BJMS
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Batna Journal of Medical Sciences 2025;12(3):26
https://doi.org/10.48087/BJMSra.2025.12326

REVIEW ARTICLE

Clinical co-management of gouty nephropathy: A bidirectional interface between rheumatology and nephrology

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ABSTRACT

Gouty nephropathy is a complex clinical condition that intertwines rheumatology and nephrology, characterized by a bidirectional pathophysiological relationship in which hyperuricemia leads to kidney damage while chronic kidney disease (CKD) exacerbates urate deposition. This intricate interplay presents unique diagnostic and therapeutic challenges that necessitate coordinated management. A comprehensive literature analysis spanning from 1970 to 2025 was conducted using PubMed and Cochrane databases, along with clinical guidelines, to synthesize evidence regarding gout pathophysiology, renal urate handling, manifestations of acute and chronic nephropathy, and management strategies in CKD. Key findings indicate that uric acid (UA) solubility is pH-dependent, with significant implications for crystal nephropathy pathogenesis. Renal handling of UA involves glomerular filtration followed by proximal tubule reabsorption, with only a small percentage ultimately excreted. In CKD, impaired urate excretion leads to disproportionate hyperuricemia. The dialysis paradox is evident, as hemodialysis (HD) can rapidly lower serum urate (SUA) levels but may trigger flares in a notable percentage of patients due to crystal mobilization. Diagnostic challenges arise because acute gout flares can present with normal UA levels during inflammation, complicating biomarker interpretation in CKD. Dual-energy CT (DECT) has demonstrated high specificity for crystal detection but reduced sensitivity in early gout. Management in advanced CKD requires careful consideration of renal dosing for xanthine oxidase inhibitors (XOIs), flare prophylaxis with low-dose colchicine or prednisone, and the use of SGLT2 inhibitors for uricosuria in diabetic patients, while avoiding NSAIDs and thiazides. Interdisciplinary coordination is crucial, requiring nephrology referrals for unexplained renal decline or stones, rheumatology referrals for refractory gout or tophi, and shared decision-making for urate-lowering therapy (ULT) selection. Effective management of gouty nephropathy ultimately depends on integrating expertise from both fields, implementing evidence-based medication adjustments for renal impairment, and establishing standardized co-management protocols to address ongoing research gaps in advanced CKD populations.

Keywords: Gouty nephropathy; hyperuricemia; CKD; gout interdisciplinary management; renal dosing.

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Received: 14 Jul 2025
Accepted: 20 Aug 2025

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1. INTRODUCTION

Gout, the most common inflammatory arthritis worldwide, and CKD share a complex bidirectional relationship with significant clinical implications. Hyperuricemia, defined as SUA > 7.0 mg/dL in men and > 6.0 mg/dL in women, affects approximately 21% of US adults and demonstrates increasing prevalence paralleling CKD rates globally. (1,2) Notably, CKD stage ≥3 elevates gout risk five-fold, while 24-39% of gout patients exhibit moderate-severe CKD, creating a challenging therapeutic landscape. (3) This interdependence stems from shared pathophysiological mechanisms: renal urate excretion impairment promotes monosodium urate (MSU) crystal deposition, while crystal-induced inflammation accelerates kidney damage through tubulointerstitial fibrosis, endothelial dysfunction, and renin-angiotensin system activation. (2)

2. METHODS

This narrative review synthesizes evidence on the pathophysiology, diagnosis, and management of gouty nephropathy. A literature search was performed using PubMed and the Cochrane Library for publications from 1970 to January 2025. Search terms included "gouty nephropathy," "hyperuricemia," "chronic kidney disease," "urate-lowering therapy," "allopurinol," "febuxostat," "dialysis AND gout," and "dual-energy CT AND gout." The search was limited to human studies and the English language. Articles were selected based on relevance to clinical co-management, including clinical trials, systematic reviews, meta-analyses, and consensus guidelines from major nephrology and rheumatology societies. Exclusion criteria included non-English articles, animal studies, and basic science research without clinical relevance. Data were extracted and synthesized to provide a clinically focused overview. However, limitations include the exclusion of non-English studies and the lack of a formal meta-analysis, which may affect the generalizability of some findings. This structured approach aims to provide a comprehensive yet practical synthesis of current evidence on gouty nephropathy and its management in CKD patients.

