Tip of the Iceberg: Understanding the Unintended Consequences of Antibiotics

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Preventing the development of antibiotic resistance is 1 of the primary goals of antimicrobial stewardship.¹ The overuse of antibiotics directly contributes to the development of resistant pathogens, and the emergence of bacterial resistance is a public health threat associated with significant morbidity and mortality.^{2,3} However, bacterial resistance is not the only unintended consequence of antibiotic overuse. Alterations in the intestinal flora can result in an immune misbalance leading to immune dysregulation and inflammation.⁴ Because antibiotic exposure results in significant intestinal dysbiosis,⁵ the relationship between antibiotic use and the development of chronic diseases has been investigated, with some convincing evidence directly associating antibiotic exposure with obesity and inflammatory bowel disease.^{6–8}

In this issue of *Pediatrics*, Horton et al⁹ evaluated the association between antibiotic exposure and a new diagnosis of juvenile idiopathic arthritis (JIA) in children aged 1 to 15 years. The authors performed a nested case-control study by using a UK population-representative medical records database. Each case of newly diagnosed JIA was compared with 10 age- and gender-matched control subjects. Antibiotic exposure was found to be associated with an increased risk of developing JIA, and the magnitude of the association increased with additional antibiotic courses. These findings remained significant after adjusting for

confounders, including infection. In an effort to minimize the potential bias in which antibiotics would have been prescribed for symptoms associated with the early manifestations of JIA, the authors used the first joint symptom or referral to rheumatology as the index date of JIA onset. Secondary analysis revealed no difference among antibiotics with or without anaerobic activity. When the authors focused specifically on the diagnosis of upper respiratory tract infections (URIs), they found that antibiotic-treated URIs were more strongly associated with the development of JIA compared with untreated URIs. The authors concluded that antibiotics could potentially be a modifiable risk factor for JIA, and overprescribing of antibiotics may be unnecessarily placing some children at risk for the development of JIA.

As the discovery of new links between antibiotics and chronic diseases continues to unfold, other facets about the undesired effects of antibiotic use are now well understood. It is estimated that ~150 000 emergency department visits are attributed to antibiotic-associated adverse events each year in the United States alone.¹⁰ The burden on the health care system, patients, and families should not be underestimated when a child prescribed an unnecessary antibiotic develops an unanticipated adverse drug event requiring immediate medical attention. Similarly, development of a *Clostridium difficile* infection after an unneeded course of antibiotic can result in significant morbidity and even mortality. Although

some may argue that these unintended consequences are relatively infrequent, the risk of developing a complication from an untreated URI is even rarer.^{11,12}

Although the study conducted by Horton et al⁹ does not confirm a causal relationship between antibiotic use and the development of JIA, it does raise further questions. Additional research is needed to fully elucidate the potential mechanisms that directly connect antibiotic use to the development of systemic inflammation. Investigation of changes in the role of indigenous intestinal microflora induced by antimicrobial agents and the resultant contribution to the development of diseases is underway. As more data become available about the potential causal relationships between antibiotics and chronic diseases, clinicians will be obligated to share this information with their patients and discuss the perceived risk and benefit at the time of antibiotic prescribing.

Both the well-recognized and currently unknown, undesired sequelae of antibiotic prescribing should give clinicians and patients pause when an antibiotic is prescribed. An association with repeated antibiotic exposure and obesity or JIA may represent the tip of the iceberg. These newly discovered unintended consequences of antibiotics reinforce the importance of judicious antibiotic use, thus providing antimicrobial stewardship

programs yet another reason to optimize therapy when indicated and to reduce unnecessary antibiotic prescribing.

ABBREVIATIONS

JIA: juvenile idiopathic arthritis
URI: upper respiratory tract infection

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