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Renal Transplant-Associated Hyperuricemia and Gout

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Gout is a common problem among renal transplant patients with a prevalence of 2 to 13%. Hyperuricemia is even more common (1–7). This association is important in two respects. First, gout is a disabling disease, and may cloud the outcome of a patient for whom rehabilitation has been particularly hard fought. Second, the treatment of gout in renal allograft recipients poses more potential pitfalls than in the general population.

This article will explore the metabolic basis of gout in allograft recipients. The currently available methods for treating gout will be examined with particular emphasis on drug interactions and specific needs of the transplant patient.

Pathophysiology of Hyperuricemia and Gout

Gout is a painful disorder caused by an inflammatory reaction to monosodium urate crystals in joint fluid and periarticular tissue. The propensity for developing gout is directly related to tissue uric acid content. Most uric acid in the extracellular fluid is in the form of monosodium urate. A uric acid concentration >7 mg/dl favors the spontaneous crystallization of monosodium urate. The actual probability of gout arising in a joint depends not only on the tissue content of urate, but the pH and temperature of the joint fluid, as well as its macromolecular constituency. However, any condition promoting increased production or reduced excretion of uric acid can predispose to gout.

In primates, the kidneys are the main route for disposal of purine metabolites. Uric acid is freely filtered by the glomerulus. Tubular processing of uric acid is complex. Secretion occurs in the early proximal tubule via an organic acid transporter. At more distal sites in the proximal tubule, reabsorption and further secretion occur. Other organic anions compete with urate for proximal secretion; thus, uric acid levels may rise in patients with lactic acidosis or ketoacidosis.

To the extent that the body's uric acid content rises with reduced excretion, one might surmise that gout is common among patients with chronic renal failure (CRF). In fact, its

prevalence is lower than expected, an observation that may have several explanations. Extrarenal disposal of uric acid is probably enhanced in CRF (8). In addition, the fractional excretion of uric acid rises in remnant nephrons (9–11). The importance of this phenomenon is upheld by the observation that tubulointerstitial renal diseases demonstrate an especially strong tendency toward hyperuricemia (12). Finally, there is evidence that the inflammatory response to monosodium urate crystals may be suppressed by the uremic state (13,14).

Hypertensive nephropathy is associated with high serum uric acid levels. It has been hypothesized that sodium-dependent hypertension and hyperuricemia may be pathogenetically linked, possibly reflecting damage to the peritubular microcirculation causing reduced delivery of uric acid to its tubular secretion sites, or increased ambient generation of lactate to compete for secretion at those sites (12).

Many drugs and toxins influence nephron handling of uric acid. Several of these deserve mention. Lead intoxication may evoke a syndrome of hypertension, progressive renal insufficiency, and hyperuricemia. Both loop and thiazide diuretics reduce uric acid excretion, presumably by causing mild volume depletion with consequent enhancement of proximal tubular reabsorption. Loop agents may also compete with uric acid for secretion by the proximal organic acid transporter.

Uric Acid and the Renal Allograft

Several factors may contribute to the high prevalence of gout among renal transplant recipients (Table 1). Renal allograft recipients are prone to hypertension and edema, and diuretics are commonly used in their management. Renal uric acid excretion may be impaired simply on the basis of poor graft function. When uric acid handling was examined in patients with functioning kidney transplants in the precyclosporine era, no consistent abnormalities in fractional reabsorption or excretion of uric acid emerged. This argues against any specific impairment in uric acid excretion inherent to transplantation itself (15–18). In occasional patients, hypouricemia and hyperuricosuria were reported and were attributed to the uricosuric effect of steroids (19) or to proximal tubular dysfunction (20).

