

## Editorial



# Can the Use of Antibiotics Alter the Susceptibility to Allergic Diseases?

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The prevalence of allergic diseases has rapidly increased in Korea and other countries. There is growing evidence that the increased prevalence of allergic disease may be attributed to the changes of lifestyle such as dietary pattern, antibiotic use and mode of delivery, which shapes microbial colonization pattern.<sup>1-3</sup> Among them, use of antibiotics, which can directly cause gut dysbiosis, is of concern in light of accumulating evidence that alteration in the human microbiome can increase risk for allergy development.<sup>4</sup> The increasing use of antibiotics has coincided with a rise in the prevalence of childhood allergic diseases.<sup>5</sup> As a result, numerous observational studies on the potential harmful effects of exposure to antibiotics in the prenatal period and early childhood and the subsequent development of allergic diseases have been conducted. However, the results of these studies are still controversial.<sup>6,7</sup>

The Korean government has implemented a variety of policy measures including antibiotic use reviews, health quality assessments, and stewardship of antibiotics to reduce the use of antibiotics, resulting in a marked decrease in the use of antibiotics for upper respiratory tract infections.<sup>8</sup> Despite the various efforts, however, infants under 2 years of age had higher antibiotic consumption than their counterparts in other developed countries.<sup>9</sup> If antibiotic exposure in early life is associated with allergic diseases, it is an additional reason to reduce unnecessary antibiotic use in children.

The “hygiene hypothesis” is a frequently cited explanation for the increasing prevalence of allergic diseases. Originally, this hypothesis claimed that limiting early-life infections impedes the development of the natural immune system and thereby predisposes individuals to allergic diseases.<sup>10</sup> The modified “microflora hypothesis” proposes that Western lifestyle limits infections as well as general microbial exposure and it alters the colonization of the human gut, which in turn disrupts the development of immune systems and ultimately leads to allergic diseases.<sup>11</sup> Infancy and early childhood have been identified as important and vulnerable periods in the development of the gut microbiota, which shapes the disposition to allergic diseases. Thus, antibiotic exposure in early life could increase the risk of allergic diseases through altered gut microbiota.<sup>4</sup>

In Korea, a previous retrospective study in 2010 has suggested that the use of antibiotics in infancy does not increase the risk of atopic dermatitis in schoolchildren.<sup>12</sup> Other previous retrospective studies have suggested that the use of antibiotics in the prenatal period and infancy is associated with the risk of allergic diseases in childhood. However, these results have limitations due to recall bias as a result of retrospective studies.

In the current issue of the *Allergy, Asthma and Immunology Research*, Kim *et al.*,<sup>13</sup> reported that antibiotic use in early life is associated with an increased risk of allergic disease, especially in young children and that the risk increases as the duration of antibiotic treatment rises, using the data from the National Health Insurance Service which covers the entire Korea population. This study also showed exposure to antibiotics over a period of 7 years affects the later development of allergic diseases. This study includes all children's claim data during the period 2006 to 2015 and followed up children and adolescents for up to 7 years. However, the reverse causation was not completely excluded in this study. In the case of asthma, for example, it is difficult to distinguish between bronchitis and early wheezing caused by respiratory infections in childhood. As a result, first symptoms of asthma might be treated with antibiotics, thereby inducing an association between antibiotics and asthma (reverse causation). Conversely, antibiotics were used to treat respiratory infections, albeit a risk factor for asthma in itself, resulting in confounding by indication. Respiratory infections in children appear to be difficult to distinguish from early symptoms of asthma and can be confused with "protopathic" biases that use antibiotics to treat early symptoms of asthma. Previous systematic reviews have also highlighted the associations between antibiotic exposure and asthma, which could be caused by bias.<sup>5,14</sup>

To rule out these biases, research on the use of antibiotics before 1 year of age, which is a relatively low risk period for symptoms of allergic diseases (such as asthma and allergic rhinitis) and an important time for gut microbial composition, should be conducted. A recent retrospective study of 30,060 children in the United States found a strong association between antibiotic use in the first 3 months of life and the subsequent development of food and nonfood allergic diseases.<sup>15</sup> Similarly, another retrospective cohort study of 792,130 children found that the prevalence of food allergy, atopic dermatitis, urticaria, contact dermatitis, medication allergy, allergic conjunctivitis and anaphylaxis increased by 9% to 51% in children who had been prescribed antibiotics during the first 6 months of life.<sup>6</sup> They also showed that the hazard ratio after antibiotic prescription in the first 6 months of life is 2.09 for asthma.<sup>6</sup> A Swedish nationwide prospective cohort study demonstrated an increased risk of asthma after antibiotic exposure in fetal life and childhood.<sup>16</sup> However, the risk for asthma was higher after childhood exposure to antibiotics used to treat respiratory infections than urinary tract and skin infection, implying confounding by indication or reverse causation.<sup>16</sup>

In conclusion, although there is still controversy in this aspect, most studies reporting a positive association between antibiotic use in early life and the development of allergic diseases later in life were based on results from retrospective studies. Therefore, further studies are necessary to confirm causality and determine the mechanism by which antibiotic use at a young age may cause changes in gut microbiota and contribute to the development of allergic diseases later in life.

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