3. PATHOPHYSIOLOGY OF GOUTY NEPHROPATHY

Uric acid metabolism and renal handling

UA is a weak organic acid (pKa 5.8) existing mainly as soluble urate anion at physiological pH (~98% at pH 7.4), but in urine its solubility falls sharply with acidity (200 mg/dL at pH 7 vs 15 mg/dL at pH 5). (4,5) It is synthesized in the liver from purine metabolism via the de novo and salvage pathways, with xanthine oxidoreductase converting purine nucleotides to UA and hypoxanthine-guanine phosphoribosyl-tranferase (HGPRT) recycling hypoxanthine. Overactivity of phosphoribosyl pyrophosphate synthetase can cause excess UA production. (6,7) Renally, urate is freely filtered, ~90% reabsorbed in the proximal tubule (URAT1, GLUT9), and partly secreted, leaving only 6–10% excreted. (5,7–9) Its handling is influenced by drugs (diuretics, salicylates), organic acids, urine pH, hydration, and renal perfusion. (7–10, 12) Acidic urine promotes crystal formation, while reduced blood flow limits secretion, explaining hyperuricemia in conditions like hypertension or sickle cell disease despite preserved filtration. (1,8)

4. CLINICAL MANIFESTATIONS

Urate nephropathy

Urate crystal deposition in the kidney can cause either acute obstruction with abrupt AKI or chronic interstitial injury leading to CKD. (13,22) Clinical patterns are broadly classified into acute and chronic forms.

-*Acute uric acid nephropathy (AUAN).* AUAN results from intratubular UA crystal precipitation, typically in tumour lysis syndrome but also in seizures, solid tumour therapy, or inherited disorders (e.g., Lesch-Nyhan). (13–17) It presents with sudden oliguria/anuria and marked hyperuricemia (>15 mg/dL); a UA:creatinine ratio >1 is suggestive. (18,19) Associated metabolic abnormalities include hyperkalaemia, hyperphosphatemia, and hypocalcaemia. (20,21) Prevention relies on hydration, rasburicase, and XOIs, while established AKI may need diuretics or dialysis; bicarbonate is reserved for acidosis. (1)

-*Chronic urate nephropathy.* This CKD form reflects urate crystal deposition in the medullary interstitium, provoking chronic inflammation and fibrosis. (22) It presents with mild proteinuria, reduced renal function, and disproportionate hyperuricemia. (3) Diagnosis can be challenging. Historically, it was often confounded by lead nephropathy (23,24), a condition now rare but once frequently associated with tophaceous gout (25). In such cases, confirmation often relied on renal biopsy. (26–28)

SUA may be affected by drugs such as diuretics (increase) or losartan (decrease). (3) The role of hyperuricemia in CKD progression and the benefit of ULT remain debated. (3,29,31)

-Dialysis paradox (lower urate but increased flares). Haemodialysis can reduce SUA by 60–70% (e.g., from ~78.8 to ~26.4 mg/L), yet paradoxically triggers flares. (32) Rapid UA shifts disturb MSU equilibrium, mobilizing crystals into joints; intravascular volume removal, haemoconcentration, and acid–base changes may also reduce MSU solubility. (33) Clinically, 35.4% of HD patients had flares after initiation (50% without ULT vs. 22.7% with ULT), (34) and population studies report incidences of 10–25% despite low SUA. (35) In contrast, some reviews note fewer flares with advanced CKD and long-term dialysis, (36) but early after initiation, gout activity often persists—highlighting the paradox that UA removal does not equal remission. (33)

5. DIAGNOSTIC CHALLENGES AND OVERLAP

Diagnosing and managing complications in patients with coexisting gout and CKD presents unique challenges due to overlapping clinical features, confounding laboratory results, and the need for specialized imaging techniques.

