Chapter 23: Hyperuricemia and Gout

23.1: We suggest treating hyperuricemia in KTRs when there are complications, such as gout, tophi, or uric acid stones. *(2D)*
- **23.1.1: We suggest colchicine for treating acute gout, with appropriate dose reduction for reduced kidney function and concomitant CNI use. *(2D)***
- **23.1.2: We recommend avoiding allopurinol in patients receiving azathioprine. *(1B)***
- **23.1.3: We suggest avoiding NSAIDs and COX-2 inhibitors whenever possible. *(2D)***

CNI, calcineurin inhibitor; COX-2, cyclo-oxygenase-2; KTRs, kidney transplant recipients; NSAID, nonsteroidal anti-inflammatory drug.

Background

Definitions of hyperuricemia differ widely. Local laboratories often report the upper normal range as a population mean plus two standard deviations (gender-specific), and this performs well in clinical practice (804). An international task force recommends that a level of >0.36 mmol/L (6.0 mg/dL) be defined as hyperuricemia in the general population (804). For each 0.06 mmol/L (1.0 mg/dL) increase above 0.06 mmol/L, the adjusted RR of gout increases by 2.33 (95% CI 2.00–2.71). The threshold of 0.36 mmol/L is associated with 67% sensitivity and 78% specificity for diagnosing gout. A threshold of 0.42 mmol/L (7.0 mg/dL) is associated with a 57% sensitivity and 92% specificity (805). However, because of gender differences, men are less likely to experience gout at level between 0.36 and 0.42 mmol/L (6.0 and 7.0 mg/dL) and a higher level (>0.42 mmol/L [7.0 mg/dL]) is generally used for men (804). Detailed information is not available in KTRs, but the Work Group chose to define hyperuricemia as >0.36 mmol/L (6.0 mg/dL) in women and >0.42 mmol/L (7.0 mg/dL) in men.

Rationale

- Hyperuricemia is very common in KTRs.
- Hyperuricemia increases the incidence of gout and other complications in KTRs, and it may be associated with loss of kidney function and CVD.
- Important drug interactions and precautions will alter treatment strategies in KTRs with gout.

The incidence of hyperuricemia approaches 80% in KTRs (806,807). A recent analysis of 29 597 US Medicare recipients found that the cumulative incidence of gout was 7.6% at 3 years after transplantation (808). This relatively high incidence is consistent with a number of smaller reports (809–812).

The mechanisms responsible for hyperuricemia and gout are complex. Several studies have shown rates to be higher with CNIs, and especially CsA, when compared to azathioprine (806,808,809,811). The incidence of hyperuricemia appears to be similar with CsA and tacrolimus regimens, both being higher compared to regimens without CNIs. For example, in a recent large RCT, uric acid levels were similar between patients treated with low-dose CsA and tacrolimus at the end of 1 year, and significantly higher in comparison to patients on sirolimus and MMF (813). Consistent with these results is a study in which 35 patients were converted from CsA to tacrolimus had no change in uric acid levels (814). However, in another report of patients converted from CNIs to sirolimus, there was a significant reduction in uric acid levels (815). Similarly, in a small (n = 28) RCT of liver transplant recipients, conversion from CNIs to MMF was associated with a 15–20% reduction in uric acid levels (816). Other risk factors associated with hyperuricemia and gout are prior history, higher BMI, diuretics, older age, more recent year of transplantation and hypertension (806–809,812, 817).

Of the clinical manifestations of hyperuricemia, gout is the most common. It can be disabling and is associated with lost time from work. Impressive tophaceous deposits in the hands can occur (806,812). Evidence that hyperuricemia causes or contributes to progressive kidney disease or CVD is weak, even in the general population (804,818,819). Acute kidney injury from very high uric acid levels has been reported (820). A large registry cohort study recently demonstrated an association of gout with elevated mortality (adjusted hazard ratio 1.26, 95% CI 1.08–1.47) and graft loss (adjusted hazard ratio 1.22, 95% CI 1.01–1.49) (808). This association with mortality, though, has not been observed in other studies. There are no RCTs to show that lowering uric acid levels is associated with better graft survival, kidney function or patient survival. There is one small (n = 54) recent RCT in nontransplant patients with kidney impairment, however, in which improved function with uric acid reduction failed to reach statistical significance (821). Case series have not shown a consistent benefit of uric acid reduction on kidney function in CKD (822).

