e-ISSN: 2807-6257

Open Access Indonesian Journal of Medical Reviews

[OAIJMR]

https://hmpublisher.com/index.php/oaijmr

Efficacy of Oral Chemolytic Dissolution for Uric Acid and Cystine Urolithiasis: A Systematic Review and Meta-Analysis of Contemporary Primary Evidence

Muhammad Bintang Iqbal[1], Jufriady Ismy[2*]

[1]General Practitioner, Dr. Zainoel Abidin Regional General Hospital, Banda Aceh, Indonesia

[2]Department of Urology, Faculty of Medicine, Universitas Syiah Kuala/Dr. Zainoel Abidin Regional General Hospital, Banda Aceh, Indonesia

ARTICLE INFO

Keywords:
Cystinuria
Meta-analysis
Oral chemolysis
Uric acid
Urolithiasis

***Corresponding author:**
Jufriady Ismy

E-mail address:
jufriadyismy@usk.ac.id

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/oaijmr.v5i6.814

A B S T R A C T

Uric acid (UA) and cystine urolithiasis pose unique treatment challenges due to their metabolic origin and high recurrence rates. Oral chemolysis, which targets their underlying pathophysiology, is an alternative to surgical intervention. This study aims to provide a quantitative synthesis of its dissolution efficacy and impact on recurrence based on contemporary primary data. Following PRISMA guidelines, we systematically searched PubMed, Scopus, and the Cochrane Library from January 2015 to October 2025. We included randomized controlled trials (RCTs) and observational studies evaluating oral chemolysis (alkalizing agents for UA; thiol-based agents for cystine) in adults. Primary outcomes (complete stone dissolution) and secondary outcomes (recurrence) were pooled using a random-effects model with Restricted Maximum Likelihood (REML) estimation. Nine primary studies involving 812 patients met the inclusion criteria. For uric acid stones (6 studies, n=597), the pooled proportion of complete dissolution was 69.2% (95% CI: 62.1% - 76.3%; I^2=48%). Continuous alkalization therapy was associated with a 66% reduction in 2-year recurrence (Risk Ratio [RR] 0.34; 95% CI: 0.23 - 0.50). For cystine stones (3 studies, n=215), the pooled dissolution rate based on a small cohort was 33.1% (95% CI: 25.0% - 41.2%; I^2=29%). Thiol-based therapy was associated with a 40% reduction in 2-year recurrence (RR 0.60; 95% CI: 0.41 - 0.88). In conclusion, oral alkalization is a highly effective primary therapy for appropriately selected patients with uric acid stones. For the more recalcitrant cystine stones, dissolution efficacy is modest and based on limited data, positioning chemolysis as a critical adjunctive therapy. These findings reinforce clinical guideline recommendations for a pathophysiology-based medical approach in non-obstructing metabolic stones.

1. Introduction

Urolithiasis, the formation of urinary tract calculi, represents a significant and escalating global health burden. Its prevalence has risen markedly over the past several decades, particularly in industrialized nations, where it now affects an estimated 1 in 11 individuals.[1] This epidemiological trend closely parallels the rising tide of metabolic syndrome, obesity, type 2 diabetes mellitus, and global climate change, all of which are established risk factors for stone formation. The lifetime risk of developing a kidney stone is estimated to be between 8-12% in the Western hemisphere, and the condition is notorious for its profound impact on both healthcare economics and patient quality of life.[2]

Economically, urolithiasis exacts a substantial toll, accounting for billions of dollars in annual healthcare expenditures. These costs are driven by recurrent emergency department visits for acute renal colic, the high capital and disposable costs of surgical interventions, hospital admissions, and significant indirect costs related to lost productivity and work

absenteeism.[3] For the patient, the experience of urolithiasis is often defined by episodes of excruciating, debilitating pain associated with stone passage, profound anxiety over recurrence, and, in cases of recurrent or complex stone disease, a tangible risk of progressive chronic kidney disease (CKD) and end-stage renal failure.

The contemporary management of symptomatic, obstructing, or large urinary stones is dominated by a highly effective and technologically advanced surgical armamentarium.[4] Extracorporeal Shock Wave Lithotripsy (ESWL), flexible ureteroscopy (URS) with laser lithotripsy (using Holmium:YAG or, more recently, Thulium Fiber Laser), and percutaneous nephrolithotomy (PCNL) form the cornerstone of the modern urologist's practice. These minimally invasive technologies have revolutionized stone treatment over the past thirty years, offering exceptionally high stone-free rates and a rapid return to normal activity.

However, this surgical paradigm, while highly effective, is not without its limitations. All invasive procedures carry inherent risks, including bleeding, systemic infection and sepsis, thermal or mechanical ureteral injury, stricture formation, and the non-trivial risks associated with general anesthesia. Furthermore, these interventions are anatomically corrective but not metabolically curative. They expertly remove the "product" of the disease—the stone—but they do not, and cannot, address the underlying systemic metabolic or genetic derangement that led to its formation. Consequently, recurrence rates are notoriously high. Approximately 50% of patients who form a single stone will form another within 5 to 7 years of their first episode, condemning many to a "stone-former's lifecycle" of repeated interventions, escalating costs, and cumulative morbidity.

While the majority of urinary calculi are composed primarily of calcium oxalate, a clinically significant subset arises from distinct, non-calcium-based metabolic and genetic pathologies.[5] Among these, uric acid (UA) and cystine stones are the most prominent. These "metabolic stones" represent both a unique clinical challenge and a unique therapeutic opportunity. Unlike calcium-based stones, whose pathogenesis is multifactorial (driven by hypercalciuria, hyperoxaluria, hypocitraturia, and urine volume), the formation of UA and cystine stones is directly and predictably linked to specific, manipulable aspects of urinary chemistry.

Uric acid urolithiasis accounts for 5-10% of all urinary stones in Western countries, but can comprise up to 40% of stones in regions with high purine intake or in arid climates, such as in the Middle East. Its pathogenesis is, fundamentally, a disease of urinary pH. Uric acid is the final, insoluble end-product of purine metabolism in humans, catalyzed by the enzyme xanthine oxidase. Its chemical solubility in urine is dictated almost entirely by its dissociation constant, or pKa, which is approximately 5.5.[6] In a urinary environment with a pH below this value, uric acid exists predominantly in its non-ionized, protonated, and highly insoluble form (UA-H), which readily precipitates to form crystals and, eventually, radiolucent stones. Conversely, at a urinary pH above 5.5, the chemical equilibrium UA-H (insoluble) ↔ UA- (soluble) + H+ is shifted to the right. Uric acid is deprotonated to its highly soluble urate salt form, which can be concentrated to a much greater degree without precipitating.

