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Managing Gout in the Post-Transplant Setting: The Role of Calcineurin Inhibitors in Hyperuricemia and Treatment Complexity

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Abstract

Introduction: Gout is the most prevalent inflammatory arthritis globally, marked by the deposition of monosodium urate (MSU) crystals due to persistently high serum uric acid levels [1]. This article reviews the burden and management of gout in solid organ transplant (SOT) recipients, a high-risk population facing up to a 12-fold increased risk of gout compared to the public [6].

Methods: A comprehensive review was conducted focusing on the pathophysiology, diagnostic challenges, and treatment strategies for gout in the post-transplant setting.

Results: The pathogenesis is multifactorial, driven primarily by the nephrotoxicity of calcineurin inhibitors (CNIs) like cyclosporine, which impairs glomerular filtration rate (GFR) and tubular urate excretion [8,13]. Diagnosis is complicated by the need to differentiate gout from septic arthritis, often requiring urgent synovial fluid analysis [23,27]. Management must balance immunosuppression maintenance with Urate-Lowering Therapy (ULT). Corticosteroids and low-dose colchicine are used for acute flares. Allopurinol is the first-line ULT, requiring careful dose adjustment and monitoring for drug interactions (e.g., with azathioprine). Febuxostat and pegloticase serve as alternatives for refractory cases. Adjusting the immunosuppressive regimen (e.g., using mTOR inhibitors) and continuous monitoring of serum uric acid (SUA) are vital for prevention and graft preservation [42]. Conclusion: Gout in SOT recipients is a major clinical issue requiring a precise, multidisciplinary approach to prevent severe morbidity and preserve graft function.

Keywords: Gout; Transplantation; Hyperuricemia; Monosodium Urate; Magnetic Resonance Imaging

Abbreviations: SOT: Solid Organ Transplant; MSU: Monosodium Urate; SUA: Serum Uric Acid; CNI: Calcineurin Inhibitor; GFR: Glomerular Filtration Rate; ULT: Urate-Lowering Therapy; mTOR: Mammalian Target of Rapamycin; DECT: Dual-Energy Computed Tomography; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; BMI: Body Mass Index; MRI: Magnetic Resonance Imaging; eGFR: Estimated Glomerular Filtration Rate

Introduction

The most prevalent type of inflammatory arthritis worldwide, gout is characterized by the accumulation of monosodium urate crystals in and around joints due to persistently high blood sugar levels [1]. According to Kuo et al. & Liu et al. [1], prevalence rates in the general population vary from less than 1% to 6.8%,

depending on geographic region and demographic parameters. This condition has become much more prevalent worldwide in recent decades [1,2]. In the United States alone, gout affects approximately 3.9% of the population, and prevalence estimates vary significantly depending on the study population and methodological techniques employed [3,4]. Men are affected by the illness at rates three to ten times higher than women, and its frequency rises with age, reaching 11–13% in people over 80 [1]. Recent epidemiological estimates suggest that between 2020 and 2050, the number of people with gout would rise by over 70%, mainly due to population aging, rising obesity rates, and an increase in the frequency of metabolic comorbidities [5].

This increasing burden emphasizes how crucial it is to comprehend how to manage gout in susceptible groups, especially those who have other risk factors that make treatment more difficult and worsen the course of the disease. Compared to the normal population, post-transplant patients have a significantly increased risk of hyperuricemia and the ensuing gout. Recipients of solid organ transplants, especially those who have received liver, heart, or kidney transplants, are at a notably higher risk of developing issues associated with uric acid. According to studies, gout affects about 25% of kidney transplant recipients at some point during their recovery, which is 12 times more common than in the general population that does not have a transplant. Up to 80% of kidney transplant recipients experience hyperuricemia after the procedure; 15% of these patients present with gout before the procedure, and 10% acquire new-onset gout an average of 1.8 years after the donation [6].

Gout prevalence varies by organ type; patients of heart transplants had higher rates than recipients of lung transplants, which is probably due to variations in underlying comorbidities and treatment needs. In these susceptible groups, serum uric acid levels above 7.0 mg/dL for males and 6.0 mg/dL for women are considered post-transplant hyperuricemia. Several transplant-specific factors, such as decreased estimated glomerular filtration rate, pre-transplant hyperuricemia, hypercalcemia, use of concurrent medications like diuretics, impaired renal function, and prolonged pre-transplant dialysis duration, cause this increased vulnerability. As a clinically relevant complication linked to increased morbidity, progression to chronic tophaceous disease, and possibly detrimental effects on graft function and patient survival, gout in transplant recipients is more than just a quality-of-life issue [7].

