REVIEW

Metaphylaxis of nephrolithiasis in percutaneous nephrolithotripsy: A narrative review

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ABSTRACT

Background and aim of the work: Urolithiasis (UC) remains a significant global public health concern, with prevalence ranging from 1.2% to 5.3% worldwide and a documented increase of 4.9% between 2017 and 2022. High recurrence rates following surgical treatment contribute substantially to long-term morbidity, healthcare costs, and reduced quality of life. Metaphylaxis has been proposed as a key strategy for preventing recurrent stone formation after percutaneous nephrolithotripsy (PCNL). The aim of this study was to assess the role of metaphylaxis in reducing UC recurrence and improving clinical outcomes after PCNL.

Research design and Methods: A narrative literature review was performed using PubMed, Embase, the Cochrane Library, Scopus, Web of Science, and Google Scholar. The search strategy included the terms "urolithiasis," "nephrolithiasis," "kidney stones," "percutaneous nephrolithotripsy," "recurrence," and "metaphylaxis." Meta-analyses, systematic reviews, original studies, and cross-sectional studies published between 2014 and 2024 were included. Non-peer-reviewed and non-evidence-based sources were excluded. In total, 50 peer-reviewed publications in English and Russian were analyzed.

Results: The reviewed evidence indicates that metaphylaxis significantly reduces the risk of UC recurrence following PCNL. Patients adhering to individualized dietary and pharmacological recommendations demonstrated a 30–50% reduction in recurrence rates within the first two years. Regular metabolic evaluation enabled early detection and correction of lithogenic risk factors, leading to improved patient-reported outcomes and reduced healthcare utilization.

Conclusions: Metaphylaxis represents a fundamental component of modern UC management after PCNL. An integrated approach combining dietary modification, targeted pharmacotherapy, and systematic metabolic

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monitoring effectively reduces recurrence rates and improves long-term outcomes. Broader implementation of metaphylaxis protocols in routine clinical practice is essential to mitigate the growing global burden of urolithiasis. (www.actabiomedica.it)

Key words: nephrolithiasis, metaphylaxis, recurrence, PCNL, prevention, kidney stones

Introduction

Nephrolithiasis is a global healthcare issue, with a lifetime risk of approximately 18.8% in men and 9.4% in women, affecting populations in both developed and developing countries (1). Regardless of age, gender, or race, kidney stone disease is becoming increasingly prevalent worldwide (1,2). Nephrolithiasis, a common urological disease globally, ranks seventh among urinary system pathologies, with a prevalence of 1.4% in Kazakhstan (3). The incidence of urolithiasis in Kazakhstan in 2015 was 76.6 per 100,000 adults (2014 - 75.5; 2013 - 73.4; 2012 - 71.8). The highest rates, similar to 2014, were recorded in the Zhambyl region (211.7) and the city of Astana (287.1), while the lowest rates were in West Kazakhstan (13.1), Karaganda (44.9), and Almaty (44.5) regions (4). The prevalence of kidney stones ranges from 1% to 15% worldwide (5). An analysis of 81,327 hospitalized patients in the Turkestan region revealed an annual increase in urological pathologies by a factor of 1.17 from 2017 to 2019 (3). Without specific treatment, the five- and twenty-five-year recurrence rates range from 40% to 75% (6,7). Urolithiasis primarily affects working-age individuals, with associated hospitalizations, surgeries, and work absences costing the U.S. economy over $5 billion annually (8-11). Despite advances in the surgical treatment of nephrolithiasis, the recurrence rate remains high, with up to 30% of patients experiencing recurrent stone formation within 5-10 years post-percutaneous nephrolithotripsy (PCNL) (12). Therefore, pharmacological prophylaxis is a desirable strategy given the high disease burden associated with kidney stone recurrences (6,7).

