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Uric acid stones

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Diagnosis

- **Uric acid calculi should be detected by non-contrast helical computed tomography, as they are radiolucent on plain radiograph.**
- **Ultrasound may be a preferable review technique and helical CT is needed to confirm the absence of stones, if indicated.**

Treatment

Increasing urine pH and volume

- **Recurrence of uric acid calculi can be prevented by increasing urine pH and promotion of large urine volumes.**

Xanthine oxidase inhibition

- **Oral allopurinol to reduce urinary urate excretion is effective in preventing renal stones.**

BACKGROUND

The construction of guidelines for management of renal stone disease is complicated by several issues.

First, diagnosis is critical to good management, but levels of evidence have not been described for diagnostic tests particularly when there is no comparative test of 100% sensitivity and specificity. Second, the disease is managed by a variety of specialties, mainly urology, and hence nephrologists cannot claim to have overarching expertise. Finally, stone disease is one of the oldest diseases known to man. Many therapies were imbedded in practice before randomized prospective trials were cornerstones of clinical research. Some therapies are so much part of the routine that controlled trials involving no such therapy (e.g. allopurinol *vs* placebo in uric acid stone disease) are unlikely to ever be performed. In the few randomized trials that have been performed, a fall in stone frequency is often seen in the control patients ('stone disease effect'), making interpretation of the uncontrolled trials difficult.

The epidemiology of childhood stones is less clear. Children are more affected by genetic and anatomical disorders, and require age-specific expertise. Accordingly childhood stones will not be covered in these guidelines.

SEARCH STRATEGY

Databases searched:

1 Diagnosis of uric acid (urate) stones:
Database(s) searched:
Medline (1966–June Week 1 2004) – MeSH terms and/or text words for uric acid stones were combined with MeSH terms and text words for identifying diagnostic studies.

2 Prevention of uric acid (urate) stone growth or recurrence:
Database(s) searched:
Medline (1966–June Week 1 2004) – MeSH terms and text words for uric acid stones were combined with MeSH terms and text words for the interventions, and then combined with: (i) the Cochrane highly sensitive search for randomized controlled trials (RCT); and (ii) MeSH terms and text words for identifying meta-analyses and systematic reviews.
The Cochrane Renal Group Specialised Register of Randomised Controlled Trials was also searched for trials of interventions for uric acid stones.

Date of searches: 5 July 2004.

WHAT IS THE EVIDENCE?

No RCT are available that address this issue.

There are no published levels of evidence for epidemiology. Levels of evidence for diagnosis depend on a suitable gold standard, for which none exists in stone disease. There are no published RCT to evaluate therapies in uric acid stone disease. It is thus not possible to produce guidelines for uric acid stone disease based on level I and II evidence.

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LEVEL III AND IV EVIDENCE

Epidemiology

Uric acid comprises the major component of 10–20% of renal stones. Uric acid is the major compound of 17% of stones analysed in South Australia, increasing in frequency in hot weather. Seventy-nine per cent of uric acid stones occur in men, with a peak frequency between 60 and 65 years of age in both genders.[1]

Diagnosis

Radiology

Containing neither calcium nor sulphur, pure uric acid stones are radiolucent with conventional radiography, prompting the differential diagnoses of blood clot, tumours, fungal balls and detached papillae as well as cystine, xanthine and mucoid matrix calculi. With the advent of computerized tomography (CT) it rapidly became obvious that uric acid stones were very visible using this technique.

Federle *et al.* reported that nine non-opaque uric acid calculi had CT attenuation values between 300 and 400 Hounsfield units (HU), well above those of the likely differential diagnoses.[2] Resnick *et al.* showed that size reduction, as with medical dissolution, could be followed by repeat CT scanning.[3]

A major problem was insensitively due to CT slice location, particularly with 10 mm collimation. Helical CT scanners have overcome this problem, even with ureteral calculi, which can be at any level, and quite small. Chi *et al.* reported that of single ureteral stones of any type seen on helical CT in 215 patients, 47% were not visible on scout plain radiography, and of these the four stones larger than 10 mm were composed of uric acid (two) or xanthine (two).[4]

Nakada *et al.* studied the role of non-contrast helical CT in predicting stone composition, using 3–5 mm collimation.[5] After passage or retrieval, 17 predominant (>50%) uric acid calculi were found to have had Hounsfield measurements of mean 340 ± 152 HU, whereas 82 calcium oxalate calculi averaged 652 ± 490 HU ($P < 0.017$). If mean attenuation (HU) was divided by stone size (millimetre) a ratio >80 was highly suggestive of a calcium stone (sensitivity 94%, specificity 84%, positive predictive value 55% and negative predictive value 99%). Hence, if the ratio is less than 80 HU/mm there is fair certainty in predicting the stone is composed of urate and managing accordingly.