It is clear that the risk of gout attributable to cyclosporine is greater than that of any other factor in renal transplantation. Cyclosporine's adverse effects on renal excretion of uric acid were recognized shortly after the drug came into widespread clinical use. The mechanism by which these effects occur has been the subject of considerable investigation, yielding a vari-

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Table 1. Prevalence of hyperuricemia and gout in renal transplant patients

Source	CsA		Non-CsA	
	↑ Uric Acid	Gout	↑ Uric Acid	Gout
Lin (1)	84	7	30	0
Ahn (2)	51	3.5	19	0
Delaney (3)	82	28	28	8
Gores (5)	80	4.6	55	0
West (6)	NR	9.7	25	0
Kahan (7)	30	2	NR	NR
Ben Hmida (4)	NR	13	NR	0

^a Figures in columns are all percentages. CsA, immunosuppressive regimen based on cyclosporin A, generally in combination with prednisone; Non-CsA, immunosuppressive regimen not containing cyclosporin A, generally comprising azathioprine and prednisone; NR, not reported.

ety of conclusions. Cohen and coworkers noted a reduction in uric acid clearance among their cyclosporine-treated transplant patients. Pyrazinamide-inhibitable uric acid secretion was higher in these patients than in non-cyclosporine-treated patients, suggesting that cyclosporine may potentiate tubular uric acid secretion. However, because fractional uric acid excretion was no different from that of patients not receiving cyclosporine, these investigators concluded that the drug must simultaneously induce an offsetting increase in uric acid reabsorption, and that the observed reduction in uric acid clearance must be attributable to reduced glomerular filtration (21). In a study by Hansen, the anti-uricosuric effect of cyclosporine also appeared to be due to a reduction in the filtered load (22).

The majority of studies have tended to implicate impaired tubular handling of uric acid in the hyperuricemia of adult and pediatric transplant patients receiving cyclosporine (10, 23–27). Marcén and colleagues reported that cyclosporine inhibits probenecid-stimulated tubular secretion (23). In other studies that used clearance techniques, however, uric acid reabsorption was found to be augmented by cyclosporine (24,26). In a study of renal transplant patients receiving cyclosporine, Zawadzki and colleagues found that probenecid-stimulated uric acid secretion was lower in patients with hyperuricemia than in normouricemic patients. These authors found that treatment for 8 d with nifedipine increased maximal stimulated uric acid secretion by 45.7%.

This response, while substantial, was not sufficient to normalize fractional uric acid excretion since the increment in secretion was largely offset by a concomitant increase in post-secretory reabsorption. In this study, it is not clear whether the enhancing effect of nifedipine on tubular secretion of uric acid derived from its ability to reverse cyclosporine-induced renal vasoconstriction or from some other action upon uric acid secretory transport (25). The pathogenesis of hyperuricemia in patients who develop fixed arteriopathic lesions from cyclosporine may have some similarity to that of patients with hypertensive nephropathy. The rarefaction of renal microvas-

culature in both settings could easily impair the delivery of uric acid to its sites of secretion (12).

The impact that cyclosporin A has had in the pathogenesis of gout and hyperuricemia among transplant patients is demonstrated in Table 1, which displays prevalence data from several studies. Most of these data represent observation periods of 5 yr or less. The incidence of gout among non-cyclosporine-treated patients may be higher than reflected in the table. In a recent report from the Cleveland Clinic of transplant patients treated solely with azathioprine and prednisone and followed for more than 20 yr, gout occurred in 23% (28). It is therefore possible that in addition to predisposing patients to gout, cyclosporine may accelerate its appearance.

It is unclear whether additional factors further amplify the risk of hyperuricemia and gout in patients receiving cyclosporine. Diuretics may heighten the risk of gout in patients on cyclosporine (1,23,29,30), but their contribution to that risk has been reported by some groups to be negligible or small (3,5,6). Few investigators have examined the relationship between cyclosporine levels and hyperuricemia or gout. West did not find evidence of such an association (6). Lin found a weak, but statistically significant, correlation between the trough cyclosporine and serum uric acid levels (1). Renal insufficiency, as defined by increased serum creatinine levels, has in most studies correlated with hyperuricemia (1,2,23,30), although serum creatinine levels may be a surrogate for cyclosporine level. Renal allograft recipients may develop their first attack of gout at any time from months to years after transplantation. Because cyclosporine doses and levels diminish with time in most immunosuppressive protocols, the logical inference is that the risk of gout depends more on exposure to cyclosporine *per se* than on its level or dose.