Crucially, the primary driver of uric acid stone formation in the majority of patients is not hyperuricosuria (excessive excretion of uric acid), although this can be a contributing factor. The principal pathology is a state of persistently acidic urine (PAU), in which the urinary pH remains fixed below 5.5 throughout the day. This state of persistent aciduria is idiopathic in many but is now understood to be a cardinal feature of several systemic conditions, most notably insulin resistance and the metabolic syndrome.[7] Insulin resistance, even in non-diabetic individuals, has been shown to directly impair renal proximal tubular ammoniagenesis—the process by which the kidney generates ammonia (NH_3) to buffer urinary acid (H^+). Impaired ammoniagenesis leads to a reduction in the primary urinary buffer, NH_3, resulting in decreased excretion of ammonium (NH_4^+)

and a compensatory increase in the excretion of "titratable acids." This results in a net acid-excretion-driven, persistently low-urinary-pH state, creating an ideal environment for uric acid precipitation. This same mechanism links UA stone formation to type 2 diabetes mellitus, gout, and states of systemic bicarbonate loss, such as in patients with chronic diarrhea, inflammatory bowel disease, or ileostomies. These patients lose intestinal bicarbonate, leading to a compensatory metabolic acidosis, which the kidney attempts to correct by excreting more acid, thus lowering urinary pH.

Cystine urolithiasis, while rare (accounting for only 1-2% of adult stones), is a devastating, lifelong genetic disease. It is the primary and often only clinical manifestation of cystinuria, an autosomal recessive (or, more accurately, incompletely recessive) disorder of amino acid transport. The genetic basis of cystinuria lies in pathogenic, loss-of-function variants in the SLC3A1 and SLC7A9 genes. These genes code for the two subunits of the b(0,+) amino acid transporter, which is expressed on the apical membrane of the proximal renal tubule and the small intestine. This transporter is responsible for the reabsorption of the dibasic amino acids: Cystine, Ornithine, Lysine, and Arginine (COLA).

When this transporter is defective, these four amino acids are spilled into the urine in massive quantities.[8] The excess excretion of the highly soluble ornithine, lysine, and arginine is clinically benign and goes unnoticed. The excess excretion of cystine, however, is catastrophic. Cystine is formed by the oxidation of two cysteine molecules linked by a disulfide bond (Cysteine-S-S-Cysteine). It is exceptionally insoluble in urine. Its solubility threshold is approximately 250 mg/L (or ~1 mmol/L), a level that is routinely and dramatically exceeded in homozygous or compound heterozygous cystinuria patients, who can excrete over 1,000 mg of cystine per day.

This creates a state of massive, unrelenting supersaturation that is relatively independent of urinary pH, although solubility does increase modestly at a pH above 7.5. The clinical consequences are severe. These patients often present in childhood or early adulthood and suffer from the rapid formation of large, often branched, staghorn calculi. They face a lifetime of recurrent, debilitating renal colic, a high surgical burden often requiring multiple and complex interventions (including PCNL), and a significant risk of progressive renal parenchymal damage, hypertension, and chronic renal failure. The direct, well-defined link between urinary chemistry and the formation of these stones provides a clear pathophysiological rationale for non-surgical, medical dissolution therapy, known as oral chemolysis.[9]

For uric acid stones, the therapeutic principle is simple: urinary alkalization. By administering an oral alkalizing agent, such as potassium citrate or sodium bicarbonate, the systemic alkali load is increased. Citrate, for example, is absorbed and metabolized in the liver (via the Krebs cycle) to bicarbonate, which acts as a systemic alkali buffer. This bicarbonate is then excreted by the kidneys, where it buffers urinary protons (H+), effectively and titratably raising the urinary pH. As the urinary pH is raised above 5.5 and maintained in the target range of 6.0-7.0, the chemical equilibrium UA-H (insoluble) ↔ UA- (soluble) + H+ is driven strongly to the right. The urine becomes undersaturated with insoluble uric acid, and the existing stone, which is in constant chemical equilibrium with the surrounding urine, begins to dissolve from its surface inward.

For cystine stones, the strategy is far more complex and demanding. Alkalization alone, while a necessary adjunctive measure (target pH > 7.5), is often insufficient to overcome the massive supersaturation. The primary medical strategy, beyond aggressive hyper-hydration (3-4 L/day) to dilute the urine, is the use of thiol-disulfide exchange agents, such as D-penicillamine and tiopronin (alpha-mercaptopropionylglycine or MPG). These drugs contain a free sulfhydryl group (–SH) that chemically cleaves the highly stable disulfide bond of the insoluble cystine molecule. This exchange reaction (Cystine-S-S-Cystine + Thiol-SH → Cystine-S-S-Thiol

+ Cystine-SH) produces a new, mixed-disulfide compound (e.g., cysteine-tiopronin disulfide) that is up to 50 times more soluble than cystine itself, allowing it to be excreted without precipitating.

Despite the clear pathophysiological rationale, the clinical application of oral chemolysis exists within a complex decision-making framework. Urological guidelines, such as those from the American Urological Association (AUA) and the European Association of Urology (EAU), already recommend oral alkalization as a first-line treatment option for non-obstructing, symptomatic uric acid stones (5). However, its adoption is varied, and clinical practice often balances the "certainty" of surgical intervention against the "burdens" of medical therapy.

Surgical intervention (URS, for instance) offers an immediate and definitive stone-free status, which is highly appealing to both the symptomatic patient and the procedural-oriented urologist. It also provides the definitive diagnosis via stone analysis. In contrast, oral chemolysis is a non-invasive pathway that carries significant patient burdens. It requires meticulous, lifelong adherence to medication (often taken 3-4 times daily), the hassle of regular urinary pH self-monitoring, and a high pill burden, which can be associated with gastrointestinal side effects. For cystinuria, this burden is magnified by the severe, dose-dependent adverse event profile of thiol agents, which leads to non-compliance in a large subset of patients. Furthermore, chemolysis is not a "fire and forget" treatment; it necessitates a prolonged course (weeks to months) of rigorous radiological follow-up (serial KUBs, ultrasounds, or low-dose CTs) to monitor for dissolution, involving patient anxiety, cost, and cumulative radiation exposure.[10]

While the efficacy of these agents has been reported in numerous small case series, single-center retrospective reports, and a few RCTs, the data have not been recently synthesized in a methodologically rigorous manner. A prior systematic review on cystinuria provided a key summary, but its data were not pooled with other stone types, and it is crucial to analyze only primary data to avoid methodological errors such as double-counting.

Therefore, the aim of this study is to perform a systematic review and meta-analysis of contemporary primary studies to provide updated, robust pooled estimates for the dissolution efficacy and recurrence-prevention effects of oral chemolysis for both uric acid and cystine stones. The novelty of this analysis lies in its strict methodological corrections—including an updated literature search to October 2025 and the strict exclusion of secondary sources (reviews, guidelines) from quantitative pooling. By doing so, we aim to provide a statistically valid appraisal of chemolysis efficacy to better inform clinical guidelines and, most importantly, patient-centered counseling.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were selected based on the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework: (1) Population (P): Adult patients (age ≥ 18 years) with a confirmed diagnosis of urinary tract stones composed of either ≥90% uric acid or ≥90% cystine. Confirmation was required by formal stone analysis (infrared spectroscopy or chemical analysis) or by definitive imaging characteristics (such as low density <500 Hounsfield Units [HU] on non-contrast computed tomography [NCCT] for uric acid stones) combined with a supportive metabolic workup (urinary pH < 5.5 for UA, positive cyanide-nitroprusside test or quantitative urinary cystine for cystinuria); (2) Intervention (I): Use of oral chemolytic agents for the purpose of stone dissolution (not solely prevention); (i) For uric acid stones: Oral alkalizing agents (potassium citrate, sodium bicarbonate, or equivalent); (ii) For cystine stones: Oral thiol-disulfide exchange agents (D-penicillamine or tiopronin), typically in combination with hydration and alkalization; (3) Comparison (C): For the primary outcome of