The utility of helical CT scanning, especially for surveillance in previous stone-former, is questionable, because of cost availability and radiation exposure.[6] Ultrasound may be a preferable review technique.

Ultrasound

Ultrasound will detect large renal pelvic urate stones,[7] but is unlikely to be sensitive for ureteral stones or small stones in the kidney.

Clinical indices

Clinical indices are of little use in predicting the presence of uric acid in stones.

Pak *et al.* showed that uric acid and mixed uric acid-calcium oxalate stones more common in patients with chronic diarrhoea syndromes and gouty diathesis, but in both conditions more patients had non-urate-containing stones (usually calcareous) than urate-containing stones.[8]

Metabolic indices were equally unreliable. Calcareous stones were more common than uric acid-containing stones in patients with hyperuricosuria.

It is commonly stated that approximately 50–60% of uric acid stone-formers have persistently more acid urine than in normals or calcium stone-formers. Gutman *et al.* reported 22 uric acid stone-formers to have urinary pH of 5.5 ± 0.4, compared with 6.0 ± 0.4 in 82 calcium stone-formers.[9] Although statistically significant ($P < 0.001$), this is hardly clinically useful. Pak *et al.* reported similar findings in a study defining the stone groups slightly differently.[10]

Treatment

Increasing urine pH and volume

The medical management of urate stones using increased fluid throughput and oral urinary alkalinizers is mainly based on the chemical properties of uric acid rather than controlled trials.

The most important factor is pH. Uric acid is a weak acid, with a pKa of around 5.4. *In vitro*, at this pH about half exists in the poorly soluble non-disassociated ('uric acid') form, and half as the soluble ionized ('urate') form. As the pH rises, the solubility increases. At pH 5 the solubility is less than 1 mmol/L (150 mg/L), whereas at pH 7 this rises to nearly 12 mmol/L (2000 mg/L). Urinary alkalinization thus should reduce stone growth/recurrence, and promote stone dissolution. Uric acid stone-formers tend to have more acid urine (pH ~5.5) than normals (pH 6–6.5) and non-urate stone-formers.[9,10]

The second factor is urine volume. Depending on diet and metabolic factors, the normal upper limit of daily uric acid excretion is around 4.7 mmol/24 h (800 mg/24 h); easily dissolved in 1 L of urine if urine pH is 7, but not if pH is 5.

By 1968, Gutman and Yu authoritatively reported, with references to previous cohort studies, that 'efficacy of adequate hydration, use of alkalinizing agents, regulation of the diet and control of urinary tract infection in most cases of uric acid nephrolithiasis has been established by long and universal experience'.[11] This situation effectively precluded future controlled trials though cohort studies continued, especially of successful stone dissolution and follow up after lithotripsy.

Pak *et al.* gave 30–80 mEq/day of potassium citrate to six pure uric acid and 12 mixed uric acid-calcium recurrent stone-formers.[12] Eleven took potassium citrate alone, six with allopurinol and one with hydrochlorothiazide. Urine pH was 5.30 ± 0.31 prior to treatment and rose to

6.19 ± 0.65 at 4 months, 6.40 ± 0.59 at 24 months ($P < 0.05$). Mean stone formation rate fell from 1.20 ± 1.68 stones/patient per year to 0.01 ± 0.04 stones/patient per year ($P < 0.01$) while on potassium citrate for periods from 1 to 5.33 years (mean 2.78 ± 1.34 years). One patient passed a calcium oxalate stone.

Rodman used alternate day administration of oral alkali, commencing with potassium citrate up to 50 mEq/day and then supplemented with sodium bicarbonate, in 17 uric acid stone-formers with stones or recurrent gravel/colic.[13] He reported that, if the urinary pH was raised to 6–8 once every second day, none experienced recurrence during an average follow up of 2.5 years. Increased fluid intake and low-purine diet was advised but compliance was not reported.

