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PEDIATRIC IMMUNE SYSTEM MATURATION

The "microbiota" is a community of microorganisms mainly composed of bacteria, fungi and viruses that synergistically inhabit the body. It is estimated that there are as many individual microbes colonizing a person as there are cells in their body (1). Now there is mounting evidence inextricably linking a person's health and their microbiota. There are several distinct ecological zones where these complex communities reside, such as the skin, mouth, and especially the gut. Within the gastrointestinal tract microorganisms help to digest food and supply the energy necessary for intestinal integrity, they produce essential vitamins and create a protective barrier against colonization by harmful bacteria, and in many cases they actively inhibit or kill non-indigenous harmful organisms (2,3).

In recent years we have learned that our microbiota is not a mere convenience, but rather an absolute necessity. We are so highly dependent on these microbial communities for our health that they should be considered an "extrinsic organ system", equally vital as our other organs. Colonization by these essential microorganisms begins immediately upon birth and continues throughout life. However, one of the most crucial periods for the establishment of our microbiota is during the early years of life. It takes approximately three years for a child's microbiota to reach a similar level of diversity and complexity as that of an adult (4). During this developmental phase the microbiota is ever changing and becoming more intricate in its population. Importantly, a child's immune system must be able to accommodate these rapid changes.

It's now understood that a child is born with an immature immune system, such that it must be "taught" and "learn" from its microbial inhabitants (5,6). We often marvel at the neurological development of a newborn as they begin to develop skills and understandings that will protect them for life. Less obvious is that a similar process is occurring at the immunological level. Approximately 70% of the immune system resides in the GI tract and during the first three years of life the immune system is adapting to a diverse commensal microbiota, in addition to distinguishing harmful microorganisms. After this early "learning phase" the immune system becomes more "fixed" and less accommodating of changes. If not properly trained initially, the later rigidity of the immune system can lead to misdirected immune responses toward benign organisms, as well as ourselves (7). These misdirected

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attacks can result in long term health consequences and may also act to prevent the subsequent colonization of beneficial organisms.

It's known that disturbances in the co-maturation of the microbiota and the immune system during the early years may bring about local and systemic inflammatory and autoimmune diseases, obesity, allergies and gastrointestinal pathologies (8,9,10,11,12). These pathologies may develop during childhood, but quite often develop later in adulthood (13,14,15). Given the potentially negative consequences, it is essential that the process of co-maturation of the microbiota and immune system not be unnecessarily interrupted. Breast feeding and proper diet help in the establishment and development of a healthy microbiota. Yet, this developmental process can be disrupted through the use of antibiotics. Antibiotics indiscriminately kill both harmful and beneficial bacteria, and as a matter of course will cause perturbations in the microbiota. Nevertheless, when used with the knowledge of their potential side effects, antibiotics can be an effective treatment against harmful pathogens and are an essential medical tool.

Unfortunately, the CDC has estimated that up to 50% of the antibiotics administered to pediatric patients are done so needlessly and inappropriately (16,17). In these cases, the child's microbiota undergoes a significant stress in its development. Repeated dosing with antibiotics can lead to substantial delays in the development and maturation of the microbiota, as well as causing "dysbiosis", which is an imbalance in the members of the microbial community; this too can lead to disease. As such, delays in the development of an "adult-like" microbiota during the first three years may lead to life-long fundamental deficits in the training and functioning of the immune system. These functional deficits may subsequently lead to chronic disease. Given the importance of the intestinal microbiota and its interplay with the immune system it is critical that this delicate, early-life, tuning process not be unnecessarily perturbed. Therefore, prior to, or during the administration of antibiotics it should be ascertained whether these powerful agents are actually warranted in an effort to forestall inappropriate usage and reduce the incidence of antibiotic-associated complications. As an analogy, surgical amputation can be a useful lifesaving measure, but it would never be used indiscriminately, nor should antibiotic therapy.

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