Cell Host & Microbe
Perspective

Antibiotics, Pediatric Dysbiosis, and Disease

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Antibiotics are by far the most common medications prescribed for children. Recent epidemiological data suggests an association between early antibiotic use and disease phenotypes in adulthood. Antibiotic use during infancy induces imbalances in gut microbiota, called dysbiosis. The gut microbiome's responses to antibiotics and its potential link to disease development are especially complex to study in the changing infant gut. Here, we synthesize current knowledge linking antibiotics, dysbiosis, and disease and propose a framework for studying antibiotic-related dysbiosis in children. We recommend future studies into the microbiome-mediated effects of antibiotics focused on four types of dysbiosis: loss of keystone taxa, loss of diversity, shifts in metabolic capacity, and blooms of pathogens. Establishment of a large and diverse baseline cohort to define healthy infant microbiome development is essential to advancing diagnosis, interpretation, and eventual treatment of pediatric dysbiosis. This approach will also help provide evidence-based recommendations for antibiotic usage in infancy.

Introduction

Antibiotics are by far the most common prescription drugs given to children (Chai et al., 2012). Epidemiological studies have identified associations between antibiotic usage in early infancy and occurrence of diseases such as obesity, diabetes, and asthma in later life. Longitudinal studies of antibiotic usage have demonstrated profound short- and long-term effects of antibiotics on the diversity and composition of the gut microbiota. Finally, a large and growing number of studies implicate a causal role for microbiome imbalance (dysbiosis) in numerous diseases (Biedermann and Rogler, 2015). Understanding the short- and long-term effects of early life antibiotic use on the diversity and composition of the gut microbiota is critical in identifying the risks associated with the emerging prescription trends. However, the existing literature is limited in directly implicating microbial dysbiosis as the link between childhood antibiotics and development of disease in later life.

In this review, we synthesize numerous complementary sources, including microecological studies linking antibiotics and dysbiosis, mechanistic studies linking specific types of dysbiosis to specific disease outcomes, and reviews of epidemiological studies supporting antibiotics and increased disease risk. By this approach, we have identified four major types of antibiotics-related dysbiosis, and we have presented a framework for discussing and measuring pediatric dysbiosis in the context of several major diseases. Our analyses indicate substantial existing evidence for a number of causal mechanisms by which the microbiome mediates antibiotic-related disease risk.

Overuse of Antibiotics

The vast majority of antibiotic use occurs in the outpatient setting, where up to a third of prescriptions are unnecessary. In 2010, children received 74.5 million outpatient antibiotic prescriptions—one for every child in the US—accounting for one fourth of all medications for children (Hicks et al., 2013). Numerous studies have demonstrated that antibiotics are often prescribed unnecessarily (Gonzales et al., 2001; McCaig et al., 2003; Nash et al., 2002), with estimates as high as 50% (Kronman et al., 2014). Nearly 30% of children receive an antibiotic prescription during an outpatient primary care visit (McCaig et al., 2003), most often inappropriately, for viral upper respiratory tract infections (Gonzales et al., 2001; Nash et al., 2002; Nyquist et al., 1998). Overuse of broad-spectrum antibiotics for conditions responsive to narrow-spectrum agents has been dramatically increasing (Hersh et al., 2013). Even after adjusting for differences in patient age, comorbidities, and sociodemographic factors, children with the same infections can receive vastly different rates of antibiotic prescriptions depending upon the practice or clinician visited (Fierro et al., 2014; Gerber et al., 2014). This phenomenon also seems to be universal: per capita antibiotic prescribing rates vary widely across US states (Hicks et al., 2013) and European countries (Goossens et al., 2005) without reasonable cause for geographic differences in bacterial infection rates.

In addition to the gut-microbiome-mediated effects as discussed in detail below, inappropriate prescribing of antibiotics can lead to both drug-related adverse effects and the promotion of antibiotic resistance. More than 140,000 emergency department (ED) visits occur annually in the US for antimicrobial-related adverse effects, comprising almost 20% of all ED visits for drug-related adverse effects (Shehab et al., 2008). In addition to this direct patient harm, antibiotic use has been associated with the emergence of antimicrobial resistance, identified by the World Health Organization (WHO) as "one of the three greatest threats to human health." Importantly, a recent study found that the prevalence of antibiotic resistance genes in the infant gut microbiome increases with age, and infants born via C-section harbored a larger proportion of antibiotic resistance genes (Bäckhed et al., 2015). Infections with resistant bacteria increase morbidity and mortality, and greatly increase the cost of medical care; the Institute of Medicine estimated that, in 2010, roughly

$20 billion was spent on the treatment of antibiotic-resistant infections. Knowledge of these facts, however, has done little to curb antimicrobial use. Improving our awareness of the long-term implications of both necessary and unnecessary antibiotic exposure is important to better inform the risk/benefit ratio for antibiotic prescribing and to improve child health.