Hyperuricemia and gout have been reported among cardiac allograft recipients treated with cyclosporine (31), as well as among nontransplant patients receiving cyclosporine for autoimmune disease (32). The related calcineurin-inhibiting immunosuppressive agent tacrolimus has also been found to cause hyperuricemia (33).

Clinical Characteristics of Gout in Renal Allograft Recipients

Gout in renal transplant patients behaves similarly to gout in other settings. As noted, the onset of the disease may occur within months of transplantation or after a period of years; it is invariably preceded by a period of hyperuricemia. The inflammatory manifestations of transplant-associated gouty arthritis may be sufficiently pronounced to raise concern regarding the possibility of septic arthritis (34). Patients may have monoarticular or oligoarticular presentations with hot, tender joints. Fever, chills, and leukocytosis are seen in particularly dramatic attacks. The intensely inflammatory nature of gout is appreciable in transplant patients as in the general population. Maintenance immunosuppression neither obviates nor mitigates symptoms in all patients. Although it is possible that a patient's threshold for manifesting clinical gout may be influenced by their immunosuppressive therapy, this remains to be proven.

Gout in allograft recipients, as in other patients, has a predilection for the first metatarsophalangeal joint, as well as wrists, knees, and elbows. There are some interesting qualitative differences, however. Cohen has described proximal distributions of gouty arthritis involving hips, shoulders, and sacroiliac joints (35). Cohen has also reported gouty enthesitis in five of seven patients who subsequently developed arthropathy (36). We have seen numerous patients in our transplant center with extra-articular gout presenting as a tenosynovitis of the dorsum of the foot and ankle.

Tophi may also be more common in the posttransplant setting than elsewhere (Figure 1). Baethge and colleagues reported four cases of tophaceous gout occurring within 5 years or less of renal transplantation (37). Although no literature exists regarding the specific prevalence of tophaceous disease among transplanted patients with gout, we have seen them frequently among our patients, and anecdotal information exchanged with other centers suggests that this experience is fairly typical. In the 1970s, the prevalence of tophaceous gout was reported to be declining in the general population, probably reflecting more effective uric acid-lowering therapy and prophylactic management (38).

The apparent increase in incidence of tophi among transplant recipients probably relates to cyclosporine's potency in promoting uric acid retention. Immunosuppressive therapy may exert a permissive effect in this regard, delaying the manifestation of overt symptoms, and recognition of the need for treatment, until an extremely large uric acid burden has been accrued. These hypotheses are not inconsistent with the relatively later appearance of gout in renal transplant patients not receiving cyclosporine (28).

The presence of tophi can simplify the diagnosis of gout and help clarify the therapeutic approach; tophi pose a clear indication for uric acid-lowering therapy. In other respects, tophi are problematic. They may be disfiguring. Tophi may also compound the discomfort of gout by virtue of their bulk; Peeters and Sennesael reported a patient with low back pain due to spinal cord compression from a large tophus (39). Subcutaneous tophi may erode through the overlying skin and



Figure 1. Digital tophi in a patient with gout. Courtesy of Dr. David F. Giansiracusa.

drain cutaneously. Such lesions can provide a nidus for serious infection and sepsis (P. Kimmel, personal communication).

Therapy of Hyperuricemia and Gout in Renal Transplant Recipients

Treatment of Gouty Arthritis

The approach to treating gout in this patient population parallels that of most patients, albeit with a few precautions. Anti-inflammatory therapy should be initiated as soon as the diagnosis is made. There are several choices. Colchicine is effective for most patients. The dose may be titrated until gastrointestinal side effects occur. A typical starting dose is 0.6 mg every 6 h. At the appearance of diarrhea, abdominal cramping, or nausea, the dose may be reduced to 0.6 mg once or twice a day and continued for the duration of symptoms.

