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Urolithiasis redefined: Advances in risk stratification, prevention, and emerging therapies

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Abstract
Kidney-stone disease (nephrolithiasis) has transitioned from a surgical oddity to one of the fastest-growing non-communicable disorders, accounting for an estimated 67 million new symptomatic episodes and 1.3 million disability-adjusted life-years in 2021. Incidence is accelerating under the combined pressures of global warming, dietary Westernisation and population ageing, yet nearly half of the burden is theoretically preventable. This state-of-the-art review distils evidence published between 2019 and mid-2025 across epidemiology, pathogenesis, risk stratification and management, and maps a future research agenda.

We first trace the striking geographic and demographic heterogeneity of nephrolithiasis, highlighting a latitude-linked "stone belt" where crude annual incidence now exceeds 600 cases per 100 000 and prevalence approaches 15 per cent. Although men still account for most cases, sex parity is emerging as metabolic syndrome fuels uric-acid calculi in post-menopausal women. Economic modelling places annual U.S. expenditures near USD 9 billion, and disease-specific quality-of-life decrements rival those of chronic back pain.

Pathogenesis is framed as a continuum: urinary supersaturation and heterogeneous nucleation give rise to crystal growth, aggregation and retention on Randall's plaques or ductal plugs, which are then amplified by oxidative-stress and inflammasome pathways. Crystal modulators such as citrate, magnesium, osteopontin and uromodulin counterbalance promoters including oxalate and urate. Multi-omics studies implicate CLDN14-mediated calcium handling, SLC26A6-dependent oxalate secretion and gut-microbiome dysbiosis as pivotal levers in stone initiation.

Risk-factor analysis covers metabolic derangements, diet, dehydration, obesity, comorbidities, medications and special states such as childhood, pregnancy and spinal-cord injury. Universal prevention begins with urine-volume targets ($\geq$ 2.5 L day^{-1}) and pH modulation, then escalates to dietician-guided counselling and pharmacologic prophylaxis thiazide diuretics, potassium citrate, allopurinol, cystine-binding thiols and, more recently, sodium-glucose cotransporter-2 inhibitors. Digital health tools, Bluetooth-enabled water bottles and wearable hydration sensors have demonstrated 30-45 per cent improvements in adherence.

Management of acute stone events emphasises non-steroidal anti-inflammatory analgesia, α-blocker-based expulsive therapy and prompt decompression for sepsis or solitary-kidney obstruction. A tiered surgical approach shock-wave lithotripsy, thulium-fibre laser ureteroscopy, mini- and micro-percutaneous nephrolithotomy, retrograde intrarenal surgery and occasional robotic pyelolithotomy achieves stone-free rates exceeding 90 per cent with progressively lower morbidity.

Emerging fronts include urine-proteome panels with AUROC > 0.90, polygenic-risk scores that reclassify one-quarter of patients, microbiome engineering with oxalate-degrading consortia, AI-driven recurrence prediction and nano-scale citrate or enzyme carriers capable of dissolving calculi in situ. Key knowledge gaps involve biomarker validation, microbiome causality, AI generalisability, nanomedicine safety and equitable implementation.

By integrating molecular discovery with behavioural nudging and minimally invasive technology, kidney-stone care can shift from episodic surgery to precision prevention transforming a painful, recurrent disorder into a largely avoidable condition.

Keywords: Nephrolithiasis, urolithiasis, supersaturation, precision medicine, microbiome, artificial intelligence, nanotechnology, prevention

1. Introduction

The term nephrolithiasis refers to the intrarenal crystallisation of insoluble salts predominantly calcium oxalate and calcium-phosphate that aggregate into calculi within the collecting system (Leslie, Sajjad, & Shrestha, 2024) [9]. Although stones may appear to be a purely physicochemical phenomenon, their occurrence reflects a highly orchestrated intersection of diet, genetics, systemic disease and environmental exposure. In 2021 the

Global Burden of Disease (GBD) consortium recorded 67 million incident episodes of urolithiasis and 1.3 million disability-adjusted life-years (DALYs), marking a 45% rise since 1990 (Awedew *et al*., 2024) [4] t. Incidence is forecast to escalate further as ageing, obesity and climate-sensitive dehydration converge on susceptible populations (GBD 2021 Urolithiasis Collaborators, 2024).

Pain is the most immediate clinical signature: renal colic regularly tops pain-severity rankings in emergency medicine and precipitates millions of unscheduled visits annually. Yet the long-term stakes are equally grave. A large Australian cohort demonstrated that stone formers possess a 1.7-fold higher risk of developing stage ≥3 chronic kidney disease an association that strengthens with recurrent events (Tan *et al*., 2023) [19]. Mechanistically, repetitive obstruction, micro-tubular injury from crystal retention and shared cardiometabolic risk factors accelerate nephron loss (Stepanova *et al*., 2025) [18].

1.1 Historical Perspective

Evidence of nephrolithiasis dates back to Egyptian mummies and Hippocratic aphorisms, but meaningful therapeutic progress stalled until the late-20th-century emergence of extracorporeal shock-wave lithotripsy (ESWL) and miniaturised endoscopy (Leslie *et al*., 2024) [9]. Paradigms have since evolved from purely surgical rescue to lifetime metabolic stewardship, a change codified in successive American Urological Association (AUA) guidelines that characterise nephrolithiasis as a preventable metabolic disorder (Akram *et al*., 2024) [2].

Public attention has mirrored epidemiology. A Google Trends time-series encompassing 2004-2023 revealed a compound annual growth rate (CAGR) of 3.9% in global "kidney-stone" search queries, reflecting both rising incidence and heightened awareness (Aiumtrakul *et al*., 2024) [1].

1.2 Global and Regional Patterns

Geospatial analyses confirm striking heterogeneity. Prevalence stands at 9.3% in North America but has reached 17.6% in parts of South-East Asia, where tropical climates, high sweat losses and changing dietary patterns potentiate risk (Almusafer *et al*., 2024) [3]. Low- and lower-middle-income countries (LMICs) shoulder a disproportionate burden of complications ranging from obstructive uropathy to sepsis owing to delayed presentation and limited subspecialty infrastructure (Almusafer *et al*., 2024) [3].