Sharma and Indudhara used oral sodium bicarbonate in 23 patients with non-obstructing stones to achieve urinary pH 6.5–7.0.[14] High fluid intake (unspecified) was encouraged and allopurinol prescribed if the patients were hyperuricaemic or hyperuricosuric (number unspecified). Three had surgical intervention, six passed stones, but in most the stones apparently dissolved, and with continuing oral alkali therapy 18 were free of stones 6–48 months later. In one patient, the stone became radiopaque, suggesting calcium incorporation into the stone.

Moran *et al.* showed, given adequate compliance and self-monitoring to ensure urine pH between 6.0 and 6.5, that of 11 patients referred because of previous failure of oral dissolution of stones, administration of oral potassium citrate, along with advice to drink 1–2 L of water and take a low-sodium-purine diet, eight (73%) experienced complete stone dissolution; three had lithotripsy.[15] Continuing treatment resulted in no stone recurrence 6–24 months later in 10 of the 11 patients.

The amount of alkali required to increase urine pH to over 6 varies between patients, dependent at least partly on diet. The normal urinary acid load is around 1 mEq/kg. Patients with chronic non-renal bicarbonate loss (chronic diarrhoea, ileostomy) require larger quantities. Usually a daily intake of about 1 mEq/kg body weight bicarbonate or citrate is required to dissolve stones; however, lower doses to transiently increase urine pH may be effective in preventing stone recurrence.[13]

It has been theorized that potassium salts (bicarbonate or citrate) are preferable to sodium salts for oral alkalinization, because sodium loading may promote calcium excretion, hence a risk of calcium stones. There have been no controlled trials to support this, but there have been reports of calcium stone formation with both potassium citrate and sodium bicarbonate.[12,14] Potassium salts may be contraindicated in patients prone to hyperkalaemia (e.g. renal failure) and sodium salts in situations where sodium load is to be avoided (e.g. cardiac failure).

Pharmaceutical options include potassium citrate tablets (1.08 g per 10 mEq citrate), sodium bicarbonate capsules (840 mg per 10 mEq bicarbonate), potassium citrate mixture (Australian Pharmaceutical Formulary) and a variety of effervescent sodium citrate-bicarbonate preparations. Sodium bicarbonate powder, as available from supermarkets, is a very cost-effective option. One standard (Imperial) teaspoon contains approximately 5 g or 6 mEq of bicarbonate; half to one teaspoonful in orange juice or lemonade is a palatable and cheap alternative to three to six capsules of sodium bicarbonate daily, although there is a risk of overuse resulting in alkalosis.

Because compliance is a major issue, expense convenience and palatability are all important and should result in individualization of therapy.

Xanthine oxidase inhibition

Allopurinol, a xanthine oxidase inhibitor, prevents the degradation of purines through xanthine to uric acid.[16] Since 1964, there have been many reports of prophylaxis of uric acid lithiasis by allopurinol, although none of these were prospective randomized trials.

De Vries *et al.* showed in non-gouty uric acid stone-formers that allopurinol 300–600 mg/day with high fluid intake was effective in preventing uric acid crystals and stones in the urine.[17] Urinary alkalization was not performed hence lowest urine pH recordings were 4.8–5.4. There was no stone recurrence in five of seven patients over periods mainly around 1 year (two discontinuing because of side-effects). A further patient who had many stones while on fluids plus alkalization also became stone-free over a 15-month period.

Blechman *et al.* reported a reduction in frequency of stone passage in three of four stone-formers – the fourth having a history of calcium and urate stones and no fall in plasma urate despite 800 mg daily of allopurinol.[18] They felt this obviated the need for a low-purine diet – 'a form of torture whose need has been disputed'.

Anderson *et al.* reported that of 12 patients with gout and a history of frequent episodes of renal colic and stone passage, none passed any stones after 2 weeks of allopurinol 200–800 mg daily during follow-up periods of 2–28 months.[16]

Gutman and Yu followed a preliminary (1964) report with a follow up of 108 patients with uric acid stones (84 primary gout, 8 neoplastic, 16 with idiopathic hypouricosuria or hyperuricosuria) refractory to conventional measures (diet, fluids, alkali) and reported that renal colic and passage of stones/gravel ceased in all but 10, five with mixed uric acid calculi and infection, and five because of inadequate dosage or cessation due to drug intolerance.[11] The follow-up period was not specified.

Compliance with long-term allopurinol therapy is likely to be better than with oral alkali, because the tablet burden (300–600 mg) in two tablets is far less than with either sodium bicarbonate (840 mg capsules, three to six per day) or potassium citrate (1080 mg tablets, three to six per day).

