# The Evaluation and Management of Urolithiasis

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## Introduction

Urolithiasis is one of the most common urologic diseases encountered by urologists worldwide. The disease has an estimated prevalence ranging from 2% to 20%, with regional differences seen across the globe. Regardless, evidence suggests that the prevalence of urolithiasis is on the rise across the world, owing to combination of several factors, encompassing changes in dietary habits, climate, social conditions, and comorbidities present in patients at risk of the disease.[1-4] Furthermore, it is noteworthy that the burden of urolithiasis might especially in precipitated in certain specific regions of the world like Asia, where India and China show high percentage of the global incident cases. This high incident burden then translates into augmented distribution of total disability adjusted life years (DALYs) in these countries.[3]

## Classification of stones

Urinary stones are of different types, classified based on their major chemical composition. In general, a majority of stones are composed of calcium oxalate or phosphate (80%), with other stone types including struvite, uric acid, and cystine stones (Table 1).[5,6]

## Clinical presentations

The most common clinical presentation seen in patients with urinary stones is acute, severe pain, which often radiates from the flank region to the abdomen and especially to the groin; and is commonly referred to as ureteric or renal colic. The pain is usually sharp and severe in nature, and it is one of the most severe pain sensations known. In addition, patients may also report symptoms of urinary urgency, restlessness, hematuria, and nausea and vomiting.[1,7] Nevertheless, asymptomatic presentation of urinary stones is also not common. Such patients have no relatable urinary symptoms of significance, and are coincidentally diagnosed to have stones when evaluated for some other clinical indication.[8]

**Table 1. Types of various common stones[5,6]**

| | |
|---|---|
| **Calcium oxalate** | Calcium oxalate monohydrate, Calcium oxalate dehydrate |
| **Calcium phosphate** | Hydroxyapatite, Brushite, Carbonate apatite, Whitlockite, Octacalcium phosphate |
| **Infection stone** | Struvite (Magnesium ammonium phosphate), Carbonate apatite |
| **Uric acid** | |
| **Cystine** | |
| **Drug-induced stones** | Xanthine, Indinavir, Triamterene, etc. |
| **Mixed stones** | Mixed calcium oxalate-phosphate, Mixed uric acid-calcium oxalate |

## Risk factors for stone formation

There are several risk factors that have been observed to increase the risk of urolithiasis in patients. These include poor dietary habits including poor oral fluid intake, high salt intake, high animal-derived protein intake; personal and family history of stones; environmental factors; medications; and medical comorbidities. Herein, a prior personal and family history of calculi is a likely consistent factor that often increases the risk of developing subsequent stones in such patients.[5] The STONE score is a validated risk assessment tool, which categorizes patients in a low, moderate, or high probability of having a stone using five criteria; sex, timing origin, nausea, and erythrocytes.[5] Recently, researchers from South Korea also developed a urolithiasis score based on age (>35 years), history of urolithiasis, pain duration (<8 h), nausea/vomiting, costovertebral angle tenderness, serum creatinine (≥0.92 mg/dL), erythrocytes (≥10/high power field), no leukocytes and any crystalluria, with its performance claimed to be better than the STONE score. However, the model requires further validation in different settings.[9]

## Diagnosis of urolithiasis

Initial evaluation of the patients suspected to have urinary stones usually starts careful medical history, followed by routine blood and urine tests including urine analysis with microscopy.[5] These tests are generally inexpensive

and essential, and should be used to screen for possible abnormalities associated with urolithiasis.[6] However, a diagnostic confirmation of urolithiasis following initial evaluation is often needed and achieved through imaging only.[10] Herein, renal ultrasound is one of the most widely used imaging methods, and provides an ideal initial imaging modality to assess urolithiasis.[5] In patients with non-conclusive diagnosis, further imaging test like non-contrast abdominal and pelvic CT scan can be used to confirm the diagnosis.[7] These two modalities – ultrasound and CT – in fact remain as first-line diagnostics for treatment planning in urolithiasis.[11] Particularly, unenhanced helical CT is highly sensitive (>95%) and specific (>96%) in the diagnosis of urolithiasis.[6]

## Pharmacotherapeutic strategies for urolithiasis

The management of patients with urolithiasis depends mainly on the patient's acute presentation and can involve both conservative and surgical approaches like shock wave lithotripsy (SWL), ureteroscopic stone removal, or percutaneous nephrolithotomy (PCNL). For conservative management, several management options are available including watchful waiting, fluid and diet modifications, disease-specific therapies, and medical expulsive therapy (MET) aimed to prevent stone recurrence or dissolve specific stones. In all such scenarios, stone size is an important factor that needs to be considered; a trial of spontaneous passage is recommended for uncomplicated ureteral stones of size 10 mm or less. Medical expulsive therapy with use of α-adrenergic blockers, such as tamsulosin, has special significance here as it can result in considerably higher passage rate of 5-10 mm ureteral stones.[5,10,12,13]

