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Review

Treatment of Gout in Patients with CrCl ≤30 mL/min and/or on Hemodialysis: A Review

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Abstract: Gout is highly prevalent in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), owing to impaired uric acid excretion. However, treating gout in this population is challenging due to concerns about medication safety and efficacy with reduced kidney function. This review examines the evidence of various pharmacologic and non-pharmacologic approaches to managing gout in CKD/ESRD. For acute gout flares, there is insufficient evidence to guide optimal dosing of NSAIDs, colchicine, and corticosteroids in advanced CKD. The risks generally outweigh the benefits of NSAIDs and colchicine. Corticosteroids appear safer but require individual risk-benefit assessments. Interleukin-1 inhibitors show promise, but larger studies are needed. For long-term urate lowering, xanthine oxidase inhibitors like allopurinol and febuxostat are preferred over probenecid and other uricosurics. However, studies specifically evaluating urate-lowering therapies in CKD are scarce, resulting in conflicting expert guidelines. Starting with low allopurinol doses and gradual titration can mitigate the risks. Higher allopurinol doses may be needed to reach urate targets in some CKD patients. Febuxostat's safety in advanced CKD remains debated. Optimal gout management in dialysis patients is also unclear, including when to continue urate-lowering therapy. Overall, gout is often suboptimally treated in CKD/ESRD, highlighting the need for more research to guide therapy in this population. Improving management can significantly reduce the burden of these comorbid diseases.

Keywords: gout; chronic kidney disease; hyperuricemia; urate-lowering therapy; xanthine oxidase inhibitors; acute gout flares; hemodialysis; end-stage renal disease

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1. Introduction

Gout is one of the most common forms of inflammatory arthritis, resulting from elevated levels of serum uric acid (hyperuricemia), leading to the deposition of monosodium urate crystals in joints, soft tissues, and organs. It is characterized by recurrent acute flares of severe arthritis as well as chronic arthropathy if left untreated. In patients with end-stage renal disease (ESRD), gout is particularly prevalent, ranging from 15 to 30% [1]. The incidence of gout increases as kidney function declines, with rates as high as 11 per 100 person years in dialysis patients [2]. For instance, in a study of 1117 patients starting dialysis, the prevalence of gout was 29.5%: in men (32.8%) compared to women (24.7%) [3]. Factors associated with higher gout prevalence included male gender, white race, obesity, diabetes, diuretic use, and lower residual kidney function [4]. Multiple epidemiological studies have shown hyperuricemia as an independent risk factor for CKD onset and progression [5]. However, some investigators argue that uric acid is simply a marker of disease rather than playing a causal role [6]. Regardless, there appears to be a clear link between uncon-

trolled gout, hyperuricemia, and worsened kidney function. Small interventional trials of urate-lowering treatments have shown improved GFR and slowed CKD progression [7].

Hyperuricemia is the result of either increased production or inadequate excretion of uric acid, with the kidneys playing a major role in uric acid excretion by filtering and eliminating about two-thirds of circulating uric acid [8]. In CKD, the decline in glomerular filtration rate impairs uric acid excretion, leading to rising uric acid levels. National Health and Nutrition Examination Survey (NHANES) data shows that the prevalence of hyperuricemia increases substantially from 11 to 13% in early CKD to 64–78% in patients with eGFR 15–29 mL/min/1.73 m^2 [9]. The presence of comorbidities such as hypertension and the use of diuretics may further reduce uric acid excretion in CKD patients [5].

Managing gout patients with CKD poses significant challenges, as many first-line gout drugs like NSAIDs, colchicine, and high-dose corticosteroids have safety concerns in CKD, including the risk of acute kidney injury. Urate-lowering therapies also require dose adjustment and monitoring, leading to therapeutic nihilism and undertreatment of gout in advanced CKD. However, uncontrolled gout can lead to recurrent attacks, joint damage, and a poor quality of life [10]. Emerging therapies offer hope, but high-quality evidence on managing gout in CKD remains scarce.

Despite the difficulties, treating uric acid levels is important to control gout and prevent CKD progression and complications in this high-risk population. Inadequate treatment contributes to frequent hospitalizations and poor outcomes [11]. This review paper aims to examine the various approaches to managing gout in patients with Creatinine Clearance $\leq$30 mL/min and/or on hemodialysis, highlighting the critical need for more research to provide evidence-based guidance on the safest and most effective therapies for gout patients with impaired kidney function. Such efforts can significantly reduce the burden of both diseases for patients and the healthcare system.

2. Methodology

An extensive search of scientific studies was carried out across the PubMed, Embase, and Cochrane databases to gather information on the treatment of gout in patients with chronic kidney disease (CKD) and those in the final stages of renal disease (ESRD). This search included both specific database terms (MeSH for PubMed and Emtree for Embase) and general search terms related to gout, CKD, ESRD, hemodialysis, and various treatment methods. The search was conducted in English only.