Kidney stones form due to urinary supersaturation with substances such as calcium, oxalate, and uric acid, leading to crystallization. Risk factors include metabolic disturbances, dietary habits, genetic predisposition, and environmental conditions (13-17). Modern minimally invasive endourological techniques enable the effective removal of virtually any calculi from the kidneys and urinary tract. However, complete removal of all stone fragments is not always achievable, and drainage devices such as nephrostomies, stents, and urethral catheters are often necessary, which increase the risk of catheter-associated bacteriuria and infections, further complicating urinary tract infections. Additionally, urease-producing microorganisms play a significant role in alkalizing the urine, creating conditions favorable for crystallization and the formation of so-called infection stones. These stones account for 20%-40% of all urinary calculi (18-20). Moreover, biofilm-induced urinary tract infections increase the risk of recurrence after surgery. Studies indicate that bacteriuria and infections caused by gram-negative bacteria, such as Klebsiella spp. and E. coli, heighten the likelihood of stone recurrence (21). Metaphylaxis, or metaphylaxis, is critical in reducing recurrence rates and improving long-term outcomes in patients following PCNL. The aim of this review article is to evaluate the effectiveness of various metaphylaxis strategies in preventing kidney stone recurrence in patients post-percutaneous nephrolithotripsy. In the United States, nephrolithiasis (NL) is relatively common, affecting approximately 1 in 11 adults. A study of 12.7 million children in the United States noted a rate of NL of 54.1 cases per 100,000 person-years in 2016. Multiple studies have noted that the incidence of NL and

nephrocalcinosis has increased over the past decade, especially in adolescents and female children. There is high morbidity associated with NL and nephrocalcinosis, including an increased risk of chronic kidney disease and kidney failure. Causative gene variants have been detected in up to 32% of children with NL (22). Nephrolithiasis remains one of the most challenging diseases for clinicians worldwide because of the high prevalence of subjects experiencing kidney stone formation (13 for men and 7% for women) and the elevated rate of reoccurrence after the first episode (approximately 50% within 5 years) 1. It is common dur-ing adulthood with a higher prevalence between 40-50 years, but its incidence is increasing in patients older than 65 year old 2. This is partly due to increase in life expectancy over the last decades, mainly in Western countries. Indeed, the general demographic statistics underline that the population aged 65 years or more will rise to the 28% of the general population in 2050 (about 2 bil-lion people), thus further increasing the prevalence of nephrolithiasis in geriatric patients 3 to 19.1% in men and 9.4% in women. It is estimated that the elderly will represent 10-12% of all stone formers 4. Elderly patients deserve specific attention in consid-eration of their frequent comorbidities, different dietary habits, with low fluid intake and decreased high-nutri-ents food consumption, physical and environmental factors and hormonal changes 5. Accordingly, the management of elderly patients requires an accurate diagnostic evaluation and tailored treatment, both pharmacological and surgical, to obtain results similar to their younger counterpart. McCarthy et al. compared patients aged 80 year-old or more with a younger cohort highlighting that, although elderly had more comorbidities, later presentation with larger and more complex stones, required early ureteric stent insertion and definitive percutaneous nephrolithotomy (PCNL), there was no difference in intraoperative Nephrolithiasis is a disease characterized by the presence of crystal concretions in the urinary tract. It is widely spread worldwide, both in the Western and non-Western countries. Several studies have pointed out a rising prevalence and incidence of kidney stone disease in the elderly population in the last several decades. Data from large cohort studies suggest an association between the increased risk of stones formation and dietary factors such as low fluid intake, low calcium intake, high sodium intake, high animal protein intake, and high fructose intake. The kidney stones risk may also be increased by medical conditions such as obesity, diabetes, primary hyperparathyroidism, and gout. Stones may be asymptomatic or may show symptoms such as abdominal and flank pain, nausea and vomiting, urinary tract obstruction, and infections (23).

Materials and methods

A structured literature search was conducted in the following databases: PubMed, Embase, Cochrane Library, Scopus, Web of Science, and Google Scholar. The search utilized a combination of Medical Subject Headings (MeSH) and keywords related to nephrolithiasis, percutaneous nephrolithotripsy, recurrence, and metaphylaxis. In planning and conducting the study, we adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and the study selection process is summarized in Figure 2. Key search terms included “nephrolithiasis,” “kidney stones,” “percutaneous nephrolithotripsy,” “recurrence,” “metaphylaxis,” and “prevention.” Studies published from January 2014 to September 2024 were considered for data relevance. Inclusion criteria covered meta-analyses, controlled and original studies, cross-sectional studies, and systematic reviews. Articles lacking an evidence base were excluded. A total of 61 sources met the inclusion criteria, including peer-reviewed articles in English and Russian.