Joint vs. Renal Flare Identification

Distinguishing an acute gout flare from renal-related pain in patients with CKD is clinically challenging. An acute gout flare typically presents with sudden, severe pain, swelling, erythema, and warmth in one or more joints—most classically the first metatarsophalangeal joint (podagra). (37) Systemic features such as fever and malaise may also occur. (38) In contrast, renal colic due to uric acid nephrolithiasis, a common complication of hyperuricemia, manifests as acute flank pain radiating to the groin, often with haematuria. (39)

In advanced CKD, atypical presentations complicate the picture: diffuse musculoskeletal pain, uraemia-related symptoms, superimposed. Careful history (pain site, nature, and radiation), urinary symptoms, and a thorough physical examination are essential. The presence of tophi strongly supports gout, though their absence does not exclude it, especially in early disease. (40,41)

Laboratory confounders.

SUA is central to gout management, with a target of <6 mg/dL. (38,42) However, during acute flares, SUA may be normal or even low in 14–50% of cases due to cytokine-driven uricosuria or sequestration of urate into joints. (43,41) Hence, SUA levels during a flare can be misleading diagnostically. In contrast, CKD itself reduces urate clearance, so hyperuricemia may persist even without flares. (42,44) Inflammatory markers (CRP, ESR) typically rise during flares but are non-specific, as CKD and infections can also elevate them. (8,91) Renal function tests (serum creatinine, eGFR) are essential for staging CKD and adjusting therapies, but acute changes may occur with NSAID use, dehydration, or intercurrent renal insults. Synovial fluid analysis remains the gold standard, demonstrating negatively birefringent, needle-shaped MSU crystals. (45) This step is particularly important when septic arthritis is a differential diagnosis.

Imaging modalities.

When laboratory and clinical findings are equivocal, imaging provides additional clarity.

- *Dual-energy CT (DECT):* Highly specific for MSU deposits, using dual spectra to color-code urate. (46–48) Sensitivity is ~90% and specificity 83–84%, though lower in early gout (<6 weeks). (38,49) It can quantify urate burden and distinguish gout from CPPD. (50)
- *Musculoskeletal ultrasound (MSKUS):* Shows the “double contour sign,” tophi, and erosions. (41) Sensitivity is ~83% and specificity 76%. (51) It surpasses plain X-rays for early erosions and can guide aspiration.
- *Renal ultrasound:* First line for nephrolithiasis and CKD changes. (38,46,52) It detects hydronephrosis and stones, though it is less sensitive than non-contrast CT (NCCT) for stones <5 mm or ureteric calculi. (53,54) It also evaluates kidney size and cortical thickness, aiding chronic damage assessment.
- *Plain radiography:* Limited in early disease but reveals classic juxta-articular erosions and “overhanging edges” in advanced gout. (41)

6. OPTIMIZING GOUT MANAGEMENTIN CKD

Pharmacologic management

The pharmacologic management of gout in CKD involves treating acute flares and long-term ULT to prevent recurrent attacks and complications (Table1).

Table 1. Pharmacologic Management of Gout in CKD.

Drug	Use	Dosing Considerations
Allopurinol	First-line urate-lowering therapy (ULT) for gout management.	Start low (≤100 mg/day, as low as 50 mg/day in CKD stage 4 or worse) and titrate every 2-5 weeks to target SUA <6 mg/dL. Testing for the HLA-B*5801 allele is recommended in high-risk populations.
Febuxostat	Alternative first-line ULT if allopurinol is contraindicated or not tolerated.	Starting dose ≤ 40 mg/day; titrate up to 80 mg/day as needed. Minimal renal excretion makes it suitable for CKD.
Pegloticase	Reserved for severe, refractory chronic gout with high tophi burden.	Administered via IV infusion; requires G6PD deficiency screening due to risk of haemolysis. Monitor for infusion reactions and anti-drug antibodies.
NSAIDs	Effective for acute gout flares but should be used cautiously in CKD.	Avoid in patients with eGFR <30-60 mL/min due to risks of acute kidney injury and gastrointestinal bleeding. Use the lowest effective dose for the shortest duration.
Colchicine	Effective for acute flares, especially if initiated early.	Requires dose adjustment in CKD to avoid toxicity (e.g., 1.2 mg followed by 0.6 mg one hour later for acute flare). Monitor for drug interactions.
Corticosteroids	Preferred for acute flares in significant CKD; can be oral or intra-articular.	Oral prednisone (30-40 mg daily for 5-10 days) or intra-articular injections are recommended. Monitor for side effects like hyperglycaemia and fluid retention.
IL-1 Inhibitors	Effective for severe or refractory flares but typically reserved for cases where other treatments are ineffective.	Expensive and not first-line; used when other options are unsuitable.