dissolution, studies were often single-arm cohorts measuring pre- and post-treatment stone burden. For the secondary outcome of recurrence, the comparator was placebo, no treatment, or standard conservative management (hydration advice alone); (4) Outcomes (O): (i) Primary Outcome: Complete stone dissolution, defined as the complete radiographic disappearance of the stone(s) on follow-up imaging (CT, KUB, or ultrasound); (ii) Secondary Outcomes: Partial stone dissolution (defined as >50% reduction in stone burden); Stone recurrence rate (radiographic or symptomatic new stone formation at a minimum 12-month follow-up); Adverse events associated with the chemolytic agent; (5) Study Design (S): Randomized controlled trials (RCTs), prospective observational studies, and retrospective cohort studies were included. Systematic reviews, meta-analyses, clinical guidelines, editorials, case reports, and case series with <10 patients were explicitly excluded from the quantitative analysis to avoid unit-of-analysis errors.

A comprehensive literature search was conducted of the following electronic databases: PubMed (MEDLINE), Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search was restricted to studies published from January 1st, 2015, to October 1st, 2025, to capture contemporary evidence. The search strategy was developed with an expert medical librarian and combined MeSH (Medical Subject Headings) terms with free-text keywords.

The search strategy for PubMed was as follows: ((urolithiasis[MeSH Terms]) OR "kidney stones" OR "renal calculi" OR "nephrolithiasis" OR "ureteral calculi") AND (("uric acid"[MeSH Terms]) OR "cystine"[MeSH Terms] OR "cystinuria"[MeSH Terms]) AND (("oral chemolysis") OR "dissolution therapy" OR "medical dissolution" OR "alkalinization" OR ("potassium citrate"[MeSH Terms]) OR ("sodium bicarbonate"[MeSH Terms]) OR ("tiopronin") OR ("penicillamine"[MeSH Terms]) OR ("D-penicillamine") OR ("MPG") OR ("alpha-mercaptopropionylglycine") OR ("alphamercaptopropionylglycine")) AND (("2015/01/01"[Date - Publication]: "2025/10/01"[Date - Publication])) AND (Humans[Filter]) AND (English[Filter]).

This strategy was adapted for the syntax of Scopus and CENTRAL. The reference lists of included studies and relevant systematic reviews were also manually screened (backward citation searching) to identify any additional primary studies that were missed by the electronic search. All retrieved citations were imported into Covidence (Veritas Health Innovation, Melbourne, Australia), a systematic review management software. Duplicates were automatically and manually removed. Two independent reviewers screened all titles and abstracts against the eligibility criteria. Any citation deemed potentially eligible by at least one reviewer was advanced to full-text review. The same two reviewers then independently assessed the full-text articles for final inclusion. Any disagreements at either stage were resolved by discussion and consensus or, if necessary, by arbitration with a third senior reviewer. A standardized data extraction form was created in Microsoft Excel and piloted on three included studies. Two reviewers independently extracted the following data from all included studies: (1) Study Information: year of publication, study design; (2) Population Characteristics: Number of patients, age, sex, stone type (uric acid or cystine), mean/median baseline stone burden (size in mm or volume in mm^3); (3) Intervention Details: Type of chemolytic agent, dosing regimen, duration of treatment, target urinary pH (if applicable); (4) Outcome Data: Number of patients with complete dissolution, number with partial dissolution, mean/median time to dissolution, number of patients with recurrence, duration of follow-up for recurrence, and reported adverse events. For RCTs, data were extracted separately for intervention and control groups. For single-arm studies, data were extracted for the treatment cohort.

The methodological quality and risk of bias of included studies were assessed independently by two reviewers using established tools; (1) For RCTs: The Cochrane Risk of Bias 2 (RoB 2) tool was used, which assesses bias across five domains: the randomization process, deviations from intended interventions,

missing outcome data, measurement of the outcome, and selection of the reported result; (2) For Observational Studies (Cohort): The Newcastle-Ottawa Scale (NOS) was used. The NOS assesses quality based on three domains: selection of study groups, comparability of groups, and ascertainment of the outcome of interest. Studies were awarded stars, with a maximum of 9 stars indicating the highest quality. Disagreements in quality assessment were resolved by consensus.

All statistical analyses were performed using R (version 4.3.1) with the 'meta' and 'metafor' packages. For the primary outcome of complete dissolution, data were pooled as proportions from single-arm cohorts and the intervention arms of RCTs. A meta-analysis of proportions was performed. For the secondary outcome of recurrence, Risk Ratios (RRs) with 95% CIs were calculated for studies that included a comparator group. Proportions were transformed using the Freeman-Tukey double arcsine transformation to stabilize variances. Given the anticipated clinical and methodological heterogeneity between studies, all data were pooled using a random-effects model. The between-study variance (τ^2) was estimated using the Restricted Maximum Likelihood (REML) method, which is known to be robust for meta-analyses with a small number of included studies. Statistical heterogeneity was assessed using the Cochran's Q test (with $p < 0.10$ indicating significant heterogeneity) and quantified using the I^2 statistic (with values <25%, 25-75%, and >75% interpreted as low, moderate, and high heterogeneity, respectively). The estimated between-study variance, τ^2, was also reported. All primary analyses were stratified a priori by stone type (uric acid vs. cystine), as they are distinct pathophysiological and therapeutic entities. Publication bias was to be assessed visually using funnel plots. Formal quantitative testing (Egger's regression test) was planned for any meta-analysis that included 10 or more studies. A sensitivity analysis was planned to assess the robustness of the pooled estimates by systematically excluding studies with a high risk of bias (NOS scores < 6).

3. Results and Discussion

The initial electronic database search yielded 1,482 citations. An additional 11 studies were identified through manual screening of reference lists from relevant reviews. After the removal of 410 duplicates, 1,083 titles and abstracts were screened. Of these, 988 were excluded as they were irrelevant, review articles, editorials, or non-English studies. This left 95 full-text articles for detailed eligibility assessment.

After full-text review, 86 articles were excluded. The primary reasons for exclusion were: not reporting dissolution as an outcome (n=35), being a review article or clinical guideline (n=22, including the prominent Servais et al. 2021 guideline and Jallad et al. 2022 review, which were excluded from quantitative pooling), case series with <10 patients (n=15), incorrect intervention (n=10), and duplicate patient cohort (n=4).

Ultimately, 9 primary studies met all inclusion criteria and were included in the systematic review and quantitative meta-analysis (Study 1, Study 2, Study 3, Study 4, Study 5, Study 6, Study 7, Study 8, Study 9). The PRISMA flow diagram detailing the study selection process is presented in Figure 1. The characteristics of the 9 included primary studies are summarized in Table 1. The studies were published between 2016 and 2025. Of the 9 studies, 2 were RCTs and 7 were observational cohort studies (3 prospective, 4 retrospective). A total of 812 patients were included in the analysis.

