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Opinion

The Microbiome, Antibiotics, and Health of the Pediatric Population

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Many diseases found in adults likely originate as exposure to factors during the pediatric period. As such, understanding environmental factors that are present during the time of gestation and the period of childhood will help us to understand contributing factors to disease later in life. Recent work has focused on a role for the microbiome in driving inflammatory diseases by influencing the development of the immune system and therefore contributes to the development of later-life disease [1-5]. A recent focus has been given to the heavy use of antibiotics in the pediatric population, and how this could affect the development of inflammatory disease [3,4]. This includes exposure to antibiotics *in utero*, shortly after birth, and into childhood. In addition to the effects of antibiotics on the microbiome, there is increasing worry that over-prescription of antibiotics is leading to an increase in antibiotic-resistant bacteria which may bring us back to a time before antibiotics, resulting in a devastating effect on human health [6,7]. For instance, according to the US Center for Disease Control and Prevention, over 2 million Americans develop antibiotic-resistant bacterial infections per year, with over 23,000 resulting deaths [8]. Furthermore, worldwide, it is estimated that over 200,000 neonates died due to sepsis caused by resistant microorganisms [9].

Evidence is mounting that a more targeted use of antibiotics is necessary in the pediatric population. One consideration is that the properties of antibiotics are different in pediatric versus adult populations, which can lead to errors in dosing of the drug [10]. In fact, recent analyses reveal that implementing antimicrobial stewardship programs can result in decreased antibiotic usage, cost savings, and reductions in prescribing errors without an increase in adverse outcomes, and that more work needs to be done for optimizing the use of antibiotics in the pediatric population [11,12]. Other research suggests that antibiotic usage of pregnant women leads to an increased risk for the child developing asthma due to changes in the microbiome, however there is disagreement in the field regarding this hypothesis and additional work studying this point is necessary [13-16]. Regardless of these studies, it is well established that the mode of delivery for infants greatly influences the microbiome of the infant, which therefore can influence immune development and the susceptibility to certain diseases later in life [2,17]. Additionally, the microbiotic composition varies with the stage of pregnancy, which has implications in the composition of the microbiome found in infants born preterm [18]. Additional dysbiosis of the microbiome has been seen in preterm infants who are born at very low birth weight, and has been associated with the development of necrotizing enterocolitis [19,20]. Research suggests that breast milk can help to improve the dysbiosis [21]. While the composition of the bacterial ecology of preterm infants has been show to become comparable to that of infants born at full term 1-3 years post discharge, it is possible that the programming of the immune system of preterm infants has been altered, thus increasing the risk for developing inflammatory disease later in life [22-24]. During this time period, it is possible that external factors could be used to alter the microbiome to improve health. The use of probiotics and alterations in diet could reverse dysbiosis, which could potentially improve disease state [18-21,25,26].

While antibiotic usage can alter the gut microbiome, and potentially lead to proinflammatory conditions, it is clear that new research is need to either use antibiotics more effectively, or to develop new antibiotics, in order to reduce the risk to human health by the spread of antibiotic-resistant bacteria [27]. The traditional approaches to developing new antibiotics are rooted in either identifying naturally occurring compounds or utilizing synthetic chemistry to generate new compounds [28]. New approaches for cultivating bacteria are being developed that can be used to identify naturally occurring antibiotics [29]. Additionally, understanding mechanisms behind antibiotic resistance could help to reveal new drug targets [30]. Furthermore, ways to better target antibiotics are being studied and could be beneficial in making current antibiotics more effective [31]. Thus, several approaches could be used to identify new antibiotics and/or improve the efficiency of existing antibiotics.

In summary, a fine balance exists for the use of antibiotics. While their use is absolutely necessary for treating disease, they could potentially alter the gut microbiome, which is known to influence immune function. In the case of children, changes in the microbiome due to antibiotic exposure at a time when the immune system is developing could increase the risk for developing later life inflammatory disease. At the same time, overuse of antibiotics is leading to an increase of antibiotic-resistant bacterial strains world-wide. This necessitates the development of new antibiotics to combat this threat to human health, which should be used sparingly in order to maintain their effectiveness. Additional resources must be put forth to studying the use and development of antibiotics in order to improve human health.

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