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The Use of Antibiotics and Risk of Kidney Stones

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Abstract

Purpose of review: The effect of the intestinal microbiome on urine chemistry and lithogenicity has been a popular topic. Here we review the evidence for exposure to antibiotics increasing the risk of nephrolithiasis.

Recent findings: Studies of the intestinal microbiome have focused on *Oxalobacter formigenes*, an anaerobe that frequently colonizes the human colon. As a degrader of fecal oxalate its presence is associated with lower urinary oxalate, which would be protective against calcium oxalate stone formation. It also appears capable of stimulating colonic oxalate secretion. A recent study showed that antibiotics can eliminate colonization with *O. formigenes*. In a case-control study, exposure to sulfa drugs, cephalosporins, fluoroquinolones, nitrofurantoin/methenamine, and broad spectrum penicillins prospectively increased the odds of nephrolithiasis. The effect was greatest for those exposed at younger ages and 3-6 months before being diagnosed with nephrolithiasis.

Summary: Recent evidence suggests a possible, causal role of antibiotics in the development of kidney stones. A possible explanation for this finding includes alterations in the microbiome, especially in oxalate-degrading bacteria like *O. formigenes*. Ample reasons to encourage antibiotic stewardship already exist, but the possible role of antibiotic exposure in contributing to the increasing prevalence of kidney stones in children and adults is another rationale.

Keywords

calculi; renal; microbiome; microbiota; nephrolithiasis; oxalate; *Oxalobacter formigenes*; urolithiasis

I. Introduction

Nephrolithiasis is a complex disorder with multiple contributing factors, including environmental, lifestyle, and genetic causes. The prevalence of nephrolithiasis has increased by 70% over the last three decades.(1) Changes in diet, increasing prevalence of overweight

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and metabolic syndrome, and diabetes are often considered likely to be causative in this observed increase.(2) While these and other variables are likely to be important, we have posited that increasing use of antibiotics is also a contributing factor in the development of nephrolithiasis. The role of antibiotics could arise from alterations in the intestinal microbiome of people who receive them for a variety of infectious diseases. The role of the intestinal microbiome as an influence on urine chemistry and lithogenicity has long been a topic of interesting speculation. Recent observational evidence has more convincingly linked oral antibiotic exposure to the development of kidney stones. In this article, we review the evidence for exposure to antibiotics increasing the risk of nephrolithiasis and possibly have a causal role.

II. The Microbiome

A potential mechanism possibly explaining the association between antibiotic exposure and nephrolithiasis is the effect of the intestinal microbiome, the community of microorganisms hosted by the human bowel, on urine chemistry. The complexity of the microbiome cannot be understated; it is home to 500-1000 bacterial species, many with symbiotic relationships that affect the health of their human host. In total, the intestinal microbiome has approximately 150 times more genes than the human genome.(3)

Studies of the gut microbiome of patients with and without kidney stones have shown differences in the patients' microbiome.(4) For example, in a study of 23 kidney stone patients and 6 non-stone forming controls, the *Prevotella* genus was one of the most abundant bacteria in those without kidney stones and the *Bacteroides* genus was most abundant in those with kidney stones. Since the metabolic effects of these differences in the microbiota on urine chemistry or other risk factors for kidney stones are not known, there is currently no clear hypothesis about the potential causality of these observations.

III. Oxalobacter formigenes

Studies of the effects of intestinal microbiota on many disease states and chronic conditions are often unable to identify the specific organisms responsible. The metabolic consequences of colonization with various organisms is not yet understood. Even the molecules mediating many of the proposed effects of the microbiome have not been determined. The situation is different in the case of kidney stone disease. In this case, microbiome studies have particularly focused on the effects of bacterial constituents on the metabolism of oxalate. The importance of this metabolite is clear since nearly 80% of kidney stones are composed of calcium oxalate.(5) In addition, studies have shown that certain gut bacteria, like *Oxalobacter*, *Bifidobacterium*, *Escherichia coli*, *Lactobacillus*, and *Eubacterium*, can degrade oxalate, and presumably reduce intestinal oxalate absorption, and thereby reduce oxalate levels in the urine.(6-9) Exposure to antibiotics can reduce levels of these bacteria in the intestine, thereby increasing levels of urinary oxalate and the risk of calcium oxalate stones. An effect of antibiotics to increase calcium oxalate kidney stone risk could then be effected by alterations in the gut microbiome. Of the oxalate-degrading bacteria, *Oxalobacter formigenes* is the most efficient at degrading oxalate and the best studied. A

