representation of their experimental design). Their study also identifies potential mechanisms underpinning the recognized shortcomings in current treatment strategies for undernutrition that use ready-to-use therapeutic food (RUTF; usually a fortified spread consisting of peanut paste, milk powder, oil, sugar, and a micronutrient supplement). The findings of Smith et al. unveil new targets in the microbiota for the treatment of kwashiorkor and suggest that preclinical screening approaches based on mouse models may be useful for guiding interventions.

The human gut microbiota make up a complex and diverse microbial community that is

notable for its variation from person to person. In a recent study from the laboratory of Jeffrey Gordon, the senior author of the study by Smith et al., deep sequencing of the gut microbiota from people from the United States, Venezuela, and Malawi identified changes in the microbiome during postnatal development.³ Previous studies of the gut microbiome have suggested that using monozygotic twins or individual persons as their own controls can help control for the effects of human genetic variation and environmental exposure on the microbiota.^{4,5} With these factors in mind, Smith et al. recruited twin pairs in rural southern Malawi for a study designed to resolve the kwashiorkor conundrum and establish the microbiota as a key player in the pathogenesis of kwashiorkor.

The study included monozygotic and dizygotic twins as well as twins discordant for kwashiorkor. When a twin with kwashiorkor began receiving RUTF, the healthy twin received it, too. A total of 15% of the twin pairs were monozygotic twins, which allowed the investigators to determine whether zygosity contributed to a propensity for malnutrition or to the discordance for kwashiorkor, but no significant differences were found. The twin pairs were followed prospectively, allowing for comparisons of the microbiota before and after the diagnosis of kwashiorkor, as well as while the children were and were not receiving RUTF. In the healthy twins, whether their twin siblings were healthy or had kwashiorkor, there were significant differences over time in the microbiota, and these patterns were consistent with developmental maturation of the gut microbiota. However, these changes were not observed in the twins with kwashiorkor, suggesting that the maturation of their microbiota was stunted.

To determine whether the composition of microbiota represents a causal factor in kwashiorkor, the investigators used fecal transplantation in gnotobiotic mice. Before undergoing

transplantation, these mice had no microbes, and during the experiments they received sterile food and water while living in specialized isolators with filtered air. One group of mice received fecal transplants from healthy persons, and the other group received transplants from persons with kwashiorkor; both groups of mice were then fed a diet that mimicked the foods consumed in rural Malawi — a critical experimental factor. The mice that received fecal transplants from human donors with kwashiorkor lost a significant amount of weight on the Malawian diet.

Several differences were noted between the two groups of mice. There were differences both in the microbiota and metabolic profiles in the mice that received transplants with microbiota from persons with kwashiorkor, as compared with those receiving transplants with microbiota from healthy persons, both when those persons were receiving RUTF and when they were not. Many of the RUTF-associated changes were transient, especially in mice receiving microbiota from the fecal-transplant donors with kwashiorkor. Metabolic analyses suggested that the microbiota of persons in whom kwashiorkor develops generate products, such as inhibitors of enzymes in the tricarboxylic acid cycle, that can compromise effective energy metabolism.

Smith et al. have identified potential targets for kwashiorkor that are rooted in the microbiota. They also found specific microbes, metabolic pathways, and metabolites that correlated with a positive response to RUTF, as well as signals that correlated with a lack of sustained improvement. Their work, and that of other microbiome researchers, not only provides a basis for understanding developmental patterns in healthy gut microbiota but also establishes robust preclinical models to improve food and microbial-based therapies for malnutrition.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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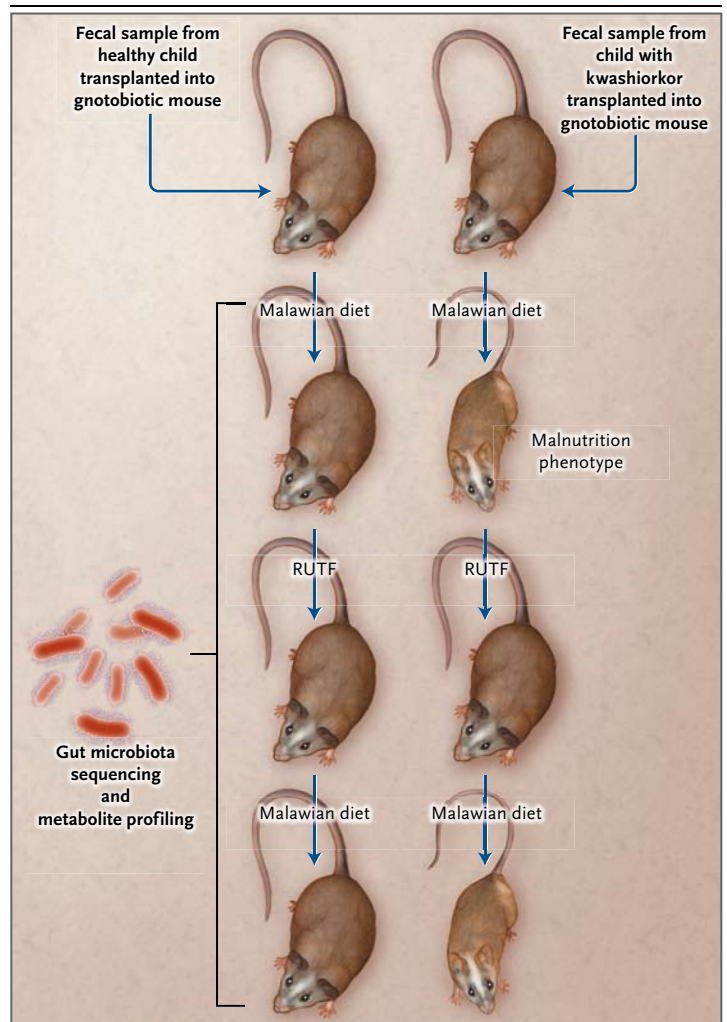


Figure 1. Gut Microbiota in Children with Kwashiorkor.

After analyzing and observing differences in the gut microbiomes of Malawian twin pairs discordant for kwashiorkor, Smith et al.¹ transplanted feces from donors with and those without kwashiorkor into gnotobiotic mice that were being fed a Malawian diet. After a few weeks on the Malawian diet, the mice were given ready-to-use therapeutic food (RUTF) for 2 weeks and were then restarted on the Malawian diet. Fecal samples from three kwashiorkor-discordant twin pairs were tested in these experiments. In two of the three pairs, the microbiota resulted in significant weight loss, which was consistent with a malnutrition phenotype. Deep sequencing allowed for detailed tracking of species-level changes during the dietary interventions. Metabolic analyses of urine samples from the mice suggested that the microbiota in persons with kwashiorkor have an altered metabolic profile that compromises efficient energy metabolism on the Malawian diet.

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DOI: [10.1056/NEJMcibr1301297](https://doi.org/10.1056/NEJMcibr1301297)

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