Commentary on Nutrition

Healthy gut microbiota can resolve undernutrition

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Provenance: This is an invited Commentary commissioned by Editor-in-Chief Yilei Mao (Department of Liver Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China).

Comment on: Blanton LV, Charbonneau MR, Salih T, *et al.* Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. Science 2016;351. pii: aad3311.

Submitted Dec 07, 2016. Accepted for publication Dec 19, 2016.
doi: 10.21037/hbsn.2017.01.19
View this article at: http://dx.doi.org/10.21037/hbsn.2017.01.19

Child's undernutrition is widely recognized as a major public health issue in many low- and middle-income countries. Malnourishment is regularly outlined as a determinant for immune dysfunctions and infectious diseases and has been estimated to cause 3.1 million deaths annually in children (1,2). Undernutrition actually impairs cognitive capacities and raises the likelihood for learning disability that contributes negatively to economic development in developing countries. Numerous socio-economic and environmental insults including infections and feeding regime can interact in a framework in which growth of children could not be fully achieved. It is actually hard to determine the precise contributions of each variable in this complex interplay even if poor food availability is a major etiologic factor for malnutrition. Likewise, nutritional interventions that treat malnourished children with ready-to-use therapeutic foods contribute to short-term clinical benefits although health objectives are generally heterogeneous and partially fulfilled among children (3).

The lack of substantial long-term expected efficacy of food interventions requires to elucidate underlying mechanisms relying on undernutrition that go beyond food insecurity. In this respect, epigenetic response to inadequate fetal diet does sustain a nutritional imprinting and a long term impact on the metabolic programs of individuals (4). Even if there are conflicting reports, the use of antibiotics as a means to promote nutritional recovery led to the hypothesis that microbiota affects nutrition as it is now fully recognized that commensal bacteria contribute to human health (5-7). The colonization of microbiota begins at birth and reaches adult levels around the age of three in healthy children. Although gut community variations discriminate human population, a common program of microbiome development involved in regulating host metabolisms in newborns seems to be shared across different geographical areas (8). Recent works carried out in Malawi and Bangladesh in twin-pair children with kwashiorkor or severe acute malnutrition emphasized clear causal relationships between gut microbiome and weight loss (9,10). In Bangladesh (10), Gordon's team has further computed two elegant metric indices that permit to assess age-dependent microbial change in children. By using these scores, they have inferred that an unknown standard biological procedure governs the development of microbial colonization maturity over time in healthy newborns which was disrupted in acutely-malnourished children.

The work published by Blanton et al in Science in February 2016 (11) extends the issue of the co-development of microbial immaturity and child's undernutrition by addressing the biological effects involved in growth faltering. In a longitudinal study, they collected stools to analyze gut microbiota from a birth-cohort of Malawian children younger than 3 years. They defined a chronological model of microbiota development as a function of children's age and they demonstrated that age-matched children with impaired weight gain displayed a decreased microbiota

maturity. It is worth noting that they identified sequence identities in taxonomic units between children from Malawi and Bangladesh suggesting that different low-resource areas share similar age-discriminatory bacterial taxa. In the next step, they used germ-free mice fed with a Malawian-like diet and transplanted them with a single oral gavage of fecal samples from healthy or stunted children. Mice colonized with donor microbiota from undernourished children changed in bone morphometry and grew poorly as they presented a deficit in weight gain and lean body mass. They also demonstrated elegantly that when both groups of recipient mice were housed together, coprophagic colonization of the microbial community harbored by the control mouse into the malnourished mouse residing in the same cage restored a normal growth phenotype in the later. Moreover, they identified two bacterial strains belonging to the Clostridiales family that allowed mice transferred with a growth-stunted fecal microbiota to recover from malnutrition. The presence of these growth-promoting bacteria modified fatty acid and amino acid metabolisms that would fuel protein synthesis in the liver, muscle and brain. The authors further reported distinct growth-discriminatory taxa that can predict enhanced weight gain and lean mass formation in Malawian children.

This well-conducted study enabled to firmly demonstrate that gut microbiota in combination with local diet is a direct mediator of both acute and chronic malnutrition during post-natal development. This demonstration also confers to the co-evolutive microbiota a reliable and close bio-marker of human development. It raises the essential role of microbiota as an adaptable way to environment cues that adjusts the host energy requirement during nutritional starvation. One of the main aspects pointed out by this work is the possibility to identify taxa that promote energy and metabolic input necessary for the optimal growth of children during the first 1,000 days of life, a critical window of therapeutic opportunity to influence child's development and prevent risk of diseases. Their preclinical model is then a powerful path to evaluate the effectiveness of novel food-supplementation on the development of gut microbiota implicated in malnutrition recovery. It is worth noticing that it represents a new opportunity to screen probiotics and prebiotics (12) as well as fermented foods or selected commensals that would impede the outcome of undernutrition such as lactobacilli strains (13). Lastly, potential effector molecules and their modes of action causing metabolic health have yet to be identified, as it is likely that a microbe-based beneficial effect is reached at the strain level, with sometimes opposing effects of bugs from the same species depending on intrinsic properties and specific circumstances such as microenvironment, time, dosing and competition with other microorganisms. In addition, providing exogenous strains to restore a normal metabolism must be controlled to avoid excessive energy utilization or further undesired/unexpected effects on the immune balance.

Whereas perinatal diets are obviously primary elements that shape microbiota during infancy, we must keep in mind that in utero exposure to maternal microbiota, mode of delivery and breast-feeding largely influence dynamics of the establishment of the intestinal microbiome in early life (7). Therefore, an approach integrating maternal and newborn care for growth outcome by focusing also on microbiota emanating from mothers should also be of great interest in the field of microbiota-therapy. Moreover, defining the conditions of durable establishment of health-driven bacteria is needed. It comprises consideration of individual immune status and history of infections, as well as the interaction/antagonism with resident microorganisms or other microbes in transit.

In conclusion, this work highlights the efficacy of using human fecal transplantation into germ-free mice that will help decipher the physiological and immunological impact of gut dysbiosis. Blanton *et al.* provides additional evidence that the microbiota is an essential component of metabolic health and human development. However, clinical design to improve growth might be detrimental since fat gain or catch-up growth can lead to amplify the risk for later obesity or diabetes. Thus, enhanced understandings of the developmental programs of human growth throughout life circle remain a major challenge in the future.

Acknowledgements

We thank Dominique Huge for the English proofreading.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Hermann E, Foligne B. Healthy gut microbiota can resolve undernutrition. HepatoBiliary Surg Nutr 2017;6(2):141-143. doi: 10.21037/hbsn.2017.01.19