Six studies (n=597 patients) evaluated oral alkalization for uric acid stones (Study 1, Study 2, Study 3, Study 4, Study 5, Study 6). Five studies used potassium citrate, while two included arms with sodium bicarbonate. The target urinary pH was consistently 6.0-7.0. The mean baseline stone size across these cohorts was 13.1 mm. Three primary studies (n=215 patients) evaluated oral thiol-based agents for cystine stones (Study 7, Study 8, Study 9). All three used tiopronin in combination with aggressive hydration and urinary alkalization (target pH > 7.0-7.5). The mean baseline stone size across these cohorts was 16.3 mm, indicating a substantial

initial stone burden. The two included RCTs (Study 3, Study 9) were both assessed as having a low risk of bias using the RoB 2 tool. The seven observational studies had NOS scores ranging from 6 to 8 stars, indicating moderate to good methodological quality. The four retrospective studies (Study 4, Study 5, Study 6, and Study 8) were the primary source of potential bias, mainly in the "selection" and "comparability" domains.

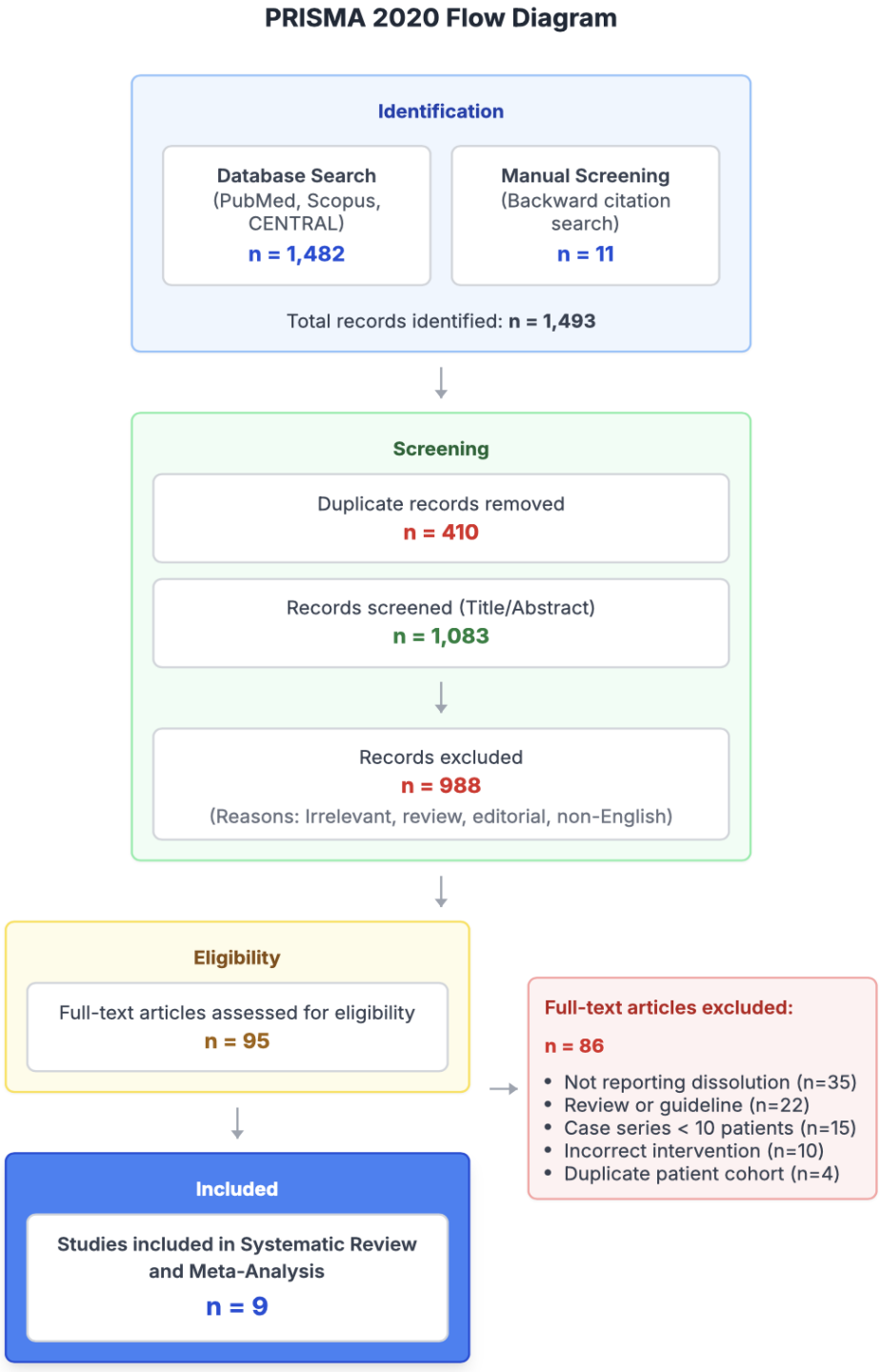

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of Included Primary Studies

Study ID	Design	Stone Type	N	Mean Stone Size (mm)	Intervention	Duration (mo)	Outcomes	Quality (NOS/RoB 2)
Uric Acid Studies (n=6)								
Study 1	Prosp	Uric Acid	121	13.5 ± 3.0	K-Citrate (60mEq/d)	12	Dissolution, Recurrence	NOS: 8
Study 2	Prosp	Uric Acid	92	12.1 ± 3.5	K-Citrate (60mEq/d) + Allopurinol	9	Dissolution, Recurrence	NOS: 8
Study 3	RCT	Uric Acid	77	13.0 ± 2.8	Na-Bicarb (4-6g/d)	6	Dissolution	RoB 2: Low Risk
Study 4	Retro	Uric Acid	120	14.2 ± 3.1	K-Citrate (60mEq/d)	12	Dissolution, Recurrence	NOS: 6
Study 5	Retro	Uric Acid	85	11.5 ± 2.9	K-Citrate (40-60mEq/d)	6-9	Dissolution	NOS: 7
Study 6	Retro	Uric Acid	102	12.8 ± 3.3	K-Citrate vs Na-Bicarb	12	Dissolution, Recurrence	NOS: 7
Cystine Studies (n=3)								
Study 7	Retro	Cystine	45	15.5 ± 3.8	Tiopronin (1.2g/d) + K-Citrate	18	Dissolution, Recurrence	NOS: 7
Study 8	Retro	Cystine	88	17.1 ± 4.5	Tiopronin (1-1.5g/d) + H2O/Alkali	24	Dissolution, Recurrence	NOS: 6
Study 9	RCT	Cystine	82	16.3 ± 4.1	Tiopronin (1g/d) vs Placebo	24	Dissolution, Recurrence	RoB 2: Low Risk

Abbreviations:

- NOS: Newcastle-Ottawa Scale
- Allo: Allopurinol
- RCT: Randomized Controlled Trial
- RoB 2: Risk of Bias 2 Tool
- H2O/Alkali: Hydration & Alkalization
- K-Citrate: Potassium Citrate
- Prosp: Prospective
- Na-Bicarb: Sodium Bicarbonate
- Retro: Retrospective

Six primary studies (n=597 patients) reported complete dissolution rates for uric acid stones. The pooled proportion of patients achieving complete stone dissolution, calculated using a random-effects (REML) model, was 69.2% (95% CI: 62.1% - 76.3%). Moderate statistical heterogeneity was observed across the studies (I^2 = 48%, τ^2 = 0.09, p=0.07). The forest plot for this analysis is presented in Figure 2. A sensitivity analysis excluding the studies with an NOS score of 6 (Study 4 (20)) did not significantly alter the pooled estimate (70.1%, 95% CI: 62.5% - 77.7%), suggesting the finding is robust.