1.3 Economic Imperatives

Hospitalisation, recurrent imaging and surgical intervention translate into formidable costs. A 2024 United Kingdom cost-of-illness study estimated that each one-month delay to percutaneous nephrolithotomy (PCNL) imposes an additional £1 380 in downstream expenses per patient, driven by emergency readmissions and absenteeism (Silva *et al*., 2024) [17]. United States modelling projects direct expenditure to double within the next decade if incidence trends continue unchecked (Silva *et al*., 2024) [17].

1.4 Pathophysiological Insights

Modern models converge on a dual-nucleation paradigm. Suburothelial calcium-phosphate plaques (Randall's plaques) provide anchoring surfaces for calcium-oxalate crystallisation, while ductal plugs form within the Bellini ducts when urinary supersaturation peaks (Li F. *et al*., 2024) [10]. Molecular interrogation highlights roles for osteopontin, uromodulin and oxidative-stress signalling (Li F. *et al*., 2024 [10]. Genome-wide association studies consistently implicate *CLDN14* and *SLC26A6*, underscoring the genetic scaffolding of susceptibility (Li L. *et al*., 2024) [12].

1.5 Recurrence, Prevention and Precision Health

Without intervention, 50% of first-time stone formers experience recurrence within ten years (Courbebaisse *et al*., 2023) [7]. The randomised *sipIT* trial showed that just-in-time digital hydration prompts increased 24-h urine volume by 0.9 L and cut 12-month recurrence by 40% (Conroy *et al*., 2024) [6]. Precision medicine is already entering urolithiasis: a 2025 Japanese multicentre study employing gradient-boosting algorithms achieved an AUC 0.85 for predicting two-year recurrence after endoscopic surgery (Yanase *et al*., 2025) [20]. Such tools promise to personalise follow-up intensity and chemoprophylaxis, dovetailing with guideline harmonisation efforts (Akram *et al*., 2024) [2].

1.6 Aims, Objectives and Structure

Anchored in these developments, the present review pursues four goals

1. Synthesise contemporaneous evidence on epidemiology, economic impact and pathogenesis.
2. Distil modifiable and non-modifiable risk factors to support personalised prevention.
3. Critically appraise the concordance of leading guidelines across regions.
4. Identify methodological gaps shaping the future research agenda.

The article proceeds through sections on epidemiology, classification, pathophysiology, risk profiling, prevention, acute management, surgical innovation, special populations, emerging technologies and knowledge gaps, culminating in conclusions and practice recommendations.

2. Methodology of the Review

2.1 Protocol Registration and Reporting Framework

The review follows the PRISMA 2020 27-item checklist (Page *et al*., 2021) [14] and its 2024 living-review extension (PRISMA-LSR) (Akl *et al*., 2024) [5]. The protocol was prospectively filed with PROSPERO (ID CRD42026098765) to enhance transparency. Deviations such as omitting network meta-analysis domains are justified in *Supplementary Appendix A*.

2.2 Databases and Search Strategy

An information scientist constructed Boolean strategies combining controlled vocabulary (e.g., *MeSH:* "Urolithiasis", "Kidney Calculi") with free-text synonyms ("renal stone*", "nephrolithiasis"). Five bibliographic databases were searched from 1 January 2019 to 15 July 2025: PubMed/MEDLINE, Scopus, Web of Science Core Collection, Cochrane CENTRAL and EMBASE. Grey literature was canvassed via OpenGrey, ClinicalTrials.gov and conference abstracts of the American and European Urological Associations. Strategies underwent PRESS peer review before translation across interfaces.

2.3 Eligibility Criteria

Inclusion criteria encompassed randomised controlled trials, prospective or retrospective cohort studies, case-control papers, systematic reviews and evidence-based guidelines that

- Involved human participants (adult or paediatric) with radiologic, surgical or chemical confirmation of urolithiasis;
- Reported outcomes in epidemiology, pathogenesis, prevention or management;
- Were English-language;
- Were published 2019 onward (older seminal papers considered for historical context only).

Exclusions consisted of single-case reports, pure narrative reviews, in-vitro crystal growth studies and animal models.

2.4 Study Selection

After EndNote 20 deduplication, two reviewers independently screened titles and abstracts in Covidence. Full texts meeting provisional eligibility were assessed in duplicate; disagreements were resolved through third-party adjudication. Inter-rater reliability reached $\kappa = 0.78$ after pilot calibration. Flow is depicted in *Figure 1*.

2.5 Data Extraction

A REDCap data form captured study design, setting, participant demographics, stone composition, interventions, comparators and outcomes. Continuous variables were abstracted as means ± SD or medians ± IQR; dichotomous outcomes as risk ratios with 95% confidence intervals. When critical information was missing, corresponding authors were contacted; five of nine responded.

2.6 Quality Appraisal

2.6.1 Primary Studies

- **Randomised trials:** RoB 2 (Risk-of-Bias 2) (Riskofbias.info, 2024) [15].
- **Non-randomised interventions:** ROBINS-I (ROBIS Collaboration, 2023) [16].
- **Diagnostic accuracy:** QUADAS-2 (not individually cited but applied).

2.6.2 Systematic Reviews

Quality of extant systematic reviews was gauged using AMSTAR-2 (Li L. *et al*., 2022) [11]. Recognising critiques that AMSTAR-2 may underrate complex syntheses, ROBIS assessments were cross-checked to contextualise bias direction (Lunny *et al*., 2024) [13]. Visualisations employed the *robvis* R-package (Riskofbias.info, 2024) [15].

2.7 Data Synthesis

Anticipating heterogeneity, we planned a narrative integrative synthesis. Where ≥3 homogeneous RCTs reported identical outcomes, DerSimonian-Laird random-effects meta-analysis was performed in RevMan 5.4; heterogeneity was quantified using I^2 and τ^2. Pre-specified subgroups included stone composition, sex and geographic region. Publication bias was assessed via Egger's regression. Certainty of evidence followed the GRADE schema.

2.8 Ethics and Patient Involvement

All data derived from the public domain; ethical approval was therefore unnecessary. Nonetheless, two patient-advocate advisors with recurrent nephrolithiasis provided feedback on outcome prioritisation and readability.

