power of genetic studies, and the ability to perform similar studies across different metabolomics platforms is a fundamental unmet need in the field. We view metabolomics studies as an important starting point for discovery and hypothesis generation, with subsequent efforts required for independent replication, individualized assay development, and mechanistic investigation.

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DISCLOSURES

None.

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Does the Receipt of Antibiotics for Common Infectious Diseases Predispose to Kidney Stones? A Cautionary Note for All Health Care Practitioners

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Nephrolithiasis is an illness of worldwide significance. Over the course of a lifetime, about 9% of the United States population will develop kidney stones, and the incidence is rising.[1] About 60%–80% of stones are composed of calcium oxalate, and urinary metabolic abnormalities, including hyperoxaluria, hypercalciuria, and hypocitraturia, increase kidney stone risk. Although nephrolithiasis can be associated with specific genetic and metabolic disorders, most stones are idiopathic; why kidney stones are becoming more common is not well understood.

In this issue of the *Journal of the American Society of Nephrology*, Tasian *et al.*[2] focused on antibiotic exposures as one explanation for an increasing stone prevalence. In the United States, >250 million courses of antibiotics are prescribed annually to outpatients,[3] with >40 million of these prescribed to children under 18 years of age.[4] A conservative estimate is that 30% of the antibiotics prescribed in the outpatient setting in the United States are unnecessary, with comparable estimates in other developed countries. Although many antibiotic courses are absolutely necessary, antibiotics are also overused for marginal indications in part on the basis of the belief that their long-term side effects are minimal. The prevailing belief for three generations has been that, after a brief period of instability accompanying an antibiotic course, "everything will bounce back to normal." However, this assumption may not be correct, and ultimately, reassessment may force changes in the practice of medicine.

We now know that the "everything" that we are counting to "bounce back to normal" refers largely to the human microbiome, the collection of microorganisms that live in and on us. The microbiome has been viewed as a "metabolic organ," providing beneficial metabolic

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and immunologic functions, and its disturbance by antibiotics has been linked to systemic diseases, including atherosclerosis, diabetes, and obesity.[5–7] Antibiotics also may affect the risk of kidney stones through altered oxalate metabolism by the microbiome. Oxalate is a common dietary constituent, and it is also produced endogenously as an end product of amino acid metabolism. Importantly, the gut microbiota can degrade dietary oxalate, involving the activities of multiple organisms that we will define as the collective "oxalobiome," which in net, reduces intestinal oxalate absorption and thus, potentially protects from calcium oxalate kidney stones. The bacterium *Oxalobacter formigenes* is perhaps the most important member of the human oxalobiome,[8] which also includes *Bifidobacterium*, *Lactobacillus*, *Escherichia coli*, and other species. *O. formigenes* is susceptible to commonly prescribed, orally administered antibiotics,[9] and it is becoming less prevalent as societies modernize.[10,11]

Tasian *et al.*[2] ask whether there is an association between antibiotic use and the risk of developing kidney stones in the subsequent months and years. They used conditional logistic regression models to compare approximately 26,000 patients with nephrolithiasis with approximately 260,000 matched controls in the large United Kingdom (UK) The Health Improvement Network (THIN) database. The three statistical models used had multiple adjustments for covariates, including clinical conditions, prescribed medications known to affect risk of stones, the presence or absence of outpatient imaging, and rate of health care encounters. To estimate the effect of the age at antibiotic exposure and the timing of the exposure on the association between kidney stones and antibiotics, they used generalized additive models, and they assessed model robustness with five sensitivity analyses. In total, the analytic approach was careful and sound.

The authors found that exposure to any of five different major antibiotic classes in the prior 3–12 months was associated with increased risk for a kidney stone. The odds ratio was highest for use of sulfa drugs followed by cephalosporins, fluoroquinolones, nitrofurantoin/methenamine, and broad spectrum penicillins. Two of the antibiotic classes with the broadest spectra—tetracyclines and macrolides—did not show any effect; thus, antibiotics were not all equal in their associations. The magnitude of the association was highest for antibiotic exposures at younger ages and antibiotic exposures 3–6 months before the kidney stone diagnosis. Importantly, even exposures up to 5 years before kidney stone diagnosis were associated with increased risk. Sensitivity analyses found that the overall findings were robust.