Results

Percutaneous nephrolithotripsy was introduced into clinical practice in the late 20th century and has since been considered the gold standard for treating large kidney stones (over 2 cm in diameter) (24). The procedure involves creating a channel through the skin to access the kidney and subsequently removing or fragmenting the stone using various energy sources, such as ultrasound, laser, and pneumatic lithotripters (25). PCNL demonstrates a high success rate and significantly

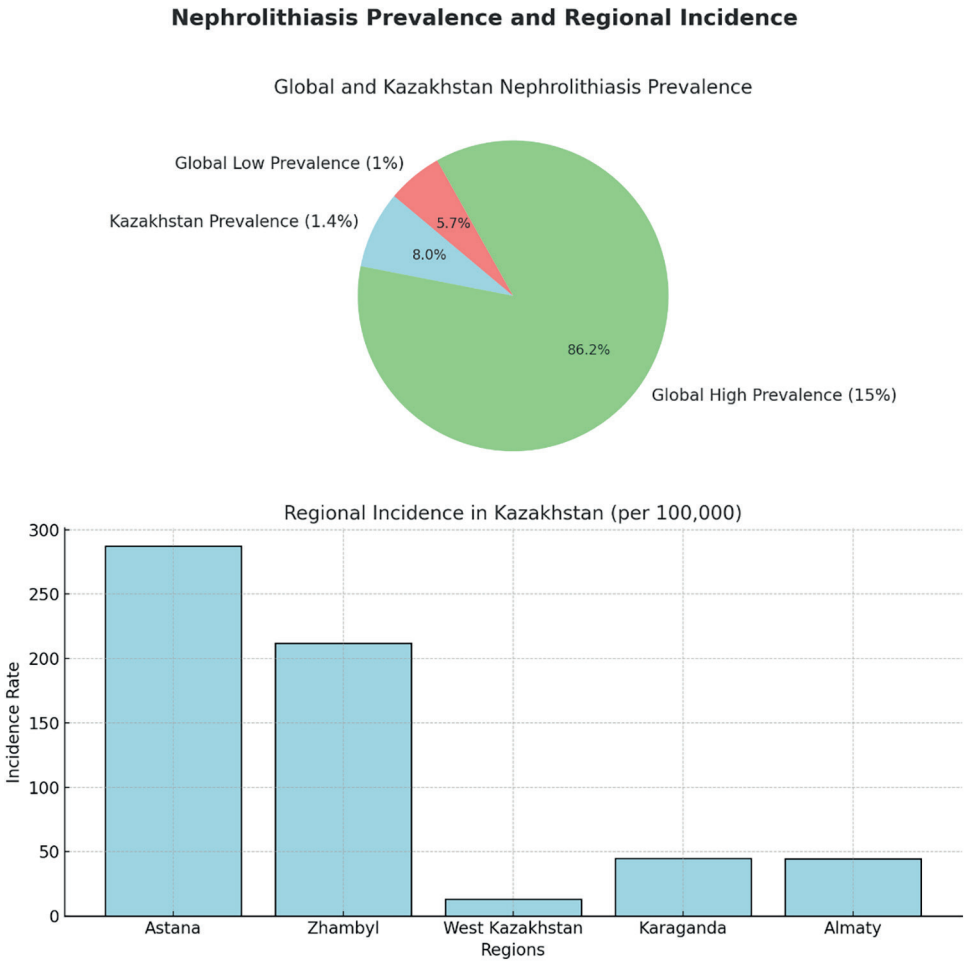

Figure 1. Nephrolithiasis and Regional Incidence. The figure illustrates the variability in nephrolithiasis prevalence across different regions, highlighting areas with high, moderate, and low incidence. Geographic and environmental factors contributing to regional differences are schematically represented.

fewer complications compared to open surgeries (26). However, PCNL does not address the underlying metabolic or environmental causes of stone formation, making metaphylaxis a critical component of treatment necessary to prevent recurrences (27). Metaphylaxis consists of strategies aimed at preventing kidney stone recurrence in individuals with a history of stone formation. These strategies typically include metabolic evaluation, dietary modification, pharmacological therapy, and lifestyle changes (28-30) (Figure 1). After PCNL, metaphylaxis is essential due to the high recurrence rate associated with nephrolithiasis. Without effective metaphylaxis, patients remain at risk for recurrent stone formation, which may necessitate additional invasive procedures (31). A key aspect of effective metaphylaxis is identifying and treating the underlying metabolic disorders that predispose patients to stone formation (32). Post-PCNL, a comprehensive metabolic evaluation should be conducted, including a 24-hour urine analysis and serum biochemical tests. This assessment helps identify risk factors such as hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria. Other factors affecting recurrence risk include patient age, stone location, and stone size (31). Once risk factors are identified, an individualized treatment plan can be developed to reduce the recurrence risk (33, 34). A 24-hour urine