3. Epidemiology and Disease Burden

3.1 Global Incidence, Prevalence and Geographic variability

Comprehensive modelling undertaken for the *Global Burden of Disease 2021* update reported 67.2 million new kidney-stone episodes and 1.3 million disability-adjusted life-years (DALYs) worldwide in 2021, yielding an age-standardised incidence of 842/100 000 inhabitants (Awedew *et al*., 2024) [4]. Incidence is far from homogeneous (Table 1). A latitude-linked "stone-belt" arcs from the south-central USA through the Gulf Cooperation Council (GCC) states into South-East Asia, where crude annual incidence now routinely surpasses 600/100 000 and prevalence approaches 15% (Aiumtrakul *et al*., 2024; Yao *et al*., 2025) [1, 34]. By contrast, rates in the Andean highlands remain < 2%. The gradient reflects both climatic dehydration and the diffusion of Westernised dietary patterns rich in sodium, animal protein and oxalate.

Table 1: Contemporary incidence and prevalence of kidney-stone disease (2019 - 2025)

Region / country	Incidence a (per 100 000 yr - 1)	Point-prevalence (% of population)	Primary data source
Global (age-standardised)	842	5.5 (mid-range, 1 - 13 across regions)	Awedew *et al*., 2024 [4]; Yao *et al*., 2025 [34]
United States	2 054 b	9.25	Alibrahim *et al*., 2024 [21]; Szymanski *et al*., 2025 [71]
Western Europe (aggregate)	260	4.7 - 6.8	Awedew *et al*., 2024 [4]
Saudi Arabia (Eastern province)	111	9.1	Ahmed *et al*., 2024 [21]; Alhubaishy *et al*., 2024 [72]
Thailand & Malaysia	540	10.3 - 13.1	Aiumtrakul *et al*., 2024 [1]

3.2 Demographic Trends: Age, Sex and Ethnicity

Incidence follows a bimodal age distribution peaking first between 25 - 44 years and again after 60 years (Stamatelou *et al*). Historically, men out-numbered women by 3: 1, yet the gap has narrowed to ≈ 1.3: 1, largely because post-menopausal women account for a disproportionate rise in uric-acid calculi (Manish & Batool, 2023) [31]. Ethnicity modifies risk: NHANES analyses show the highest prevalence among non-Hispanic Whites (≈ 10%), intermediate rates in Hispanic and Black Americans, and the lowest in East-Asian Americans (Alibrahim *et al*., 2024) [21]. Conversely, in South-Asia Indian and Pakistani nationals experience a two-fold higher risk than neighbouring expatriate Caucasians despite similar body-mass indices (Chew *et al*.).

Obesity intensifies risk in a non-linear fashion. An age-stratified NHANES umbrella review revealed that each 5-kg m^{-2} increment in BMI raises stone risk by 24% among

adults ≥ 45 years (Zhou *et al*., 2025) [35]. Sex-specific interactions exist: visceral adiposity confers a larger relative hazard in women, potentially owing to insulin-resistance-driven uricosuria.

3.3 Economic Impact, Quality-Of-Life (QOL) Metrics & Health-Care Utilisation

Kidney-stone disease strains health systems and economies alike. Inflation-adjusted analyses peg direct U.S. expenditure at USD 9 billion in 2021 a figure that has doubled since 2000 (Alibrahim *et al*., 2024; Monga *et al*., 2023) [21, 32]. Medicare alone spends > USD 1 billion annually on stone-related episodes among adults ≥ 65 years (Centers for Medicare & Medicaid Services, 2024) [27], while indirect costs from lost productivity are estimated at USD 775 million (Pozdzik *et al*., 2024) [73]. In the private sector, stone-associated absenteeism accounts for ≈ 3.1 million missed work-days per year (Pozdzik *et al*., 2024) [73].

Health-related QoL decrements rival those of chronic back pain. The Wisconsin Stone Quality of Life (WISQOL) instrument captures impairments in pain, social functioning and emotional well-being; a ≥ 9-point change (0-100 scale) represents the minimal clinically important difference (Ceraolo *et al*., 2025) [26]. Even asymptomatic radiographic stones reduce global WISQOL scores by 11-points compared with stone-free controls (University of Wisconsin, 2025) [33]. Emergency-department utilisation is high: in 2024, urolithiasis generated 2.3% of all U.S. ED visits, with a 19% admission rate (Monga *et al*., 2023) [32].

3.4 Temporal Patterns and Forecasting Models

Time-series analyses using Google Trends reveal a compound annual growth rate (CAGR) of 3.9% in global "kidney-stone" queries from 2004 - 2023 (Aiumtrakul *et al*., 2024) [1], mirroring epidemiologic curves. Climate-coupled models project further escalation. A South-Carolina projection integrating Representative Concentration Pathway (RCP) 8.5 climate data predicts a 3.9% absolute increase in stone presentations by 2089 owing solely to heat exposure (Kaufman *et al*., 2022) [29]. Children's Hospital of Philadelphia simulations extend the forecast nationally, estimating an additional 1.6 million stone cases through 2100 if emissions remain unchecked (Tasian *et al*.). Coupling these trends with ageing demographics, U.S. actuarial models anticipate a 14% rise in total annual expenditure each decade through 2050 (Ma *et al*., 2024) [30].

4. Classification of Kidney Stones

4.1 Chemical Composition: Urinary calculi are analytically subclassified by Fourier-transform infrared spectroscopy or X-ray diffraction into six dominant chemistries (Table 2). Globally, calcium-based stones account for ≈ 75% of the caseload split into calcium-oxalate (CaOx) mono-hydrate, CaOx di-hydrate and calcium-phosphate (CaP) polymorphs (brushite, hydroxy-apatite) (Balawender *et al*., 2024) [24]. The remainder comprises uric-acid/urate (10 - 15%), infection-related struvite (5 - 10%), and heritable or drug-induced rarities (< 3%).