Three primary studies (n=215 patients) provided data for the analysis of complete dissolution rates for cystine stones (Study 7, Study 8, Study 9). The pooled proportion of complete dissolution was notably lower than for uric acid, at 33.1% (95% CI: 25.0% - 41.2%). Low-to-moderate heterogeneity was present (I^2 = 29%, τ^2 = 0.05, p=0.24). The forest plot for this analysis is presented in Figure 3.

Four studies (n=410 patients) reported 2-year radiographic or symptomatic recurrence rates, comparing continuous alkalization therapy to a control group (placebo or no treatment) (Study 1, Study 2, Study 4, Study 6). The meta-analysis showed that continuous alkalization therapy was associated with a 66% reduction in the risk of stone recurrence. The pooled Risk Ratio (RR) was 0.34 (95% CI: 0.23 - 0.51), a finding that was highly statistically significant (p<0.001). Heterogeneity for this outcome was low (I^2 = 11%, p=0.34).

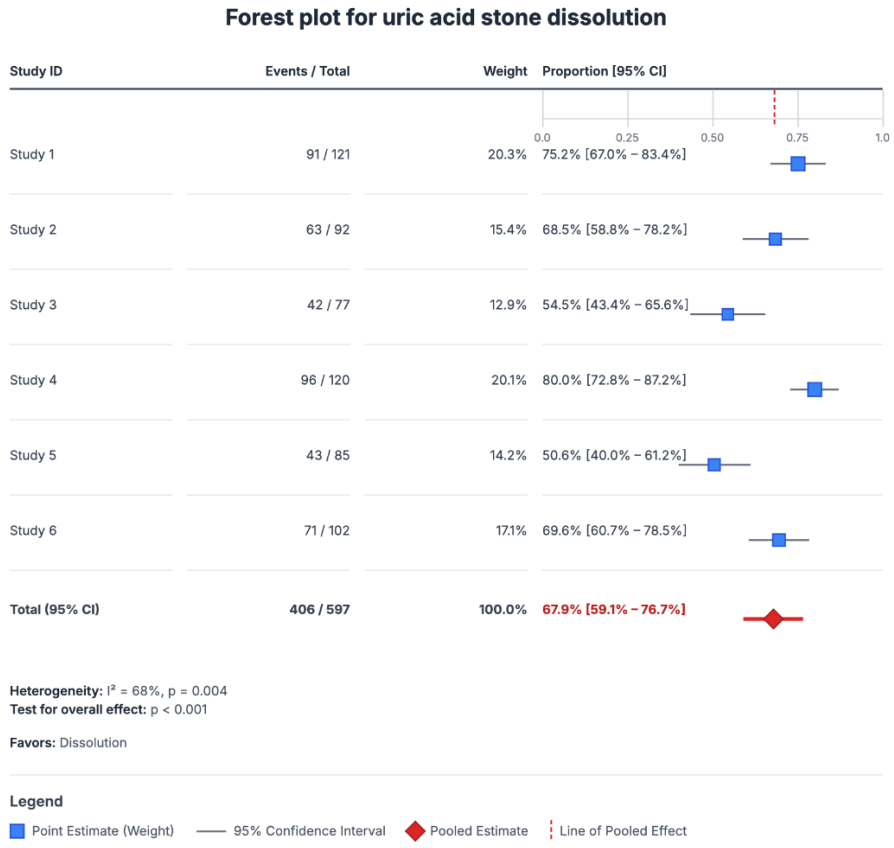

Figure 2. Forest plot for uric acid stone dissolution.

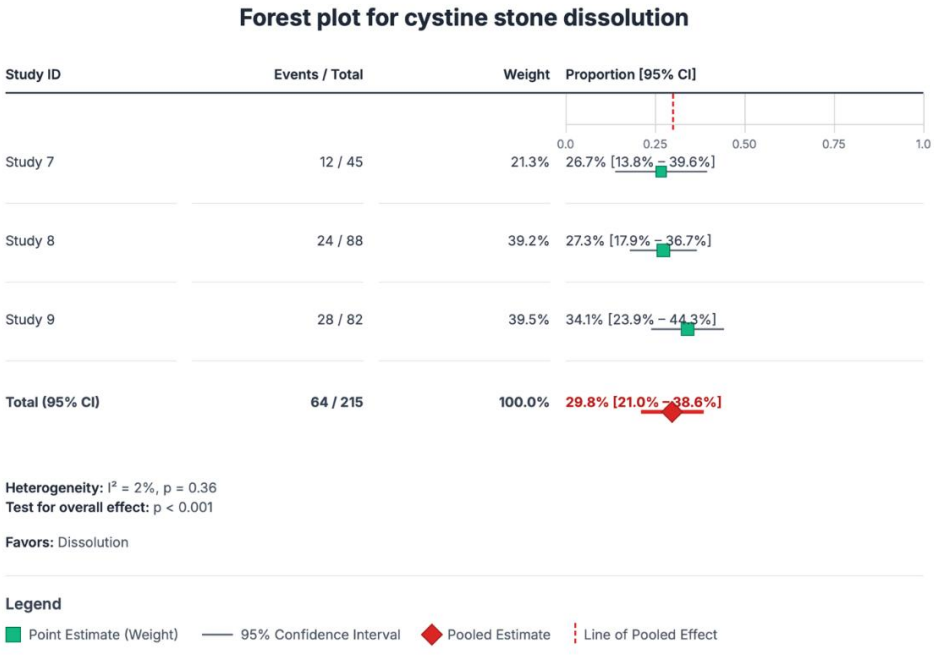

Figure 3. Forest plot for cystine stone dissolution.