Urate-lowering therapy management in CKD

ULT in CKD with symptomatic hyperuricemia

Patients with CKD and symptomatic hyperuricemia should receive ULT. Strong evidence supports its use in those with tophi, radiographic damage, or recurrent flares—many of whom also have CKD. (55) Safety analyses indicate no increased risk of hypersensitivity, liver toxicity, cardiovascular events, or mortality. (56–58) This aligns with the ALL-HEART trial findings, which showed no cardiovascular risk difference with allopurinol in older patients with ischemic heart disease and varying kidney function. (59)

Initiation after first gout episode in CKD

Although not universally recommended after a first gout attack, ULT is suggested in CKD stages G3–G5 when SUA exceeds 9 mg/dL or if urolithiasis is present, due to higher risk of disease progression. (55) Initial therapy may trigger flares, requiring patient counseling. Initiating therapy during a flare does not prolong it (60,61**),** and once started, treatment should continue long-term (55).

Drug choice: Xanthine oxidase inhibitors over uricosurics

XOIs are the foundation of ULT**. Allopurinol** remains the first-line agent, even in moderate-to-severe CKD (stage ≥3) (5), using a "start low, go slow" strategy starting at ≤100 mg/day (≤50 mg/day in stage 4 or worse) and titrating every 2–5 weeks to reach SUA < 6 mg/dL. (42) HLA-B*5801 testing is advised in high-risk ethnic groups (e.g., Han Chinese, Koreans, and Thai with CKD ≥ stage 3) to reduce the risk of allopurinol hypersensitivity syndrome (AHS). (5,12) Studies show allopurinol can be safely used in CKD without accelerating renal decline. (62)

Febuxostat, metabolized primarily in the liver, is an alternative first-line XOI, especially when allopurinol is not tolerated. (63) Starting at 40 mg/day, it may be titrated to 80 mg/day. Although initially thought superior to fixed-dose allopurinol in CKD, trials show similar efficacy when allopurinol is dose-escalated. (21) Cardiovascular safety concerns raised by the CARES trial (64) remain debated; thus, febuxostat use should be individualized, particularly in those with high cardiovascular risk. (65)

Pegloticase, a recombinant uricase, is reserved for severe, refractory gout in patients unresponsive to XOIs. (66) Administered IV, it rapidly lowers SUA but is limited by immunogenicity, infusion reactions, and the need for G6PD screening. (67,68) Co-therapy with immunosuppressants (e.g., methotrexate) is under investigation. (69)

Acute gout management in CKD

Managing gout flares in CKD is challenging**. NSAIDs** should be avoided or used cautiously due to nephrotoxicity, hyperkalaemia, and cardiovascular risk, especially at eGFR <30–60 mL/min. (69) **Colchicine,** though effective, requires dose reduction in CKD to avoid toxicity; caution is needed with interacting drugs (e.g., CYP3A4 or P-gp inhibitors). (70–72**) Oral or intra-articular corticosteroids** are often preferred in advanced CKD due to their non-renal metabolism, though side effects include hyperglycaemia, fluid retention, and infection risk. (73,74**) ACTH and IL-1 inhibitors** (e.g., anakinra) are alternative options for refractory flares. (74)

Managing gout in CKD, particularly in dialysis patients

It requires balancing efficacy and safety due to altered pharmacokinetics and comorbidities. Key principles and evidence-based recommendations are synthesized below: continue ULT in dialysis patients using renal-dosed allopurinol (e.g., 100 mg thrice weekly post-dialysis) or febuxostat (20-40 mg daily, liver-metabolized). Employ a "start low, go slow" titration strategy (increments ≤ 50-100 mg, intervals ≥ 2-5 weeks) to achieve SUA targets (< 6 mg/dL, or < 5 mg/dL with tophi). (33)

Non-Pharmacologic Strategies: Adjunctive measures include limiting alcohol (especially beer/spirits), red meat, seafood high in purines, and high-fructose corn syrup; encourage low-fat dairy, vegetables, cherries, and the DASH diet. (75-78) Maintain hydration to reduce urolithiasis risk. (79) Implement supervised weight loss to lower SUA and flare frequency, avoiding rapid loss. (80)

Asymptomatic hyperuricemia: KDIGO does not recommend ULT solely for asymptomatic hyperuricemia to delay CKD progression due to lack of proven benefit. (57)

Comorbidity management

Gout and CKD are frequently associated with metabolic and cardiovascular comorbidities, including hypertension, diabetes mellitus, dyslipidaemia, and metabolic syndrome (86). Effective management is crucial for overall health and may positively impact both conditions.