figure summarizing oxalate metabolism and the potential effects of the microbiota and *O. formigenes* appears in another paper in this issue. (10)

O. formigenes is a gram-negative, obligate anaerobic bacterium that requires oxalate uptake for a source of carbon and for the generation of ATP.(11) Colonization rates of the bacterium vary from undetectable levels to 10^7 per gram of feces. The levels of the bacterium in fecal samples are also affected by the presence of dietary oxalate, which is their only required substrate.(12) Abundance of *O. formigenes* can increase by about ten-fold with a ten-fold increase in dietary oxalate and decrease with increasing oral calcium intake by the host, which binds oxalate and renders it unavailable for uptake by the bacteria.

Consumption of oxalate by *O. formigenes* is thought to reduce the amount of intestinal oxalate available for absorption and excretion in the urine. In addition, the bacterium appears able to stimulate intestinal secretion of oxalate, which may ultimately reduce urinary oxalate levels.(13) This appears to occur via production of an as-yet unidentified secretagogue that stimulates the intestinal chloride-oxalate exchanger SLC26A6 present in the apical or luminal intestinal epithelium. (14)

Colonization of the human intestine with *O. formigenes* has been associated with fewer stones. A case-control study of 247 patients with recurrent calcium oxalate stones and 259 controls without nephrolithiasis matched for age, gender, and region found a strong inverse association between colonization with *O. formigenes* and recurrent calcium oxalate stones. (7) Those colonized with the bacterium had a 70% reduction in risk of becoming a recurrent calcium oxalate stone former. Among controls, those who consumed more oxalate had an increased prevalence of *O. formigenes* whereas the opposite was seen with antibiotic use. However, median urine oxalate excretion was not different between those colonized with *O. formigenes* and those who were not. The lack of difference in urinary oxalate excretion could be related to dietary differences. Another study of 37 calcium oxalate stone formers showed no differences in urinary oxalate excretion between those colonized and not colonized with *O. formigenes* while on a self-selected diet.(15) However, when participants consumed a controlled, standardized diet, urinary oxalate concentrations were lower in those colonized with *O. formigenes* compared to those who were not. Further, those colonized with *O. formigenes* were associated with a significant lower number of stone episodes compared to those who were not colonized with the bacterium.

IV. The Effect of Antibiotics on *O. formigenes*

In adults from USA, colonization rates vary from 38 to 62% of individuals.(16, 17) A recent study analyzing the abundance and stability of *O. formigenes* in 242 healthy young adults in the United States using data from fecal samples from the Human Microbiome Project revealed that whole-genomic shotgun sequencing had the best sensitivity in detecting the bacterium.(17) In this dataset, 29 of 94 participants (31%) tested positive for *O. formigenes*, a value which may have been reduced by prior antibiotic exposure. Globally, higher rates are seen in populations with less antibiotic use.(18, 19)

It is not surprising that antibiotics would reduce the prevalence of *O. formigenes*. Amerindians, for example, have higher rates of *O. formigenes* colonization, which is attributed to less antibiotic availability in this population.(20) Amerindians of the Yanomami-Sanema, Yekwana ethnic groups in Venezuela, and the Hadza in Tanzania all had higher rates of detection of *O. formigenes* than adults from the USA.(20, 21) Another example is the children of Ukraine, who have limited access to antibiotics, and have universal colonization at age 3-4 years which declines with time.(22)