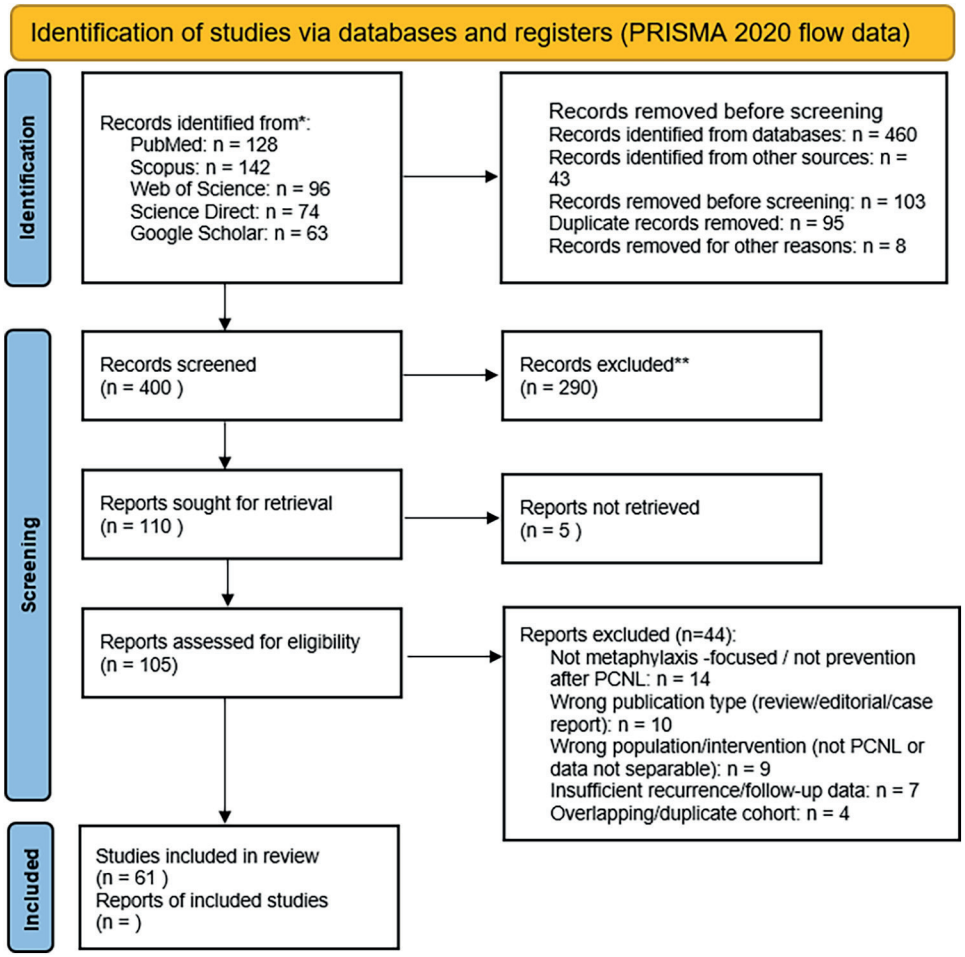

Figure 2. Research flowchart Literature search and study selection process. This flowchart summarizes the databases searched, screening process, eligibility assessment, and final inclusion of studies in this narrative review.