The danger with colchicine resides in its ability to induce myoneuropathy (40–47). A reversible disorder, it may nevertheless be highly disabling. It should be suspected in any colchicine-treated patient developing weakness and an elevated serum creatine kinase level. The diagnosis may be confirmed by muscle biopsy, which reveals a characteristic vacuolated myopathy. Impaired renal function clearly enhances the risk for this complication, which may explain the number of reports occurring in the setting of renal transplantation (40,41,44–47). For this reason, the Cleveland Clinic group has recommended the sparing approach to colchicine use in renal transplant patients outlined in Table 2 (28). Some patients are unable to tolerate even modest exposure to colchicine. One of our renal allograft recipients developed biopsy-proven colchicine myopathy while being treated for gout. This patient improved after cessation of colchicine therapy, but relapsed when challenged with a dose as small as 0.6 mg/d.

Nonsteroidal anti-inflammatory drugs (NSAID) are an effective alternative to colchicine in treating gouty arthritis. These agents can adversely affect renal hemodynamics in susceptible individuals, and may also cause hyperkalemia (48,49). Because these same effects occur in association with cyclosporine, NSAID must be used extremely cautiously in renal transplant patients, particularly those with compromised graft function (50). One of the more “renal sparing NSAID” such as sulindac or a nonacetylated salicylate may be administered, but these are not always effective against a full-blown, established attack of gout. Clinicians using salicylates should be aware of their odd dose-dependent effects on uric acid

Table 2. Protocol for the use of colchicine in the treatment of acute gout in renal transplant recipients^a

Day	Dosage Regimen
1	Colchicine 0.6 mg/h ×2 maximum; stop if diarrhea occurs
2	Colchicine 0.6 mg/h ×2 maximum; stop if diarrhea occurs
3 to 10	Colchicine 0.6 mg/d; stop if diarrhea occurs

^a Modified from reference 28, with permission.

metabolism. At low doses, these agents inhibit urate excretion and may raise plasma urate concentrations. Their effect on uric acid handling is neutral at intermediate-range doses, but large doses may actually be uricosuric (51).

If a more potent NSAID is administered, we recommend monitoring blood chemistry and renal function at least weekly for the duration of therapy. Although their specific risks have not been fully studied, the new cyclooxygenase-2 inhibitors, such as celecoxib, may be less likely to induce deleterious renal side effects than conventional NSAID (52,53). In the future, these agents may prove a safe means for treating gout in transplant patients. They are presently approved only for use in rheumatoid arthritis and osteoarthritis and, for now, their expense is unlikely to be borne by insurers for use in gout.

Corticosteroids constitute yet another therapeutic choice for the management of an acute gouty attack. Most transplant patients are already on small, maintenance regimens of prednisone or methylprednisolone. An acute gouty episode may be treated by increasing the steroid regimen to the equivalent of 0.5 to 1.0 mg/kg per d of prednisone given for 3 to 7 d and then tapered to the maintenance steroid dose within a 14-d period. Adrenocorticotrophic hormone (ACTH), 40 to 80 IU given intramuscularly, is a reasonable alternative to a course of prednisone for patients on low maintenance steroid doses. The injection may be repeated if necessary. Unfortunately, ACTH is subject to variations in availability.

Antihyperuricemic Therapy and Prophylaxis against Gout

Daily small doses of colchicine, generally 0.5 or 0.6 mg/d, are often effective in prophylaxing against recurrent gouty attacks. The use of this agent, even in small doses, is to be avoided in patients with a previous history of colchicine-induced myoneuropathy.