Monitoring patients for hyperuricemia at the time of other routine blood monitoring might help prevent further increases in uric acid levels and greater risks for gout. There is evidence that dietary interventions (losing weight and reduced meat and alcohol consumption) and avoiding diuretics in the general population can lower uric acid levels (804). There are no studies in KTRs. Several medications used in KTRs can lower uric acid levels. For example, in a randomized crossover trial of 26 KTRs, losartan was associated with an 8% fall in uric acid levels (823). The uric acid lowering effect would not be the sole reason for using these medications, but could be substituted if these medications were needed for other indications. Monitoring might also give clinicians an increased level of suspicion for dealing with atypical symptoms of gout. Measuring uric acid levels is indicated in patients with suspected gout; however, during an acute gouty attack, levels may be normal (804). Treatment of asymptomatic hyperuricemia has not been generally recommended in the general population or KTRs, but it is advocated in those with recurrent symptomatic episodes of gout, tophi or radiographic changes of gout (627,804,824).

Treatment of gout is beyond the scope of these guidelines. There are evidence-based reviews on the treatment of hyperurcemia and gout (824). Briefly, oral colchicines and/or nonsteroidal anti-inflammatory agents are recommended as first-line agents for gout (824). Nonsteroidal anti-inflammatory agents and cyclo-oxygenase-2 inhibitors can be associated with significant reductions in kidney function and acute kidney injury (825–827). Patients with normal kidney function may use these agents in moderate doses for short periods of time, but nonsteroidal anti-inflammatory agents should be avoided in KTRs whenever possible (806).

Cochicine levels may be increased in patients with reduced kidney function and in patients treated with CsA (and presumably tacrolimus). Life-threatening colchicine toxicity has been described in patients with reduced kidney function receiving colchicine 1 mg/day for only 5–8 days (828). A disabling myoneuropathy has also been described in patients with reduced kidney function receiving long-term colchicine therapy (829,830). Therefore, prolonged use of colchicine should be avoided in patients with eGFR <60 mL/min/1.73 m^2. However, colchicine can be used at reduced doses for <1 week in patients with eGFR >10 mL/min/1.73 m^2 not requiring dialysis. In patients with eGFR <60 mL/min/1.73 m^2, avoid doses higher than 0.6 mg/day. Intraarticular or short-term systemic steroids have also been used if the above therapies are contraindicated or not tolerated (824).

Allopurinol is a common uric acid lowering agent (804). However, allopurinol and azathioprine used together can result in profound, life-threatening pancytopenia (627,753), and thus this combination should be used with extreme caution, or not at all. If used together, azathioprine should be reduced by at least 50% and frequent complete blood counts should be used to monitor the interaction (806). Further dose reductions may be needed. Mycophenolate does not interact with allopurinol and can be used in place of azathioprine if an antiproliferative agent is necessary for immunosuppression (831). Patients allergic to allopurinol may be given benziodarone (832,833).

The American Society of Transplantation guidelines recommended measuring uric acid levels once 2–3 months after transplantation, with additional screening in patients with reduced function and on diuretics (627). The Caring for Australasians with Renal Impairment guidelines for patients with CKD state that treating hyperuricemia does not retard progression and cannot be recommended; patients on protein-restricted diets treated with allopurinol may require dose reductions (822). The European Best Practice guideline on kidney transplantation recommends that the combination of allopurinol and azathioprine be avoided (708).

Research Recommendations

- A RCT with adequate statistical power is needed to study the effect of treating asymptomatic hyperuricemia on preventing loss of kidney function, gout and CVD.