Pathophysiology of Gout in the Post-Transplant Setting

Uric acid metabolism and excretion are tightly regulated by renal physiology. Uric acid is the end-product of purine metabolism, and its serum concentration is determined by the balance between production and renal excretion. In healthy individuals, uric acid is freely filtered at the glomerulus, with subsequent reabsorption and secretion in the proximal tubule mediated by specific transporters such as URAT1, OAT4, and GLUT9. The kidney is responsible for most of the urate excretion, and declining glomerular filtration rate (GFR) post-transplant impairs uric acid clearance, leading to hyperuricemia. This relationship is directly proportional as GFR decreases, serum uric acid rises, and transplant recipients with reduced allograft function are at increased risk for gout [8-10,12,13,18-19].

Calcineurin inhibitors (CNIs), particularly cyclosporine, are a major contributor to post-transplant hyperuricemia. Cyclosporine and tacrolimus both elevate serum uric acid, but cyclosporine is associated with a higher risk and greater severity of gout [8-11,13,14,17]. The mechanisms include CNI-induced nephrotoxicity, which reduces GFR and impairs tubular secretion of uric acid. Cyclosporine may also cause irreversible tubular damage, further decreasing urate clearance [15,16]. Volume depletion secondary to nephrotoxicity exacerbates proximal tubular reabsorption of uric acid. While both CNIs increase uric acid, studies show that switching from cyclosporine to tacrolimus does not significantly lower uric acid levels, indicating similar effects on urate handling. However, cyclosporine may have a more pronounced impact [9,13,17]. In contrast, regimens without CNIs (e.g., sirolimus or mycophenolate mofetil) are associated with lower uric acid levels [9,10].

Interaction with other risk factors further complicates gout management in the post-transplant setting. Diuretic therapy, commonly used for hypertension, increases the risk of gout by promoting extracellular volume contraction and enhancing proximal tubular urate reabsorption [8-10,18-22]. Additional risk factors include older age, male sex, higher BMI, hypertension, and metabolic syndrome, all of which are prevalent in transplant recipients and independently associated with hyperuricemia [9,10,13,14]. Allograft rejection and ischemia-reperfusion injury also contribute to renal inflammation and dysfunction, amplifying the risk of hyperuricemia and subsequent gout [22]. The cumulative effect of these factors underscores the complexity of gout pathophysiology in the post-transplant population and the need for individualized management strategies.

Clinical Manifestations and Epidemiology

Gout and asymptomatic hyperuricemia are frequent complications in solid organ transplant recipients, with prevalence rates of hyperuricemia ranging from 5% to 84% and gout from 1.7% to 28% depending on organ type and immunosuppressive regimen. Kidney and heart transplant recipients are at highest risk, while liver transplant recipients have lower but still significant rates. The incidence of new-onset gout in kidney transplant recipients is approximately 7.6% at three years post-transplant, and hyperuricemia may affect up to 80% of this population. Key risk factors include baseline renal dysfunction, cyclosporine use, diuretic therapy, higher body mass index, older age, male sex, hypertension, and metabolic syndrome

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[15,9,16,8,12]. Cyclosporine is a particularly strong risk factor, with studies showing a higher incidence of gout compared to tacrolimus or azathioprine-based regimens. Diuretic use further increases risk by promoting urate retention [9,15-19].

The clinical presentation of gout in immunosuppressed transplant recipients is like that in the general population but may be more severe and progress rapidly to chronic tophaceous gout. Acute gout flares typically present as sudden onset monoarthritis, most often affecting the first metatarsophalangeal joint, but polyarticular involvement and tophus formation are more common in this population, sometimes within months of onset. Chronic tophaceous gout may develop earlier and be more extensive, with tophi affecting joints and soft tissues. Diagnostic challenges arise due to overlapping symptoms with infection (e.g., septic arthritis, cellulitis) and drug-induced arthropathy, as both can present with fever, leukocytosis, and joint inflammation. The coexistence of gout and infection is possible, and distinguishing between these entities is critical, often requiring synovial fluid analysis [10,20,23].

