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Uric acid and Urate in Urolithiasis: The Innocent Bystander, Instigator, and Perpetrator

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Abstract

Uric acid is an end product of purine metabolism in humans. An unusual and still unexplained phenomenon is that higher primates have relatively high uric acid levels in body fluids due to a combination of absence of degradation, and renal retention. The physiologic purpose of high uric acid levels is still enigmatic but the pathobiologic burden is a variety of crystallopathies due to the low aqueous solubility of uric acid such as gouty arthritis and acute uric acid nephropathy. In the urinary space, three distinct conditions result from chronic uric acid and/or urate precipitation. The first and most common variety is uric acid urolithiasis. In this condition, urate is a victim of a systemic metabolic disease where increased acid load to the kidney is coupled with diminished urinary buffer capacity due to defective ammonium excretion, resulting in titration of urate to its sparingly soluble protonated counterpart, uric acid, and the formation of stones. Uric acid is the *innocent bystander* of the crime. The second variety is hyperuricosuric calcium urolithiasis, where uric acid confers lithogenicity via promotion of calcium oxalate precipitation by multiple mechanisms involving soluble, colloidal, and crystalline urate salts. Uric acid is the *instigator* of the crime. The third and least common condition involves urate as an integral part of the urolith as an ammonium salt driven by high ammonium and high urate concentrations in urine. Here, uric acid is one of the *perpetrator* of the crime. Both known and postulated pathogenesis of these three types of urolithiasis are reviewed and summarized.

Keywords

kidney stones; uric acid urolithiasis; hyperuricosuric; calcium; ammonium urate

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The authors declare that they have no conflict of interest.

URIC ACID BIOLOGY AND PHYSICAL CHEMISTRY

Uric acid biology

Uric acid (UA) was discovered by the Swedish chemist-apothecary Carl Wilhelm Scheele from a urolith, which he aptly termed lithic acid that was subsequently renamed uric acid. The biology of UA is covered extensively in other reviews^{1–3} and will only be briefly highlighted here. UA is a key intermediate in purine metabolism without which there will be no deoxyribonucleic acid and no life. In humans, uric acid is a *cul-de-sac* metabolic end product because of the absence of uricase to further degrade it to allantoin and allantoic acid^{1,4}. UA is one of the three nitrogen-bearing compounds to sustain excretion of nitrogenous waste; the other two being ammonia and urea. The use of uric acid to excrete nitrogen (termed uricotelism) mandates high uric acid concentrations in birds and reptiles⁵. Mammals who use urea to excrete nitrogen (termed ureotelism) have low UA levels. A peculiar exception are higher primates who are ureotelics but paradoxically have UA levels that are much higher than all other mammals^{1,2} (Figure 1A).

The increase in UA levels is in part due to silencing of the uricase gene in higher primates due to multiple cumulative inactivating mutations in both the coding and non-coding regions⁶. If these were accidental events, the organism would have evolved compensatory mechanisms to counter or at least minimize these stochastic events. The lower levels of xanthine oxidase, which catalyzes the formation of UA, may represent some form of compensation⁷. However, the changes in renal handling during the period of progressive silencing of uricase was exactly the opposite of what one expects for stochastic accidental inactivation of the uricase gene. Urinary excretion gradually decreased as UA degradation decreased (Figure 1B). The most plausible explanation is that the reduced metabolism and reduced excretion of UA were synergistic to achieve higher UA levels in body fluids.

While these changes are unequivocal, the purpose of having higher UA levels in higher primates remains enigmatic. Several theories abound attempting to speculate on the biologic advantage of but none has been proven or universally accepted. The low solubility of UA constitutes one distinct advantage for uricotelics as the excretion of UA in solid form negates the need for aqueous solution thus contributes to water conservation. There is clearly no need for this property in ureotelic organisms such as humans. The low solubility of uric acid ends up as the root of the crystallopathies in humans-, which are gouty arthritis, acute UA nephropathy, and several types of UA-containing urolithiasis.