analysis allows for the assessment of various salt and mineral levels, which is important for identifying specific stone types. For instance, hypercalciuria is one of the most common metabolic disorders associated with calcium stone formation. Studies indicate that 30-50% of nephrolithiasis patients have elevated urinary calcium levels, necessitating further evaluation and dietary adjustment or medication (35,36). Skolarikos et al. recommend stone composition analysis and metabolic assessment for all patients after stone formation episodes. Patients are classified as low-risk or high-risk; for low-risk patients, general dietary and lifestyle recommendations are sufficient, whereas high-risk patients require in-depth metabolic evaluation, including 24-hour urine collection, and, if needed, pharmacotherapy (30). Hyperoxaluria is also a critical factor, particularly among patients with calcium oxalate stones. Excessive consumption of oxalate-rich foods (such as spinach, nuts, and chocolate) can lead to stone formation, warranting dietary restrictions. Citrate levels should also be checked, as low urinary citrate levels may contribute to stone formation, given that citrates help dissolve calcium and prevent its crystallization (37, 38). Blood analysis is essential for evaluating levels of uric acid and other substances such as creatinine and electrolytes. Hyperuricemia, an elevated blood uric acid level, can lead to the formation of urate stones, and patients with this condition often require dietary adjustments and medications to lower blood uric acid levels

(39, 40). Adequate hydration reduces the concentration of lithogenic substances in urine, lowering the risk of stone formation. It is recommended to consume at least 2-2.5 liters of fluid daily, preferably water. High sodium intake increases urinary calcium excretion, which raises the risk of calcium stones. It is recommended to limit salt consumption to 2-3 grams per day. Adequate calcium intake (1,000 - 1,200 mg per day) helps bind oxalates in the gut, reducing their absorption and subsequent excretion in urine (41). Limiting foods high in oxalates, such as spinach, beets, nuts, and chocolate, reduces the risk of calcium oxalate stones. (42) High intake of animal protein increases urine acidity and calcium excretion, promoting stone formation. Moderate consumption of meat, fish, and poultry is recommended (43). Citrates found in citrus fruits inhibit crystal formation in urine. Incorporating lemons, oranges, and other citrus fruits into the diet can help prevent stone formation. Consumption of sugary soft drinks is associated with an increased risk of stone formation. It is recommended to limit or eliminate them from the diet (44). These dietary recommendations, based on the latest research, contribute to reducing the recurrence risk of nephrolithiasis and improving the quality of life for patients. Cystinuria is an autosomal inherited aminoaciduria caused by mutations in one or both subunits of the amino acid transport system b0, +, and has a global prevalence ranging from 1 in 2000 to 1 in 100000, depending on the population1. It results in a failure to reabsorb freely filtered cystine in the proximal tubule of the kidney, causing increased urinary excretion of cystine and the dibasic aminoacids, lysine, arginine and ornithine. Cystine is a dimer of cysteine formed by oxidation of their sulphydryl groups to form a disulphide bond. It is poorly soluble in water in the physiological pH range. Its solubility limit in urine is ~1 mM and it forms a microcrystalline precipitate above this limit. This insoluble cystine can form recurrent stones that may cause kidney obstruction and lead eventually to irreversible damage and loss of function (45).

Diet modification

Diet plays a key role in preventing kidney stone formation, with a balanced diet being crucial for preventing recurrence (45,46). Increased fluid intake is universally recommended to dilute urinary substances and reduce the risk of kidney stones (47-50). A balanced diet with low protein, salt, moderate dairy intake, increased fluid intake can reduce kidney stone risk by 13% (51,52). A meta-analysis found that low-protein, high-fiber diets do not reduce stone recurrence (OR = 2.32; P = 0.34). Meanwhile, a low-sodium, normal-calcium diet reduces recurrence compared to a standard calcium diet. Additionally, increased fluid intake significantly lowers the risk of stone formation (OR = 0.39; P = 0.01) (53). Limiting foods high in oxalates is also essential. If dietary modifications are insufficient, pharmacological interventions, such as thiazides or potassium citrate for hypercalciuria, may be required. Overall, an effective approach considers individual stone types and metabolic factors (54,55). Soft drinks and citrus juices are linked to an increased risk of urinary stones (49). A balanced diet with dairy products can reduce intestinal oxalate absorption and urinary excretion, offering protection against nephrolithiasis (56). Vegetarian and Mediterranean diets are recommended for stone prevention, while Western diets are associated with higher stone risk. A general recommendation of at least 2-3 liters of fluid per day suits all stone-forming patients (57). This helps dilute urine, actively preventing new stones by reducing crystallization and aggregation risk (23,58-60). Encourage patients to increase fluid intake to 2-3 liters daily, prioritizing water over sugary or citrus-based soft drinks, to reduce stone formation risk . Recommend a balanced diet with low protein, low sodium, moderate calcium (1,000-1,200 mg/day), and avoidance of high-oxalate foods like spinach and nuts (61). Advocate for vegetarian or Mediterranean diets while discouraging Western-style diets rich in animal protein. Include calcium-rich foods such as dairy to reduce intestinal oxalate absorption. For high-risk patients, a low-sodium, normal-calcium diet and pharmacological interventions like thiazides or potassium citrate may be necessary. Use tools like hydration trackers to monitor adherence and regularly assess urinary parameters to guide further adjustments.

