REVIEW ARTICLE

CLINICAL ADVANCES IN NEPHROLITHIASIS

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Abstract:

Nephrolithiasis, or kidney stone disease, is a common and recurrent urological disorder influenced by urinary supersaturation, pH, anatomical factors, infections, genetics, and diet. Calcium-containing stones (oxalate and phosphate) are most prevalent, followed by uric acid, struvite, cystine, and rare stones. Diagnosis relies on clinical assessment, urine and serum studies, and imaging techniques such as ultrasound, CT, and endoscopy, with advanced tools like dual-energy CT, FTIR, and AI improving detection and risk stratification. Stone formation involves nucleation, growth, and aggregation, promoted by supersaturation, Randall's plaques, infections, and deficiencies in inhibitors like citrate and magnesium. Management combines pharmacotherapy (thiazides, potassium citrate, allopurinol, thiol drugs), minimally invasive surgery (ESWL, ureteroscopy, PCNL), and preventive strategies including hydration, dietary modifications, and correction of metabolic abnormalities. Despite advances, recurrence remains high, highlighting the importance of tailored therapy and lifestyle interventions.

Keywords: Nephrolithiasis, Kidney Stones, Pharmacotherapy, Dietary Modification.

Introduction:

Nephrolithiasis, commonly referred to as kidney stone disease, represents one of the most prevalent and recurrent urological disorders worldwide. Characterized by the formation of crystalline concretions within the urinary tract, it imposes a substantial clinical and economic burden on healthcare systems. are classified based on their chemical composition, with calcium-containing stones being the most prevalent worldwide. Calcium oxalate stones account for approximately 60% of adult cases and typically form in acidic urine, appearing black or dark brown with monohydrate 'dumbbell' or dihydrate tetragonal crystals, while calcium phosphate stones constitute 10–20% of cases, forming in alkaline urine and often associated with infections such as Proteus, presenting as dirty white, radio-opaque stones. Uric acid stones, representing 5–10% of cases, develop in persistently acidic urine, particularly in individuals with metabolic disorders or high purine intake, and are radiolucent, yellow to reddish-brown, with pleomorphic crystals. Struvite stones, comprising 3–15% of stones, form in alkaline urine

due to urease-producing bacterial infections and exhibit a characteristic 'coffin-lid' morphology; they can rapidly grow into large staghorn calculi. Rare stones, including cystine, xanthine, and those associated with metabolic disorders or certain drugs, are less common but clinically significant, with cystine stones appearing pink-yellow and hexagonal under microscopy. Stone location varies across the urinary tract, with small stones (<5 mm) often passing spontaneously, whereas larger calculi, especially staghorn stones, typically require surgical intervention.

Kidney stones are a common urological condition that affects all geographical, cultural, and racial groups. The global lifetime risk of nephrolithiasis is estimated to range between 10% and 15%, with higher prevalence observed in industrialized nations and regions with hot climates where dehydration is common, but it can reach 20–25% in the Middle East. The higher prevalence in hot climates is primarily due to increased risk of dehydration, compounded by dietary patterns that are roughly 50% lower in calcium and 250% higher in oxalates compared to Western diets. Consequently, uric acid stones are more common than calcium-containing stones in the Middle East. Globally, the number of deaths attributable to kidney stones is estimated at approximately 19,000 annually, a figure that has remained fairly stable between 1990 and 2010.Recurrence is particularly problematic: nearly 50% of patients experience another episode within 5–10 years of the initial stone event, underscoring its chronic and relapsing nature. [1-2]

Aetiological Insights of Nephrolithiasis:

Renal calculi develop due to an imbalance in the concentration of stone-forming substances in the urine. Their formation is influenced by multiple factors, including metabolic, dietary, genetic, and environmental causes. [3-10]

Table 1: Comprehensive Aetiological insights of Nephrolithiasis

Etiological Factor	Mechanism	Clinical Implications
Low Fluid Intake & Dehydration	↓ Urine volume → ↑ concentration of calcium, oxalate, uric acid → supersaturation and crystallization. Occupational factors (e.g., surgeons, drivers) limit hydration.	RCTs & meta-analyses show ≥2–2.5 L/day urine output reduces recurrence; cystinuria patients require ≥3 L/day.
Supersaturation of Urine	Excess calcium, oxalate, phosphate, uric acid exceed solubility → nucleation, crystal growth, aggregation. COD → COM transition stabilizes stones.	Central driving force of stone formation; protein–crystal interactions stabilize stone matrix.
Deficiency of Inhibitory Substances	↓ Citrate → less calcium–citrate complex formation; ↓ Magnesium → less Mg–oxalate binding. Both enhance calcium oxalate/phosphate precipitation.	Hypocitraturia and hypomagnesuria are strong risk factors; supplementation reduces recurrence.

