A new reason to reconsider that antibiotic prescription: The microbiome

Of all the drugs I prescribe, I had been particularly comfortable with antibiotics. I may not recall in entirety their individual molecular mechanisms of action, but I can choose an appropriate antibiotic based, ideally, on bacterial identification and sensitivity data from our microbiology lab or, at the least, on epidemiologic information suggesting the more likely bacterial causes of the infection and current local microbiologic sensitivities. There are reasonable evidence-based guidelines for the prophylactic and therapeutic use of antibiotics based on clinical scenarios and for when to avoid prescribing them reflexively. I am aware of the issues mandating antibiotic stewardship to limit the spread of antibiotic resistance and of the links between nephrotoxicity, *Clostridium difficile*-related colitis, and tendon rupture with certain antibiotics.

But, after the results of many recent studies, it turns out I should not have been so comfortable after all. This should not be a surprise. We should never be overly confident with our understanding of anything in clinical practice.

In this issue (page 928), Dr. Martin Blaser discusses his work, which supports the hypothesis that the currently increased prevalence of obesity and diabetes is at least in part due to reduced diversity in the gut microbiome. The increased exposure to antibiotics through prescriptions for women before and during pregnancy, as well as perhaps their exposure to antibiotics in the environment, results in changes to the gut and vaginal flora that influence the developing gut and likely other anatomic microbiomes in the neonate and infant. Fascinating research done in mice, utilizing fecal transfer experiments, is building an evidence trail to support the concept that the microbiome plays a major role in the development of childhood and adult obesity, and the gut microbiome is influenced by its exposure to antibiotics, perhaps given years earlier.

Knowledge of the gastrointestinal and other human microbiomes is exploding. I now wonder how many seemingly random clinical events associated with antibiotic use that were not understood and were easily dismissed as stochastic warrant formal study. Some of my patients with rheumatoid arthritis have described flares after eating certain foods and transient remissions or exacerbations after treatment with antibiotics. An epidemiologic study has linked the likelihood of developing childhood inflammatory bowel disease with exposure to antibiotics. Even more fascinating are observations that the microbiota composition (influenced by antibiotics) can influence the outcome of cardiac allografts in a murine model and the response of certain tumors to immune checkpoint inhibitors in murine and human studies. The mechanism may relate to the effects of the microbiome on immune cell activation and migration. Several disorders have been linked to specific bacteria in the gut microbiome, and others as diverse as cardiovascular events and the acute inflammatory response to monosodium urate crystals (gout) are affected by metabolites generated by bacteria in the gut.

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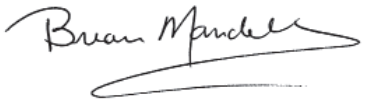
The use of germ-free and antibiotic-treated mice in the laboratory, with selective repopulation of their gut microbiome with flora harvested from other strains of mice or selected humans, will continue to teach us much about the role that these microbes and other inhabitants play in controlling normal and disease-disrupted homeostasis. *C difficile* overgrowth after antibiotic exposure, and the successful treatment of refractory *C difficile* with fecal transplantation,[1] was just the beginning.

The simple writing of a prescription for an antibiotic is a far more complicated and long-lasting affair than most of us have thought.



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1. **Agito MD, Atreja A, Rizk MK**. Fecal microbiota transplantation for recurrent *C difficile* infection: ready for prime time? Cleve Clin J Med 2013; 80(2):101–108. doi:10.3949/ccjm.80a.12110