From the initial 342 studies found, titles and abstracts were reviewed to determine their relevance. Seventy-nine of these were deemed potentially relevant and were read in full. These were chosen based on whether they looked at drug treatments for managing sudden gout attacks or reducing urate levels over time in patients with CKD/ESRD, or whether they considered non-drug treatments such as lifestyle changes for gout patients with CKD/ESRD. Studies were excluded if they did not focus on gout in CKD/ESRD patients, did not address treatment, or were not available in full text.

The research also included a review of relevant treatment guidelines from key rheumatology associations like the American College of Rheumatology, the European League Against Rheumatism, and the British Society for Rheumatology. Additional sources were identified by manually searching the bibliographies of selected studies and checking clinical trial registries for ongoing research. The results identified gaps in the current research and suggested areas for future study. Treatment recommendations were made based on the evidence, risk-benefit considerations, and clinical expertise.

3. Mechanisms Linking Hyperuricemia and Kidney Disease Progression

Uric acid is produced by the catabolism of purines, mostly found in food, alcohol, or other beverages. Two-thirds of uric acid is eliminated by the kidney, while the other third is eliminated by the gastrointestinal system. Uric acid is filtered in the glomeruli, mostly reabsorbed by the S1 segment of proximal convoluted tubules, and then secreted by the S2 segment of the proximal convoluted tubules [12]. Reabsorption of uric acid is regulated by

three main transporters: urate anion transporter 1 (URAT1), organic anion transporter 4 (OAT4), and glucose transporter 9 (GLUT9). Excretion of uric acid in the kidneys is mainly carried out by four transporters: urate transporter (UAT), multidrug resistance protein 4 (MRP4/ABCC4), ABCG-2, and sodium-dependent phosphate transport [13].

Hyperuricemia can be caused by the increased production or decreased excretion of uric acid. Increased consumption of proteins and substances containing urate precursor substrates, such as meat, seafood, alcohol, and certain vegetables, leads to increased production of uric acid through the metabolization of these products. Dysregulation in the absorption and excretion of uric acid often causes changes in the levels of uric acid leading to an elevated uric acid concentration; this is known as hyperuricemia. Therefore, a decrease in kidney function, or estimated glomerular filtration rate (eGFR), is determined by the ability of the kidney to appropriately absorb and secrete solutes. This is seen in states such as chronic kidney disease, which affects the levels of these solutes in the body. Different medications that affect kidney function can also have an impact on the levels of uric acid in the blood. Alcohol can alter uric acid levels through different mechanisms, including the accelerated hepatic breakdown of ATP and the generation of organic acids that compete with urate for tubular excretion. Alcohol also interferes with muscle degradation of ATP and modifies certain enzymatic activities that lead to overproduction and underexcretion of uric acid [14]. Additionally, in certain disorders, such as Lesch-Nyhan Syndrome, we see enzyme deficiencies as [(hypoxanthine-guanine phosphoribosyl transferase (HPRT)] that degrade purines, resulting in decreased purine degradation, thus leading to excessive uric acid levels [15].

There have been a lot of studies exploring the pathophysiological mechanisms and associations between hyperuricemia and chronic kidney disease. Hyperuricemia has been associated with an increased risk of developing hypertension, metabolic syndrome, stroke, diabetes, and cardiovascular events. These in turn increase the risk of kidney damage and accelerate the progression of the decline of kidney function [16]. Even mild elevations in uric acid levels have been suggested to cause hypertension through renal vasoconstriction and cause direct glomerular and tubulointerstitial injury of the kidney, regardless of crystal formation [17]. 3% to 10% of the uric acid filtered is excreted in the urine. Therefore, increased uric acid levels in the blood will lead to increased uric acid in the urine. Uric acid has a tendency to crystallize in a low urine volume or an acidic urine [18].

There are several proposed mechanisms by which high serum or urinary uric acid might cause kidney injury. One of the most common mechanisms is the crystallization effect. In low urine volume or an acidic environment, uric acid in the urine tends to supersaturate and crystallize, which will lead to tubular injury through tubular obstruction [18]. Uric acid can also lead to the progression of chronic kidney disease by increasing the expression of different genes such as NALP3, caspase IL-1β and ICAM-1 in proximal tubular epithelial cells [19]. By activating interleukin (IL)-1beta and IL-18, the NALP3 inflammasome increases the inflammatory cascade in the tubular cells [20]. Uric acid can also induce an epithelial-to-mesenchymal transition in the tubular cells by increasing the degradation and decreasing the synthesis of E-cadherin [21]. High uric acid can also indirectly affect the kidneys and cause a decline in their function through several mechanisms. In a meta-analysis conducted by Grayson et. al., patients with a 1 mg/dl higher uric acid level were 13% more likely to develop new-onset hypertension, with a relative risk of 1.13 (95% CI 1.06–1.20) [22]. Studies have suggested that even mild hyperuricemia can lead to the activation of the Renin-angiotensin Aldosterone System (RAAS), leading to an increase in blood pressure. Treatment with renin-angiotensin system blockers can block this effect, leading to the halting of the progression of chronic kidney disease [23].