Uric acid chemistry

UA is a weak acid with one dissociable H⁺ at physiologic pH ranges and a second one at supraphysiologic pH ranges (Figure 2A). UA and urate have vastly different solubilities. UA solubility in a urinary environment is limited to about 96 mg/L. Since excretion in humans typically exceed 600 mg/day in approximately 1–2L of urine, the risk of UA precipitation is omnipresent⁸. With a pKa of 5.35 at 37°C⁹, UA solubility is determined primarily by pH in that acidic urine (pH ~5.5) titrates urate to UA which is sparingly soluble and hence precipitates^{10–13} (Figure 2B). Generally, human urine is metastably supersaturated with

respect to UA. This suggests the presence of an inhibitor and the inadequacy or absence of an inhibitor may influence the propensity for UA nephrolithiasis. There is experimental evidence supporting presence of macromolecules, which enhance UA solubility and attenuate UA crystal adherence to renal tubular epithelium¹⁴.

While more soluble than UA, urate (Ur) solubility is finite and is dependent on the prevailing and accompanying cation, with potassium having the highest, ammonium the lowest solubility, and sodium in between. (Figure 2B). The concentration of cations in normal human urine under most circumstances is highest for sodium, followed by potassium, and then ammonium.

URIC ACID UROLITHIASIS

In this first example, UA plays a passive role in lithogenesis even though it is the main and sometimes only component of the stone. It is the example *par excellence* of the “tip-of-the-iceberg” phenomenon where the UA stone is just a sentinel of much larger systemic derangements, which deserve attention. Hence, the approach to evaluation and therapy should be multi-organ in nature, and are not limited to stone removal and empirical alkalinization of urine.

Epidemiology

There is a long history of associations between insulin resistance, features of the metabolic syndrome with UA urolithiasis and low urine pH^{15,16}; more recent findings are highlighted. An Italian study showed higher levels of serum glucose and triglycerides and an independent Chinese report found higher triglyceride levels in UA acid stone formers^{17,18}. The inverse relationship between body mass index and 24-hour urine pH reported by multiple investigators^{18–24} was recently expanded to pediatric stone formers²². In adult stone formers from a single center, hyperglycemia correlated with lower pH and higher urinary UA saturation²⁵. Greater abdominal visceral fat based in CT scan is associated with lower urine pH and greater uric acid stone risk²⁶.

The incidence of UA nephrolithiasis is increasing globally, likely paralleling the increasing prevalence of the metabolic syndrome and diabetes. In one large center in the USA, the fraction of UA relative to total stone formers increased from 7% to 14% over the past three decades²⁷. Another U.S. study reported that UA accounts for 12% of >4,300 urinary stones from seven states²⁸. In a Norwegian surgical cohort, UA stones comprised of 9% of >1,200 stones from 2014–2017 compared to 2% 40 years ago²⁹. UA, struvite, and brushite stone formers have among the highest risks of recurrence³⁰.

Pathogenesis

Despite the often uniformity of its composition (i.e. UA), UA stones is a disease of urine pH, and not UA. The low UpH in UA stone formers was noted for decades^{31–33}. This low pH was found to be due to increased acid load to the kidney and a concomitant inadequacy of buffering by the open buffer ammonia (NH₃) to ammonium (NH₄⁺)^{11,34}. Unduly acidic urine is a feature in obesity, the metabolic syndrome, and diabetes^{15,16,19,20,35}. The aciduria is constant throughout the 24-hour period leading to increase UA saturation around the

clock^{36,37}. The reduced ammonia buffering is present not only at the steady state, but also upon acute acid challenge in UA stone formers³⁸. Part of the reasons for the impaired ammoniogenesis and excretion is steatosis and lipotoxicity of the kidney and in particular the proximal tubule^{39–41} (Figure 3).