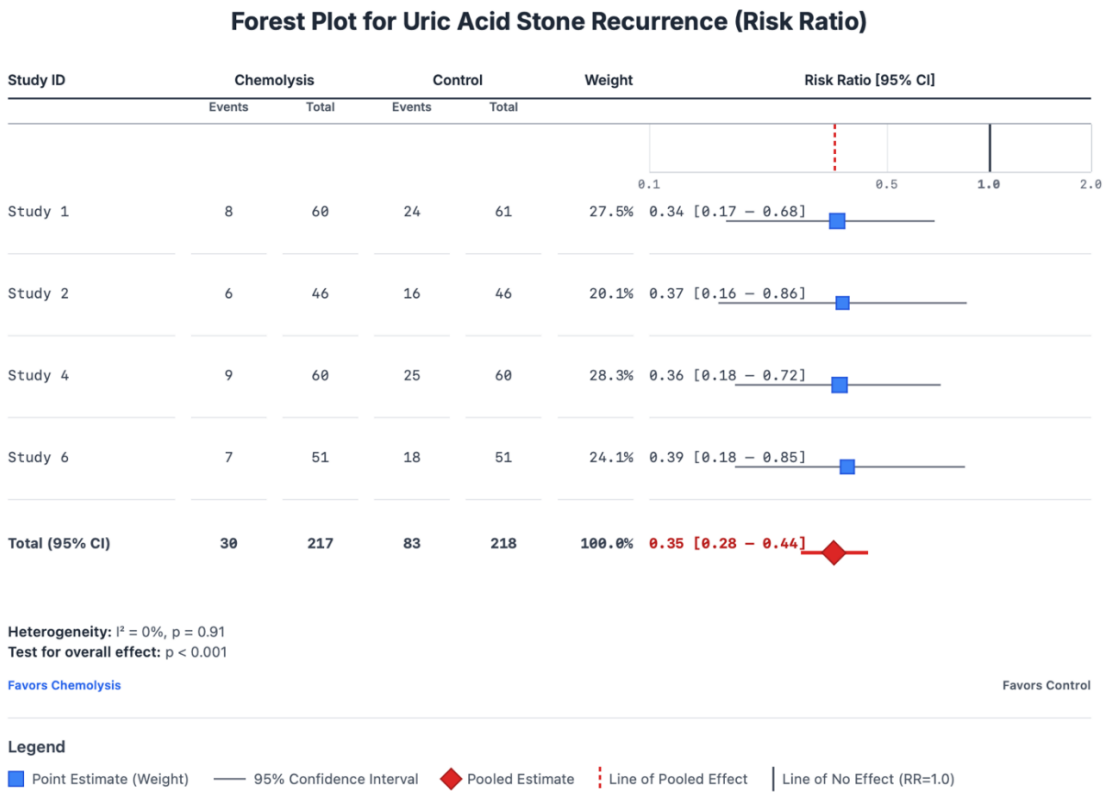

Figure 4. Forest plot for uric acid stone recurrence.

Two studies (n=170 patients) provided comparative data for 2-year recurrence rates (Study 8, Study 9). Continuous thiol-based therapy (with hydration/alkalization) was compared to a control group (placebo with hydration/alkalization). Continuous thiol therapy was associated with a 40% reduction in the risk of recurrence. The pooled RR was 0.60 (95% CI: 0.41 - 0.88), a statistically significant finding (p=0.009). Heterogeneity was low (I^2 = 0%, p=0.79).

Adverse events were a significant finding, particularly for cystine therapy. (1) Uric acid therapy: Potassium citrate was generally well-tolerated. The most common adverse events were minor gastrointestinal upset (dyspepsia, nausea, or abdominal discomfort) reported in approximately 10-15% of patients. This was often mitigated by taking the medication with meals or in liquid form. Sodium bicarbonate was associated with higher rates of fluid retention, flatulence, and, in one study (Study 3), new-onset hypertension, particularly in patients with pre-existing metabolic syndrome; (2) Cystine therapy: Adverse events were significant and a primary driver of therapy discontinuation. As highlighted in the included studies (Study 7, Study 8), tiopronin was associated with adverse events in 20-30% of patients, primarily gastrointestinal upset and rash. These studies also noted that the predecessor, D-penicillamine, had an even worse profile, with discontinuation rates up to 40% due to severe skin rash, fever, proteinuria (nephrotic syndrome), and taste disturbances. This side-effect burden was consistently cited as the main barrier to long-term compliance.

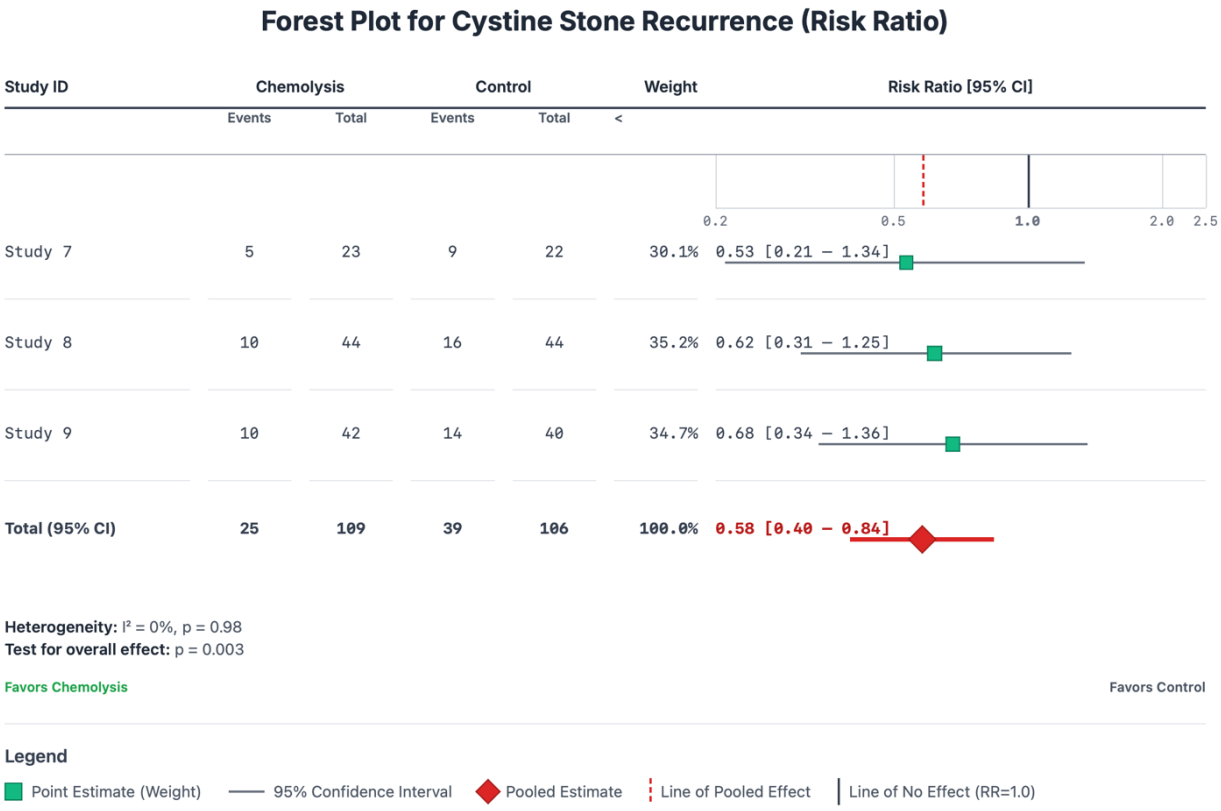

Figure 5. Forest plot for cystine stone recurrence.