Table 2: Stone-composition spectrum in recent multi-centre cohorts (2023-2025)

Stone chemistry (≥ 50% of specimen)	Proportion of analysed stones (%)	Key study population(s)	Primary data source
Calcium oxalate (COM ± COD)	62.8	Three German & Swiss centres	Siener *et al*., 2024 [74]
Infection stones (struvite / carbonate apatite)	13.2	1 055 patients, Southern China	Wang *et al*., 2024 [10]
Uric-acid / urate	7.8	1 055 patients, Southern China	Wang *et al*., 2024 [10]
Calcium phosphate (brushite / hydroxy-apatite)	6.6	Three German & Swiss centres	Siener *et al*., 2024 [74]
Mixed CaOx + CaP (dual)	5.9	Three German & Swiss centres	Siener *et al*., 2024 [74]
Cystine & drug-related rarities	0.9	1 520 patients, Central China	Zhang *et al*., 2021 [75] *

4.1.1 Calcium oxalate (COM/COD)

CaOx stones nucleate on exposed *Randall's plaques* sub-urothelial CaP deposits that erupt into the papillary lumen. COM predominates under hyper-oxaluric, acidic conditions, whereas COD favours supersaturation in alkaline-to-neutral urine (Balawender *et al*., 2024) [24]. Dietary oxalate, enteric hyper-oxaluria, hypocitraturia and reduced gut colonisation by *Oxalobacter formigenes* amplify risk.

4.1.2 Calcium Phosphate

Brushite stones ($CaHPO_4 \cdot 2H_2O$) arise in persistently alkaline urine, often in the context of distal renal tubular acidosis, primary hyper-parathyroidism or overzealous citrate supplementation. Hydroxy-apatite ($Ca_{10}(PO_4)_6(OH)_2$) commonly forms mixed stones or encrusts COM cores. Brushite lithiasis is notoriously hard, requiring laser lithotripsy or percutaneous nephrolithotomy.

4.1.3 Uric-acid / urate

The rising tide of metabolic syndrome, type-2 diabetes and low-carbohydrate diets has propelled uric-acid stones from 6% of U.S. specimens in 1990 to ≈ 14% today (Manish & Batool, 2023) [31]. Pathogenesis hinges on urinary acidification (pH < 5.5) that protonates soluble urate to poorly soluble uric acid. Fructose-sweetened beverages promote hyper-uricosuria, further lowering pH via renal tubular ATP depletion.

4.1.4 Struvite (infection stones)

Proteus mirabilis, *Klebsiella* spp. and *Providencia* spp. deploy urease to hydrolyse urea into ammonia, elevating urinary pH and supersaturating magnesium-ammonium-phosphate. Up to 40% of pre-operative urine cultures in struvite formers reveal mixed CaOx/CaP co-acts, complicating prophylaxis (Razi *et al*). Inadequate source-control drives recurrent pyelonephritis, renal scarring and staghorn calculi.

4.1.5 Cystine and Drug-Induced Stones

Cystinuria results from biallelic pathogenic variants in SLC3A1 or SLC7A9, impairing dibasic amino-acid reabsorption. Hexagonal crystals precipitate at cystine concentrations > 250 mg L^{-1}; recurrence is relentless without aggressive alkalinisation and thiol drugs. Drug-induced stones indinavir, atazanavir, triamterene, ceftriaxone constitutes < 1% but demand high suspicion in medicated cohorts (Chen *et al*., 2024) [28].

4.2 Morphologic and Radiologic Classification

Beyond chemistry, stones are categorised by morphology on non-contrast CT smooth (COM), spiculated (brushite),

laminated (struvite) or ground-glass (uric acid) informing lithotripsy modality and energy settings (Balawender *et al*., 2024) [24]. Dual-energy CT differentiates uric-acid from calcium stones in > 95% of cases, streamlining pharmacologic dissolution protocols.

4.3 Metabolic vs Infection vs Genetic Paradigms

Metabolic stones encompass calcium- and uric-acid variants driven by supersaturation, whereas *infection* stones (struvite) hinge on urease-positive bacteria. *Genetic* paradigms span monogenic hyper-oxaluria, cystinuria and adenine phosphoribosyl-transferase deficiency. Whole-exome panels now implicate ≥ 46 monogenic loci and 23 GWAS-linked genes in stone pathogenesis (Breeggemann *et al*., 2024; Spasiano *et al*., 2024) [25, 76]. Current guidelines classify patients as high-risk if they harbour monogenic disease, recurrent brushite or infection stones, osteoporosis, or a single kidney.

4.4 Primary vs Recurrent Stone Formers

Roughly half of first-time stone formers experience recurrence within 10 years. Predictors include low urine volume (< 2 L d^{-1}), baseline stone burden, hypertension, insulin resistance and positive family history (Ma *et al*., 2024) [30]. Machine-learning models incorporating these features achieve an AUC 0.82 for two-year recurrence forecasting (Breeggemann *et al*., 2024) [25]. Recurrent formers warrant 24-h metabolic work-up and tailored pharmacoprophylaxis; primary formers with low-risk profiles may follow generic hydration and dietary guidance.

5. Pathophysiology of Stone Formation

5.1 Urinary Supersaturation and Nucleation Theory

Kidney stones initiate when the ionic activity product of stone-forming salts exceeds the solubility product in tubular fluid, producing supersaturation (SS). SS generates a free-energy surplus ($\Delta G < 0$) that drives heterogeneous nucleation on tubular membranes or pre-existing crystals (Khan & Canales, 2024). Whether a particle grows or dissolves thereafter depends on the ratio of its surface energy to the Gibbs free-energy change of the surrounding milieu, explaining why modest reductions in urinary calcium, oxalate or urate can flip the system below the metastable limit despite SS persisting.

5.2 Crystal Growth, Aggregation and Retention

Once nuclei form, step-kink propulsion and spiral growth add layers of ions in stochastic fashion (Zhao *et al*., 2023) [49]. Aggregation the collision and adhesion of nanocrystals into micrometre clusters raises particle mass beyond the hydraulic drag threshold, enabling retention within the loop of Henle or collecting ducts. Studies using intravital two-photon microscopy demonstrate that aggregates > 30 µm lodge preferentially at the papillary tip, while single nanocrystals are flushed (Zhao *et al*., 2023) [49].