Diabetes	Insulin resistance → impaired ammoniagenesis → persistently acidic urine; ↑ oxalate excretion.	↑ Risk of calcium oxalate and uric acid stones; uric acid nephrolithiasis most common in diabetics.
Cardiovascular Disease	Shared risk factors: hypertension, vascular calcification, oxidative stress. Randall's plaques parallel vascular calcification.	Stone formers have higher risk of hypertension, MI, and stroke; particularly strong in women.
Metabolic Syndrome / Obesity	Obesity → ↑ urinary calcium, oxalate, uric acid, sodium; ↓ urinary citrate; persistent acidic urine.	NHANES data: stone risk rises with number of metabolic syndrome traits; bariatric surgery may cause enteric hyperoxaluria.
Hyperparathyroidism	↑ PTH → ↑ bone resorption, intestinal calcium absorption, renal calcium reabsorption → hypercalciuria.	Leads to calcium oxalate ± phosphate stones; alkaline urine favors CaP formation.
Climate / Environment	Hot climate & summer → dehydration, concentrated urine → ↑ supersaturation.	Stone "belts" (e.g., SE USA). Climate change projected to increase global stone prevalence.
Lithogenic Drugs	Drugs precipitate directly (indinavir, triamterene, sulfadiazine) or alter urine chemistry (Ca/Vit D supplements).	1–2% of stones; HIV drugs now commonest cause; metabolic alteration or direct crystallization.
Genetic / Family History	Hereditary disorders: cystinuria, primary hyperoxaluria. GWAS: mutations in AGXT, GRHPR, SLC3A1, TRPV5, etc.	Familial clustering; early-onset and recurrent stones; monogenic causes in ~30% of pediatric/young adults.
Infections	Urease-producing bacteria (Proteus, Klebsiella, Pseudomonas) → alkaline urine → struvite & carbonate apatite stones. Non-urease bacteria (E. coli) adhere to crystals and promote biofilms.	Causes staghorn calculi; recurrent UTIs; biofilms shield bacteria → chronic infection–stone cycle.
Dietary Factors	High sodium → hypercalciuria; animal protein → ↑ uric acid, ↓ citrate; excess vitamin C/oxalate → hyperoxaluria; low Ca diet → ↑ oxalate absorption.	Diet central in prevention: hydration, moderate calcium, low sodium/animal protein, citrate-rich fruits protective.
Sedentary Lifestyle	Low activity → ↓ bone Ca deposition, ↑ urine concentration. Vigorous activity protective; excessive sweating can worsen risk.	Prolonged sitting linked to higher stone risk; moderate exercise beneficial.

Diagnosis of Nephrolithiasis – Clinical and Diagnostic Overview:

The diagnosis of nephrolithiasis involves a combination of clinical assessment, laboratory evaluation, and imaging studies to accurately identify the presence, location, and composition of urinary

stones. The evaluation of nephrolithiasis begins with a thorough assessment of clinical presentation, which differs between children and adults. In children, older individuals may present with colicky flank or abdominal pain and macroscopic hematuria, while younger children often exhibit nonspecific symptoms such as vomiting and irritability; stones in young children are frequently discovered following a urinary tract infection (UTI) or incidentally. Adults typically present with the classic acute-onset flank pain radiating to the groin, accompanied by hematuria and colicky pain. [11-12]

A detailed history is essential in both populations, focusing on diet, fluid intake, medications, and family history. In children, comorbidities such as inflammatory bowel disease, cystic fibrosis, Dent's disease, primary hyperoxaluria, ketogenic diet use, and prolonged immobilization may predispose to stone formation, while family history is positive in 50–75% of pediatric cases. Adults require a similar assessment for metabolic and lifestyle risk factors. Identifying modifiable dietary and metabolic contributors, along with genetic predisposition, can guide preventive strategies.