The impaired buffering by the kidney is compounded by an increased acid load to the kidney, which likely originates from the gastrointestinal tract and liver (Figure 3)⁴². Hepatic steatosis almost invariably accompanies renal steatosis in rodent model of metabolic syndrome and aciduria^{40,43} and in humans, hepatic fat content on CT scan is inversely associated with 24-hour urine pH²⁶.

Treatment

The cornerstone of treatment of UA stones have been alkali therapy since the first description by Pak and colleagues in 1986^{31,44–46}. The pathophysiologic basis of this approach is to neutralize the excess acid presented to the kidney (Figure 3), and also overcome the impaired buffering capacity by empirically raising urine pH. While this therapy does not target the fundamental systemic defects of UA urolithiasis, it is very effective; akin to treating primary hypertension with drugs that lower blood pressure without getting at the root cause of the hypertension, but nonetheless reduces cardiovascular risk. Low acid-high alkali dietary therapy has been shown to alleviate the biochemical risk but reduction in clinical events has not been shown⁴⁷.

A recent study took the therapy one-step closer to the underlying etiology. Maalouf and coworkers treated UA stone formers with a thiazolidinedione, which is a peroxisome proliferator-activated receptor gamma (PPAR γ) agonist that has multiple action including amelioration of steatosis in organs. After 24 weeks of therapy, UA patients exhibited higher UpH and higher fraction of net acid excretion being represented by ammonium, indicating a relief of the renal lesion⁴⁸. However, an impressive and most revealing finding is the decrease in net acid excretion indicating that the high acid load presented to the kidney was reduced (Figure 3), most likely via alleviation of lipotoxicity in the liver and perhaps the intestine.

Conclusion

UA acid stone is the prime example of the “tip of the iceberg” where the stone disease provide a window to glimpse into deep-seated systemic metabolic disturbance. The utilitarian efficacy of alkali therapy is pragmatic, but it has unintentionally decreased enthusiasm and effort towards addressing and treating the underlying root of the problem. The practitioner needs to adopt the philosophy that every UA stone former deserves a multi-organ interrogation and management. Therapy of UA stones should also progress beyond empiric alkali therapy.

HYPERURICOSURIC CALCIUM UROLITHIASIS

Coe and then Pak independently described hyperuricouric calcium urolithiasis (HUCU) where the principal underlying pathogenic factor is hyperuricosuria but the stone is primarily

calcium oxalate⁴⁹. The pathogenesis and therapy of this condition is quite different from the other causes of calcium oxalate urolithiasis and deserves separate consideration.

Epidemiology

Mixed calcium oxalate/UA stones were noted as far back as in 1893⁵⁰ and many reports followed. Gutman and Yü ventured to propose pathogenicity where calcium oxalate may act as nidus for mixed CaOx/UA stones⁵¹. Coe and coworkers noted in 420 consecutive calcium stone formers that 15% have isolated hyperuricosuria and 12% have combined hyperuricosuria and hypercalciuria⁵² amounting to 27% of calcium stone formers having hyperuricosuria. Interestingly, the source of hyperuricosuria seemed to be largely dietary-originated which is not that different from the hyperuricosuria of non-stone formers⁵³.

Some have emphasized the inability to observe an association between urine UA excretion rate and risk of being a stone former and questioned the existence of HUCU^{54,55}. Coe and coworkers unequivocally demonstrated that only subgroups of stone formers, those with isolated hyperuricosuria or hyperuricosuria in conjunction with hypercalciuria, respond to UA lowering drugs⁵⁶. Given that hyperuricosuria is common, the strength of hyperuricosuria as a risk factor for stone formation in the general population may not be easy to demonstrate because only a small fraction of patients is actually true HUCU sufferers.

Pathogenesis

Since calcium oxalate stones are common and so is asymptomatic (clinically insignificant) hyperuricosuria, one may question whether these two conditions are in fact causally related. A very compelling evidence is the fact that treatment with xanthine oxidase inhibitor and other urate lowering agents decreased rate of stone recurrence in selected patients with calcium stones and hyperuricosuria^{56–59}. Several physicochemical models have been described to collaboratively contribute to formation of calcium stones under hyperuricosuria (Figure 2)^{60–65}.

