Editorial

The link between antibiotic exposure and kidney stone disease

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Tasian and colleagues have recently undertaken an interesting investigation, studying the association between antibiotic administration and diagnosis of nephrolithiasis (1). They have shown statistically significant correlations between exposure to antibiotics, particularly at young ages, and subsequent diagnosis of kidney stones. Specifically, they showed that the association between antibiotic therapy and kidney stone disease diagnosis is highest with more recent antibiotic exposure (3–6 months) prior to stone diagnosis. While these data do not identify specific mechanisms of how antibiotic exposure may directly promote the formation of stones, there is no doubt that it is associated with a significant increase in stone formation risk.

Precedence for antibiotic exposure and the risk for disease development has been set for other disease states including asthma and inflammatory bowel disease, where antibiotic-induced changes in the intestinal microbiome were linked with increased risk and incidence of disease (2,3). The intestinal microbiome is very complex, consisting of 500–1,000 different bacterial species which form symbiotic networks that collectively are determinants of overall health. Overall, the intestinal microbiome was shown to consist of 3.3 million unique genes, roughly 150 times more genes than the human genome (4). The importance of the microbiome to the human host is evident in the fact that these genes encode proteins and enzymes that we do not have, thereby allowing us to metabolize components that we would otherwise not be able to utilize, creating an overall well balanced healthy environment. What constitutes a normal or healthy intestinal microbiome is still under investigation, with all research to date pointing towards a broad rather than specific composition where key characteristics include diversity, richness and overall resilience when confronted with factors that may lead to significant changes in composition and overall function. While antibiotics are one of the most powerful weapons we have to combat "invading" pathogenic bacterial species, their inability to distinguish between good and bad bacteria and lack of localized antimicrobial activity results in the unfavourable "side effect" of disturbing the well balanced intestinal microbiome "designed" to keep us healthy. The end result is increased risk for the development of other disease states that may have been kept at bay by the function of the "healthy" intestinal microbiome.

The more research that is being conducted in this area, the more it becomes evident that imbalances in the intestinal microbiome are associated with a number of conditions. Recently a link between intestinal bacteria, mainly *Oxalobacter formigenes* (*O. formigenes*), and the maintenance of overall oxalate homeostasis has been made with a loss of this bacterial species being associated with increased risk for recurrent calcium oxalate (CaOx) stone episodes (5,6). Subsequent studies, including the one by Tasian *et al.*, went on to show that antibiotic exposure is one factor associated with the loss of this important bacterial species and subsequent risk for CaOx kidney stone formation (7-9). While the susceptibility of *O. formigenes* to commonly prescribed antibiotics likely plays a significant role in the increased risk for CaOx stone disease, increased systemic oxalate levels are likely the result of antibiotic-induced disturbances of the intestinal microbiome as a whole. Recent work has gone beyond *O. formigenes*, and found differences in overall intestinal microbiome composition in recurrent kidney stone formers compared to controls (10-12). For all these studies, the *Bacteroides* genus were enriched in urinary stone disease (USD) patients, while *Prevotella* was enriched in healthy individuals. Furthermore, among patients who had

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24-hour urine results, the presence of *Eubacterium* species was inversely correlated with urine oxalate (10). In two studies, no significant difference for *Oxalobacter* colonization was noted between healthy and stone former groups, while the third did not report a result for this genus, implying no significant difference (10-12). However, in one study, when *Oxalobacter*-specific primers were used, 100% of healthy individuals were colonized by *O. formigenes* compared to only 17% of patients (13). This result is interesting, as the likelihood that at least a subset of non-stone formers have been exposed to antibiotic treatment with similar classes of drugs as the patient population is high, yet colonization by *O. formigenes* appears unaffected. This suggests that while antibiotic exposure may account for the loss of *O. formigenes* colonization in some individuals, it does not in others. In that same study, patients were found to harbor a diversity of other oxalate-degrading bacteria, as assessed by the presence of the *frc* gene, suggesting a role for other bacterial species in regulating oxalate homeostasis (14,15). Collectively, these studies indicate a broader role for the intestinal microbiome in recurrent kidney stone disease than originally thought, and further investigation into key bacterial networks required for overall oxalate homeostasis is warranted.

Despite the fact that our understanding of the bacterial networks involved in maintaining healthy systemic oxalate levels is limited, there is no doubt that antibiotic exposure is a key factor that leads to significant disruption of overall intestinal microbiome composition, likely including members of a potential oxalate metabolic network. Given that Tasian *et al.* found a correlation between different antibiotic classes and increased risk for kidney stone disease, the level and degree of dysbiosis associated with this in the microbiome is likely to differ between patients, meaning that specific microbiome "dysbiosis signatures" that may serve as biomarkers for increased stone risk likely do not exist.