Laboratory evaluation includes urine and serum studies. Urine analysis with microscopy in children can reveal microhematuria, pyuria, bacteriuria, and pathognomonic crystals such as hexagonal cystine or coffin-lid struvite, indicating metabolic abnormalities or infection. Adults also undergo urinalysis and microscopy to assess hematuria and urinary tract infections. Serum studies in children focus on creatinine to detect acute kidney injury, with additional testing including CBC, electrolytes, calcium, and uric acid as indicated; adults receive similar testing along with parathyroid hormone (PTH) levels to identify obstruction, infection, or metabolic derangements.

Table 2: Comprehensive Diagnostic Overview of Nephrolithiasis

Diagnostic Method	Advanced Techniques / Tools	Clinical Relevance (Imaging / Example)	Paediatric vs Adult Considerations
Computed Tomography (CT)	Dual-Energy CT (DECT), Low-Dose CT	Differentiates stone composition (uric acid vs. calcium), guides therapy, reduces unnecessary interventions; low-dose protocols reduce radiation in recurrent stone formers (DECT color-coded image distinguishing uric acid (red) vs. calcium (blue) stones)	Adults: gold standard; Children: reserved if US non-diagnostic or for surgical planning due to radiation risk
Ultrasound (USG)	3D Ultrasound, Contrast-Enhanced Ultrasound (CEUS); Doppler twinkling artifact	Improves detection of small stones, hydronephrosis, complex anatomy; radiation-free; first-line in children (3D renal USG showing multiple calyceal stones)	Preferred initial imaging in children; adequate for clinically significant stones; may miss ≤3 mm stones

X-ray / KUB	Digital radiography with enhanced software	Quick initial screening for radiopaque stones; baseline follow-up for recurrence (High-resolution KUB X-ray showing radiopaque calcium stones)	Limited role in children; mainly follow-up of radiopaque stones
Endoscopy	Digital Flexible Ureteroscopy with laser integration	Real-time visualization and simultaneous therapeutic intervention (Ureteroscopic image showing stone in mid-ureter)	Used in both adults and children when intervention required
Stone Composition Analysis	Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD)	Accurate determination of stone type for tailored prevention and therapy (Spectroscopic graph identifying calcium oxalate vs. uric acid)	Important for recurrent stones or pediatric metabolic evaluation
Metabolic Evaluation	Automated 24-hour urine analyzers, genetic screening	Detects metabolic abnormalities (hypercalciuria, hyperoxaluria) and inherited disorders (cystinuria, primary hyperoxaluria) (Table of urine chemistry profile indicating high oxalate excretion)	Particularly important in children with recurrent stones or underlying metabolic/genetic disorders
Biomarker Detection	Urinary NGAL, osteopontin, cystatin C	Early detection, risk stratification, and monitoring of recurrence (Graph showing elevated urinary biomarker levels in stone formers)	Promising in pediatric risk assessment; not yet routine
Artificial Intelligence (AI) & Software	AI-assisted imaging analysis, predictive recurrence models	Enhances detection accuracy, quantifies stone burden, predicts recurrence risk (AI-generated CT segmentation highlighting all stones in the kidney)	Applicable to both adults and children; can reduce missed stones and optimize management
Urine Studies	Microscopy, urinalysis	Detect hematuria, infection, crystals; indicates metabolic cause	Pediatric: crystals may indicate metabolic disorders; adults: routine evaluation for stones and infection

Serum Studies	Creatinine, electrolytes, calcium, uric acid, CBC	Detect obstruction, acute kidney injury, infection, metabolic derangements	Critical in children with obstruction or infection; adults: used for baseline and recurrent stone workup

Pathophysiology:

Nephrolithiasis, are primarily composed of calcium salts, with calcium oxalate accounting for 70–80% of cases, followed by calcium phosphate and uric acid. Nephrolithiasis arises from a complex interplay of urinary supersaturation, crystal nucleation and aggregation, anatomical factors such as Randall's plaques, bacterial influences, and deficiencies in natural inhibitors like citrate and magnesium. Stone formation is a multistep process involving nucleation, growth, and aggregation. Nucleation represents the initial formation of microscopic crystals, which can grow individually or aggregate into larger masses. Supersaturation of urine with calculogenic substances is a necessary prerequisite for stone formation, as it promotes crystal nucleation. Heterogeneous nucleation, in which crystals form on a preexisting solid surface, is energetically favored over homogeneous nucleation in a liquid medium, allowing crystals to adhere to renal papillae and aggregate into clinically significant stones. The process is strongly influenced by urine pH; for example, uric acid solubility decreases from 158 mg/100 mL at pH 7.0 to less than 8 mg/100 mL at pH 5.0. Hyperuricosuria combined with acidic urine promotes uric acid stone formation, whereas hyperuricosuria alone is insufficient if the urine is alkaline. While supersaturation is necessary, it is not sufficient for stone formation; calcium-based stones, particularly calcium oxalate, often arise through additional mechanisms beyond simple crystalluria.

Randall's plaques, first described in 1937, are calcium phosphate deposits in the papillary interstitium that serve as a nidus for stone formation. Randall's plugs in the ducts of Bellini may similarly act as foci for stone development. These structures can generate reactive oxygen species, further promoting crystallization and stone growth. Bacterial factors also contribute to stone formation. Urease-positive bacteria, such as *Proteus mirabilis*, hydrolyze urea to ammonia and carbon dioxide, increasing urinary pH and facilitating struvite stone formation. Non-urease-producing bacteria can also promote calcium oxalate crystallization, although the mechanisms remain poorly understood.

Endogenous inhibitors in urine play a critical role in preventing stone formation. Citrate, a natural chelator, binds calcium ions, reducing supersaturation and inhibiting crystal growth and aggregation. Other inhibitory molecules include calgranulin, Tamm–Horsfall protein, glycosaminoglycans, uropontin, nephrocalcin, prothrombin F1 peptide, and bikunin, though their precise biochemical mechanisms are not fully elucidated. Deficiencies in these inhibitors, whether due to dietary insufficiency or metabolic disturbances, increase the risk of stone formation. Magnesium and citrate intake synergistically reduce the risk of calcium oxalate and calcium phosphate stones, with magnesium's effect being dose-dependent.

Hypocitraturia, defined as low urinary citrate excretion (often <320 mg/day), is observed in up to two-thirds of stone formers and is a significant risk factor. Citrate's protective effect stems from its

ability to form soluble complexes with calcium ions and to inhibit crystal nucleation, growth, and aggregation. Clinically, potassium citrate or other alkali citrate preparations are frequently administered to correct hypocitraturia, raise urinary citrate levels, and reduce the risk of recurrent stones. These interventions may be provided in prescription or over-the-counter forms, including tablets, powders, and liquids. [13-14]

Treatment / Management

Pharmacological Therapy:

Kidney stones are a heterogeneous group of crystalline disorders with distinct compositions, including calcium, uric acid, cystine, and struvite stones, each requiring targeted pharmacological strategies for prevention and management. Treatment primarily aims to modify urinary risk factors such as supersaturation, pH, and solute excretion, using agents like thiazides, potassium citrate, allopurinol, or cystine-binding drugs, depending on stone type and underlying metabolic abnormalities. [15-16]