Laboratory and imaging findings play a central role in diagnosis. Serum uric acid monitoring is essential, but levels may be normal during acute flares and should be rechecked after resolution. The gold standard for diagnosis remains identification of monosodium urate crystals in synovial fluid or tophi by polarizing microscopy. Imaging modalities such as ultrasound and dual-energy CT (DECT) are increasingly used to detect urate deposits, with ultrasound findings including the double contour sign and snowstorm appearance, and DECT providing high sensitivity for crystal detection [10,20]. Conventional radiography is less sensitive to early diseases but may reveal joint erosions in advanced cases. In summary, the epidemiology and clinical manifestations of gout in post-transplant patients are shaped by immunosuppressive regimens and comorbidities, necessitating a high index of suspicion and multimodal diagnostic approach for optimal management [15,24].

Diagnostic Considerations

Differentiating a gout flare from septic arthritis in post-transplant patients represents a significant diagnostic challenge. Both conditions may present with acute monoarthritis, erythema, and elevated inflammatory markers. However, in individuals receiving immunosuppressive therapy, classic systemic signs such as fever or leukocytosis may be attenuated or absent, which can delay recognition of infection [25,26]. The identification of monosodium urate crystals in synovial fluid supports the diagnosis of gout but does not exclude concomitant infection, as both entities may occur simultaneously [27]. Therefore, arthrocentesis with synovial fluid analysis remains essential for establishing an accurate diagnosis. The evaluation should include total and differential cell counts, Gram stain, and culture [28-31]. It is also important to recognize that traditional inflammatory thresholds may be unreliable in transplant recipients [25].

Immunosuppressive medications, particularly corticosteroids and calcineurin inhibitors such as cyclosporine and tacrolimus, can further complicate the diagnostic process by masking infection and promoting hyperuricemia [25]. These overlapping effects highlight the need for a comprehensive clinical assessment that integrates laboratory findings with patient history and medication exposure. Imaging modalities such as ultrasound or magnetic resonance imaging (MRI) can be useful when aspiration is not immediately feasible, though synovial fluid analysis remains the diagnostic gold standard [28-30]. Emerging biomarkers including pentraxin-3, interleukin-6, and presepsin have shown potential to enhance diagnostic precision, especially in patients with atypical presentations [32]. Ultimately, accurate diagnosis depends on maintaining a high index of suspicion for infection and correlating clinical, laboratory, and microbiological findings. Early distinction between these entities is crucial to ensure appropriate management and prevent irreversible joint or systemic complications [26,28].

Management Strategies

General Principles

Management of gout in post-transplant patients involves balancing inflammation control, uric acid reduction, and graft preservation [33]. Hyperuricemia is common in transplant recipients, particularly those on calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus, which impair renal urate excretion and contribute to gout flares [33]. Duan et al. opined that "Calcineurin is expressed in the kidney and regulates renal Na+ and K+ transport" [34]. The authors elaborated that, in the thick ascending limb of the kidney, calcineurin inhibition by CNIs enhances NKCC2 dephosphorylation, and an intracellular sorting receptor, sorting-related receptor with A-type repeats (SORLA), modifies calcineurin's potency on NKCC2 [34]. Also, CNIs are attributed with increasing tubular reabsorption of uric acid, exacerbating hyperuricemia [34]. Hence, CNIs cause hypertension, compromise renal K^+ excretion, and induce hyperkalemia [34], and treatment modalities must be tailored towards minimizing nephrotoxicity while maintaining immunosuppressive efficacy.

Acute Gout Treatment

NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are traditionally used for acute gout but pose significant risks in transplant recipients due to nephrotoxicity. Their use is generally limited or avoided to prevent further renal compromise and protect graft function [35].

Colchicine

Drug interactions with CNIs, particularly cyclosporine, can elevate colchicine levels due to P-glycoprotein inhibition,

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increasing the risk of toxicity [34]. Colchicine also reduces the activation of the NLRP3 inflammasome and the generation of IL-1β [36]. Utilizing low-dose regimens and close monitoring are precautions to mitigate adverse effects [34].

Corticosteroids

According to studies, corticosteroids are very effective in the treatment of gout and are an accepted treatment for acute gout in transplant patients due to their potent anti-inflammatory effects and minimal nephrotoxicity [33,34]. Again, short-term use of prednisone or methylprednisolone can effectively manage flares without compromising graft function [33]. However, long-term use should be avoided due to risks of metabolic complications and immunosuppression.

IL-1 Inhibitors

The interleukin-1 (IL-1) inhibitors are emerging as practical alternatives for refractory gout in transplant recipients, including anakinra. IL-1 targets the inflammatory cascade without significant renal toxicity and is effective in patients with low tolerance to colchicine or corticosteroids [24]. Although long-term data are limited, IL-1 blockade may offer a safer therapeutic option in complex cases [24].