Antihyperuricemic therapy represents another approach to preventing gout. In a typical patient population, this may be accomplished in either of two ways: increasing uric acid excretion through the use of uricosuric agents, or attenuating the production of uric acid with allopurinol. The drug reduces the metabolism of purines to uric acid by inhibiting the activity of the enzyme xanthine oxidase. This action of allopurinol also enables it to retard the breakdown of the purine antimetabolite azathioprine, which remains in widespread use among transplant patients for antirejection chemoprophylaxis. Extreme care should therefore be exercised when introducing allopurinol to the regimen of a patient receiving azathioprine (52). If excessive myelosuppression is to be avoided, the azathioprine dose should be lowered to 25 to 50% of the usual amount, and blood cell counts should be followed closely. Renal insufficiency predisposes to severe allopurinol toxicity, by permitting retention of the metabolite oxipurinol (54,55). Therefore, the starting dose of allopurinol should also be reduced in the transplant setting (100 to 200 mg/d) (28). Mycophenolate mofetil has replaced azathioprine for chemoprophylaxis of rejection in many protocols. The pharmacologic benefit of this agent also resides in its ability to alter purine metabolism. It is much more selective in this regard than allopurinol, inhibiting

only the *de novo* path of purine synthesis. For this reason, plus the absence of an effect of allopurinol on mycophenolate metabolism, these two drugs are easier to use safely in combination than are allopurinol and azathioprine (56).

Allopurinol is generally more effective than uricosuric therapy because its antihyperuricemic effect is independent of renal function. Patients allergic to allopurinol, or in whom the drug has proven difficult to use safely, may be given uricosuric agents, recognizing that such agents may fail to promote the desired uricosuric response. Uricosurics are unlikely to be effective in patients with significant graft dysfunction, *i.e.*, creatinine clearance <30 ml/min. Furthermore, as already noted, probenecid may be ineffective in stimulating uric acid secretion in the presence of cyclosporine. Occasionally, the opposite condition may prove true. In rare cyclosporine-treated transplant patients, excessive uric acid excretion has been reported to cause uric acid lithiasis (57–59) and even acute uric acid nephropathy (60). Uric acid excretion should be measured periodically in transplant patients receiving drugs such as probenecid, and they should be monitored sonographically at regular intervals for urinary calculi. In hyperuricosuric patients (24-h uric acid excretion >750 mg) or those with a history of uric acid calculi, a prudently high fluid intake should be recommended, and consideration should be given to alkalization of the urine with acetazolamide or sodium bicarbonate.

Cyclosporine withdrawal may be considered for transplant patients with recurrent, severe gout that cannot be managed safely or effectively through any of the above means. Hyperuricemia due to cyclosporine generally reverses upon discontinuation of the drug (61–65). The risks and utility of this maneuver obviously warrant careful consideration by both patient and transplant clinician. Substitution of tacrolimus would probably offer no advantage, because it, too, can cause hyperuricemia (33).

Conclusion

Hyperuricemia and gout are common problems among renal transplant recipients. Their prevalence is clearly attributable to cyclosporine use, although individual patients may have other risk factors as well. Cyclosporine lowers urinary clearance of uric acid; the specific mechanism for this is unknown, but may involve alterations in tubular transport. The therapy, both preventive and remedial, of gout may be particularly challenging in these patients. Barring specific contraindications, patients with an established history of hyperuricemia or gout at the time of transplantation should probably be on uric acid-lowering therapy at the same time cyclosporine treatment is initiated.

References

1. Lin H-Y, Rocher LL, McQuillan MA, Schmaltz S, Palella TD, Fox IH: Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 321: 287–292, 1989
2. Ahn KJ, Kim YS, Lee HC, Park K, Huh KB: Cyclosporine-induced hyperuricemia after renal transplant: Clinical characteristics and mechanisms. *Transplant Proc* 24: 1391–1392, 1992
3. Delaney V, Sumrani N, Daskalakis P, Hong JH, Sommer BG:

- Hyperuricemia and gout in renal allograft recipients. *Transplant Proc* 24: 1773–1774, 1992
4. Ben Hmida M, Hachicha J, Bahloul Z, Kaddour N, Kharrat M, Jarraya F, Jarraya A: Cyclosporine-induced hyperuricemia and gout in renal transplants. *Transplant Proc* 27: 2722–2724, 1995
 5. Gores PF, Fryd DS, Sutherland DE, Najarian JS, Simmons RL: Hyperuricemia after renal transplantation. *Am J Surg* 156: 397–400, 1988
 6. West C, Carpenter BJ, Hakala TR: The incidence of gout in renal transplant recipients. *Am J Kidney Dis* 10: 369–372, 1987
 7. Kahan BD, Flechner SM, Lorber MI, Golden D, Conley S, Van Buren CT: Complications of cyclosporine-prednisone immunosuppression in 402 renal allograft recipients exclusively followed at a single center for from one to five years. *Transplantation* 43: 197–204, 1987
 8. Sorensen LB, Levinson DJ: Origin and extrarenal elimination of uric acid in man. *Nephron* 14: 7–20, 1975
 9. Garyfallos A, Magoula I, Tsapas G: Evaluation of the renal mechanisms for urate homeostasis in uremic patients by probenecid and pyrazinamide test. *Nephron* 46: 273–280, 1987
 10. Steidel K, Brandis M, Kramer M, Leititis JU, Zimmerhackl LB: Cyclosporine inhibits renal uric acid transport in renal transplants not in children treated for nephrotic syndrome. *Ren Failure* 12: 193–198, 1990
 11. Steele TH, Rieselbach RE: The contribution of residual nephrons within the chronically diseased kidney to urate homeostasis in man. *Am J Med* 43: 876–886, 1967
 12. Johnson RJ, Kivlighn SD, Kim Y-G, Suga S, Fogo AB: Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. *Am J Kidney Dis* 33: 225–234, 1999
 13. Ifudu O, Tan CC, Dulin AL, Delano BG, Friedman EA: Gouty arthritis in end-stage renal disease: Clinical course and rarity of new cases. *Am J Kidney Dis* 23: 347–351, 1994
 14. Buchanan WW, Klinenberg JR, Seegmiller JE: The inflammatory response to injected microcrystalline monosodium urate in normal, hyperuricemic, gouty and uremic subjects. *Arthritis Rheum* 8: 361–367, 1995
 15. Better OS: Tubular dysfunction following kidney transplantation. *Nephron* 25: 209–213, 1980
 16. Better OS, Chaimowitz C, Naveh Y, Stein A, Nahir AM, Barzilai A, Erlik D: Syndrome of incomplete renal tubular acidosis after cadaver kidney transplantation. *Ann Intern Med* 71: 39–46, 1969
 17. Vaziri ND, Nellans RE, Brueggemann RM, Barton CH, Martin DC: Renal tubular dysfunction in transplanted kidneys. *South Med J* 72: 530–534, 1979
 18. Györy AZ, Stewart JH, George CRP, Tiller DJ, Edwards KDG: Renal tubular acidosis, acidosis due to hyperkalemia, hypercalcemia, disordered citrate metabolism and other tubular dysfunctions following human renal transplantation. *Q J Med* 38: 231–254, 1969
 19. Schmidt P, Zazgornik J, Kopsa H: Hypouricemia after renal transplantation. *N Engl J Med* 289: 1373, 1973
 20. Vertuno LL, Preuss HG, Argy WP Jr, Schreiner GE: Fanconi syndrome following homotransplantation. *Arch Intern Med* 133: 302–305, 1974
 21. Cohen SL, Boner G, Rosenfeld JB, Shmueli D: The mechanism of hyperuricemia in cyclosporine-treated renal transplant recipients. *Transplant Proc* 29: 1829–1830, 1987
 22. Hansen JM, Fogh-Andersen N, Leyssac PP, Strandgaard S: Glomerular and tubular function in renal transplant patients treated with and without cyclosporin A. *Nephron* 80: 450–457, 1998