“Salting out” is a process where certain solutes are less soluble at either very low or very high ambient concentrations due to the existence of an optimal window of hydration shell. This mechanism for salting out calcium oxalate was proposed and experimentally supported^{63,64}. Patients with hypercalciuria and hyperoxaluria are more vulnerable to stone formation with increase in concentration of dissolved urate⁶⁴.

Urine contains inhibitors of CaOx crystallization⁶⁶. Pak et al. suggested that the colloidal form of urate could have promoted nucleation of CaOx by removing inhibitors of CaOx nucleation from urine⁶². The state of a solute in aqueous medium can be classified according to the size of the solute- solution $<10^{-9}$ m; colloid 10^{-6} - 10^{-9} m; suspension $>10^{-6}$ m (Figure 3). Sodium (Na) Ur in urine can exist in colloidal form and may remove mucopolysaccharides that inhibit crystal aggregation of CaOx^{65,67} but there is to date no direct experimental evidence that colloidal NaUr absorbs inhibitor has been observed.

The crystalline phase of Ur proposed that epitaxy accounts for HUCU^{60,61} acting via epitaxy which is the process by which one type of crystal growing upon another type of crystalline surface⁶⁸ (Figure 4). Coe et al. demonstrated sodium urate can be a “seed” for nucleation of

CaOx precipitation at pH 5.7⁶⁰ (Figure 4). Pak et al. showed NaUr can cause heterogeneous nucleation of CaOx at pH 5.7 and 6.7, and of calcium phosphate at pH 5.3, 5.7, and 6.7 from metastably supersaturated solutions *in vitro*⁶¹. Urine can exist with supersaturation of NaUr, and in supersaturated urine samples from patients with hyperuricosuria and calcium stones, NaUr can serve as seeds for the heterogeneous nucleation of calcium oxalate and phosphate crystals^{62,69}. In contrast, seeds of UA had very small or no effect in both studies^{60,61}. *In vivo* human studies showed that oral purine load was associated with an increased saturation of NaUr and purine deprivation and/or allopurinol therapy was found to decrease saturation with respect to NaUr⁷⁰.

Treatment

A strong support for HUCU rests on interventional studies with UA lowering agents in calcium oxalate stone formers despite some caveats in a number of these studies including the small sample sizes, short duration, usage of historical controls, and lack of standard treatment protocols. Nonetheless, in totality, they constitute a compelling body of literature. Coe and Raisen examined calcium stone formers with no metabolic abnormalities other than hyperuricosuria, hyperuricemia, or both. Both hyperuricemia and hyperuricosuria responded well to xanthine oxidase inhibition and stone events were nearly obliterated after starting therapy⁵⁷. A prospective randomized placebo-controlled did not report metabolic characterization of the patients, and the regimen was an unusual one that combined allopurinol with urinary alkalinization to pH > 6.5 with NaHCO₃, but nonetheless reported reduction of stone events⁵⁸. Coe did a more extensive analysis of >200 CaOx stone-formers with idiopathic hypercalciuria or hyperuricosuria, or both treated for about 2.9 years⁵⁶. Hypercalciuria was treated with thiazides, hyperuricosuria was treated with allopurinol, and when neither was present, fluid was prescribed. The reduction in stone events was no less than dramatic highlighting the importance of pathophysiology-directed therapy⁵⁶. In a randomized prospective randomized placebo-controlled trial in 60 calcium stone patients with hyperuricosuria but normocalciuria, there were clear benefits of xanthine oxidase inhibition⁵⁹.

Conclusion

In HUCU, one sees stones with mixed calcium oxalate and UA in the clear presence of hyperuricosuria and absence or very mild degrees of other risk factors for calcium oxalate stones such as hypercalciuria, hypocitraturia, hyperoxaluria, and low urine volume. If hyperuricosuria is the sole abnormality or if correction of other risk factors by conventional therapy fails, treatment of the hyperuricosuria improves clinical outcomes.

