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Prophylaxis of infection-induced kidney stone formation

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Summary. Lowering supersaturation with respect to struvite and carbonate apatite is the most important prophylactic measure in patients with infection-induced kidney stone disease. This is best achieved by combining culture-specific antibiotics with urinary acidification. Urinary infection with non-urease-producing *Escherichia coli,* probably promoting struvite particle formation, must be eradicated. Possible measures for improving urothelial anti-adherence properties or reducing bacterial adherence are discussed.

Key words: Infection-induced kidney stone formation – Lowering struvite/carbonate apatite supersaturation – Urinary inhibitors and promoters – Urothelial anti-adherence properties and bacterial adherence

Any prophylactic measure in patients with kidney stones has to be based on the general physico-chemical principles of kidney stone formation (Fig. 1). Primarily, urinary *supersaturation,* the "driving force" of stone formation, induces *particle formation*; subsequently, the growth and aggregation of nucleated microcrystals forms crystalline particles of larger sizes. Only particles that are *retained* within the urinary tract finally grow into full-sized stones.

The term "infection stones" is used for kidney stones either induced by urinary tract infection of *associated* with infected urine. This review focuses only on infection-*induced* stones, also called struvite, urease or "triple-phosphate" stones [2, 6]. As a consequence of *urealysis*, caused by a urinary tract infection with urease-producing bacteria [2, 6, 14], unique physico-chemical conditions develop: at the same time, urinary concentrations of ammonium, hydroxyl and carbonate ions are elevated, rendering urine supersaturated with magnesium ammonium phosphate (struvite) and carbonate apatite [14].

Patients with infection-induced stone disease primarily need adequate *treatment*, which consists of a combination of stone removal (as complete as possible) and eradication of urinary infection by culture-specific antibiotics [7].

Prophylactic measures, which are discussed along the pathophysiologic cascade of events outlined in Fig. 1, may interfere at all three physico-chemical levels of stone formation (Fig. 2): supersaturation is lowered by a reduction in the concentrations of stone components (antibiotics, urease inhibitors) or by as increase in their solubility (urinary acidification). Particle formation is regulated by urinary inhibitors and promoters, whereas urothelial defense mechanisms and bacterial adherence properties, balanced against each other, oppose or favor the process of particle retention.

Lowering urinary supersaturation

Antibiotics

Long-term administration (> 6 months) of antibiotics, the most obvious measure for the reduction of urinary supersaturation, produced sterile urine only in 8 cases and partial or complete stone dissolution in 5 of 31 patients

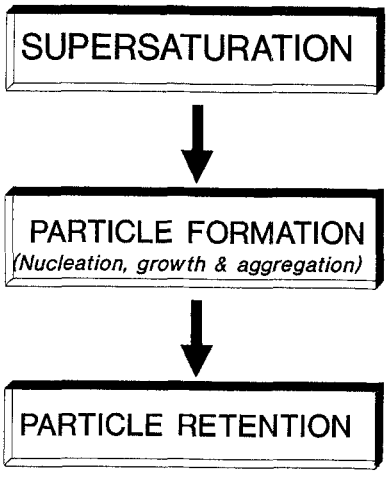

Fig. 1. General physico-chemical pathogenesis of kidney stones

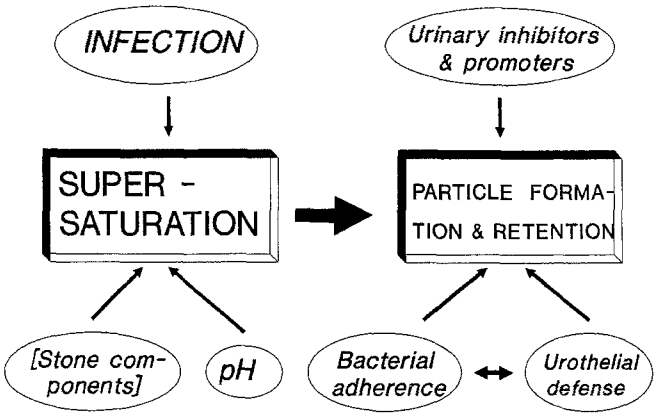

Fig. 2. Factors regulating infection-induced stone formation

with residual stone material [5]. Therefore, although they are of utmost importance, antibiotics may be insufficient if not combined with other treatment modalities.

