Impact of Antibiotics on Necrotizing Enterocolitis and Antibiotic-Associated Diarrhea

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KEYWORDS

• Antibiotics • Microbiome • Necrotizing enterocolitis • Antibiotic-associated diarrhea • *Clostridium difficile* • Probiotics

KEY POINTS

- Antibiotics induce microbial dysbiosis.
- Neonatal intestinal dysbiosis may contribute to necrotizing enterocolitis (NEC).
- Microbiome information may help predict risk for antibiotic-associated diarrhea (AAD) and NEC.
- Microbiome modulation may help prevent disease.
- Antibiotics induce AAD by disrupting microbiota's metabolic functions.

INTRODUCTION

Antibiotics are commonly prescribed medications that have saved countless lives, yet their side effects pose significant health challenges. Antibiotics are the most frequently prescribed medications in children[1] and constitute a significant amount in adults.[2] Antibiotics function by either direct killing or inhibiting growth of bacteria. In either case, they work in conjunction with the host's immune system to resolve infections.

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Antibiotics and the Microbiome

The intestinal microbiome is a complex ecosystem in which there is tremendous interdependence and crosstalk between microbial species, and between the microbes and their host. Although antibiotics target specific types of microbes (eg, vancomycin and gram-positive organisms), their effects on the microbiome go beyond just those clinically targeted microbes. For example, removing certain species of bacteria opens niches for other microbes to expand, which, in turn, can result in microbiome disruptions or microbial dysbiosis, such as when treatment with the gram-positive microbe-targeted antibiotic vancomycin leads to loss of some gram-negative taxa.[3] Not all antibiotics affect intestinal microbiota to the same degree. For example, vancomycin and metronidazole both drastically change the composition of the microbiota (in different ways) but the overall bacterial density is less following metronidazole treatment yet remains the same following vancomycin treatment.[3] The route of exposure also matters because parenteral antibiotic treatment can affect the intestinal microbiome via biliary excretion of antibiotic into the intestinal lumen.[4] Thus, although antibiotics are intended to target specific pathogenic microbes, their effects can be much more extensive, long-lasting, and unpredictable.[5] Antibiotic-induced dysbiosis contributes in the shorter term to antibiotic-associated diarrhea (AAD) and is epidemiologically linked to a variety of longer-term health problems, including obesity, asthma, allergy, and inflammatory bowel disease.[5,6]

Microbiome of the Neonate

Neonates face enormous challenges at parturition, including developing tolerance to their new microbiota while maintaining immunity against infection. The initial colonization of the gastrointestinal (GI) tract is an intricate balance between the colonization of commensal bacteria that leads to the establishment of tolerance and the prevention of infections secondary to the selective recognition of pathogenic microbes by the host. These host-microbial interactions are critical for the development and function of both the GI tract and the immune system. For example, the microbiota of the GI tract regulates angiogenesis,[7] enterocyte proliferation, and proper crypt formation,[8] along with development and function of gut-associated lymphoid tissue and the intestinal T cell populations that prevent intestinal inflammation.[9,10] In a healthy neonate, this early crosstalk between commensal bacteria and the host leads to pathogen recognition, epithelial barrier maturation, immune system development, and development of tolerance to food antigens and commensal bacteria.[11]

Microbial exposures early in ontogeny are associated with a range of diseases from atopy and autoimmune disorders to obesity and cancer.[12] This process is thought to occur either through epigenetic epithelial and/or immune system changes or by providing a niche for specific microbial colonization that influences long-term health outcomes.[11] However, exactly how the microbiome is established, and the impact of prenatal and postnatal exposures on the development of the microbiome, is only starting to be elucidated but offers great promise in predicting, preventing, and treating a variety of diseases.

The neonatal GI tract rapidly becomes colonized with microbiota. Newborn's initial microbiota is acquired by vertical transmission of the maternal microbiome during delivery,[13–16] although there is evidence for[17–19] and against[20] low-level microbial colonization of the placenta in utero. The mode of delivery, either via vaginal or caesarian section, influences the acquisition of most of the initial microbes.[13,14,16] As such, prenatal factors that affect the maternal microbiome also influence the newborn's microbiome.[6]