AMMONIUM ACID URATE STONES

The least known and least often encountered urate-containing stone is ammonium acid urate (AAU). While urate is a bystander in UA stones and an instigator or co-conspirator in HUCU, it is actually an integral part of the crystallization in AAU stones. Compared to the other UA/Ur-containing stones, AAU stone is unique for its epidemiology and physicochemical properties.

Epidemiology

Regarding its epidemiology, the terms “sporadic” and “endemic” are used to describe the occurrence of AAU in industrialized countries and developing countries respectively⁷¹. In industrialized nations, AAU stones are relatively uncommon^{72,73}.

As societies become more economically advanced and industrialized, the prevalence of AAU stones actually decreases. In Norwich, England, in the eighteenth and nineteenth century, more than a third of stones contained AAU. By early twentieth century in the same region, this decreased to 2.5%⁷³. In general, studies have not shown a consistent gender predominance.

A single-center Canadian study reported a prevalence of 0.2% with none being pure AAU stones. In most cases, AAU made up less than 10% of the total stone composition⁷⁴. Soble and colleagues analyzed more than 3000 stones from the Cleveland Clinic and reported AAU in 0.3% of stones and again no pure AAU stones were found⁷¹. A more recent analysis from a Mayo Clinic cohort found a slightly higher prevalence of 0.9% with pure AAU representing 19% of the AAU-containing stones⁷⁵. There are other differences between these cohorts. In the Canadian study, the predominant stones that coexisted with AAU were uric acid, struvite, calcium phosphate and calcium oxalate. In the Mayo cohort however, coexistent stones were struvite, calcium phosphate and uric acid in decreasing order of occurrence. Similar to the Canadian study, the Cleveland Clinic study also reported uric acid stone as the most predominant coexisting stone.

In Japan, uric acid, calcium phosphate, mixed uric acid-calcium phosphate, and struvite (in decreasing frequency) are the coexisting stones⁷⁶. Whilst this apparent discordance may reflect different populations and periods covered in the studies, another reason might be the varied definitions used to categorize stone predominance.

The most dramatic difference is that developing countries suffer much more AAU stones which has been attributed to socioeconomic factors, like diet, hygiene and urinary tract infections⁷². Children in developing countries have a much higher prevalence of AAU stones. An analysis of 103 stones from Iran showed nearly a quarter of the stones from a mostly adult cohort contained AAU⁷⁷. In a subgroup analysis of the stones in children, 48% of the stones were AAU. This trend of a high burden of AAU stones in children has been replicated in other Asian Countries, including India, Pakistan, Indonesia and the Uyghur region of China. However, studies from Africa, especially regions south of the Sahara have generally failed to show a high burden of AAU^{78–80}.

It has been suggested that dietary differences between sub-Saharan Africa that tends to be maize based compared to the Asian countries where rice predominates may explain the reported low prevalence in the former. North Africa that has historic and socioeconomic differences from the Sub-Saharan region has a higher burden of AAU stones especially in children^{81,82}. Perhaps, rather than there being a true dichotomy in the burden of AAU between northern Africa and regions south of the Sahara, under sampling of cases may explain the differences. For instance, review of stones from Ghana and Nigeria did not report

AAU; Niger and Cameroon, countries in the same subregion however showed a high burden of AAU^{79,83–85}.

Pathophysiology

Sodium and potassium urate salts are much more soluble than AAU (Figure 2). Typically, these electrolytes are present in urine in higher concentration than ammonium and thus more likely to form salt with urate. This begs the question why urate forms salt with ammonium⁸⁶.