 23. Marcén R, Gallego N, Orofino L, Gamez C, Estepa MR, Teruel JL, Ortuño J: Impairment of tubular secretion of urate in renal transplant patients on cyclosporine. *Nephron* 70: 307–313, 1995
 24. Hoyer PF, Lee IJ, Oemar BS, Krohn HP, Offner G, Brodehl J: Renal handling of uric acid under cyclosporin A treatment. *Pediatr Nephrol* 2: 18–21, 1988
 25. Zawadzki J, Grenda R, Januszewicz P: Effect of nifedipine on tubular handling of uric acid in transplanted kidney on cyclosporine A treatment. *Nephron* 70: 77–82, 1995
 26. Laine J, Holmberg C: Tubular effects of cyclosporine in pediatric renal transplant recipients. *Transplant Proc* 28: 2104–2106, 1996
 27. Laine J, Holmberg C: Mechanisms of hyperuricemia in cyclosporine-treated renal transplanted children. *Nephron* 74: 318–323, 1996
 28. Braun WE, Richmond BJ, Protiva DA, Gifford WA, Straffon RA: The incidence and management of osteoporosis, gout, and avascular necrosis in recipients of renal allografts functioning more than 20 years treated with prednisone and azathioprine. *Transplant Proc* 31: 1366–1369, 1999
 29. Edvardsson VO, Kaiser BA, Polinsky MJ, Palmer J, Quien R, Baluarte HJ: Natural history and etiology of hyperuricemia following pediatric renal transplantation. *Pediatr Nephrol* 9: 57–60, 1995
 30. Noordzij TC, Leunissen KML, Van Hooff J: Renal handling of urate and the incidence of gouty arthritis during cyclosporine and diuretic use. *Transplantation* 52: 64–67, 1991
 31. Kahl L, Thompson ME, Griffith BP: Gout in the heart transplant recipient: Physiologic puzzle and therapeutic challenge. *Am J Med* 87: 289–294, 1989
 32. Palestine AG, Nussenblatt RS, Chan CC: Side effects of systemic cyclosporine in patients not undergoing transplantation. *Am J Med* 77: 652–656, 1984
 33. Ochiai T, Ishibashi M, Fukao K, Takahashi K, Endo T: Japanese multicenter studies of FK 506 in renal transplantation. *Transplant Proc* 27: 50–52, 1995
 34. Daniels ID, Friedman EA: Missed diagnosis of acute arthritic gout in kidney transplant recipients. *NY State J Med* 93: 55–57, 1993
 35. Cohen MR: Proximal gout following renal transplantation [Abstract]. *Arthritis Rheum* 37: 1709, 1994
 36. Cohen MR: Entesopathy and atypical gouty arthritis following renal transplantation: A case control study. *Rev Rhum Engl Ed* 62: 86–90, 1995
 37. Baethge BA, Work J, Landreneau MD, McDonald JC: Tophaceous gout in patients with renal transplants treated with cyclosporine-A. *J Rheumatol* 20: 718–720, 1993
 38. O'Duffy JD, Hunder GG, Kelly PJ: Decreasing prevalence of tophaceous gout. *Mayo Clin Proc* 50: 227–228, 1975
 39. Peeters P, Sennesael J: Low-back pain caused by spinal tophus: A complication of gout in a kidney transplant recipient. *Nephrol Dial Transplant* 13: 3245–3247, 1998
 40. Jagose JT, Bailey RR: Muscle weakness due to colchicine in a renal transplant recipient. *N Med J* 110: 343, 1997
 41. Lee BI, Shin SJ, Yoon SN: Acute myopathy induced by colchicine in a cyclosporine-treated renal transplant recipient: A case report and review of the literature. *J Korean Med Sci* 12: 160–161, 1997
 42. Tapal MF: Colchicine myopathy. *Scand J Rheum* 25: 105–106, 1996
 43. Kuncel RW, Duncan G, Watson D, Alderson K: Colchicine myopathy and neuropathy. *N Engl J Med* 316: 1562–1568, 1987