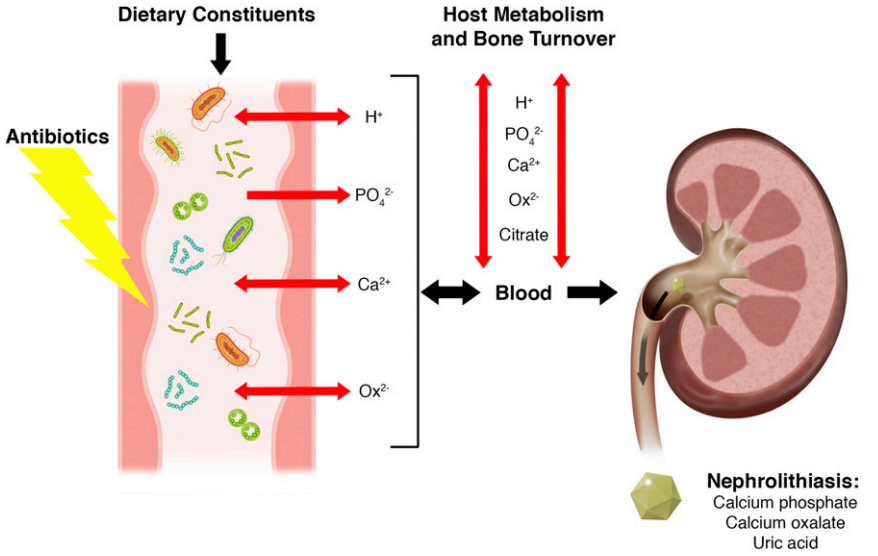

Figure 1. Proposed model linking antibiotic exposures to heightened kidney stone risk. The intestinal microbiota contains multiple species that, by their actions on dietary constituents and mucosal epithelial cells, can affect the absorption and secretion of ions into the bloodstream. Collectively, they influence the homeostasis of these electrolytes in the host that, in turn, affects the risk of specific forms of nephrolithiasis. By their collateral effects on the microbiome, antibiotic treatments will select for microbial taxa that can affect multiple physiologic processes. The microbiota perturbations may be brief or prolonged, and they can lead to either short- or long-term physiologic changes that can promote metabolic diseases.

Confidence in the findings from this epidemiologic study is bolstered by their internal consistency and biologic plausibility. Antibiotic effects on the microbiome could be explained at least in part by an effect on the "oxalobiome," which diminishes microbial oxalate consumption in the intestine, leading to increasing oxalate absorption, and by urinary excretion. The lack of association of some of the broad spectrum antibiotics that are known to affect colonization by *O. formigenes* and other members of the oxalobiome suggests that those antibiotics may have selected for microbes with countervailing activities.

Although the study was performed on a United Kingdom cohort, we would expect similar results in United States subjects who have similar lifestyle, diet, and antibiotic exposure profiles. However, although we consider that this study was conducted in an exemplary manner, there are multiple limitations common to all epidemiologic studies. Most importantly, the study design precludes inferences about causal roles of the exposures. Although the authors extensively controlled for known confounders, unidentified confounders cannot be ruled out.

Because information on stone types was not available, associations of specific stone composition with specific antibiotics were not ascertainable. With their broad effects on the gut microbiome,[12] antibiotics might also affect other metabolic parameters that were not available in this study, including urine pH, phosphate, calcium, and citrate. Changes in

these urine electrolytes can, in particular, associate with the risk of uric acid and calcium phosphate stones (Figure 1). Many commonly used antibiotics have broad effects on the microbiome, even if they are considered "narrow spectrum" against potential pathogens. Differential microbiome effects could explain the variable associations by antibiotic class. The finding of antibiotic exposure effects on stone risk decreasing over time is consistent with microbiome resilience, representing the anticipated "bounce back." The finding that associations of stones with antibiotic exposures were stronger in children could relate to synergistic effects from the higher use of antibiotics in this age group and with children's lower microbiome resilience.[13] Thus, these interactions may partially explain the dramatic rise in stone incidence in children.[14]

This study is important, because it analyzes a large database to address a question highly relevant to clinical practice. These results suggest that previously unrecognized long-term side effects of common antibiotic treatments may include increased nephrolithiasis risk. Recent large epidemiologic studies have associated prior antibiotic use with increased risk of diabetes, which manifests up to 15 years after the identified exposures.[15] Taken together, these studies of kidney stones and diabetes support the hypothesis that, by affecting the microbiome and its metabolic properties beyond just the intended effect of treating infections, health providers may be unintentionally contributing to chronic diseases. Because the consequences may be delayed by months or even years, these outcomes could have slid under the radar of health practitioners. Because antibiotic use is so ubiquitous, indeed central to the modern practice of medicine, long-term harm may be substantial. A growing body of evidence, including well conducted investigations, such as this study,[2] provide support for this very idea.

Considering the enormous scale of worldwide antibiotic usage, further research is needed to clarify these issues. Whether clinicians should recommend preventive measures, including increased fluid intake or low-oxalate diets, or specific probiotics after antibiotic use to mitigate increased kidney stone risk will require further investigation and in particular, mechanistic studies.

If these findings are confirmed, both clinicians and the public must be educated about the risks of harm with antibiotics. Such considerations are especially important when the indication for antibiotics is marginal or indeed, absent. As in this study, the most common use of antibiotics is to treat upper respiratory tract infections, most of which are viral, where the antibiotics used are ineffective.

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DISCLOSURES

None.

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See related article, "Oral Antibiotic Exposure and Kidney Stone Disease," on pages 1731–1740.