We have long recognized the association between bacterial infections and nephrolithiasis, both with struvite and calcium-based stones (16). These infections had generally been thought to be secondary to the calculi. However, anecdotally, urologists have long noted that bacterial culture patterns from extracted calculi can differ from that of urine cultures from the same patient, suggesting the presence of multiple bacterial species in the urinary tract in addition to the pathogen. Recent work by Tavichakorntrakool and colleagues has confirmed these findings and made clear that the association between nephrolithiasis and urinary tract infections is far more complex than initially supposed (17).

While most microbiome research in nephrolithiasis has focused on intestinal flora, recent advances in the identification of a urinary microbiome has resulted in hypotheses that bacteria that naturally inhabit the urinary tract may also play a role in kidney stone formation. The urinary microbiome has only recently been identified by utilizing sophisticated genome sequencing techniques (18). Presumably, these bacteria have evolved to adapt to the urinary environment and have a symbiotic arrangement with the human host. A perfect example of this is the well-established role of the female urinary microbiota in urinary tract infections (19). Perturbations of this homeostatic condition are postulated to result in adverse effects for the host. Tasian and colleagues, in showing an association between antibiotic administration and subsequent stone diagnosis (1), open the door to speculation that disruption of genitourinary bacteria may perturb the system such that the urinary environment becomes more supportive of calculus formation. It is intriguing to contemplate whether an alteration in urinary microbiota composition affects stone initiation or aggregation. Previous studies have identified the presence of bacteria in non-infection kidney stones, suggesting that members of the urinary microbiome may play some role in stone formation (17,20).

We cannot ignore the possibility that those patients in the study by Tasian and colleagues who received antibiotics just months prior to an initial diagnosis of nephrolithiasis may in fact already have had calculi present. However, the continued significance of this correlation up to 5 years prior to diagnosis does support the assertion that this may well be an independent association (1). Further studies are needed to determine whether these bacteria directly promote stone formation or are incorporated into the stone matrix as "innocent bystanders" are still required to improve our understanding of the role these bacteria play in stone formation.

Of particular interest is the finding that antibiotic exposure at younger ages results in a higher risk for the development of kidney stone disease compared to exposure at older ages. This can likely be attributed to the fact that the intestinal microbiome may still be developing in younger individuals and is therefore not very stable and/or diverse. As mentioned previously, one characteristic believed to be important for a "healthy" or "normal" microbiome is the ability to resist change due to outside pressures, which itself can be shaped by prior antibiotic exposure. Prior exposure to antibiotics, and particularly to a variety of classes, is greater in the older population, increasing the development of resistance mechanisms by members of the intestinal

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microbiome. As a result, antibiotic exposure at older ages may result in less "significant" dysbiosis of the intestinal microbiome, compared to that of younger and less resistant intestinal microbiomes and hence result in an increased risk for stone disease development in the latter. Alternatively, in the context of bacteria that colonize the urinary tract, some bacteria respond to antibiotic exposure by triggering their internalization into uroepithelial cells for protection, forming internalized biofilm-like pods (21). While this type of mechanism has been proposed mainly for uropathogens causing recurrent urinary tract infections, it may be possible that similar intracellular bacterial communities may directly serve as a nidus for stone growth or indirectly promote stone formation while inside the cells (i.e., forming attached stones) or once released from the cells. Previous work using hyperoxaluric mice has shown that the presence of bacteria in the urinary tract resulted in increased numbers of CaOx deposits and increased renal gene expression of inner stone core matrix proteins (22). Lastly, much like for the intestinal microbiome, antibiotic exposure may shift the balance of the urinary microbiome by selecting for resistant species that changes the overall genitourinary milieu to one that favors stone formation through whatever mechanism.

While all of this is purely speculative, the data presented by Tasian *et al*. certainly do raise some very important questions that remain to be answered. Most importantly, what these data do show is a broader negative effect of antibiotic exposure on overall health beyond the development of resistant infections, but also an increased risk for the development of diseases such as recurrent kidney stone disease. While the exact mechanisms by which antibiotic exposure increases the risk for kidney stone disease remain to be elucidated, practicing good antibiotic stewardship is something clinicians can do to help minimize antibiotic "side effects" of increasing stone risk. Despite raising awareness of the importance of antibiotic stewardship in decreasing the spread of resistance, the incidence of antibiotic exposure is still on the rise and along with it so is the risk for the development of recurrent kidney stone disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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