44. Rieger EH, Halasz NA, Wahlstrom HE: Colchicine neuromyopathy after renal transplantation. *Transplantation* 49: 1196–1198, 1990
45. Johnsson J, Gekpi JR, Light JA: Colchicine-induced myoneuropathy in a renal transplant patient. *Transplantation* 53: 1369–1371, 1992
46. Cook M, Ramos E, Peterson J, Croker B: Colchicine neuromyopathy in a renal transplant patient with normal muscle enzyme levels. *Clin Nephrol* 42: 67–68, 1994
47. Rumpf KW, Henning HV: Is myopathy in renal transplant patients induced by cyclosporin or colchicine? *Lancet* 335: 800–801, 1990
48. Clive DM, Stoff JS: Renal syndromes associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 310: 563–572, 1984
49. Palmer BF: Renal complications associated with use of nonsteroidal anti-inflammatory agents. *J Invest Med* 43: 516–533, 1995
50. Harris KP, Jenkins D, Walls J: Non-steroidal anti-inflammatory drugs and cyclosporine: A potentially serious adverse interaction. *Transplantation* 46: 598–599, 1988
51. Flower RJ, Moncada S, Vane JR: Analgesic-antipyretics and anti-inflammatory agents: Drugs employed in the treatment of gout. In: *The Pharmacologic Basis of Therapeutics*, 7th Ed., edited by Gilman AG, Goodman LS, Rall TW, Murad F, New York, Macmillan, 1985, pp 674–715
52. Kömhoff M, Gröne H-J, Klein T, Seyberth HW, Nüsing RM: Localization of cyclooxygenase-1 and -2 in adult and fetal human kidney: Implications for renal function. *Am J Physiol* 272: F460–F468, 1997
53. Schneider A, Stahl RAK: Cyclooxygenase-2 (COX-2) and the kidney: Current status and potential perspectives. *Nephrol Dial Transplant* 13: 10–12, 1998
54. Venkat Raman G, Sharman VL, Lee HA: Azathioprine and allopurinol: A potentially dangerous combination. *J Intern Med* 228: 69–71, 1990
55. Wilson JD, Simmonds HA, North JD: Allopurinol in the treatment of uraemic patients with gout. *Ann Rheum Dis* 26: 136–142, 1967
56. Jacobs F, Mamzer-Bruneel MF, Skhiri H, Thervet E, Legendre C, Kreis H: Safety of the mycophenolate mofetil-allopurinol combination in kidney transplant recipients with gout. *Transplantation* 64: 1087–1088, 1997
57. Norlén BJ, Hellstrom M, Nisa M, Robertson WG: Uric acid stone formation in a patient after kidney transplantation: Metabolic and therapeutic considerations. *Scand J Urol Nephrol* 29: 335–337, 1995
58. Cantarell MC, Capdevila L, Morlans M, Piera L: Uric acid calculus in renal transplant patients treated with cyclosporine. *Clin Nephrol* 35: 288, 1991
59. Hayes JM, Strem SB, Graneto D, Steinmuller DR, Novick AC: Urolithiasis after renal transplantation. *Transplant Proc* 21: 1960–1961, 1989
60. Venkatesh VS, Feingold R, Dikman S, Churg J: Acute hyperuricemic nephropathy and renal failure after transplantation. *Nephron* 56: 317–321, 1990
61. Leunissen KML, Bosman F, van Hoof JP: Cyclosporin metabolites and nephrotoxicity. *Lancet* 1: 702, 1985
62. Chapman JR, Harding NGL, Griffith D: Reversibility of cyclosporin nephrotoxicity after three months' treatment. *Lancet* 1: 128, 1985
63. Versluis DJ, Wenting GJ, Jeekel J, Weimar W: The influence of cyclosporine A on proximal tubular function in renal allografts. *Transplant Proc* 20[Suppl 3]: 686–690, 1988
64. Hollander AAMJ, van Saase JLCM, Kootte AMM, van Dorp WJ, van Bockel HJ: Beneficial effects of conversion from cyclosporin to azathioprine after kidney transplantation. *Lancet* 345: 610–614, 1995
65. Hilbrands LB, Hoitsma AG, Wetzels JF, Koene RA: Detailed study of changes in renal function after conversion from cyclosporine to azathioprine. *Clin Nephrol* 45: 230–235, 1996