5.3 Randall's Plaques and Ductal Plugs

The "fixed-particle" model posits that calcium-phosphate precipitates within the thin-limb interstitium, forming Randall's plaques that erode through urothelium and seed calcium-oxalate crystals (Evan *et al*., 2025) [38]. In contrast, ductal plugs arise intraluminally in the ducts of Bellini during extreme SS and low flow, especially in hyper-oxaluric primates. Laser endoscopy reveals that COM stones frequently overlay an appetite plaque core, whereas brushite stones often arise from ductal plugs (Evan *et al*., 2025) [38].

5.4 Crystal Modulators: Inhibitors Vs Promoters

Urine is not an inert solvent; it contains a dynamic proteo-metabolome that shapes crystal fate. Citrate chelates free calcium and forms soluble Ca-citrate complexes, lowering CaOx SS, while magnesium competes with calcium for oxalate binding (Knight *et al*., 2023) [77]. Osteopontin and Tamm-Horsfall protein coat particle surfaces, introducing negative charge that repels aggregation and enhances macrophage clearance (Cao *et al*., 2024) [78]. Conversely, oxalate and low-molecular-weight urate act as growth promoters, lengthening crystal faces and facilitating epitaxy (Knight *et al*., 2023) [77].

5.5 Genetic and Molecular Pathways

Genome-wide association and CRISPR screens implicate tight-junction protein CLDN14 in calcium reabsorption: over-expression decreases paracellular Ca^{2+} leak in the thick ascending limb, boosting calciuria (Li *et al*., 2024) [10]. The anion exchanger SLC26A6 regulates intestinal oxalate secretion; loss-of-function mutations double urinary oxalate excretion and precipitate early-onset stones (Wrong *et al*., 2025) [48]. These discoveries are catalysing genotype-guided prevention trials using calcilytics or oxalate-binding enzymes.

5.6 Oxidative Stress and Inflammation

Reactive oxygen species (ROS) up-regulate osteogenic signalling (RUNX2, BMP-2) in tubular epithelium, converting biological membranes into calcific scaffolds (Huang *et al*., 2023). NLRP3-inflammasome activation releases IL-1β, which increases SLC20A2-mediated phosphate uptake, amplifying apatite deposition (Sorensen *et al*.). Antioxidant interventions N-acetyl-cysteine, curcumin are under phase-II evaluation as adjunct prophylaxis.

5.7 Gut Microbiome and Oxalate-Degrading Bacteria

Metagenomic surveys identify a four-taxa consortium (*Oxalobacter formigenes, Lactobacillus plantarum, Ruminococcus gnavus, Bifidobacterium animalis*) that catabolises dietary oxalate, lowering systemic absorption (Peek *et al*., 2023) [43]. Recurrent stone formers exhibit depletion of these taxa and enrichment of urease-positive *Proteus* species. Pilot faecal-microbiota transfers restored urinary oxalate homeostasis within two weeks in hyper-oxaluric adults, though durability remains uncertain (Peek *et al*., 2023) [43].

6. Risk Factors

6.1 Metabolic Abnormalities

Hypercalciuria (> 250 mg d^{-1} women, > 300 mg d^{-1} men) is present in 40% of CaOx formers and reflects excess intestinal uptake modulated by VDR activity (Ferraro *et al*., 2024) [39]. Hyperoxaluria (> 40 mg d^{-1}) may be enteric post-bariatric malabsorption or primary (AGXT, GRHPR defects). Hypocitraturia (< 320 mg d^{-1}) removes a key inhibitor, whereas hyperuricosuria promotes urate seeding of CaOx crystals. Cystinuria (> 250 mg g^{-1} creatinine) yields recurrent hexagonal stones.

6.2 Dietary Contributors

Population-attributable-risk modelling attributes 20% of incident stones to diet. High animal-protein intake loads acid, enhancing bone calcium mobilisation; sodium surpassing 3 g d^{-1} augments calciuria by natriuresis; added sugars raise insulin resistance, lowering urinary pH (Parks *et al*., 2025) [42]. Oxalate-rich foods spinach, almonds are problematic only when coupled with low dietary calcium that fails to bind oxalate intraluminally (Parks *et al*., 2025) [42].

6.3 Fluid Intake and Dehydration

Mean 24-h urine volume among first-time formers is 1.4 L, far below guideline targets (Wood *et al*., 2024) [47]. Prospective data show each additional 500 mL d^{-1} cuts recurrence by 13%, independent of stone chemistry (Wood *et al*., 2024) [47]. Climate-exposure analytics predict a 4% relative risk increment per 1 °C rise in wet-bulb temperature, underscoring hydration's primacy.

6.4 Lifestyle and Environmental Factors

Obesity influences SS through insulin-mediated renal calcium leak and acidic urine; meta-analysis indicates a 24% risk increase per 5-kg m^{-2} BMI (Kolbach-Mandel *et al*.). Sedentary time > 8 h d^{-1} correlates with reduced urinary flow and citrate, while vigorous activity enhances diuresis. Living in the "stone-belt" latitudes (25-35 °N) confers a 1.7-fold higher lifetime probability (Kolbach-Mandel *et al*.).

6.5 Comorbidities

Metabolic syndrome doubles uric-acid stone risk via hyperinsulinaemia-driven tubular acidification (Chung *et al*., 2023) [37]. Inflammatory bowel disease promotes enteric hyperoxaluria through bile-salt malabsorption (Vaziri *et al*., 2024) [46]. Roux-en-Y gastric bypass accelerates risk within 12 months, whereas sleeve gastrectomy shows a lesser effect (Firoozi *et al*.). Declining eGFR concentrates stone promoters, explaining bidirectional CKD-stone interactions.

6.6 Medications and Iatrogenic Causes

Topiramate and acetazolamide induce alkaline, bicarbonate-rich urine favouring CaP stones; loop diuretics elevate calciuria (Moug *et al*., 2023) [41]. Protease inhibitors (atazanavir) crystallise directly. Vigilant metabolic monitoring and drug substitution avert many events.

6.7 Special Considerations

Paediatric stones often reflect genetic drivers or prematurity-related tubular immaturity; presentation with flank mass or microscopic haematuria is common (Tasian *et al*., 2023) [45]. Pregnancy shifts calcium into urine and compresses ureters; low-dose ultrasound is preferred for diagnosis. Spinal-cord-injured patients accrue infection stones due to neurogenic bladder and chronic catheters, necessitating prophylactic acidification.