Long-Term Uric Acid–Lowering Therapy

Long-term management of gout in post-transplant patients aims to maintain serum uric acid below 6 mg/dL to prevent flares and tophus formation [10,20,37,39]. Allopurinol remains the first-line urate-lowering agent and is recommended for most patients, including those with moderate-to-severe chronic kidney disease, provided dosing is started low (≤100 mg daily, or lower in advanced CKD) and titrated gradually. However, allopurinol must not be co-administered with azathioprine due to the risk of severe bone marrow suppression; substitution of mycophenolate mofetil for azathioprine is preferred if allopurinol is required [10,39].

HLA-B5801 testing should be considered in patients of Southeast Asian or African American descent to mitigate hypersensitivity risk [8,15,10,14,38]. Febuxostat is an alternative xanthine oxidase inhibitor for patient's intolerant to allopurinol or with contraindications, but its use is limited by an FDA black box warning for increased cardiovascular and all-cause mortality in patients with established cardiovascular disease. Febuxostat should be reserved for those who cannot tolerate or do not respond to allopurinol, with close cardiovascular monitoring. Both allopurinol and febuxostat should be avoided in combination with azathioprine or mercaptopurine [10,39].

For patients with severe or refractory gout-such as those with persistent tophi or frequent flares despite maximally tolerated oral therapy-pegloticase (an intravenous uricase) may be considered. Pegloticase is not recommended as first-line therapy due to high cost and risk of infusion reactions, but it can be effective in those failing conventional agents [14,20,37,39,40]. Durability of pegloticase may be improved by coadministration of immunosuppressants such as methotrexate or mycophenolate mofetil. Uricosuric agents are generally less effective in transplant recipients with renal impairment, though benzbromarone may be considered in select cases outside the United States [10,15,37].

Adjustment of Immunosuppressive Regimen

Immunosuppressive regimen modification is a key strategy for managing post-transplant hyperuricemia and gout. Cyclosporine is strongly associated with increased uric acid levels and gout risk, primarily due to its nephrotoxic effects and impaired tubular urate secretion. Switching from cyclosporine to tacrolimus or to mammalian target of rapamycin (mTOR) inhibitors such as sirolimus or everolimus may be considered to improve hyperuricemia. However, evidence suggests that tacrolimus does not consistently lower uric acid compared to cyclosporine, and both agents may increase uric acid over time. mTOR inhibitors may offer metabolic advantages, but their use must be balanced against the risk of acute rejection and other adverse effects [14,20,15,17,9,11].

Adjustment of immunosuppression should be individualized, weighing the risk of graft rejection against the potential for improved metabolic outcomes. Avoidance of diuretics and optimization of antihypertensive therapy (e.g., use of losartan or amlodipine) may further help control uric acid levels. Close monitoring of graft function and serum uric acid is essential during any regimen change [9,11,15]. In summary, successful long-term management of gout in post-transplant patients requires a combination of urate-lowering therapy, careful drug interaction monitoring, and judicious adjustment of immunosuppressive regimens, always prioritizing graft preservation and patient safety [11,14].

Prevention and Monitoring

Effective prevention and vigilant monitoring are essential components in reducing the burden of gout and hyperuricemia among post-transplant recipients. The pathogenesis of post-transplant gout is inherently multifactorial shaped by calcineurin inhibitor induced renal vasoconstriction, impaired urate excretion, and overlapping metabolic disturbances requiring a proactive, structured approach to patient management [41]. Routine monitoring of serum uric acid levels should be embedded in post-transplant follow-up protocols. Early detection of rising urate levels provides an opportunity for timely intervention before the development of acute flares or irreversible joint and renal injury. Current evidence supports obtaining baseline uric acid measurement at discharge and reassessing at regular intervals every 1 to 3 months during the first post-transplant year, and thereafter in parallel with routine renal function testing or following modifications in immunosuppressive or diuretic

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therapy [42,43]. This continuous surveillance allows clinicians to identify subtle metabolic trends and adjust treatment before clinical manifestations emerge.