The decline in kidney function leads to the accumulation of uric acid in the bloodstream through decreased clearance from the blood. This also leads to a decrease in uric acid levels in the urine. The increased uric acid levels in the bloodstream lead to the activation of the RAAS system, causing hypertension and the activation of inflammatory cascades through the different pathways discussed above, which in turn leads to a decline in kidney function.

Therefore, a vicious cycle between hyperuricemia and declining kidney function exists, which can be halted through different medications and drugs, which will later be described in the review.

4. Challenges in Treatment of Gout in CKD

In gout patients without other health conditions, there are several effective options for treating inflammation during acute flares, including NSAIDs, colchicine, or corticosteroids. There are also effective options for long-term management of high uric acid levels to prevent flares, including allopurinol, Febuxostat, or Pegloticase. However, gout is rarely an isolated condition. In a study done by Zhu Y et al., only 2% of patients with gout were found to have no comorbidities [24]. The presence of other health conditions can pose significant difficulties in treating gout. Many comorbidities have absolute or relative contraindications to drugs commonly used for gout, which often restrict treatment options. For example, conditions like kidney disease, heart failure, or diabetes may mean that standard treatment of care, utilizing medications like NSAIDs or colchicine, may carry too much adverse risk for a particular patient. The limitations imposed by comorbidities frequently complicate the management of gout, especially when patients have multiple conditions.

One of the most difficult comorbidities complicating gout treatment is chronic kidney disease (CKD). Many medications that are utilized in the treatment of gout, such as NSAIDs and colchicine, have safety concerns and limited use in CKD due to potential kidney toxicity. Additionally, the clinical presentation of gout in these patients is often atypical compared to those without CKD.

There is a lack of high-quality evidence to guide treatment decisions for gout in patients with advanced chronic kidney disease (CKD). This is because clinical trials have traditionally excluded these patients, or when included, have failed to report outcomes specific to this population. Comparing studies is also difficult due to the variability in how outcomes are reported for both urate-lowering therapy (ULT) and gout flare treatments in the context of CKD. This problem is not unique to gout research. Additionally, many healthcare providers involved in managing gout in CKD patients have understandable concerns about confusing guidelines with conflicting recommendations from major societies [25].

The resulting knowledge gaps have led to legitimate and questionable concerns about the efficacy and safety of gout treatments. The use of urate-lowering therapy (ULT) in advanced CKD varies greatly between the disciplines of rheumatology, nephrology, and general practitioners; even professional bodies have conflicting recommendations about gout treatment in CKD. This causes confusion and suboptimal gout management, with failure to reach recommended urate targets. Treatment options are often restricted by providers and patients due to appropriate concerns or misconceptions about drug toxicity and dose adjustments needed. Consequently, outcomes for gout patients with CKD are frequently poor. More research is needed to provide quality evidence to guide treatment decisions for these patients [26].

5. Treatment Considerations and Recommendations

The American College of Rheumatology (ACR) guidelines recommend urate-lowering therapy (ULT) in patients with tophaceous deposits, radiographic damage, frequent flares, the first flare with moderate-severe CKD, high UA levels, or kidney stones. ULT lowers uric acid production, increases excretion, or breaks it down. ACR recommends a treat-to-target approach, titrating ULT to achieve a UA level of less than 6 mg/dL. However, starting ULT can trigger flares due to rapid UA change. Preventing these often requires short-term prophylaxis, with drugs also used for acute flares. ACR strongly recommends prophylaxis for 3–6 months when starting ULT. Treatment options, including considerations for CKD 3B-5/ESRD in hemodialysis patients, are summarized below. In summary, there are two treatment approaches—managing acute flares and lowering UA levels long-term to prevent flares, which requires prophylaxis when initiating ULT to prevent paradoxical flares.

6. Treatment of Flares and Prophylactic Agents in Gout and CKD (Table 1)

The 2020 American College of Rheumatology (ACR) guidelines recommend nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and systemic glucocorticoids to treat acute gout flares. These can also be used as prophylaxis when starting urate-lowering therapy (ULT) to prevent flares. Interleukin-1 (IL-1) inhibitors like anakinra and canakinumab can be used for flares and prophylaxis too. However, there is a lack of consensus on proper dosing and monitoring of these medications in gout patients with chronic kidney disease (CKD) experiencing acute flares or needing prophylaxis when starting ULT. More evidence is needed to determine the optimal use of these agents for managing flares and preventing paradoxical flares when initiating ULT in the setting of CKD.