Patients with cystic fibrosis are known to have higher rates of kidney stones and antibiotic exposure. In one study, 71% of patients without cystic fibrosis were colonized by *O. formigenes*, while only 16% of patients with cystic fibrosis were colonized.(23) Those patients who had both cystic fibrosis and *O. formigenes* colonization demonstrated normal urinary oxalate excretion, whereas 53% of patients not colonized by the bacterium had hyperoxaluria. However these data were not collected prospectively or longitudinally and could have represented associations of disease severity with antibiotic use, rather than a causal phenomenon. Patients with cystic fibrosis have additional reasons related to their phenotype, and possibly to their genotype, that could represent kidney stone risk factors.(24)

The only longitudinal data to examine the effects of antibiotic exposure on *O. formigenes* in humans comes from a study in which we selected patients who were found to have intestinal colonization, after undergoing upper endoscopy for indications independent of the study. The persistence of *O. formigenes* colonization was compared between those who were treated with antibiotics for *H. pylori* and those who did not have it and therefore did not receive antibiotics. Patients receiving antibiotics in the two years prior to the study were excluded. All patients underwent stool sampling at baseline and 1 and 6 months afterwards, with detection of *O. formigenes* by polymerase chain reaction. Those treated with antibiotics (predominantly amoxicillin and clarithromycin; metronidazole, tetracycline, and bismuth; or metronidazole and clarithromycin) had a substantially reduced colonization of *O. formigenes* at 1 and 6 months: from 100% to 36.8%. Of those who did not receive antibiotics, 91.7% remained colonized. We did not have 24 hour urine oxalate excretion or dietary information to determine if the loss of *O. formigenes* colonization was associated with a greater risk of higher urinary oxalate excretion or the development of stones, but the study was suggestive that these developments were plausible.

The lasting effects are consistent with other reports of reductions in gut bacteria persisting months after antibiotic exposure.(25)

V. Antibiotics and Nephrolithiasis

Despite the aforementioned associations with absence of *O. formigenes* and nephrolithiasis, not all studies have shown such association. For example, in a recent study, three bacterial taxa (*Faecalibacterium*, *Enterobacter*, *Dorea*), but not *Oxalobacter* were significantly less represented in the fecal samples of calcium stone formers.(26) One possible explanation has been the resistance of *O. formigenes* to antibiotics. *O. formigenes* is generally sensitive to a variety of antibiotics commonly used to treat infections, but resistance has been documented with cephalosporins, nitrofurantoin, and broad-spectrum penicillins.(27, 28) However, all

antibiotics have effects on the abundance of other bacteria in the microbiome, which then may mediate the pathogenesis of nephrolithiasis. Given the complexity of the gut microbiota, it is likely that other taxa and species and not *Oxalobacter* alone have a role, even in determining stool degradation of oxalate and the resulting urinary excretion.(4, 29, 30)

Many of these issues were recently highlighted in a recent nested case-control study.(31) Using The Health Improvement Network (THIN) database of children and adults in the UK, exposure to antibiotics was shown to prospectively increase the odds of nephrolithiasis. The study included 25,981 patients with nephrolithiasis and 259,797 controls matched for age, sex, and practice. Twelve classes of oral antibiotics were evaluated for an association with stones of oral antibiotics. Exposure to any of five different antibiotic classes (sulfas, cephalosporins, fluoroquinolones, nitrofurantoin/methenamine, and broad-spectrum penicillins) 3 to 12 months before being diagnosed with nephrolithiasis was associated with kidney stones. The magnitude of the association was greatest for those exposed at younger ages and 3-6 months before being diagnosed with nephrolithiasis. Importantly, while the strengths of the associations decreased with time since the antibiotic exposure, an association for the development of nephrolithiasis persisted for up to 5 years after receiving antibiotics from all classes except for broad-spectrum antibiotics.