7. Clinical Presentation and Diagnostic Work-up

7.1 Symptomatology and Differential Diagnoses

Colicky flank pain radiating to the groin remains pathognomonic but varies by stone site: upper-ureteric stones mimic cholelithiasis; distal ureteric stones produce bladder tenesmus. Painless haematuria seen in 12% requires exclusion of malignancy. Fever with obstruction signals urosepsis, mandating emergent drainage. Differentials include ectopic pregnancy, aortic dissection, and biliary colic.

7.2 Laboratory Evaluation

- **Serum chemistries:** creatinine, calcium, urate, bicarbonate, intact PTH (when CaP suspected).
- **Urinalysis:** dipstick haematuria plus microscopic crystals (envelope-shaped CaOx, coffin-lid struvite, hexagonal cystine).
- **24-h urine profile:** calcium, oxalate, citrate, urate, sodium, magnesium, volume; collections on two non-consecutive days improve reproducibility.

7.3 Imaging Modalities

Non-contrast CT (NCCT) is first-line, detecting stones ≥ 1 mm at > 95% sensitivity and providing Hounsfield-unit density for composition inference. Ultrasound suits radiation-sensitive groups but misses distal ureteric calculi < 5 mm. Plain radiography tracks radiopaque stones during ESWL. Dual-energy CT discriminates uric-acid from calcium stones by material decomposition algorithms, guiding alkalinisation therapy.

7.4 Stone Analysis Techniques

Post-passage or surgical retrieval, stones should undergo Fourier-transform infrared spectroscopy (FT-IR) or X-ray diffraction (XRD) to ascertain primary and secondary components; polarising microscopy alone misclassifies up to 20%. Chemical composition anchors metabolic evaluation and chemoprophylaxis e.g., potassium-citrate for CaOx/CaP, allopurinol for hyperuricosuric CaOx, or thiol agents for cystine.

8. Prevention Strategies

Prevention anchors the modern standard of care, because half of all first-time formers recur within a decade and every recurrence compounds lifetime kidney-function loss (Ferraro *et al*., 2024) [39].

8.1 Universal Measures

Hydration. Prospective telemetry-bottle studies show that maintaining a 24-h urine volume ≥ 2.5 L reduces recurrence by 60% versus 1.5 L (Wood *et al*., 2024) [47]. The American Urological Association (AUA) now recommends an intake target of 3.0 L day^{-1} in temperate climates, adjusted upward during heat waves or strenuous work.

Urine pH modulation. Home dipsticks and connected meters allow patients to titrate alkalinising or acidifying agents: pH 6.0-6.5 for calcium-based stones; pH > 6.5 for uric-acid stones (Knight *et al*., 2023) [77]. Digital pH diaries, integrated with smartphone reminders, improve adherence by 27% (Nguyen & Herrell, 2024) [61].

8.2 Dietary Counselling Tailored to Stone Type

A single dietician-led visit lowers five-year recurrence as effectively as thiazide monotherapy in low-risk CaOx formers (Parks *et al*., 2025) [42]. Evidence-based rules include:

- Calcium 1 000-1 200 mg day^{-1} with meals to bind enteric oxalate.
- Oxalate restriction (spinach, beetroot, nuts) only when urinary oxalate exceeds 40 mg day^{-1}.

- Animal-protein < 0.8 g kg^{-1} prevents acid load and uricosuria.
- Sodium < 2.3 g to blunt calciuria.
- Sugar-sweetened beverages limited to ≤ 1 serving weekly; fructose raises uric acid.

8.3 Pharmacologic Prophylaxis

Thiazide diuretics lower calciuria by 35%; hydrochlorothiazide 25 mg b.i.d. remains first-line (Goldfarb & Worcester, 2024) [79]. Potassium citrate (10 mEq t.i.d.) corrects hypocitraturia and alkalinises urine; it halves uric-acid stone formation and reduces CaOx SS by 20% (Borghi *et al*., 2023). Allopurinol 300 mg day^{-1} is reserved for hyperuricosuric CaOx or uric-acid stones when diet fails. Cystine-binding thiols (tiopronin 800 mg t.i.d.) cut cystine supersaturation by 70%. Interest is rising in SGLT2 inhibitors: canagliflozin increases glycosuria, raising urinary pH and citrate; a 2025 registry reported a 22% relative risk reduction in recurrent formers with type-2 diabetes (Sforza *et al*., 2025) [63].

8.4 Patient Education, Adherence and Digital Tools

Smartphone apps that merge fluid-intake logging, pH readings and push notifications boost 12-month adherence to > 80% (Nguyen & Herrell, 2024) [61]. Wearable devices estimating sweat loss tailor real-time hydration prompts.

9. Management of Acute Stone Events

9.1 Pain Control and Supportive Care

Renal colic is mediated by prostaglandin-induced ureteric spasm and capsular stretch. NSAIDs (e.g., ketorolac 30 mg IV) outperform opioids for pain relief and lower repeat ED visits (Drożdż *et al*.). In opioid-contraindicated patients, intranasal ketamine provides comparable analgesia.

9.2 Medical Expulsive Therapy (MET)

A network meta-analysis of 23 RCTs confirms tamsulosin 0.4 mg or silodosin 8 mg daily shortens expulsion time by 4.3 days and raises passage rates from 62% to 79% for distal ureteric stones 5-10 mm (Ferri & Preminger, 2025). Nifedipine 30 mg is second-line when α-blockers are intolerable.

9.3 Indications for Urgent Intervention

Immediate decompression is mandatory for: (1) obstructed kidney with fever; (2) solitary or transplanted kidney obstruction; (3) intractable pain, vomiting or rising creatinine (Assimos & Pearle, 2023) [32].

9.4 Emergency Drainage Options

Retrograde ureteric stenting under local-spinal anaesthesia provides swift relief; percutaneous nephrostomy is favoured when urosepsis precludes cystoscopy or distal obstruction prevents stent placement. Randomised data show no mortality difference but faster sepsis resolution (12 h vs 17 h) with nephrostomy.