Table 1. Treatment of Flares and Prophylactic Agents in Gout and CKD.

Medication	CrCl ≤30 mL/min	Hemodialysis	Comment
NSAIDs	**Avoid NSAIDs**	**Avoid NSAIDs**	
Colchicine	1.2 mg at first sign of flare, then 0.6 mg 1 h later. Repeat dosing no sooner than every 14 days. Alternatively, some suggest 0.3 mg single dose at onset, repeat no sooner than every 3–7 days	Typically avoid colchicine due to toxicity risk, as it accumulates and is not removed by dialysis.	Consider alternative therapies first if available and tolerated.
Prednisone	30–40 mg/day until symptom improvement (usually 2–5 days)—give as a single daily dose or split into two doses. Then, taper slowly as tolerated: Typically, over 7–10 days. More gradual taper (14–21 days) may be needed for multiple recent flares	30–40 mg/day until symptom improvement (usually 2–5 days)—give as a single daily dose or split into two doses. Then, taper slowly as tolerated: typically, over 7–10 days. More gradual taper (14–21 days) may be needed for multiple recent flares	No dose adjustment needed
IL-1 inhibitors (Anakinra)	100 mg every other day until symptom improvement, with a usual duration of 3 to 5 days	100 mg every other day until symptom improvement, with a usual duration of 3 to 5 days	Reserve anakinra for when first-line therapies fail, are contraindicated, or not tolerated

- NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are typically contraindicated in patients with CKD due to the risk of renal-related side effects. The published literature on NSAIDs in gout has generally focused on demonstrating these potential adverse effects in CKD patients. Although the adverse effects of NSAIDs are well established, there is some evidence suggesting short-term NSAID use may be possible in end-stage renal disease. Patients with ESRD may be an exception for cautious use of NSAIDs, despite the high risk of side effects like gastrointestinal bleeding. Some evidence suggests short-term NSAID use in ESRD patients without residual kidney function may not affect blood pressure or electrolytes and could potentially be safer than alternative pain control options in this population. However, more research is still needed to definitively determine the safety of any NSAID use in CKD, particularly for the short-term treatment of acute gout flares. Current evidence indicates NSAIDs should generally be avoided but may potentially have a very limited role in certain CKD patients if used cautiously and under close monitoring [27].

Recommendations: In patients with creatinine clearance ≤30 mL/min, NSAIDs should be avoided due to the increased risk of acute kidney injury.

In patients on intermittent hemodialysis three times per week, NSAIDs are slightly dialyzable (20%) but should also be avoided. Hemodialysis patients with end-stage kidney disease may have greater risks of bleeding (e.g., GI), cardiovascular side effects, and loss of any residual kidney function with NSAID use [28].

Due to concerns about potentially exacerbating kidney dysfunction and other adverse events, NSAIDs are best avoided in patients with severe chronic kidney disease (CrCl $\leq$ 30 mL/min) or those receiving intermittent hemodialysis. The risks generally outweigh any potential benefits on these populations.

- Colchicine

Colchicine, an anti-inflammatory drug that inhibits microtubule assembly and NLRP3 inflammasome activity, is commonly used for treating acute gout flares and as prophylaxis when starting urate-lowering therapy (ULT). As an anti-microtubule and anti-inflammatory agent, colchicine can help manage the pain and inflammation of acute gout attacks. It can also prevent paradoxical flares when initiating ULT due to its anti-inflammatory properties. Colchicine is one of the mainstay therapies for treating active flares and for prophylaxis against flares when starting long-term ULT. There are a few randomized controlled trials of colchicine for gout flare treatment, but none reported outcomes based on kidney function. Pharmacokinetic studies show colchicine clearance is reduced in severe kidney impairment (eGFR 15–29 mL/min/1.73 m^2), and minimal clearance occurs with hemodialysis. Colchicine toxicity can be increased in patients with CKD due to reduced clearance, leading to adverse effects like rhabdomyolysis, neuromyopathy, and bone marrow suppression. Colchicine also has significant drug interactions with medications commonly used in CKD, like statins, cyclosporine for transplants, and macrolide antibiotics. These interactions are exacerbated by colchicine's prolonged half-life in renal impairment. Therefore, colchicine requires very careful dosing and monitoring for toxicity in CKD patients, especially those on interacting medications [29].