Pharmacological therapy

Pharmacological therapy is a core component of recurrence prevention after PCNL and should be individualized to metabolic abnormalities and monitored

for efficacy and adverse effects. Allopurinol is indicated for hyperuricosuria/uric acid stones, while urine alkalinization (potassium citrate or sodium bicarbonate) is used for uric acid or cystine stones. Observational data suggest prophylactic pharmacotherapy lowers recurrence risk after stone removal (≈19% overall), with particularly strong benefit from alkaline therapy in hypocitraturia (≈26%), mainly within 12–36 months. In a large cohort (Hollingsworth et al.; 13,942 patients), prophylaxis was associated with reduced recurrence and fewer emergency visits in patients with hypercalciuria and low urine pH, supporting targeted use of thiazides and alkaline therapy; effects were not observed for hypocitraturia or hyperuricosuria in that analysis. Evidence is mixed for thiazides: a double-blind trial found hydrochlorothiazide (12.5–50 mg) did not reduce recurrence versus placebo over ~2.9 years and increased adverse events (e.g., hypokalemia, gout). The NOSTONE trial (multicenter, double-blind, placebo-controlled; 416 recurrent calcium-stone formers) was designed to compare placebo with hydrochlorothiazide 12.5/25/50 mg using combined radiologic and symptomatic recurrence as the primary outcome. Adjunct and emerging approaches include phytotherapy and supplements (e.g., Phyllanthus niruri, Tribulus terrestris; citrate from citrus juices, magnesium, vitamin B6, omega-3), though evidence is generally preliminary. Growing interest also focuses on gut factors: intestinal absorption and transport of oxalate and the GI microbiome may influence hyperoxaluria; probiotics have shown inconsistent results due to survival/colonization limitations, and candidate strains require careful preclinical characterization. Microbiological factors may be important in infection-related stones: studies report distinct urinary microbiomes in stone formers, with urease-producing bacteria (e.g., Proteus) and biofilms implicated in infectious stones (up to ~20%) and recurrence, supporting consideration of targeted antibacterial strategies and local resistance patterns. Newer pharmacologic signals include SGLT-2 inhibitors, which were associated with ~33% lower risk of recurrent nephrolithiasis versus other antidiabetic drugs in a 2024 study, and commercial combination approaches for calcium oxalate prevention (e.g., Lit-Control®). Overall, these findings reinforce a personalized, etiology-driven prevention strategy after PCNL. Pharmacological therapy plays a vital role in preventing nephrolithiasis recurrence, with treatments tailored to metabolic abnormalities like hypercalciuria, hypocitraturia, and hyperuricosuria. Thiazide diuretics, potassium citrate, and allopurinol are commonly used, with urine alkalinization (e.g., potassium citrate, sodium bicarbonate) proving effective for uric acid and cystine stones. Emerging therapies, such as SGLT2 inhibitors for diabetes-related nephrolithiasis and probiotics targeting oxalate metabolism, show promise. Non-traditional approaches like phytotherapy (e.g., Phyllanthus niruri, Tribulus terrestris) and products like Lit-Control® Litura® further expand options. Clinicians should combine pharmacological treatments with tailored dietary interventions, monitor efficacy and side effects, and explore innovative strategies to reduce recurrence risks, ensuring a personalized, evidence-based approach to metaphylaxis.