1. **Calcium Stones (Calcium Oxalate and Calcium Phosphate):** Calcium stones are the most common type of kidney stones, accounting for about 70–80% of cases. Pharmacological therapy primarily targets hypercalciuria, hypocitraturia, and hyperuricosuria, which are major risk factors for recurrent stone formation. Thiazide and thiazide-like diuretics (e.g., hydrochlorothiazide, indapamide, chlorthalidone) are the mainstay for patients with recurrent calcium stones, especially those with hypercalciuria. These drugs act on the distal renal tubules to enhance calcium reabsorption, reducing urinary calcium excretion. By lowering urinary calcium, thiazides decrease supersaturation of calcium salts, thereby preventing crystal nucleation and growth. Long-term therapy with thiazides has also been shown to improve bone mineral density, providing additional benefit in patients at risk for osteoporosis. However, these drugs can cause hypokalemia, which may promote hypocitraturia; therefore, concomitant use of potassium supplements or potassium-sparing diuretics such as amiloride is often recommended. Another cornerstone in calcium stone prevention is alkali therapy, primarily with potassium citrate. Potassium citrate increases urinary citrate levels and alkalinizes urine, both of which inhibit calcium crystal formation and aggregation. Citrate binds calcium in the urine, reducing free ionic calcium available to form stones. Potassium citrate also improves bone health by neutralizing acid load and reducing bone resorption. In patients with hyperuricosuria, xanthine oxidase inhibitors such as allopurinol are effective in lowering uric acid levels, thereby decreasing uric acid–induced calcium stone formation. For patients with primary hyperoxaluria type 1, pyridoxine (vitamin B6) can significantly reduce urinary oxalate excretion by enhancing the residual activity of the defective enzyme, thereby decreasing calcium oxalate supersaturation.
2. **Uric Acid Stones:** Uric acid stones are typically associated with persistently acidic urine (pH <5.5) and hyperuricosuria. The primary pharmacological approach involves urinary alkalinization, which increases the solubility of uric acid, allowing existing stones to dissolve and preventing new stone formation. Potassium citrate or sodium bicarbonate is commonly used to maintain urine pH between 6.5 and 7.0. In addition, allopurinol is prescribed for patients with high urinary uric acid levels that are not adequately controlled by alkalinization alone. By inhibiting xanthine oxidase, allopurinol

reduces uric acid production, thereby decreasing the risk of stone recurrence. Adequate hydration is always recommended to maintain dilute urine and reduce supersaturation of uric acid.

3. **Cystine Stones:** Cystine stones are rare but often recurrent and challenging to manage due to the low solubility of cystine. Pharmacological therapy focuses on increasing cystine solubility and urine alkalinization. Patients are advised to maintain high fluid intake to achieve urine output above 3 liters per day. Potassium citrate is used to raise urine pH to at least 7.5, which enhances cystine solubility. In patients with persistent or recurrent stones despite these measures, thiol-containing drugs such as tiopronin or D-penicillamine are administered. These agents form soluble complexes with cystine, significantly reducing stone formation. Close monitoring is necessary due to potential side effects, including proteinuria, rash, or hematologic abnormalities.
4. **Struvite Stones:** Struvite stones, also called infection stones, form in the presence of urease-producing bacteria, such as Proteus species. Pharmacological therapy alone is generally insufficient; however, antibiotics are essential for controlling infection and preventing stone growth. Long-term or suppressive antibiotic therapy may be used in selected cases, especially if surgical removal is incomplete or not feasible. In rare circumstances, acetohydroxamic acid, a urease inhibitor, may be used to reduce stone growth in patients who cannot undergo surgery. Nevertheless, complete stone removal remains the cornerstone of treatment, as pharmacotherapy cannot reliably dissolve these stones.

Surgical Management:

While most kidney stones smaller than 5 mm pass spontaneously, surgical intervention becomes necessary in specific circumstances, such as in patients with a single functioning kidney, bilateral obstruction, intractable pain, or concurrent urinary tract infection suggesting an infected kidney. Since the mid-1980s, less invasive techniques—including extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, and percutaneous nephrolithotomy (PCNL)—have largely replaced open surgery as the preferred methods for stone removal. Flexible ureteroscopy has also been adapted for retrograde nephrostomy creation in PCNL, though this approach is still under investigation. Large or complex stones, such as calyceal staghorn calculi, or stones resistant to less invasive procedures are typically managed with PCNL, and rarely, anatrophic nephrolithotomy. [17]

Ureteroscopic surgery has gained popularity with the advent of smaller, flexible, and rigid fibreoptic ureteroscopes. One common approach is the placement of a ureteral stent—a small, double-J-shaped tube extending from the bladder to the kidney—to relieve obstruction, reduce hydrostatic pressure, and prevent complications such as pyelonephritis or postrenal acute kidney injury. Stents are usually retained for days to weeks, facilitating urine flow and allowing stone fragmentation by ESWL or laser lithotripsy. While stents can cause mild discomfort, frequency, urgency, or infection, these issues typically resolve upon removal, which can often be performed in an outpatient setting. Definitive ureteroscopic stone extraction can involve basket retrieval, ultrasound lithotripsy, or holmium:yttrium aluminium garnet (Ho:YAG) laser lithotripsy. Ureteroscopic techniques are particularly effective for distal ureteral stones, with success rates of 93–100%, and are preferred in pregnant, morbidly obese, or bleeding-prone patients.