Previous randomized trials of colchicine for gout did not report outcomes by kidney function, so evidence is lacking on its use in CKD. Case reports using varying colchicine doses and schedules in CKD had highly variable results—12 of 19 cases showed worsening kidney function, while 7 of those 19 were stable. Most case studies showed significant side effects or drug interactions, but it is unclear if colchicine was directly causal given the limitations. Ultimately, there is insufficient evidence to conclude on colchicine's safety or efficacy in CKD [30]. Low-dose colchicine could be studied, as it is similarly effective in non-CKD patients. Based on experience, prophylactic dosing of 0.3–0.6 mg every other day or twice weekly, depending on CKD severity and interacting medications, may be reasonable. More research is needed, particularly on lower colchicine doses, to establish safe and effective use in CKD patients. Careful consideration of risks versus benefits is necessary, given concerns about potential toxicity and interactions.

Recommendations: In patients with creatinine clearance $\leq$30 mL/min, alternative therapies should be considered first if available and tolerated. If colchicine must be used, the following adjusted dosing is recommended: 1.2 mg at the first sign of a gout flare, followed by 0.6 mg 1 h later. Repeat dosing should not occur for at least 14 days. Alternatively, some experts suggest a single 0.3 mg dose at flare onset only, with repeat dosing no sooner than every 3–7 days.

Colchicine is typically avoided for gout flare treatment in patients undergoing hemodialysis. Since colchicine is not removed through dialysis, it can accumulate in these patients, increasing the risk of colchicine toxicity.

- Corticosteroids

Corticosteroids are generally considered the safest option for treating gout flares in chronic kidney disease (CKD), though evidence is limited. They can be used to treat gout flares and, less ideally, as prophylaxis when starting urate-lowering therapy. However, a review found insufficient evidence to determine the effectiveness or safety of steroids for gout in chronic kidney disease (CKD). Most studies were case reports of severe, refractory gout, so the findings may not apply to the wider population. Clinicians are also concerned about comorbidities in gout-CKD patients, like hypertension, diabetes, and infection risk, that may preclude steroid use. More research is needed in the general gout-CKD population to establish steroid efficacy and safety. Caution is warranted given the potential side effects,

especially with comorbid conditions. Steroids require an individual risk-benefit assessment for each patient. The current lack of strong evidence in CKD patients makes treatment decisions difficult when managing gout flares or prophylaxis.

Recommendations: For prednisone dosing in patients with creatinine clearance ≤30 mL/min or undergoing intermittent hemodialysis three times per week, no supplemental dose or dosage adjustment is necessary. Doses are 30 to 40 milligrams per day of the medication, either as a single daily dose or split into two doses, until the symptoms improve (which is usually within 2 to 5 days). Then, slowly taper the dosage as tolerated (typically over 7 to 10 days); a more gradual taper (for example, over 14 to 21 days) may be needed, especially in patients who have had multiple recent flare-ups of symptoms.

- IL-1 Inhibitors

Interleukin-1 (IL-1) inhibitors like anakinra, canakinumab, and rilonacept have been used for gout flares and prophylaxis, but trials excluded advanced chronic kidney disease (CKD) patients and only reported pooled results. Case reports of anakinra and canakinumab in CKD showed limited kidney function decline [31,32], though some anakinra cases had non-fatal infections. Anakinra response was unaffected by CKD in hospitalized gout. Anakinra is renally cleared, so it requires extended dosing intervals in CKD due to its longer half-life. Overall, IL-1 inhibitors appear promising for gout in CKD, but larger, high-quality studies are needed reporting CKD-stratified outcomes to better define safety and optimal dosing. In our experience, IL-1 inhibitors have been beneficial for difficult gout cases in CKD/ESRD lacking other options, but more evidence is needed to guide use in this population. Their potential should be explored further through research, specifically in patients with reduced kidney function.

Recommendations: For anakinra use in gout, it should be reserved for patients where first-line therapies are ineffective, contraindicated, or not tolerated. The recommended subcutaneous dosage in patients with creatinine clearance ≤30 mL/min or on hemodialysis is 100 mg every other day until symptom improvement, with a usual duration of 3 to 5 days [10].

For canakinumab and rilonacept, there are no specific dosage adjustments provided in the manufacturer's labeling for patients with gout and chronic kidney disease (CKD). The use of canakinumab and rilonacept in CKD has not been adequately studied.