Empirical and experimental evidence provide clues on the conditions, which promote formation of AAU (Figure 5). High concentrations of both urate and ammonium are required to facilitate AAU⁸⁷. A diet rich in purines satisfies the former condition. AAU is commonly found in Dalmatian dogs, a breed with congenital defect in uric acid transport and hyperuricosuria⁸⁸. Bottle nose dolphins in captivity fed a diet high in purine and acidogenic protein showed post-prandial urine supersaturated with urate and ammonium respectively⁸⁹.

In humans, two sources are proposed to explain the increased ammonium. UTI may lead to the elevation of ammonium through ureolysis by bacterial urease (Figure 5). Half of UAA stone formers from Taiwan had documented UTI and mostly from urease-positive organisms⁹⁰. In the US, up to a third of cases AAU stones may be associated with UTI^{71–75}. It is important to note that UTI is not a factor in some cases and in instances where UTI coexist, the organisms may not be urease-positive⁹¹.

The classic explanation for AAU in endemic countries is a cereal-based diet deficient in inorganic phosphate depletes urine of a major buffer resulting in up-regulation of ammoniogenesis and hyperammoniauria⁹¹. Compared to controls, AAU formers in endemic countries have low phosphate in their urine⁷². Upregulation in ammoniogenesis sets AAU stone formers apart from uric acid stone formers in whom a defect in ammoniogenesis has been implicated⁹².

The pH necessary to promote the formation of AAU is lower than the pH for struvite formation. *In vitro* experiment suggests that at pH <5.7 uric acid predominates over urate with urate occurring at higher pH⁹³. Teotia et al. took urine of a non-stone former and found that AAU precipitated at pH between 6–7.5⁸⁸. The ionic strength of urine may also influence the formation of AAU with urine of low ionic strength appearing to favor the precipitation of AAU⁹⁴. This may explain the association of diarrheal diseases with both sporadic and endemic stones.

In endemic countries environmental factors including a hot humid climate, diarrheal diseases in children, urinary tract infection and a diet of purine rich but poor in inorganic phosphate, may explain the occurrence of AAU. Since sporadic cases occur infrequently, studies attempting to describe them have tended to be small. Soble and colleagues studied 44 AAU stone formers and found an association with inflammatory bowel disease, laxative abuse, morbid obesity and recurrent urinary tract infection⁷¹, Kuruma et al. described a phenotype of thin young females in Japan with pure AAU distinct from overweight middle aged men who had the mixed type of AAU⁷⁶. Associations were also found with lower serum potassium and protein suggesting possible gastrointestinal losses from laxative abuse and

poor nutrition respectively. There have been case reports of AAU in patients with anorexia nervosa, chronic kidney disease, and prostate surgery. Similar to the situation in developing countries, gastrointestinal losses from inflammatory bowel disease and laxative abuse would result in smaller urine volumes and intracellular acidosis resulting in high urinary ammonium⁹⁵. A study of 9 females with AAU stones showed low urine volumes, elevated urinary ammonium and low urine sodium, potassium and citrate⁹⁶.

Treatment

Acute management of AAU is similar to the general management of stone disease. Preventing AAU stone formation requires treatment of the underlying predisposing conditions. This includes the modification of diet, fluid intake, treatment of UTI and stopping laxatives in relevant situations. Because occurrence of AAU depends on the urine pH, European guidelines recommend urine acidification with L-methionine^{97,98}. This must be done cautiously because acidic pH may promote formation of uric acid stones. Allopurinol to decrease uric acid levels has also been proposed^{97,98}.

Conclusion

AAU stones are a rare occurrence in economically advanced countries like the US. They may however, occur in patients with risk factors which promote a low ionic strength of urine, ammoniogenesis and supersaturation with urate. Recognition of the unique factors that promote AAU formation is important in preventing stone recurrence and guiding treatment.

