

Uric acid

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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 sources)

- **Treating hyperuricaemia does not retard the progression of renal failure and cannot be recommended for this indication. (Level IV evidence; limited case series; clinically relevant outcomes; consistent effects)**
- **Physicians should be aware that the use of protein-restricted diets in chronic renal patients treated with allopurinol may require further reduction of the dose of allopurinol due to inhibition of urinary excretion of oxypurinol. (Level II evidence; single randomised cross-over study; surrogate outcome; Moderate effect)**

Background

Hyperuricaemia is an almost invariable feature of renal failure (Ifudu et al 1994). Long-standing hyperuricaemia has occasionally been associated with the development of Chronic Kidney Disease (CKD) (Foreman and Yudkoff 1990, Yu and Berger 1975, Coombs et al 1940, Gutman and Yu 1957, Talbott and Terplan 1960, Barlow and Beilin 1968, Duncan and Dixon 1960, Rosenbloom et al 1967, Van Goor et al 1971, Massari et al 1980), although it has been difficult to establish whether the elevated plasma urate levels in these patients reflect a cause, consequence or accelerant of renal dysfunction. The aim of this guideline is to evaluate the available clinical evidence that treatment of hyperuricaemia retards the progression of CKD.

Search strategy

Databases searched: Medline (1999 to November Week 2, 2003). MeSH terms for kidney diseases were combined with MeSH terms and text words for allopurinol and hyperuricaemia. The results were then combined with the Cochrane highly sensitive search strategy for randomised controlled trials and 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 relevant trials not indexed by Medline.

Date of search: 16 December 2003.

What is the evidence?

There are no randomised or prospective controlled trials addressing the effect of treatment of hyperuricaemia on progression of renal failure.

Occasional renal patients with hyperuricaemia and CKD have demonstrated histologic findings of urate crystals in the renal cortical, medullary or papillary interstitium with surrounding giant cell reaction (Talbot and Terplan 1960, Sokoloff 1957, Brown et al 1950). It is uncertain whether this contributes to renal dysfunction, is a consequence of renal injury or is merely an epiphenomenon.

A case-control study by Fessel (1979) demonstrated that azotaemia occurred in only 2 of 113 patients with asymptomatic hyperuricaemia compared with 4 of 193 normouricaemic controls over a mean follow-up period of 8 years. Similarly, long-term follow-up studies of 524 gouty patients failed to demonstrate any adverse effect of hyper-uricaemia on renal function (Berger and Yu 1979).

Therapy directed at lowering plasma urate levels (uricosurics or allopurinol) in patients with familial hyperuricaemia has not been successful in preventing the development of renal insufficiency (Van Goor et al 1971, Massari et al 1980).

Case series reports (Emmerson 1999) have generally not observed an alteration in the rate of progression of renal disease after correction of hyperuricaemia by allopurinol.

In a retrospective case series, Fairbanks et al (2002) examined the effects of allopurinol commencement in 32 patients with familial juvenile hyperuricaemic nephropathy. Twenty-seven patients started immediately on allopurinol (serum creatinine < 0.2 mmol/L) experienced mild deterioration of renal function compared with five patients who commenced allopurinol with a serum creatinine concentration > 0.2 mmol/L, all of whom progressed to end-stage kidney disease (ESKD) with an average period of 6 years. The study's results were significantly limited by the absence of a control group and lead-time bias.

The unproven benefit of allopurinol in preventing renal failure progression in the setting of asymptomatic hyperuricaemia must be balanced against the documented small incidence of serious adverse reactions to allopurinol, including drug hypersensitivity syndromes. For example, a review of allopurinol hypersensitivity reactions by Lupton and Odom (1979) reported that 97% of such reactions occurred in the setting of pre-existing renal failure and that in over 60% of cases, allopurinol was prescribed for the treatment of asymptomatic hyperuricaemia; 10% of the reported patients died from allopurinol hypersensitivity.

The use of protein-restricted diets has been shown in a randomised crossover trial (Berlinger et al 1985) to significantly diminish the excretion of allopurinol and its active metabolite oxypurinol by 28% and 64%, respectively. This results in a 3-fold increase in the half-life of oxypurinol.

Summary of the evidence

There are no randomised or prospective controlled trials addressing the effect of treatment of hyperuricaemia on progression of renal failure. The majority of the small numbers of published case series and anecdotal reports suggest that treatment of hyperuricaemia per se does not appreciably influence renal failure progression.

What do the other guidelines say?

Kidney Diseases Outcome 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

No recommendation.

Suggestions for future research

A multicentre, prospective, randomised controlled trial of allopurinol therapy on the progression of renal failure would help to clarify the issue, although such a study would not be a very high priority. The study would need to be stratified for sex, diabetes and severity of renal dysfunction.

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