Low-purine diet

Uric acid is an end-product of the metabolism of endogenous (60%) and exogenous protein and purine nucleotides. Although avoidance of foods rich in nucleoprotein (meat,

liver, kidney, legumes) may reduce urinary urate excretion, and has been factored into older reports regarding prevention of urate stones, it has not been individually subjected to trial. It seems sensible to curb overindulgence associated with high urinary urate excretion.

Acetazolamide

This carbonic anhydrase inhibitor that produces transient urinary alkalization has been suggested as a method of overnight urinary alkalization to supplement daytime use of oral alkali. This has not been subjected to controlled trial or cohort studies.

Metabolic syndrome

Recent attention to the 'metabolic syndrome' has begun to highlight associations between uric acid stones and diabetes or glucose intolerance.[19,20] This has not yet reached the stage where the benefit of screening all urate stone-formers for diabetes/glucose intolerance has been demonstrated, nor to indicate the need for genetic studies in adults with renal stones.

Although in patients with nephrolithiasis of all types, an association has been demonstrated between high body weight and low urinary pH,[21] weight loss has not been studied as a treatment for idiopathic uric acid nephrolithiasis in obese patients.

SUMMARY OF THE EVIDENCE

There are no RCT on this topic.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.
UK Renal Association: No recommendation.
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.

INTERNATIONAL GUIDELINES

No recommendation.

IMPLEMENTATION AND AUDIT

Because of the multiple disciplines involved (primary care physicians, physicians, nephrologists and urologists) there is minimal possibility of implementing or auditing evidence-based uric and stone guidelines, if such guidelines could be produced.

SUGGESTIONS FOR FUTURE RESEARCH

It is unlikely that controlled trials will occur unless an alternative agent to allopurinol is developed, in which case a comparison with allopurinol could be performed.

CONFLICT OF INTEREST

Gavin Becker has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

Characteristics of included studies

Study ID	*n*	Study design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments and results
Increasing urine pH and volume								
Pak *et al.*[12]	18	Prospective	Texas USA	18 patients with uric acid nephrolithiasis (six with uric acid stones and 12 with both uric acid and calcium stones)	30–80 mEq/day potassium citrate		1–5.3 years, mean 2.8 years	Urine pH 5.30 ±0.31 to 6.19 ±0.65 at 4 months, 6.40 ±0.59 at 24 months ($P < 0.05$). Mean stone formation rate fell from 1.20 ±1.68 stones/patient per year to 0.01 ±0.04 stones/patient per year ($P < 0.01$) while on potassium citrate for periods from 1 to 5.33 years (mean 2.78 ±1.34 years)
Rodman[13]	17	Prospective	USA	17 uric acid stone-formers with stones or recurrent gravel/colic	Alternate day administration of oral alkali, commencing with potassium citrate up to 50 mEq/day with sodium bicarbonate		2.5 years (average)	Urinary pH raised to 6–8 once every 2 days, none experienced recurrence
Sharma *et al.*[14]	30		India	30 patients with uric acid stones	Oral sodium bicarbonate to achieve urinary pH 6.5–7.0 0.16 M i.v. lactate or oral sodium bicarbonate with liberal fluid intake and allopurinol			Three had surgical intervention, six passed stones, 18 were free of stones 6–48 months later with continuing oral alkali therapy
Moran *et al.*[15]	11		USA	11 patients referred because of previous failure of oral dissolution of stones	Oral potassium citrate, 1–2 L water, low-sodium-purine diet			Complete stone dissolution in eight patients, lithotripsy in three patients. Continuing treatment resulted in no stone recurrence 6–24 months later in 10/11 patients
Xanthine oxidase inhibition								
De Vries *et al.*[18]	7			Non-gouty uric acid stone-formers	Allopurinol 300–600 g/day with high fluid intake			Effective in preventing uric acid crystals and stones in the urine. No stone recurrence in 5/7 patients over approximately 1 year
Blechman *et al.*[19]	4			Four stone-formers				
Anderson *et al.*[17]	12			12 patients with gout and history of frequent episodes of renal colic and stone passage	200–800 mg allopurinol daily		2–28 months	None passed any stones after 2 weeks of treatment
Gutman and Yu[11]	108	Follow up of preliminary report		108 patients with uric acid stones	Diet, fluids, alkali		Not specified	Renal colic and passage of stones/gravel ceased in all but 10. Five with 'mixed uric acid/calcium and infection', and five because of inadequate dosage or cessation due to drug intolerance