10. Surgical and Minimally Invasive Interventions

10.1 Extracorporeal Shock-Wave Lithotripsy (ESWL)

Recent registries reveal a 78% stone-free rate (SFR) for renal stones ≤ 10 mm, declining to 55% at 15 mm (Geraghty *et al*.). Dual-pulse platforms shorten sessions and cut retreatment by 15%. Contraindications include pregnancy and uncorrected coagulopathy.

10.2 Ureteroscopy (URS) and Intracorporeal Laser Lithotripsy

The TOWER registry (60 000 URS) reports an overall SFR of 92% with holmium:YAG dusting, climbing to 96% with thulium-fibre lasers (Traxer *et al*.). Access-sheath use halves intrarenal pressure and infectious complications.

10.3 Percutaneous Nephrolithotomy (PCNL) Variants

A 2023 RCT comparing mini-PCNL (16 Fr) to standard (24 Fr) for 2-3 cm stones demonstrated equal SFR (94%) but 38% lower transfusion with mini-PCNL (Jessen *et al*.). Micro-PCNL (4.8 Fr) targets < 1.5 cm lower-pole residues; ultra-mini (11-13 Fr) balances visualisation with haemostasis.

10.4 Retrograde Intrarenal Surgery (RIRS)

Digital single-use flexible ureteroscopes, combined with thulium-fibre lasers, achieve 90% SFR for 1-2 cm stones and allow same-day discharge (Giusti & Proietti, 2025) [80].

10.5 Open, Laparoscopic and Robotic Surgery

Reserved for anatomic anomalies or encrusted staghorn calculi refractory to endoscopy. Robotic pyelolithotomy offers magnified suturing and faster convalescence (Wright & Monga, 2024) [28].

10.6 Post-Operative Care and Complications

Routine post-PCNL CT at 4 weeks detects clinically significant fragments (> 4 mm) in 18% despite ultrasound clearance (Matlaga & Krambeck). Low-dose trimethoprim-sulfamethoxazole for 3 days reduces post-URS UTI from 6.2% to 2.3%.

11. Emerging Concepts and Future Directions

11.1 Novel Biomarkers and Multi-Omics Signatures

The past two years have witnessed an explosion of discovery-scale urine proteomics and metabolomics projects directed at kidney-stone disease (KSD). A bilateral renal-pelvis study that paired liquid-chromatography tandem mass-spectrometry with targeted metabolomics identified a 12-protein "uric-acid stone" panel (including periostin, cathepsin D and fetuin-A) whose composite AUROC reached 0.93 for discriminating patients with unilateral uric-acid calculi from the contralateral non-stone kidney. Parallel shotgun proteomics reviews catalogue > 2 000 consistently detected urinary proteins, 94 of which differ by ≥ 2-fold between stone formers and controls; osteopontin, bikunin and uromodulin remain the most reproducible core inhibitors.

Metabolomics has moved beyond oxalate and citrate to highlight sphingomyelin and tryptophan-kynurenine dysregulation as potential early harbingers of supersaturation. Integrative "urine-exosome-omics" now links microRNA-21 and lncRNA-MEG3 to Randall's-plaque osteogenesis, a pathway validated in CRISPR-edited tubular organoids. While analytical depth is no longer limiting, translation into point-of-care assays demands harmonised pre-analytics and multi-centre validation gaps addressed in Section 12.

11.2 Genetic and Precision-Medicine Frontiers

A 2025 trans-ancestry GWAS meta-analysis comprising 1.1 million participants uncovered 71 genome-wide significant loci, several mapping to calcium-sensing and phosphate-

transport pathways (e.g., DGKD, SLC34A1, CYP24A1). Mendelian-randomisation analyses indicate that alleles raising serum calcium by 0.1 mmol L^{-1} heighten stone risk by 28%. The same consortium's functional validation in zebrafish crispants confirmed CYP24A1 loss to induce hypercalcaemia and nephrocalcinosis.

Gene-panel testing is consequently being trialled for "precision prophylaxis." Prototype protocols stratify high-risk individuals (< 30 y, bilateral stones, strong family history) for CLDN14-guided thiazide initiation and SLC26A6 variant carriers for gut-restricted oxalate-esterases. Beyond monogenics, polygenic-risk scores (PRS) explain 11-14% of variance in stone susceptibility and, when combined with 24-h urine profiles, reclassify 23% of patients from intermediate to high prevention tiers.

11.3 Microbiome Manipulation and Probiotic Therapeutics

Interest in the gut-kidney axis has re-intensified. A proof-of-concept trial colonising healthy adults with *Oxalobacter formigenes* reduced fasting urinary oxalate by 28% within two weeks, an effect sustained only while colonisation persisted. A meta-analysis published in 2024 nonetheless cautioned that *O. formigenes* alone may be insufficient given variability in host bile-acid milieu and microbial cross-feeding networks. Phase I/II data in primary hyperoxaluria found *O. formigenes* safe but ineffectual at lowering systemic oxalate, underscoring a need for multi-strain or engineered consortia approaches.

Emerging synbiotics pair oxalate-degrading species (*Oxalobacter*, *Lactobacillus*, *Bifidobacterium*) with inulin-type fructans to improve engraftment durability. Parallel research explores bacteriophage cocktails to suppress urease-positive *Proteus* spp., aiming to curb struvite lithogenesis without broad-spectrum antibiotics.

11.4 AI-Driven Prediction and Decision Support

Machine-learning (ML) pipelines now ingest a mosaic of variables clinical, imaging radiomics, multi-omics, wearable-captured hydration metrics to predict recurrence or acute events. In 2025 Yanase *et al*. reported that a TabNet deep-learning model trained on 235 peri-operative attributes achieved an AUC 0.89 for two-year symptomatic recurrence and produced interpretable SHAP rankings that mirrored known metabolic drivers.

EHR-based random-forest models have shown similar promise (AUC 0.82) when retrained on community cohorts but degrade if 24-h urine data are omitted. To broaden applicability, Mahmoodi *et al*. built a six-variable logistic model (sex, BMI, serum calcium, urine pH, stone HU density, family history) that still attains AUC 0.78 in primary-care settings. Real-time decision-support prototypes now flag high-risk ED patients for early nephrology referral and personalised prevention bundles.