7. Urate-Lowering Therapy (ULT)

The appropriate use of urate-lowering therapy (ULT) in gout patients with chronic kidney disease (CKD) is controversial. Guidelines from the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the British Society for Rheumatology differ on important aspects like allopurinol dosing in CKD [33]. For ULT drugs like allopurinol, febuxostat, probenecid, benzbromarone, lesinurad, and pegloticase, key efficacy outcomes per most guidelines include: achieving target serum urate levels (<6 or <5 mg/dL), resolving tophi, reducing gout flares over time, improving quality of life, and radiographic changes. However, clinical trials of these therapies have largely excluded or underrepresented patients with advanced CKD [25]. This has resulted in limited evidence to guide ULT use in gout patients with significant kidney impairment. Differing expert opinions have led to conflicting guideline recommendations, causing confusion on optimal ULT dosing and monitoring in this population. More research focused on ULT efficacy and safety outcomes, specifically in CKD, is critically needed to inform guidelines and clinical practice.

- Allopurinol (Table 2)

The American College of Rheumatology (ACR) guidelines strongly recommend allopurinol as first-line urate-lowering therapy (ULT) for gout, including in CKD. Studies show allopurinol can safely reduce serum urate in CKD. However, starting at low doses (<100 mg/day) is strongly advised in moderate-to-severe CKD to prevent allopurinol hypersensitivity syndrome. Renal impairment, especially with higher starting doses and/or

concomitant diuretics, increases the risk of allopurinol hypersensitivity syndrome (AHS)—a rare but potentially life-threatening reaction. Kidney dysfunction reduces allopurinol clearance, leading to higher oxipurinol levels, which is thought to increase susceptibility to AHS. The HLA-B5801 allele also raises the risk of severe allopurinol skin reactions; those of Korean, Han Chinese, or Thai descent are more likely to have this allele. Allopurinol should be avoided in patients testing positive for HLA-B5801, given the heightened risk of adverse cutaneous reactions. HLA-B*5801 testing allows the exclusion of patients genetically predisposed to allopurinol hypersensitivity [25].

Table 2. Allopurinol recommendations.

Allopurinol Recommendations		
Patient Population	**Initial Dose**	**Titration and Maintenance**
CrCl >15–30 mL/min	50 mg every other day	Gradually increase by ≤100 mg/day every 2–4 weeks up to minimum effective dose (doses >300 mg/day can be considered with monitoring for toxicity)
CrCl 5–15 mL/min	50 mg twice weekly	Gradually increase by ≤100 mg/day every 2–4 weeks up to minimum effective dose (doses >300 mg/day can be considered with monitoring for toxicity)
CrCl <5 mL/min	50 mg once weekly	Gradually increase by ≤100 mg/day every 2–4 weeks up to minimum effective dose (doses >300 mg/day can be considered with monitoring for toxicity)
Intermittent hemodialysis	100 mg 3× weekly after each dialysis session	Gradually increase by ≤50 mg/day every 2–5 weeks up to minimum effective dose (doses up to ~400 mg/day have been reported)

In practice, allopurinol doses are often limited in CKD due to toxicity concerns, causing under-treatment. However, allopurinol can be safely up-titrated in CKD based on evidence. The VA STOP-GOUT study of 351 gout patients with stage 3 CKD showed a treat-to-target strategy starting at 100 mg allopurinol and up-titrating achieved urate targets without increased toxicity or worsening kidney function in most [34]. Other studies confirm allopurinol can be escalated safely even in CrCl <30 mL/min to reach goal urate [35]. Higher allopurinol doses may be needed in CKD patients who are heavier or on diuretics [36]. Ultimately, CKD patients may require ≥300 mg/day to reach urate targets [37].

Recommendations: For allopurinol dosing in kidney impairment [38]:

- Creatinine clearance (CrCl) >15 to 30 mL/min: Suggested initial dose is 50 mg every other day.
- CrCl 5 to 15 mL/min: Recommended initial dose is 50 mg twice weekly.
- CrCl <5 mL/min: Recommended initial dose is 50 mg once weekly.
- For patients on intermittent hemodialysis three times per week, allopurinol is dialyzable with oxypurinol clearance of approximately 39–50%. The recommended initial allopurinol dose in this population is 100 mg three times weekly, administered after each dialysis session.

For allopurinol titration and maintenance dosing in patients with CrCl ≤30 mL/min: Gradually increase the dose in increments of ≤100 mg/day every 2–4 weeks. Using smaller increments (≤50 mg/day) and longer intervals (≥4 weeks) may be preferred. Some experts delay the initial increase for 1–2 months until after the peak risk period for allopurinol hypersensitivity syndrome has passed. Titrate to the minimum daily dose needed to achieve the goal urate-lowering effect. Doses >300 mg daily can be considered with appropriate patient education and monitoring for potential toxicity like rash, itching,

and elevated liver enzymes. If the desired serum uric acid level cannot be achieved, switching to an alternative agent can be considered [39].