Hypertension: Blood pressure control is vital. Losartan is unique among ARBs for promoting UA excretion, making it advantageous for hypertensive gout patients. (3) Diuretics (thiazides/loop) increase SUA and should be avoided unless essential for volume control. (81)

Diabetes Mellitus: SGLT2 inhibitors (e.g., empagliflozin) lower SUA levels and reduce gout risk. (82)

Dyslipidaemia: Fenofibrate has uricosuric effects and benefits patients with gout and hypertriglyceridemia. (83)

Metabolic syndrome: Address all components (obesity, hypertension, insulin resistance, dyslipidaemia) through lifestyle modifications like exercise and diet. (84)

A "treat-to-target" ULT strategy, combined with appropriate flare prophylaxis, safe acute management, non-pharmacologic interventions, and comorbidity control, optimizes outcomes in CKD patients with gout, including those on dialysis. (85)

7. Interdisciplinary coordination in gout and CKD management

Gout and CKD frequently coexist, creating complex clinical scenarios that require close coordination between rheumatologists and nephrologists. Effective collaboration enhances diagnostic accuracy, individualizes therapy, reduces medication-related risks, and improves long-term outcomes. (85) Despite the high prevalence of gout in CKD, it is often undertreated; nephrologists may defer management to rheumatologists or primary care, while rheumatologists may need nephrology input for CKD complications. (85)

Referral timing between rheumatologists and nephrologists

Timely, bidirectional referral is essential for optimal care (Figure 1)

Rheumatologist to nephrologist:

- New or established gout with unassessed CKD (eGFR <60 mL/min/1.73 m^2, persistent proteinuria, or abnormal renal imaging).
- Progressive renal decline, resistant hypertension, or fluid imbalance despite gout therapy.
- Suspected urate nephropathy or recurrent UA stones.
- Severe CKD or dialysis patients requiring ULT or steroid adjustment.
- Concerns about drug nephrotoxicity or assessment of ULT's potential renoprotective effects.

Nephrologist to rheumatologist:

- CKD patients with acute arthritis of unclear cause, especially when arthrocentesis is not feasible.
- Hyperuricemic CKD patients with recurrent flares, tophi, or gouty arthropathy for ULT initiation and treat-to-target monitoring.
- Refractory gout or intolerance to standard ULT, or need for advanced agents like pegloticase.
- Complex differential diagnosis (e.g., distinguishing gout from lupus nephritis or vasculitis).

Proactive referral and co-management improve flare prevention, medication safety, and patient outcomes in both specialties.