Urease inhibitors

Almost 30 years ago, hydroxamic acids were demonstrated to inhibit bacteria-induced urease production [13]. Thus far, three substances have undergone clinical trials: acetohydroxamic acid, hydroxyurea, and propionohydroxamic acid.

The efficacy of *acetohydroxamic acid (AHA)*, the compound most extensively studied, has been confirmed by two double-blind, placebo-controlled trials: Williams et al. [32], who studied 39 patients, observed no stone growth and no surgical intervention in AHA-treated patients; however, almost 50% of them (as compared with none of the placebo-receiving patients) had adverse reactions, mainly tremulousness and deep-vein thrombosis. Griffith et al. [8] who studied 210 men with spinal cord injuries found a significant reduction of stone growth in AHA-treated patients at 12 months, but no more at 24 months. Premature termination of the study, however, occured in 62% of AHA-treated patients as compared with 31% of placebo-receiving subjects. In about half of the cases, treatment discontinuation was due to AHA-induced adverse reactions such as gastrointestinal and neurosensory side effects, phlebitis and hemolytic anemia [8]. In addition, AHA is teratogenic and mutagenic in animals [14].

Propionohydroxamic acid (PHA) has not been studied in a controlled manner. At a daily dose of 375 mg, urinary pH and ammonium ion excretion were reduced, but urinary sterilization was achieved only in association with antibiotics [16]. A reduced dose of 120 mg/day for 1 week followed by 60 mg daily was found to have the same anti-urease activity, and no adverse side effects were reported [17]. In addition, PHA seems to be the only hydroxamic acid without teratogenic or mutagenic properties in animals [16]. The use of *hydroxyurea* carries a higher risk of complications and toxicity with less efficacy [2, 14].

Phosphate depletion

Despite shrinkage or disappearance of stones in 23% of the cases, the combination of a low-phosphorus diet and aluminum hydroxide as a phosphate binder [28] is no longer recommendable, since chronic phosphate-binder administration may lead to a phosphorus-depletion syndrome, with weakness, bone pain, increased bone resorption and hypercalciuria [15].

Urinary acidification

Increased urinary acidity raises the solubility of struvite and carbonate apatite. *Ascorbic acid* at a dose of 3 g/day acidified non-infected urine in one study [18] but did not lower the pH of infected urine without concomitant antibiotic treatment [19]. The effect of *ammonium chloride* does not seem to be sustained for longer than several days [14]. *Ammonium sulfate* at a dose of 2–3 g/day produced sustained acidification for up to 17 years in patients with phosphate stones; the stone-recurrence rate fell by 64% in patients with simultaneous infection and antibiotic treatment and by 77% in non-infected subjects [26]. *Ammonium nitrate* also successfully acidifies urine in patients with kidney stones (cited in [14]).

Monotherapy with *L-methionine* at 3 × 1 g/day lowers urinary pH within 1–2 days [31], but the effect is not sustained in infected urine after 12 weeks of treatment [1]. In patients with renal insufficiency, urinary pH did not decrease significantly, but slight systemic acidosis developed [1]. Adverse effects (dizziness, indigestion) seemed to be rare. However, urine might become more supersaturated with calcium oxalate, since calciuria – at least at the beginning of L-methionine treatment – increases and citraturia falls [1, 12].

Decreasing the rate of particle formation

Crystallization inhibitors

The addition of human urine inhibits the urease-induced precipitation of calcium phosphate and magnesium ammonium phosphate crystals in vitro [3]. Calcium phosphate crystallization may primarily be inhibited by yet unidentified macromolecules, whereas the urease-induced formation of struvite crystals seems to be retarded by macromolecules as well as small molecules [11]. It is not known whether or not such inhibitors are deficient in infection stone disease.