For patients with obstructive stones and concurrent infection, urgent decompression with a ureteral stent or nephrostomy tube is a urological emergency. Initial management includes urine and blood cultures, broad-spectrum intravenous antibiotics, fluid resuscitation, and intensive monitoring, with definitive stone removal delayed until infection resolves. Stones up to 10 mm in uncomplicated cases may be managed with a trial of passage combined with medical expulsive therapy using NSAIDs and, in some cases, α-blockers to facilitate ureteral relaxation. α-blockers can reduce stone passage time and improve clearance, particularly for stones 6–10 mm in size, though their effect on smaller stones is minimal. Pain control is primarily achieved with NSAIDs, with opioids reserved for refractory cases, and intravenous lidocaine as a non-opioid alternative in emergency settings.

Surgical decision-making depends on stone size, location, and composition. For ureteral stones, medical expulsive therapy is typically offered for stones ≤10 mm without infection or obstruction, while ureteroscopy is indicated for stones >10 mm, mid- or distal ureteral stones, or stones unresponsive to conservative therapy. Renal stones are managed conservatively if <15 mm and asymptomatic, while symptomatic stones ≤20 mm may be treated with ESWL or ureteroscopy, and those >20 mm generally require PCNL. Lower pole stones ≤10 mm can be treated with ESWL or ureteroscopy, whereas larger lower pole stones may require ureteroscopy or PCNL. Staghorn calculi almost always necessitate PCNL, and nephrectomy may be considered in cases of negligible renal function accompanied by recurrent infection or pain. ESWL remains a less invasive option with lower morbidity but may have a lower single-procedure stone-free rate, particularly for hard stones such as calcium oxalate monohydrate, brushite, or cystine, which are often resistant to fragmentation.

Prevention and Supportive Measures:

Prevention of kidney stones depends largely on the type of stone and the underlying metabolic abnormalities. For individuals prone to calcium stones, strategies such as increased fluid intake, thiazide diuretics, and citrate supplementation have proven effective. In patients with elevated urinary uric acid levels, allopurinol may help reduce the risk of stone formation. The overarching goal of prevention is to reduce the excretory load of calculogenic substances, maintain urine dilution, and correct metabolic disturbances that predispose to stone formation. [18-19]

Dietary modifications play a central role in prevention. Increasing total fluid intake to achieve at least 2 liters of urine output daily is the cornerstone for all stone types, as dilute urine reduces supersaturation of stone-forming salts. Consumption of sugar-sweetened soft drinks, particularly colas, should be limited to less than one liter per week. Intake of animal protein should be restricted to no more than two meals per day, as excessive protein increases the risk of stone recurrence. Alkaline-rich foods, including fruits and vegetables, help prevent uric acid stones by increasing urinary pH, while citrate-rich foods such as lemons and limes coat calcium oxalate crystals, inhibit crystal growth, and reduce aggregation within the renal tubules. Sodium restriction also plays a role by lowering urinary calcium excretion.

Calcium intake should not be excessively restricted; dietary calcium binds oxalate in the gut, preventing its absorption and subsequent urinary excretion. Dairy products or calcium citrate supplements taken with high-oxalate meals are preferred, particularly for individuals with lactose

intolerance. Calcium citrate is favored over calcium carbonate because it enhances urinary citrate, providing an additional protective effect against stone formation. Limiting high doses of supplemental vitamin C and avoiding oxalate-rich foods—such as spinach, rhubarb, soy products, and chocolate—may further reduce stone risk. Magnesium intake has also been associated with a lower risk of symptomatic kidney stones.

Conclusion:

Nephrolithiasis is a multifactorial and recurrent disorder influenced by metabolic, genetic, dietary, and environmental factors, with stone type guiding both management and prevention strategies. Early diagnosis, targeted pharmacotherapy, minimally invasive surgical techniques, and lifestyle modifications are essential to reduce recurrence and improve patient outcomes.

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