Normal Host-Microbiome Development

Gastrointestinal Development

Gastrointestinal (GI) development occurs throughout embryonic life, and its basic structure is first formed by the end of the first gestational trimester (Montgomery et al., 1999). Tight junctions are present by 10 weeks of gestation, and intestinal villi are formed by weeks 12–19 (Maheshwari and Zemlin, 2009; Montgomery et al., 1999). Postnatally, an abrupt shift in exposure from amniotic fluid to first foods occurs in the GI tract. This induces many changes along the GI tract, including a change in pH of the stomach. For example, some reports state the pH of the stomach is initially in the range of 6 to 8 (Avery et al., 1966), likely due to buffering by the amniotic fluid, which decreases to that of an adult (pH 1.5–2.5) within the first hours following birth (Lebenthal and Lebenthal, 1999; Ménard, 2004). However, due to the consumption of milk, and its buffering capabilities, the pH of the infant stomach often returns to a high level of 7–7.6 (Hibberd et al., 1982). The higher pH of the stomach early in life has a meaningful impact, including a higher absorption rate of nutrients and a diminished digestive capacity compared to later in life, which may support transit of ingested bacteria to colonize the lower GI tract. Throughout postnatal development, the infant GI tract also increases in size in both longitude and in diameter and loses most of its early-stage porosity within days post-birth due to milk-borne growth factors and hormones that stimulate growth and development (Cummins and Thompson, 2002).

Development of the GI-associated lymphoid tissue (GALT), including mesenteric lymph nodes, Peyer's patches, and lymphocytes in the lamina propria is complete in full-term infants at birth (Forchielli and Walker, 2005). For example, goblet cells, responsible for mucin production, are functional by 12 weeks of gestation (Montgomery et al., 1999), as are paneth cells, which can secrete defensins and lysozymes by gestational weeks 13 and 20, respectively (Louis and Lin, 2009; Maheshwari and Zemlin, 2009; Rumbo and Schiffrin, 2005). Although full-term infants are born with fully developed digestive tracts, exogenous stimulation through exposure to dietary antigens, hormones, growth factors, and bacteria is required to elicit proper function throughout life (Forchielli and Walker, 2005).

Microbiome Development

Although the GI tract of a healthy infant is generally considered to be sterile before birth, recent work suggests that initial colonization may take place in-utero (Aagaard et al., 2014; Funkhouser and Bordenstein, 2013; Matamoros et al., 2013). Hours after birth, microorganisms from the mother's vaginal, fecal, and/or skin microbiome and the environment are important colonizers of the infant gut (Penders et al., 2006), with actual contributions depending on mode of delivery. Several other factors including prematurity, infant diet (breast milk or formula), hygiene, and use of antibiotics will ultimately impact the composition of the infant gut microbiome. Despite a seemingly chaotic colonization with large swings in composition over time, gut microbiome development is governed by Darwinian dynamics: microbes best adapted for the changing conditions of the gut will be most likely to survive. We can see this clearly throughout the first few weeks of life, as the colonization of facultative aerobes reduces the availability of oxygen, which then permit the growth of strict anaerobes (Bezirtzoglou, 1997). As illustrated in Figure 1, we can also see compositional changes in response to diet and host development throughout the first year of life. In the United States, the infant gut is initially colonized with Proteobacteria and Firmicutes, followed by a gradual increase in Actinobacteria (potentially due to the introduction of breast milk) (Sela et al., 2008). By 6 months of age, Bacteroidetes dominate while Proteobacteria and Actinobacteria gradually decline, which may be attributed to the abundance of carbohydrates in solid foods that coincides with weaning (Koenig et al., 2011; Vaishampayan et al., 2010). By the end of the first year of life, the infant gut is dominated by bacteria from the phyla Bacteroides and Firmicutes (Figure 1). The healthy infant gut continues with dramatic compositional changes throughout the first 2 years of life before becoming indistinguishable from an adult gut microbiome at age three (Yatsunenko et al., 2012).

Important Host-Microbiome Interactions

Maturation of the intestinal immune system is contingent on parallel development of the gut microbiome (Figure 1); germ-free animals have been found with significant immunological defects in the GALT (Macpherson and Harris, 2004) as well as improper development of Peyer's patches and mesenteric lymph nodes (Round and Mazmanian, 2009). Peyer's patches and the mesenteric lymph nodes develop prenatally, and isolated lymphoid follicles develop postnatally, but all of these tissues require interaction with key members of the gut microbiome in order to ensure proper differentiation and specification and complete development of adaptive immunity (Cherrier and Eberl, 2012; Maynard et al., 2012). The immune system must maintain an anti-inflammatory state (Tsuji and Kosaka, 2008) in the gut, especially during exposure to the considerable number of innocuous antigens from commensals, hormones, and food.

The interactions of diverse cell types are necessary to carry out the complex functions of the immune system (Adkins et al., 2004); we highlight several immune cell types with important dependencies on the gut microbiome. Dendritic cells (DCs), one of the most important types of antigen-presenting cells, sample the lumen and are responsible for orchestrating inflammatory or tolerogenic responses. To help the immune system carry out appropriate responses, DCs can suppress or induce the activation of antigen-specific T cells and have the unique ability to differentiate naive T cells into effector or regulatory T cells to target specific antigens (Lanzavecchia and Sallusto, 2001; Macatonia et al., 1995). T helper cells are critical in processing presented antigens into specific cytokines that provide direction for other immune cells and to eventually generate an immunological response. Members of the gut microbiome have been found to differentiate Th17 cells, a class of T helper cells, which secrete IL-17 to produce defensins (Kao et al., 2004) and recruit neutrophils (Aujla et al., 2007) to fight infections at mucosal surfaces (Atarashi et al., 2008; Ivanov et al., 2009). Pro-inflammatory Th17 cells must maintain balance with anti-inflammatory regulatory T cells, particularly for the prevention of autoimmune disorders. Certain Clostridia strains have been