This study was remarkable in its size, longitudinal nature, and ability to evaluate exposure to specific antibiotics. Other strengths of this study included its use of UK data set, which due to regional factors, allowed for patient matching within practices, adjusting for prior urinary tract infections, and reducing differential ascertainment of antibiotic exposure. However, the study had important limitations, including missing intravenous antibiotic use; lack of stone composition information, microbiome data, and urine chemistries. It potentially did not account for individuals with asymptomatic stones prior to antibiotic prescription. Nonetheless, the study remains one of the more important pieces of evidence in the link between antibiotic use and stone formation.

Similarly, a recent abstract prospectively examined the Nurses' Health Study I and Nurses' Health Study II (NHS II), analyzing 141,518 women over 14 years of follow-up.(32) The result documented 1,318 incident kidney stones, of which greater than 77% were composed of calcium. Those women in NHS II who used antibiotics for greater than or equal to two months between ages 40 to 59 had an increased relative risk of developing kidney stones (RR 1.62, 95% CI 1.01- 2.60).

There are other possible antibiotic-related factors influencing the development of nephrolithiasis. For example, 70% of bacteria isolated from calcium oxalate stones were resistant to multiple antibiotics, suggesting that surviving bacteria may have a role in stone formation. While urine in healthy people is generally assumed to be sterile, studies to determine if a urinary microbiome actually exists and has a role in stone formation are ongoing. Another possible variable in some cases could be the direct crystallization of antibiotics, which has occurred with ciprofloxacin and sulfamethoxazole-trimethoprim, and could serve as the basis for heterogeneous nucleation of calcium oxalate or even form stones themselves.(33) Finally, the circumstances of antibiotic usage for infections, which could

result in transient periods of increased insensible fluid losses and reduced hydration, may further encourage stone formation.

VII. Therapeutic Implications

The factors that affect the ability of the microbiome to rebound from courses of antibiotics are not known, but could include the diversity of the microbiota constituents, and various host factors including diet. Exposure to antibiotics at a younger age may produce larger changes in the host's metabolism than those that occur at an older age.(34) It may be possible to recolonize people after courses of antibiotics with *O. formigenes*, and other oxalate degraders and restore the oxalate-degrading capability of their stool.(35) However, the practicality of such a therapy remains unproven, particularly since successful colonization could require the patient's ingestion of sufficient oxalate (with low dietary calcium content).(36) A recent study in rats demonstrated that fecal transplants from one strain into another changed urinary chemistry in the recipients in such a way that theoretically could influence the risk of kidney stones.(37)

VI Conclusion

Recent evidence suggests a possible, causal role of antibiotics in the development of kidney stones. A plausible explanation for this finding includes alterations in the microbiome, especially in oxalate-degrading bacteria like *O. formigenes*, and others, leading to increased urinary oxalate excretion, and ultimately, the development of nephrolithiasis. Other effects on the microbiome are possible but not yet supported. Antibiotics are widely prescribed, with children receiving more antibiotics than other age groups, often for inappropriate reasons. Ample reasons to encourage antibiotic stewardship already exist, but the possible role of antibiotic exposure in contributing to the increasing prevalence of kidney stones in children and adults is one additional rationale.

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Key points:

- The intestinal microbiome influences urine chemistry and lithogenicity, providing a rationale for considering an effect of antibiotics on stone incidence and prevalence.
- Studies of the intestinal microbiome have focused on *Oxalobacter formigenes*, an anaerobe that frequently colonizes the human colon, degrades oxalate and reduces urinary oxalate excretion.
- A recent study showed that commonly prescribed antibiotics can eliminate colonization with *O. formigenes*.
- In a case-control study, exposure to sulfa drugs, cephalosporins, fluoroquinolones, nitrofurantoin/methenamine, and broad-spectrum penicillins prospectively increased the odds of nephrolithiasis, especially for those exposed at younger ages and 3-6 months before being diagnosed with nephrolithiasis.
- Antibiotic exposure may contribute to the increasing prevalence of kidney stones in children and adults.