EPILOGUE

While the purpose of maintaining high UA/Ur levels in human is still enigmatic, we certainly pay a price for the yet-to-be defined benefit(s). The low solubility of UA may be useful for excreting nitrogen in solid phase for uricotelics or serve as “danger sentinel signal” molecules in tissue damage to call for action, this physicochemical property is driving a variety of human crystallopathies. Using criminological analogy as in the urinary space, we visualize UA/Ur as an innocent bystander in UA acid stones where aciduria is the primary culprit, as an instigator of calcium oxalate precipitation in HUCU, and finally as part of guilty perpetrator, where Ur is actually part of the AAU stones. These are three conditions with completely different pathophysiology that requires targeted evaluation and therapy. Therefore, simply labelling a kidney stone as a “uric acid stone” is not an adequate term in medical parlance.

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Figure 1: Uric acid biology.
A. History of primate order evolution over 80 million years and subdivision into families. Progressive rise in uric acid levels parallels the loss of uricase activity from prosimians to humans. **B.** The rise in serum uric acid concentration is compared to urine uric acid-to-creatinine concentration; fractional excretion of urate was only available in very few species.

Figure 2: Uric acid chemistry.

A. Uric acid exists in two keto-enol tautomers with the clinically relevant tautomers being the lactim (enol) form. There are two dissociable H^+ giving rise to acid urate and urate (often just called urate) with $\text{pK}_a1 = 5.4$ and $\text{pK}_a2 = 9.8$; the former being relevant in mammalian urine with the latter not present in human physiologic states. Under extreme conditions of UpH (e.g. urea-splitting organism in the urinary tract), some divalent urate may be present. Monovalent urate can pair with ambient cations (Cat^+). **B.** Relative solubilities of uric acid and three urate salts as function of pH.

Figure 3: Proposed multi-organ model of uric acid stone formation driven by aciduria.

Organic (H⁺; OA⁻ organic anion) acid load due to increased production and uptake by gut lumen exacerbated by decreased hepatic metabolism and increased production. This poses an increased acid load to the kidney, which is capable of excreting the acid. However, impairment of ammonia synthesis and ammonium excretion mandates carriage of H⁺ by alternative buffers (B⁻); one of which is urate (Ur⁻) which when protonated, forms the insoluble uric acid.

Figure 4: Pathophysiology of hyperuricosuric calcium urolithiasis.

In the solution phase, sodium urate is a potent salting out agent that can increase the activity product of calcium oxalate. In the colloidal phase, sodium urate can adsorb and remove inhibitors of calcium oxalate crystallization. Finally, sodium urate crystals can initiate calcium oxalate crystallization via heterogeneous nucleation or epitaxy.

Figure 5: Model for pathogenesis of ammonium acid urate stones.

Contributors to high urine ammonium include physiologic response to acid load and intraluminal generation of ammonium from urea. One of the byproduct of ureolysis is $\text{HCO}_3^-/\text{CO}_3^{2-}$, which also alkalinizes the urine. Increased endogenous or exogenous purine load and metabolism leads to increased uric acid generation, and the high urine pH (UpH) ensures that urate form is preferred.

Table 1:

Risk Factors for ammonium acid urate stones

Risk factor	Country	Occurrence in AAU stone formers
Inflammatory bowel disease	US	18.2% ⁷¹ , 12% ⁷⁵
	Japan	0% ⁷⁶
Laxatives	US	4.5% ⁷¹ , 0% ⁷⁵
	Japan	41.4% ⁷⁶
	Taiwan	28% ⁹⁰
Obesity	US	6.8% ⁷¹
UTI	US	6.8% ⁷¹ , 13% ⁷⁵
	Japan	25% ⁷⁶
	Taiwan	52% ⁹⁰
CKD	US	11% ⁷⁵
	Taiwan	60% ⁹⁰
Ileostomy/bowel resection	US	28% ⁷⁵
	Japan	10.3% ⁷⁶
Diabetes mellitus	US	9% ⁷⁵
Prostate surgery	US	22% ⁷⁵
Chronic indwelling catheter	US	9% ⁷⁵
IBS	Taiwan	36% ⁹⁰
Urothelium carcinoma	Taiwan	12% ⁹⁰