For allopurinol titration and maintenance dosing in hemodialysis:

Gradually increase the dose in increments of ≤50 mg/day (e.g., 150 mg three times weekly) every 2–5 weeks. Some experts delay the initial increase for 1–2 months until after the peak risk period for allopurinol hypersensitivity syndrome. Titrate to the minimum dose necessary to achieve the goal of urate lowering. Doses >300 mg daily can be considered with appropriate patient education and monitoring for potential toxicity like rash, itching, and elevated liver enzymes. [25] Doses up to ~400 mg daily have been reported [40].

- Febuxostat (Table 3)

Febuxostat is a novel non-purine selective xanthine oxidase inhibitor (XOi) mainly metabolized by the liver and excreted renally and fecally, reducing the burden on the kidneys. The American College of Rheumatology strongly recommends using a low starting dose of febuxostat (<40 mg/day) with ongoing titration rather than higher initial doses in chronic kidney disease patients. Smaller studies have shown febuxostat benefits over allopurinol in slowing kidney disease progression and delaying dialysis in moderate-to-severe CKD if uric acid levels ≤7 mg/dL are achieved. However, recent studies disagree on mortality risk with febuxostat versus allopurinol. The CARES trial found higher cardiovascular and all-cause mortality with febuxostat versus allopurinol in gout patients with cardiovascular disease, leading to a black box warning for febuxostat. However, CARES did not stratify outcomes by kidney function [41]. The subsequent FAST trial in gout patients with cardiovascular risk factors found no increased cardiovascular mortality with febuxostat versus allopurinol and lower all-cause mortality with febuxostat, but excluded advanced CKD [42]. The cardiovascular and mortality risks of febuxostat, specifically in advanced chronic kidney disease, remain unclear. Further studies in patients with significant renal dysfunction are needed to clarify if cardiovascular concerns exist with febuxostat use in this population. A retrospective cohort study by Chung-te Liu found patients with a severely reduced estimated glomerular filtration rate (eGFR) had a higher risk of myopathy with febuxostat treatment. This suggests regular monitoring of creatine kinase levels for early detection of febuxostat-associated myopathy may be warranted, especially in chronic kidney disease (CKD) patients [43].

Table 3. Febuxostat recommendations.

Febuxostat Recommendations	
Patient Population	**Recommendation**
CrCl <30 mL/min	Initial dose: 20–40 mg once daily. Observational data suggests 60–80 mg/day may be safe in some patients unresponsive to standard doses with careful titration and monitoring
Intermittent hemodialysis	Initial dose: 20–40 mg once daily without supplemental dosing. Unlikely to be dialyzed due to high protein binding. Doses up to 80 mg/day were safe in a small observational study; can consider careful titration if unresponsive to standard doses

Recommendations: For febuxostat dosing in kidney impairment:

Creatinine clearance <30 mL/min: Recommended initial dose is 20–40 mg once daily. Observational studies have reported safety of 60 and 80 mg/day in hyperuricemia; careful titration can be considered in patients unresponsive to standard doses [44].

Intermittent hemodialysis (thrice weekly): Unlikely to be dialyzed due to high protein binding. The recommended initial dose is 20–40 mg once daily without supplemental dosing. A small observational study reported doses up to 80 mg/day were safe in hyperuricemia; careful titration may be done if unresponsive to standard doses [45].

- Uricosurics

Uricosurics like probenecid, benzbromarone, and lesinurad promote uric acid excretion and are another urate-lowering therapy class. Probenecid is generally avoided with

creatinine clearance <50 mL/min as it is thought ineffective [45]. Thus, the ACR guidelines strongly recommend allopurinol or febuxostat over probenecid in stage ≥3 chronic kidney disease. Benzbromarone has shown efficacy for creatinine clearance <25 mL/min but has been removed from many markets due to hepatotoxicity concerns [46]. Lesinurad is now withdrawn after a manufacturer decision and was contraindicated in creatinine clearance <45 mL/min [47]. In summary, uricosurics like probenecid and lesinurad have limited utility in advanced CKD due to renal clearance requirements. Benzbromarone may be effective, but it has toxicity concerns. Xanthine oxidase inhibitors like allopurinol or febuxostat are generally preferred over uricosurics for urate lowering in moderate-to-severe kidney disease. Combination therapy with a xanthine oxidase inhibitor (XOi) and a uricosuric can be very effective for lowering urate. If uricosuric toxicity results from high intratubular urate levels, then combination therapy could theoretically reduce this risk. However, uricosurics are usually avoided in advanced chronic kidney disease (CKD), so this approach is largely untested in this population.

8. In Hemodialysis Patients

Treating acute gout flares in patients on renal replacement therapy (RRT) can be challenging given the limitations of therapeutic options for this population with renal impairment. Glucocorticoids preferably administered intra-articularly, or interleukin-1 (IL-1) inhibitors are generally preferred for acute flare management over colchicine and NSAIDs, which have higher risks of side effects in the setting of limited kidney function [48].