Lifestyle changes

Regular physical activity and maintaining a healthy weight can reduce stone recurrence after surgery. In postmenopausal women, activity levels ≥10 MET/week were associated with up to a 31% lower risk of kidney stone formation, while higher BMI and greater calorie intake increased risk. Other studies also identify BMI >25 kg/m² as a risk factor for recurrence after endourological treatment. Routine imaging and metabolic evaluation are needed to monitor recurrence. Preventing relapse depends on adherence to dietary and pharmacologic recommendations; pharmacologic prophylaxis helps stabilize urolithiasis and reduce the need for repeat surgery. Complete stone clearance during the primary PCNL and regular kidney function monitoring are also critical. Despite well-established preventive principles, improving adherence and developing more effective strategies remain challenges. Future directions include molecular genetics and personalized medicine to enable targeted therapies, as well as advanced imaging and biomarkers to predict recurrence and assess prophylaxis. AI and machine-learning models may further support risk stratification and proactive, individualized prevention.

Discussion

This review emphasizes the critical role of metaprophylaxis in preventing urolithiasis recurrence after PCNL. Although PCNL is highly effective for removing large stones with fewer complications than open surgery, it does not address the metabolic and environmental drivers of stone formation, making prevention strategies essential. Metaprophylaxis reduces recurrence by targeting modifiable risk factors through individualized dietary, pharmacologic, and lifestyle measures, but long-term adherence remains a key challenge. Dietary counseling is foundational: higher fluid intake consistently lowers risk by diluting urinary solutes, and diets low in sodium and oxalate with moderate calcium intake reduce recurrence. Because responses vary (e.g., low-protein or high-fiber regimens), recommendations should be tailored to metabolic evaluation and stone composition. Healthier patterns such as Mediterranean or vegetarian diets appear protective, whereas Western diets and soft drinks increase risk. Pharmacologic therapy is indispensable for metabolic abnormalities: thiazides, potassium citrate, and allopurinol address hypercalciuria, hypocitraturia, and hyperuricosuria, respectively. Recent data (e.g., the NOSTONE trial) underscore the need to optimize dosing and continuously reassess protocols. For infection-related stones, recognition of urease-producing, biofilm-forming bacteria supports incorporating microbiology-guided antimicrobial strategies when appropriate. Lifestyle changes-regular physical activity and weight control-may further reduce recurrence, and emerging tools (advanced imaging, biomarkers, AI-based prediction) could improve monitoring and personalization. Improving adherence is crucial; patient-centered education, motivational interviewing, mobile apps (reminders and hydration tracking), and telemedicine follow-up can strengthen persistence with preventive measures. Overall, integrating individualized metaprophylaxis into routine post-PCNL care can reduce recurrence, improve outcomes, and lower healthcare costs, while future advances in molecular genetics may enable prevention strategies targeting underlying predisposition.

Conclusion

The findings of this review highlight the pivotal role of personalized metaphylaxis in reducing nephrolithiasis recurrence and improving patient outcomes; however, optimal results require an interdisciplinary approach. Dietitians can provide tailored nutritional counseling based on individual metabolic profiles and cultural preferences, while nephrologists and urologists oversee evaluation and medical management of factors driving stone formation. General practitioners support continuity of care by monitoring adherence and addressing barriers to lifestyle change. Integrating these disciplines into a unified care model can improve education, adherence, and clinical outcomes and should be central to future metaphylaxis strategies. PCNL is the gold standard for treating large kidney stones, offering high success rates and fewer complications than open surgery, but it does not address the metabolic and environmental causes of recurrence, underscoring the need for metaprophylaxis. Individualized strategies combining dietary modification, pharmacotherapy, and lifestyle changes are essential to reduce recurrence risk. Increased fluid intake and reduced sodium and oxalate consumption remain foundational, while thiazide diuretics and potassium citrate can correct key metabolic abnormalities; regular exercise and weight management further improve outcomes. Emerging molecular genetics and predictive modeling may refine prevention, but sustained benefit will depend on effective adherence and the use of advanced diagnostics to personalize prophylaxis and reduce the burden of recurrent nephrolithiasis.

Conflict of interest: Each author declares that he or she has no commercial associations that might pose a con-flict of interest in connection with the submitted article.

Author contributions: T.I. - conceptualization, methodology, literature search, manuscript writing, final approval; B.Zh - supervision, critical revision; O.K. - data curation, literature analysis; M.N. - methodological support, editing; V.N. - expert consultation, review and editing; A.M. - data curation, validation; A.M. - validation, corresponding. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Declaration on the Use of AI: Chat GPT4o was used only to re-phrase or improve clarity of some sentences. Examples of Prompt used were "Rephrase this sentence" or "make this sentence clearer". AI was not used to generate original sentences or produce ideas.

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