Lifestyle modification remains a cornerstone of gout prevention and should be viewed as an integral part of long-term transplant care. Adequate hydration facilitates urate clearance and counteracts the nephrotoxic impact of calcineurin inhibitors. Nutritional counseling focusing on reduced consumption of purine-rich foods (such as organ meats and certain seafoods) and moderation of alcohol intake particularly beer and spirits has consistently been associated with lower serum uric acid concentrations [44]. Maintaining appropriate body weight, reducing the intake of fructose-sweetened beverages, and promoting regular physical activity can further decrease urate levels and reduce the frequency of gout flares [45]. While lifestyle interventions alone are rarely sufficient to normalize uric acid in transplant recipients, they represent a safe, patient-centered, and sustainable adjunct to pharmacologic therapy. Regular reinforcement of these behaviors through multidisciplinary education sessions can significantly enhance adherence and long-term outcomes.

Equally important is the periodic assessment of renal function and a systematic review of ongoing medications. Calcineurin inhibitors such as cyclosporine and tacrolimus impair urate excretion through their effects on tubular handling, while concomitant administration of diuretics or renin–angiotensin system blockers can exacerbate this imbalance [46]. Therefore, individualized review of immunosuppressive regimens and concurrent therapies should be routine in post-transplant care. When clinically feasible, dose adjustments or substitution with less urate-retentive agents may mitigate hyperuricemia risk.

Monitoring should also include serum creatinine and estimated glomerular filtration rate (eGFR), as progressive renal impairment remains one of the strongest predictors of chronic hyperuricemia and recurrent gout episodes [42,46]. In summary, prevention and monitoring strategies for gout in post-transplant patients require an integrated, multidisciplinary approach that unites biochemical surveillance, lifestyle modification, and judicious pharmacologic oversight. Embedding structured uric acid monitoring, patient-tailored education, and periodic renal and medication review within post-transplant pathways has been shown to reduce the incidence of gout, preserve graft function, and simplify overall management in this complex patient population [41,43,44].

Emerging Therapies and Future Directions

The management of gout in post-transplant patients is entering a new era, driven by the development of novel urate-lowering agents and advances in immunomodulatory strategies. Lesinurad, a selective uric acid reabsorption inhibitor targeting URAT1, was approved for use in the United States as an adjunct to xanthine oxidase inhibitors, offering an additional mechanism for lowering serum urate in patients with refractory gout. Although lesinurad was withdrawn from the market for business reasons rather than safety or efficacy concerns, its mechanism exemplifies the potential of next generation uricosurics to address unmet needs in complex cases, including those with impaired renal function or drug intolerance [47,48]. The urate-lowering drug pipeline continues to expand, with agents targeting intestinal urate transport, purine-degrading gut microbiota, and liver-specific xanthine oxidoreductase mRNA knockdown under investigation [48].

Personalized immunosuppression regimens represent a promising future direction for gout management in transplant recipients. The interplay between immunosuppressive agents and uric acid metabolism is well established, with calcineurin inhibitors-especially cyclosporine-contributing significantly to hyperuricemia and gout risk [9,14,15]. Emerging evidence supports the use of biomarker-guided approaches and combination therapies, including biologics targeting IL-1, TNF-α, and IL-6, to tailor anti-inflammatory and urate-lowering strategies to individual patient profiles [47,49]. Such precision medicine approaches may optimize graft survival while minimizing metabolic complications and drug interactions.

Despite these advances, there remains a critical need for multicenter, prospective studies evaluating the efficacy, safety, and long-term outcomes of gout management strategies in transplant populations. Most available data are derived from small cohorts or retrospective analyses, limiting generalizability and the ability to establish best practices [8,11,15]. Large-scale studies are essential to clarify the impact of novel agents, personalized regimens, and immunomodulatory therapies on patient and graft outcomes, as well as to inform guideline development and clinical decision-making. The future of gout management in post-transplant patients will be shaped by the integration of innovative urate-lowering agents, individualized immunosuppression, and robust multicenter research to improve quality of life and preserve graft function in this high-risk population.

Conclusion

Gout in the solid organ transplant setting is a clinically relevant and complex complication that extends beyond a quality-of-life issue, significantly impacting morbidity and potentially compromising graft survival. The high incidence of hyperuricemia and gout in this population is driven by the synergistic interaction of underlying renal dysfunction, CNI-induced nephrotoxicity (primarily cyclosporine), and concurrent metabolic comorbidities. Successful management requires an integrated, multifaceted approach: ensuring accurate diagnosis through timely differentiation from septic arthritis, implementing cautious and gradual urate-lowering therapy (with allopurinol as the first-line agent), and considering the judicious adjustment of the immunosuppressive regimen to mitigate urate retention. Finally, proactive surveillance of serum uric acid levels and lifestyle

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interventions are essential for prevention and for optimizing the long-term outcomes for both the patient and the graft function.

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