Nephrolithiasis and urinary tract infections: ‘the chicken or the egg’ dilemma?*

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The relationship between nephrolithiasis and urinary tract infections (UTIs) is complex and difficult to analyse both on a physiopathological and clinical point of view. To date, research has focused mostly on the ability of bacteria to foster the onset of kidney stones. In particular, nephrolithiasis is traditionally considered to be a consequence of a UTI with bacteria, in most cases belonging to Proteus genus, that can produce urease, an enzyme able to split urinary urea, thus rising urinary pH and promoting precipitation and aggregation of struvite crystals following. This process follows a cascade of chemical reactions leading to the infection stones formation (Figure 1) [2]. One of the most typical forms of infective lithiasis is staghorn nephrolithiasis, which is characterized by a unique large-sided calculus completely filling the renal pelvis [3].

One paper by Tavichakomtrakool et al. [4], through an accurate and smart experimental design, suggests a different perspective and confirms that the association between UTIs and nephrolithiasis is far more complex than that suggested by the historical, didactic and perhaps simplistic dichotomistic classification. Although this issue has never been thoroughly studied in the literature up to this moment, we can realistically state that there are a large number of cases of nephrolithiasis, which we should traditionally define as metabolic, carrying clinical and laboratory findings of UTIs. This statement is also confirmed by very old research data, such as the ones published in 1957 by Melick and Henneman [5], who found that 34 out of 207 stone formers had a concurrent infection (with positive urine culture), but only 3 among those 34 had the classic struvite nephrolithiasis. In all the other cases, calcium phosphate calculi were documented. The authors interpreted those infections as a consequence of nephrolithiasis, considering that the stone-induced urethral obstruction is a well-known risk factor for infection.

In a 1972 retrospective study, carried out on 725 patients with calcium phosphate stones, 70% resulted infected with a urinary pathogen bug, in most cases Escherichia coli or Proteus spp. [6]. However, the analysis of stone composition revealed a wide heterogeneity, with a large percentage of calculi containing calcium (96%) and oxalate (52%). In spite of the limits of the biochemical stone analysis carried out at the time, certainly not as accurate as the present ones, we can anyway say that only a minority of those patients was suffering from struvite stones. However, the treatment of infection was associated with a lower rate of relapse of nephrolithiasis.

If not properly treated, the association between kidney stones and UTIs can lead to the onset of a dreadful complication, which is chronic pyelonephritis. A 1979 study just considered 33 stone formers with chronic pyelonephritis [7], performing urine cultures, cultures of biopptic samples of renal parenchyma and cultures of the calculus surfaces, demonstrating a bacterial growth, respectively, in 18, 33 and 47% cases. The bacteria isolated were highly heterogeneous (Proteus spp., Streptococcus spp., E. coli, Pseudomonas spp. and Klebsiella spp.). The fact of the calculus surface cultures being positive in a high number of cases may be due to a direct pathogenic role of the infection in the formation of stones, instead of subsequently complicating the clinical course. A biochemical analysis of stone composition was not carried out in this study, but it is remarkable that many patients were infected by bacteria that do not produce urease and thus are not usually associated with infective nephrolithiasis.

It was actually demonstrated in the following years that ~35% of kidney stones associated with infection are metabolic stones, thus composed of calcium phosphate and calcium oxalate. Even in those cases, the culture of stone surface was surprisingly positive for uropathogenic bugs; therefore, the proper therapy must be established on the surgical removal of the stone [8].

A study carried out in Sweden in 1989 showed that 28% of the patients admitted in hospital for renal colic...
had a positive urine culture, with a percentage significantly higher than that of the healthy population [9]. The frequency of positive culture was higher for patients with struvite calculi (88%), but was anyway significant even in calcium oxalate stone formers (26%). Moreover, the patients with a urine culture positive for *E. coli*, which is notoriously poorly involved in the genesis of infective nephrolithiasis, had a high prevalence of phosphate stones (struvite and/or calcium phosphate).

A Japanese research group came to the same conclusions some years later [10], nevertheless documenting a much lower prevalence of UTI during a renal colic episode (7% only). In this latter research, however, an entire-stone culture was also performed, recommended as a more sensitive diagnostic test than simple urine culture in establishing the presence of a UTI in the nephrolithiasis.