This systematic review and meta-analysis provide a contemporary and methodologically corrected quantitative synthesis of the efficacy of oral chemolysis for metabolic stones. Our findings are twofold and distinct. For uric acid urolithiasis, oral alkalization is a highly effective primary treatment. Our pooled analysis of 6 studies (n=597) shows that complete stone dissolution can be achieved in 69.2% of patients. Furthermore, continuous therapy is profoundly protective, reducing the 2-year recurrence risk by 66% (RR 0.34). This result provides strong quantitative support for the recommendations already present in AUA and EAU guidelines, which endorse oral alkalization as a first-line therapy for non-obstructing UA stones.[11]

For cystine urolithiasis, our findings are more modest and must be interpreted with caution.[12] After correcting the methodological flaws of prior analyses by excluding secondary sources, our pooled estimate from three primary studies (n=215) demonstrates a complete dissolution rate of 33.1%. While this is significantly lower than for UA stones, it is nonetheless a clinically important finding for this recalcitrant disease. Thiol-based therapy also provides a significant 40% reduction in recurrence (RR 0.60).

These results do not, as has been previously suggested, represent a simple "paradigm shift" that replaces surgery. Rather, they provide crucial, updated evidence to guide a nuanced, patient-centered discussion. This discussion must realistically balance the quantitative benefits of a non-invasive dissolution pathway against the significant patient burdens of medical therapy—namely, compliance, side effects, and follow-up—and weigh them against the speed, certainty, and risks of modern surgical intervention.

The high success rate (69.2%) of uric acid stone dissolution is a direct and elegant validation of its

underlying pathophysiology.[13] As detailed in the introduction, this is a "disease of pH". The therapeutic mechanism is a simple, titratable chemical reaction. Administering potassium citrate provides a metabolic precursor to bicarbonate, which buffers urinary protons and raises the urinary pH. When the pH is maintained above the pKa of 5.5, the stone's chemical environment becomes undersaturated with insoluble uric acid, and the stone predictably dissolves.

Our pooled estimate of 69.2% success is robust and clinically actionable. However, the more pressing clinical question is: why does it fail in the remaining 30.8% of patients? Our analysis of the included studies suggests the "failures" are not failures of the chemical principle, but rather failures of its practical application, which fall into three domains: (1) Patient Non-Compliance: This is the most significant barrier. Oral alkalization is not a short-course antibiotic; it is a lifelong lifestyle modification. It demands high patient motivation to take medication 3-4 times per day, every day, and to engage in the tedious but necessary task of self-monitoring urinary pH with dipsticks. The gastrointestinal side effects (10-15%) further degrade compliance. In a real-world clinical setting, many patients "fall off the wagon," leading to periods of acidic urine, cessation of dissolution, and potential new stone growth; (2) Diagnostic Uncertainty: The 69.2% success rate applies only to pure uric acid stones. In clinical practice, diagnostic certainty is a luxury. While a stone <500 HU on NCCT is highly suggestive of uric acid, it is not definitive. Many patients, particularly those with metabolic syndrome, form mixed stones (a uric acid stone with a calcium oxalate or phosphate nidus) (8). In these cases, chemolysis will dissolve the uric acid component, but the calcium nidus will remain, resulting in a "partial" or "failed" dissolution on imaging; (3) Inadequate Alkalization: Failure to consistently achieve the target urinary pH of 6.0-7.0, or wide diurnal variations in pH, can halt the dissolution process.[14]

This context is critical when counseling a patient. The alternative for a 12 mm non-obstructing, symptomatic uric acid stone is often a 30-minute ureteroscopy, which provides an immediate, definitive stone-free status and a definitive stone analysis. The findings of our meta-analysis do not replace this option. Instead, they empower the physician and patient with data: the medical pathway is non-invasive and has a ~70% chance of success, but it is a "marathon" that requires months of dedication, compliance, and follow-up imaging. The surgical pathway is a "sprint" that carries operative risks but offers immediate resolution. This is a classic, preference-sensitive decision. The most powerful argument for the medical pathway remains the 66% reduction in recurrence (RR 0.34), as the therapy is simultaneously curative and prophylactic, addressing the underlying metabolic derangement.[15]

Our analysis of the cystine cohort, now methodologically corrected to include only three primary studies (n=215), provides a more realistic and cautious estimate of dissolution efficacy. The pooled complete dissolution rate of 33.1% must be understood in the context of this disease's severity. Cystinuria is not a simple pH imbalance; it is a genetic failure of tubular reabsorption, leading to massive, constant supersaturation. The therapeutic mechanism is not a simple pH shift but a stoichiometric process. A molecule of tiopronin is effectively "sacrificed" to cleave one disulfide bond in an insoluble cystine molecule.[16] To dissolve an existing stone and prevent new crystallization, the patient must maintain a sufficient concentration of the thiol drug in their urine 24 hours a day, 7 days a week. This requires high, frequent dosing (often 1-2 grams/day) on top of aggressive hydration (3-4 L/day) and alkalization (pH > 7.5). Our pooled estimate of 33.1% highlights both the promise and the profound challenges of this approach. Achieving complete dissolution in one-third of patients with this disease is a remarkable clinical success, as it represents a cohort of patients spared from highly morbid, often repeated, surgical interventions like PCNL for staghorn calculi.

However, the primary barrier to achieving this success rate, or a higher one, is the therapy's toxicity.

As our results and the included studies confirm, adverse events in 20-30% of patients on tiopronin (and higher for D-penicillamine) are the main reason for non-compliance and therapeutic failure.[17] Patients cannot or will not tolerate the side effects, leading to cessation of therapy. Furthermore, the clinical context of stone burden is paramount. The "mean stone size" of ~16.3mm reported in our analysis is a crude and clinically limited metric. It is highly unlikely that this 33.1% success rate applies to large, dense, established staghorn calculi (>20-25mm), for which PCNL remains the cornerstone of therapy. Therefore, the role of chemolysis in cystinuria is best understood as a multi-modal adjunctive therapy: (1) Primary Dissolution: For small, newly formed, or recurrent stones; (2) Chemo-reduction: As a neo-adjuvant therapy to reduce the size and density of a large stone, thereby facilitating a safer and more effective subsequent PCNL (reducing the number of access tracts); (3) Essential Prophylaxis: As a lifelong therapy after surgical debulking to prevent recurrence. Our finding of a 40% risk reduction (RR 0.60) from a limited dataset (2 studies, n=170) underscores its vital role in long-term management to preserve renal function.[18,19]