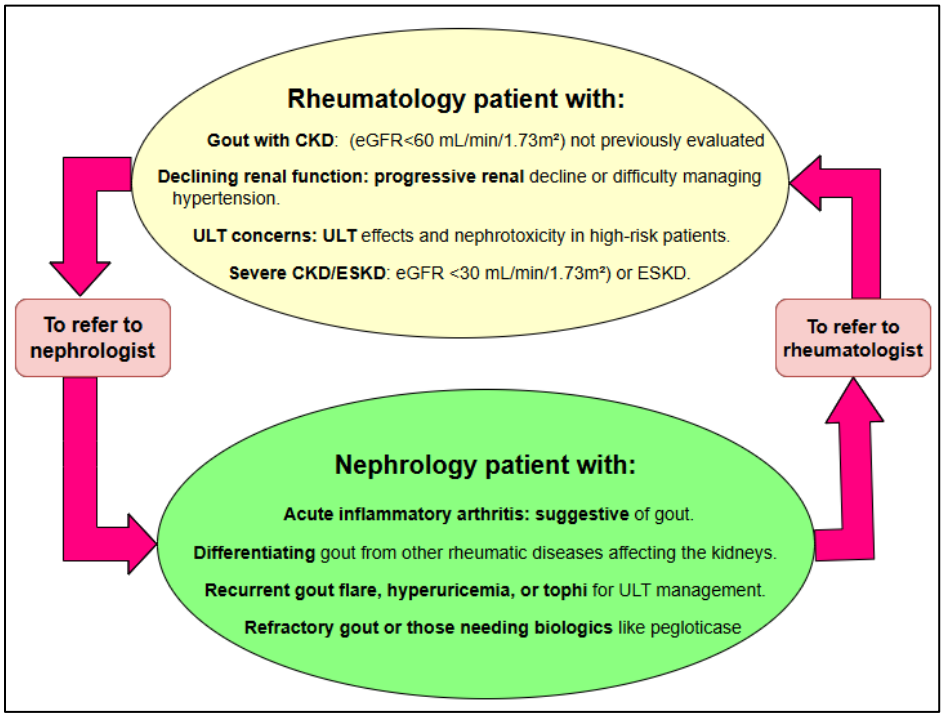

Figure 1. Referral timing: when should rheumatologists consult nephrologists, and vice versa.

Shared decision-making and integrated care models

Shared decision-making (SDM) is pivotal when selecting ULT (e.g., allopurinol vs. febuxostat), considering cardiovascular risk, renal function, genetic factors like HLA-B*5801, and patient preferences. (86) It also guides choices in acute flare treatments with renal safety in mind, lifestyle strategies based on adherence capacity, and use of pegloticase in refractory cases requiring careful planning.

Integrated care is best delivered through formal co-management models: joint rheumatology-nephrology clinics, shared electronic health records, and regular case discussions improve coordination. Telehealth consultations extend access in underserved areas, while nurse-led ULT programs and multidisciplinary input (from pharmacists, dietitians, and primary care) enhance education and follow-up.

8. RESEARCH GAPS AND FUTURE DIRECTIONS

Despite advances, critical evidence gaps remain. Most randomized controlled trials (RCTs) exclude patients with CKD, especially eGFR <30 mL/min/1.73 m², limiting guidance on the safety and efficacy of ULTs and anti-inflammatory agents in this population. (87,88) Future studies must include all CKD stages and evaluate colchicine, corticosteroids, and IL-1 inhibitors for acute gout in renally impaired patients. (89) Clarifying whether SUA target achievement improves renal outcomes requires RCT validation (90), along with standardized outcome measures to enable meta-analysis(35).

Genetic studies (e.g., ABCG2, SLC2A9 variants) and pharmacogenomics (e.g., HLA-B*5801 testing) offer personalization opportunities in ULT. (91) Advanced imaging, like DECT, may support diagnosis and treatment monitoring. (92) A coordinated, patient-centered research agenda is essential to optimize gout and CKD outcomes across care settings.

9. CONCLUSION

Gouty nephropathy represents a multifaceted clinical interface between rheumatology and nephrology, underscoring the importance of an integrated approach to diagnosis, treatment, and long-term management. The bidirectional relationship between hyperuricemia and CKD complicates both the presentation and therapeutic options, necessitating individualized care that accounts for altered pharmacokinetics, diagnostic challenges, and overlapping comorbidities. Current evidence emphasizes the need for careful interpretation of SUA levels, particularly during acute flares and in the context of advanced renal dysfunction. Diagnostic advances such as DECT and MSKUS, along with renal imaging, enhance detection and monitoring, yet access and sensitivity limitations persist.

Management strategies must balance efficacy with renal safety, employing renal-dosed XOIs, cautious flare prophylaxis, and non-pharmacologic interventions while avoiding nephrotoxic agents. Interdisciplinary coordination between rheumatologists and nephrologists is critical for optimizing treatment, ensuring timely referrals, and implementing SDM for complex cases. Despite progress, significant research gaps remain, particularly in the inclusion of patients with advanced CKD in clinical trials and the validation of treat-to-target urate strategies within this population. Ultimately, improving outcomes in gouty nephropathy will require not only collaborative clinical care models but also a unified research agenda that prioritizes patient-centered, evidence-based protocols for this underserved and often undertreated cohort.

Competing interests: The authors declare that they have no competing interest.

Funding: This research received no external funding.

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