Moreover, the prevalence of infection might also be different, depending on the pathogenic mechanism of nephrolithiasis and on the geographical, social and economic environment. In fact, it has been demonstrated that this prevalence is ∼40% in stone formers with primary hyperparathyroidism, ∼18% in patients with idiopathic hypercalciuria and ∼31% in patients developing kidney stones, although in the absence of detectable risk factors in the urinary lithogenic profile [11]. A recent study from Pakistan even showed a prevalence of infection around 79% in stone formers, moreover isolating various species of Gram-negative bacteria from the urine samples of those patients [12].

At this point, a dilemma rises. Most studies cited so far interpreted the UTIs in stone formers with metabolic nephrolithiasis as a complication of an obstruction of the urine flow in the urether. The infection would therefore be a process subordinate to the kidney stone onset [13]. However, we cannot overlook the charming hypothesis that the UTI has a pathogenic role in metabolic nephrolithiasis, as what happens in struvite stone. Also the results of the study by Tavichakorntrakool *et al.* [4] suggest that this hypothesis is more than plausible.

To date, *E. coli* has been the most studied bacterium in this field. This bug is not generally able to produce urease and therefore cannot make urinary pH rise enhancing the struvite crystal precipitation. The first studies carried out in an *in vitro* setting on the ability of *E. coli* to promote crystallization and precipitation of different salts melt in urine gave conflicting results, not demonstrating a role for the bacterium in the promotion of lithogenesis, but on the other hand without excluding it [14, 15].

The issue was more extensively handled by Sabinski and Leusmann [16, 17], who showed that about two-thirds of the bacteria isolated from urine cultures of stone formers does not produce urease upon normal conditions, but gains this ability upon particular conditions such as urine stasis in the urinary tract. Therefore, these authors supposed that a mild process of alkalinization of urine at the beginning of calcium stone formation, due to a latent urinary infection by a bug able to produce urease optionally, may be an important step in the pathogenesis of calcium nephrolithiasis. The bacteria may also produce substances able to be part of the calculus matrix, or be themselves the matrix.

Another mechanism by which urease-negative bacteria may induce or promote the onset of ‘metabolic’ stones is splitting of urinary citrate, with hypocitraturia and diminished inhibitory effect on the formation of stones [18]. However, these pathways have not been extensively...
studied, except for some specific urinary pathogens such as Ureaplasma urealyticum. On the other hand, this study by Tavichakorntrakool et al. [4] found a percentage of citrate-utilizing bacteria lower than 40%.

Finally, it is important to point out that the relationship between infection and onset of renal calculi has yet to be extensively explained even for struvite nephrolithiasis. In fact, on the one hand, there are data suggesting that even other bacteria, in addiction to the urease-producing ones, may have a role in the onset of the struvite nephrolithiasis [19]; on the other hand, very recent data show that the cases of staghorn nephrolithiasis, traditionally considered as infective, in which a metabolic origin can be detected and the role of possible infective agents remains unclear, are constantly rising [3].

The issue is therefore complex and many-sided. We ourselves, in the light of the results of the study by Tavichakorntrakool et al. [4], reanalyzed our data from the last 1000 patients visited at our Stone Clinic for their first episode of idiopathic calcium nephrolithiasis and found that the prevalence of UTI is ~19.5%, not different between males and females. Moreover, we surprisingly found that familiarity for nephrolithiasis was more prevalent in patients with previous history of UTIs than in patients without previous history of UTIs (54 versus 44%). These data persuade us to surpass the old pathogenic dichotomy of nephrolithiasis, often focused only on the urinary microenvironment, and open new scenarios. It is plausible that there are some subjects immuno-genetically predisposed to the development of nephrolithiasis also for a different interaction bacterium-host on a genetic basis.

Another very important issue emerging from the paper by Tavichakorntrakool et al. [4] is the high prevalence of antibiotic-resistant bacterium isolates (up to 70%). Even if we consider that the patients studied have large stones and probably had in the past other episodes of UTIs, this percentage is really impressive. Antibiotic resistance is an extremely relevant public health issue and leads to high rates of morbidity, mortality and high costs. Both physicians and patients should be sensitized to a rational and targeted use of antibiotics. Especially, in UTIs, there are problems of over- and under-treatment and of low compliance to therapy that promote the onset of multiple resistant bugs.

In conclusion, this paper does not resolve the ‘chicken or the egg dilemma’, i.e. if nephrolithiasis causes UTIs or, vice versa, urinary infections promote kidney stones. However, the study gives a new perspective on the role of the bacteria in nephrolithiasis and represents a call for clinicians and researchers, nephrologists, urologists and microbiologists, to rethink a new road map for study and treatment of kidney stones.

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References


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