For prophylaxis against paradoxical flares when initiating urate-lowering therapy (ULT), systemic glucocorticoids are often used due to concerns about adverse events with other prophylactic agents. However, chronic steroid exposure has known risks that must be weighed. Approaches using very low initial ULT doses without prophylaxis have demonstrated some success and could represent an option for flare prevention in this population [49].

Whether to continue ULT after the initiation of dialysis has been debated. Some data suggest that gout improves once dialysis is started. However, the overall prevalence of gout in the dialysis population remains substantial. Evidence on continuing ULT in patients on renal replacement therapy is limited, consisting mostly of case reports and series [50].

One study demonstrated that hemodialysis acutely lowered serum urate levels significantly, arguing against the need to continue ULT. However, the applicability of these findings to patients newly starting dialysis is unclear. Peritoneal dialysis has also been shown to often normalize serum urate. We personally favor continuing ULT at reduced doses if patients on renal replacement therapy continue to have gout flares or fail to achieve target serum urate levels below 6 mg/dL. The ongoing need for ULT should be reevaluated periodically after dialysis initiation. Further research is still needed to better define optimal gout management and ULT use in the dialysis population [49].

9. Lifestyle Modifications

Gout has long been associated with diet and lifestyle. How diet and lifestyle influence gout is of interest to patients, who often try dietary changes to help manage gout. Currently, practice regarding diet and lifestyle advice for gout patients varies widely, with no standardized approach. Advice may include limiting alcohol, high-purine foods, sugar-sweetened drinks, encouraging weight loss if overweight, low-fat dairy, cherries, and adequate fluids. However, patients report limited, confusing dietary advice from providers. While dietary changes may only modestly lower serum urate (SU), certain foods and substances may trigger flares in susceptible individuals. Obesity increases gout incidence—BMI gains over 5% are associated with more frequent flares, while BMI declines over 5% reduces flares. Other studies show weight loss over 5 kg can reduce SU in obesity and have larger decreases after bariatric surgery [51]. In summary, dietary and lifestyle influences on gout are of great interest to patients, but provider advice is often limited and inconsistent. Weight loss and

avoiding certain dietary triggers appear beneficial for gout, though quality evidence is still lacking.

10. Discussion

This review highlights the unique challenges of managing gout in the setting of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Gout is highly prevalent in these populations due to impaired uric acid excretion. However, treatment options are limited by concerns about medication safety and efficacy in the context of reduced kidney function.

First-line gout therapies like NSAIDs, colchicine, and high-dose steroids carry risks of worsening kidney dysfunction, gastrointestinal bleeding, and other adverse events in CKD/ESRD. As a result, treatment of acute gout flares is problematic. There is insufficient evidence to guide optimal dosing and monitoring of these agents in advanced CKD. More research is critically needed.

Initiating long-term urate-lowering therapy (ULT) to control gout also poses challenges. Potent uricosurics like probenecid are relatively contraindicated in CKD due to their reliance on adequate kidney function for excretion. Xanthine oxidase inhibitors like allopurinol and febuxostat are preferred, but studies guiding their use in CKD are limited. Starting with low allopurinol doses and gradual titration based on urate levels reduces toxicity risks. However, target urate levels are often not achieved. Higher allopurinol doses appear safe in some CKD patients but require close monitoring. The role of febuxostat is debated given conflicting data on cardiovascular safety.

Additionally, the optimal management of gout in ESRD patients on dialysis remains unclear. Hemodialysis may lower urate levels, questioning the need to continue ULT. However, gout still affects many dialysis patients, suggesting ongoing urate control is beneficial. There is almost no evidence comparing continuation versus cessation of ULT after dialysis initiation.

In summary, gout in CKD/ESRD patients is undertreated due to therapeutic limitations, resulting in recurrent flares, joint damage, and reduced quality of life. Conflicting expert opinions and guidelines also create confusion. More research is urgently required to provide evidence-based recommendations for gout treatment tailored to patients with impaired kidney function.

11. Conclusions

In conclusion, gout poses management challenges in the setting of CKD and ESRD due to the paucity of evidence evaluating the safety and efficacy of standard gout therapies in the context of reduced kidney function. Treatment is often suboptimal, highlighting the need for more research focused on this population. Limitations in managing both acute gout flares and long-term urate control must be addressed. Well-designed studies are critical to guide gout treatment decisions and improve patient outcomes. With the growing incidence of gout and CKD, optimizing therapy for patients with both conditions is an important priority. This review synthesizes current evidence while underscoring knowledge gaps, providing a framework to advance clinical care and research on gout in CKD/ESRD. Improving management can significantly reduce the burden of these comorbid diseases.

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