Promoters of crystallization

According to clinical experience, *Escherichia coli* – a non-urease-producing germ – was the only microorganism cultered from stone material in >20% of a series of struvite stones [9]. After preincubation with *E. coli* for 20 h, urease-induced crystal precipitation in filter-sterilized urine was significantly increased, despite the absence

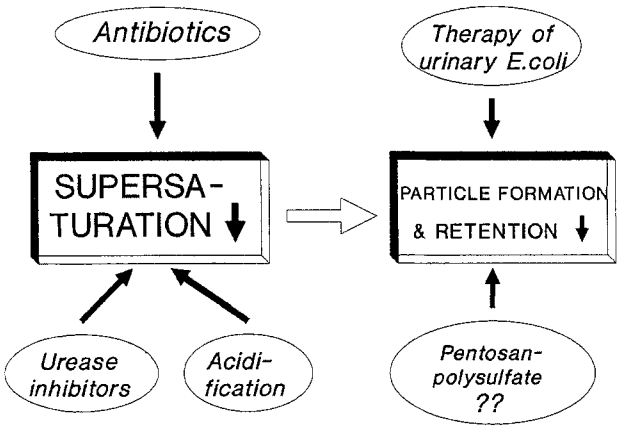

Fig. 3. Prophylaxis of infection-induced stone formation

of a change in pH [10]. Because of this probable promoting effect of these organisms on urease-induced crystallization, the eradication of any *E. coli* infection within the urinary tract may be important.

Prevention of particle retention

Urothelial anti-adherence properties

Transitional cells are covered by a layer of glycosaminoglycans (GAGs) that have unspecific anti-adherence properties against crystals and bacteria [4, 23]. Hydrochloric acid treatment and ammonium ions damage the GAG layer at the cell surface [23, 25]. Such denuded cell surfaces facilitate the adherence of struvite crystals and *Escherichia coli* [4, 25].

Anti-adherence properties of GAG-deficient urothelial cell surfaces in animals have been restored by the addition of exogenous GAGs such as heparin [4] or *sodium pentosan polysulfate (PPS)*, a heparin analogue [22]. Clinically, PPS (3×100 mg daily) seems to be an effective therapy for interstitial cystitis [24]. It is not known whether natural GAGs in human infections with urease-producing bacteria are deficient, or – if so – whether PPS treatment would restore such a defect.

Recently, *phosphocitrate* combined with antibiotics has been shown to reduce the growth rate of infection stones in rats, possibly by inhibiting crystal adherence to urothelial cells [27]. To date, no experience with this non-toxic treatment in humans has been published.

Bacterial cell-surface adherence mechanisms

Following bacteria-induced urealysis, urinary ammonium concentration rises, damaging the GAG-mediated unspecific anti-adherence properties of urothelial cell surfaces [6]. Thus, bacterial infection itself facilitates the adherence of further germs, thereby provoking more local inflammatory reaction. Local inflammation stimulates the production of organic compounds that serve as matrices of struvite stones [6].

Adherence of a bacterium to intact urothelial cells is mediated by filamentous appendages of the bacterial cell membrane called *pili* [20, 23, 29]. Adherence to cells does not necessarily mean disease: some pili simply mediate unspecific adherence [20] to a variety of cells (animal, plant, fungal) or epithelia (gastrointestinal, respiratory or urogenital) as well as to urothelial mucus, including Tamm-Horsfall glycoprotein [21, 23].

Other types of pili, however, are *virulence factors;* they are expressed more frequently in strains of bacteria associated with pyelonephritis [23] and bind specifically to urothelial-cell membrane receptors [20, 23, 29]. In an in vivo experiment in mice, ascending urinary tract infection by *E. coli* has been successfully blocked using a glycolipid analogue of host-cell membrane receptors [30]. No experience with this kind of compound in human urinary tract infection has been reported.

Conclusions

Prophylactic measures that are clinically applicable in infection-induced stone disease are summarized in Fig. 3. Besides the removal of all stone material, the *reduction of supersaturation* by eradication or suppression of infection is most important; antibiotics alone, however, may not be successful in many cases. It therefore seems recommendable to combine antibiotics with either urinary acidification or urease inhibitors. Urinary acidification is preferable because the lower frequency of side effects. To date, eradication of any *Escherichia coli* infection seems to be the only clinical way of possibly retarding struvite *particle formation*. It remains to be seen whether compounds such as pentosanpolysulfate or phosphocitrate might play a role in improving urothelial defense mechanisms against *particle retention*.

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