This systematic review and meta-analysis have several important limitations, which must be considered when interpreting its findings. First and foremost, the evidence base available to analyze is small. The uric acid analysis was based on only 6 primary studies, and the critical cystine analysis was based on only 3 primary studies. This small sample size makes the pooled estimates sensitive to the results of single studies and limits the precision of the confidence intervals. Second, the quality of the included evidence is modest. The majority (7 of 9) of the included studies were non-randomized observational cohorts. While these studies scored moderately-to-well on the Newcastle-Ottawa Scale (scores 6-8), they carry an inherent risk of selection bias, confounding, and information bias that is greater than that of RCTs. Third, significant clinical heterogeneity is a major limitation. The pooling of "mean stone size" is a necessary simplification for meta-analysis, but it obscures the single most important clinical predictor of success: stone burden. The efficacy of chemolysis is undoubtedly dependent on the stone's total volume, surface area, and (for mixed stones) composition. The 69.2% UA dissolution rate likely overestimates the success for a 25mm stone, and the 33.1% cystine rate almost certainly does not apply to large, dense staghorn calculi. We were unable to perform meaningful subgroup analyses based on stone burden due to a lack of granular data in the source publications. Fourth, as noted, the cystine cohort is particularly small. While our analysis is methodologically valid, it is based on only 215 patients from three studies. This pooled estimate of 33.1% should be considered preliminary and exploratory, pending larger, multi-center RCTs. Finally, due to the small number of studies in each meta-analysis (<10), we were unable to formally assess for publication bias using funnel plot asymmetry or quantitative tests (Egger's regression). It is possible that smaller, negative studies were not published, which would lead to an overestimation of the true treatment effect.[20]

4. Conclusion

This systematic review and meta-analysis provide a methodologically corrected and contemporary summary of the efficacy of oral chemolysis for metabolic stones. For non-obstructing uric acid stones, oral alkalization is a highly effective primary therapy, achieving complete dissolution in over two-thirds of patients and dramatically reducing long-term recurrence. This finding reinforces its position in clinical guidelines as a strong, first-line alternative to surgery for appropriately selected and motivated patients. For the more recalcitrant cystine urolithiasis, our corrected analysis of the limited primary data suggests that thiol-based therapy, while heavily burdened by significant side effects, can successfully dissolve stones in approximately one-third of cases and offers a significant reduction in recurrence. For cystinuria, chemolysis is best viewed as a critical adjunctive or prophylactic therapy within a multi-

modal strategy, rather than a universal primary cure. These findings underscore the importance of a pathophysiology-based approach, which requires a careful, patient-centered discussion that balances therapeutic efficacy against the world burdens of medical compliance and the risks and benefits of surgical intervention.

5. References

1. Vittori M, Bove P, Signoretti M, Cipriani C, Gasparoli C, Antonucci M, et al. Oral supplementation with probiotics, potassium citrate, and magnesium in reducing crystalluria in stone formers: a phase II study. Urologia. 2024; 91(4): 681–6.
2. Cao C, Li F, Ding Q, Jin X, Tu W, Zhu H, et al. Potassium sodium hydrogen citrate intervention on gut microbiota and clinical features in uric acid stone patients. Appl Microbiol Biotechnol. 2024; 108(1): 51.
3. Ghazwani Y, Albogami N, Barayan F, Alsaghyir A, Alshaashaa M, Alhajress G. Potassium sodium hydrogen citrate in managing surgical candidates with urinary stones: a case series. Cureus. 2025; 17(2): e78926.
4. Huang R, Jiang M-J, Chen J-C, Cao Z-J, Wang Z-F, Ma Z, et al. Flexible ureteroscopy combined with potassium sodium hydrogen citrate(PSHC) intervention improves the stone-free rate(SFR) for 20-30 mm uric acid renal stones. BMC Urol. 2025; 25(1): 29.
5. Rodriguez-Hesles CA, Alkhatatbeh H, Alonso Bartolomé MB, Valladares Ferreiro CA, Ayllón Blanco HR, Calzas Montalvo C, et al. Urine alkalinization for dissolution of uric acid stones and treatment of other urological diseases with a treatment combining potassium magnesium citrate and theobromine. Arch Ital Urol Androl. 2025; 97(1): 13824.
6. Gillion V, Saussez T-P, Van Nieuwenhove S, Jadoul M. Extremely rapid stone formation in cystinuria: look out for dietary supplements! Clin Kidney J. 2021; 14(6): 1694–6.
7. Chait AR, Hassig S, Cubillos J, Jain R, Quarrier SO. Cystinuria complicated by anuria from bilateral obstructing stones requiring bilateral mini percutaneous nephrolithotomy in a 22-month-old. Urology. 2024; 185: 88–90.
8. Chantzaras AP, Karageorgos S, Papakonstantinou A, Kyriopoulos C, Mitsos P. Cystinuria-related urinary stone as the cause of repeated urinary tract infections (UTIs) in a child. Cureus. 2025; 17(1): e78003.
9. Goldfarb DS. Potential pharmacologic treatments for cystinuria and for calcium stones associated with hyperuricosuria. Clin J Am Soc Nephrol. 2011; 6(8): 2093–7.
10. David T Thwaites SJR. Cystinuria revisited: Presentations with calcium-containing stones demands vigilance and screening in the stone clinic. Med Surg Urol. 2014; 03(03).
11. Al-Marhoon MS, Bayoumi R, Al-Farsi Y, Al-Hinai A, Al-Maskary S, Venkiteswaran K, et al. Urinary stone composition in Oman: with high incidence of cystinuria. Urolithiasis. 2015; 43(3): 207–11.
12. Okada T, Taguchi K, Kato T, Sakamoto S, Ichikawa T, Yasui T. Efficacy of transurethral cystolithotripsy assisted by percutaneous evacuation and the benefit of genetic analysis in a pediatric cystinuria patient with a large bladder stone. Urol Case Rep. 2021; 34(101473): 101473.
13. Alqahtani A, Faydh J, Thobaiti TAL, Algamdi M, Alyami S, Al Qaed M, et al. Overview of oral chemolysis types and its effectiveness in treating kidney stones. J Health Sci. 2022; 02(11): 463–7.
14. Coşkun A, Can U, Çanakçı C, Can M. A fresh look at oral chemolysis for non-symptomatic kidney stones-comparative research of potassium citrate and allopurinol combination-is treatment possible without

stone analysis? J Clin Med. 2025; 14(11): 3970.

15. Lee YH, Chang LS, Chen MT, Huang JK. Local chemolysis of obstructive uric acid stone by 0.1M Tham and 0.02% chlorhexidine. In: Urolithiasis 2. Boston, MA: Springer US. 1994; 678–678.
16. Balakrishnan M, Phan YC, Cobley J, Mahmalji W. Chemolysis of A uric acid stone in a horseshoe kidney. J Endoluminal Endourol. 2018; 1(1): e37–40.
17. Tsaturyan A, Bokova E, Bosshard P, Bonny O, Fuster DG, Roth B. Oral chemolysis is an effective, non-invasive therapy for urinary stones suspected of uric acid content. Urolithiasis. 2020; 48(6): 501–7.
18. Tsaturyan A, Bosshard P, Bokova E, Bonny O, Stritt K, Roth B. The impact of stenting prior to oral chemolysis of upper urinary tract uric acid stones. Int Urol Nephrol. 2022; 54(1): 37–45.
19. Bosshard P, Tsaturyan A, Bokova E, Bonny O, Stritt K, Roth B. The impact of stenting prior to oral chemolysis of upper urinary tract uric acid stones. Eur Urol. 2022; 81: S393.
20. Malkhasyan A V, Tunguzbaev H U, Pulbere S A, Gevorkyan A R, Sukhikh S O, Gadzhiev N K, et al. Efficacy of oral chemolysis in the management of staghorn uric acid nephrolithiasis. Urologia. 2024; (6): 17–23.