11.5 Nanotechnology for Targeted Delivery and Surface Engineering

Nanomedicine is expanding from oncology to urolithiasis. Citrate-loaded supramolecular nanoparticles measuring 120 nm penetrate CaOx lattices, delivering local chelation that dissolves 2 mm fragments ex vivo without altering systemic calcium. Magnetic soft micro-robots, 1.5 mm long, can adhere to calculi under MR navigation and release alginate-oxalate oxidase payloads, fragmenting uric-acid stones in porcine kidneys with no mucosal injury.

On the preventive front, mesoporous silica carriers loaded with silymarin quench tubular oxidative stress and reduce crystal adhesion in murine hyperoxaluria models by 58%. Translational hurdles renal clearance, immunogenicity, scalable manufacturing remains but early pharmacokinetics appear favourable.

11.6 Digital Health, Wearables and Behavioural Nudging

The *sipIT* ecosystem integrates a Bluetooth-enabled water-bottle, smartphone app and cloud analytics to deliver just-in-time adaptive prompts. Interim analysis of the multicentre PUSH-II trial shows a 45% rise in mean fluid intake and 0.7 L increase in urine volume over six months compared with usual care. Complementary trials evaluate a wrist-worn capacitance sensor that estimates sweat-driven fluid losses and adjusts hydration goals in real time.

11.7 Convergence Toward Precision Prevention

The vanguard of stone research is converging: omics-defined risk endotypes, AI-driven prediction, microbiome engineering and nano-therapeutics. The ultimate vision is a precision-prevention framework in which a newly diagnosed stone former receives

1. a blood/urine multi-omics panel;
2. a PRS-weighted genetic dashboard;
3. a wearable-linked hydration and dietary coach;
4. risk-tailored pharmacologic or probiotic interventions; and
5. dynamic AI monitoring that recalibrates recommendations as physiology and environment change.

12. Knowledge Gaps and Research Agenda

12.1 Biomarker Validation and Regulatory Readiness

Despite hundreds of putative urinary markers, none has yet cleared FDA 510(k) pathways. Key deficits include small convenience cohorts, inconsistent pre-analytical processing, and lack of external validation. A harmonised consortium akin to the Cancer Moonshot's BloodPAC linking reference labs and cloud repositories could accelerate clinical-grade assay development.

12.2 Microbiome Causality Vs Correlation

Whether dysbiosis is a cause or consequence of lithogenesis remains unresolved. The heterogeneity of *O. formigenes* trials positive in healthy volunteers but neutral in hyperoxaluric and primary hyperoxaluria cohorts' underscores colonisation bottlenecks and host-microbe metabolite crosstalk. Future work should explore engineered "living therapeutics" that secrete oxalate decarboxylase or urease inhibitors in situ, with CRISPR-based biocontainment.

12.3 AI Generalisability and Health-System Integration

ML models trained on tertiary-centre databases rarely account for missing urine chemistries in primary care. External validation across diverse EHR vendors and socioeconomic strata is critical; federated-learning pipelines may permit cross-institution training without data-sharing barriers. Regulatory frameworks for "learning" algorithms must balance performance drift monitoring with real-world adaptability.

12.4 Nanomedicine Safety and Manufacturing Scale-Up

Nanoparticle dissolution platforms excel ex vivo yet face translational gaps: ensuring renal clearance < 6 nm or biodegradation, mitigating complement activation and mapping long-term retention. Good-Manufacturing-Practice (GMP) protocols for citrate-polymer conjugates must demonstrate batch consistency, while magnetic robot deployment requires MRI-compatible actuation standards.

12.5 Clinical-Trial Design for Precision Interventions

Adaptive platform trials that stratify by genetics, urine-omics and microbiome state could test multiple agents in parallel, shortening timelines. Hydration-intervention studies like PUSH leverage behavioural science but need longer follow-up to link urine volume changes with hard outcomes. Wearable hydration devices promise objective adherence data yet raise data-privacy and equity concerns.

12.6 Equity and Implementation Science

Precision tools must translate across rural and low-resource settings where imaging and metabolic work-ups are scarce. Community-health-worker-led fluid-intake coaching and SMS pH reminders could bridge digital divides. Implementation science frameworks (RE-AIM) should accompany efficacy trials from inception.

Priority Agenda for 2025-2030

1. Multicentre validation of urinary proteo-metabolomic panels.
2. Engineered multi-strain probiotic or synbiotic RCTs with oxalate-reduction endpoints.
3. Federated AI algorithms tested prospectively across three continents.
4. First-in-human studies of citrate-nanoparticle dissolution under image guidance.
5. Pragmatic trials integrating PRS with lifestyle and pharmacologic prevention to quantify incremental benefit.

13. Conclusion

Kidney-stone science is in the midst of a remarkable paradigm shift. Traditional approaches that centred on generic diet advice, static urine chemistries and episodic surgery are giving way to a future of precision, prevention and patient-centred care. Multi-omics technologies now illuminate the molecular fingerprints that distinguish calcium-oxalate from uric-acid or infection stones, while large-scale genomics clarifies who is born biologically prone to lithogenesis. These insights feed novel decision-support algorithms that can flag high-risk individuals long before the first colic attack. At the same time, the microbiome revolution offers a tantalising prospect: reshaping gut ecology to siphon off oxalate or blunt urease activity, thereby neutralising potent lithogenic drivers internally. Add to this the engineering strides of nano-sized citrate carriers and magnetically guided micro-robots capable of dissolving or dislodging calculi with surgical precision but without scalpels, and the therapeutic horizon shifts even further.

Yet promise will translate into population impact only if rigorous validation, equitable implementation and sustainable cost structures accompany innovation. The immediate task is to weave emerging biomarkers, genetic scores and digital-health nudges into integrated care pathways that function just as well in primary care clinics and low-resource settings as they do in tertiary stone centres. If the field meets this challenge, recurrent nephrolithiasis could move from a chronic, painful, progressively injurious disease to a largely preventable condition managed by personalised, minimally invasive strategies. The research roadmap laid out here provides a strategic blueprint for that transformation, signalling an era in which precision prevention becomes the new clinical standard and kidney stones move decisively from inevitability to rarity.

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