## Medical expulsive therapy: Focus on tamsulosin

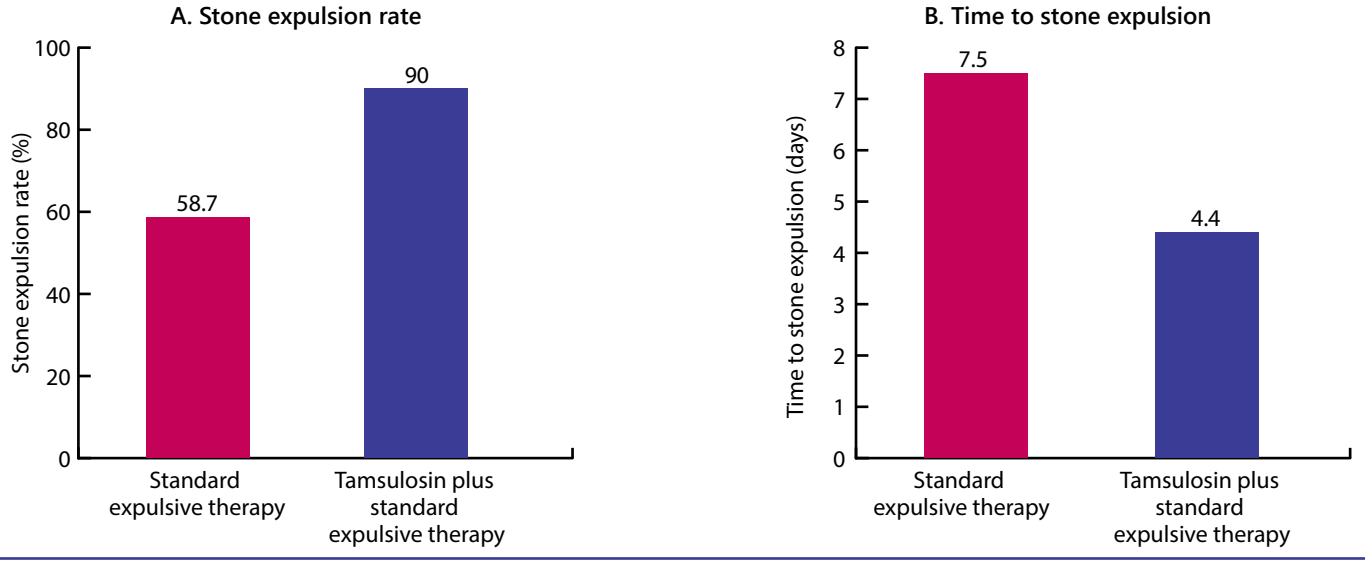
As mentioned earlier, MET is an effective conservative management approach for the initial management of patients with urinary stones. It combines the watchful waiting with combination of drugs aimed to facilitate spontaneous passage of the urinary stones.[13,14] Several drug classes are available that can be used in MET; however, most data and guidelines recommend alpha-blockers as a preferred option to facilitate passage of ureteral stones <10 mm in diameter in carefully selected patients.[14-17]

Furthermore, amongst the alpha-blockers, tamsulosin, a selective alpha-1 receptor antagonist, has been the most widely studied drug in the treatment of ureteral stones, with increased rates of spontaneous stone expulsion.[18] Tamsulosin acts on alpha-adrenergic receptors present on ureteral smooth muscles, resulting in dilatation of lumen and inhibition of spasms, especially in the distal part of the ureter.[19] It is therefore effective as MET increases the passage rate for stones up to 10 mm.[20] The treatment not only increases the rate of spontaneous stone expulsion but also decreases the time to stone expulsion.[18]

### Clinical evidences

***1. Tamsulosin for distal ureteral stone:*** MET with tamsulosin has well-documented evidence for managing distal ureteral stone. In a single-center study, De Sio and colleagues[21] demonstrated that addition of tamsulosin to standard expulsive pharmacologic therapy for treatment of distal-ureteral stones resulted in a significant higher expulsion rate (90%) as compared to standard expulsive therapy only (58.7%). In addition, tamsulosin therapy

**Figure 1: Efficacy of tamsulosin in MET for distal ureteral stones[21]**



was associated with a shorter stone passage time (mean 4.4 days) than standard therapy (mean 7.5 days) (Figure 1). Moreover, tamsulosin add-on group demonstrated lower analgesic use and significantly fewer hospitalizations for recurrent colic. In conclusion, the study thus showed that tamsulosin is effective for the conservative management of uncomplicated distal-ureteral stones.[21]

***2. Tamsulosin for proximal ureteral stone:*** Tamsulosin is effective for MET not only for distal ureter stone but in the proximal ureter stone management as well. In a study including patients with proximal ureteral calculi, Yencilek F, *et al*[22] demonstrated that addition of tamsulosin to conservative approach led to considerable increase in stone expulsion rate and a decrease in time to stone expulsion. Among the stones less than 5 mm, patients receiving tamsulosin add-on to conservative approach showed higher rate of spontaneous stone passage (71.4%) as compared to conservative approach only (50%) (Figure 2).

## Tamsulosin with ADS technology

Advances in drug pharmacology have resulted in improved methods for enhanced delivery of the drugs to target tissues. Tamsulosin with ADS technology represents an innovation designed to ensure continuous and consistent release of the drug throughout the entire length of gastrointestinal tract, including the colon where water is poorly available. This formulation thus overcomes the well-known limitation of conventional formulations, which require presence of water in the gastrointestinal tract to release the active ingredient (Box 1). In all, the ADS advantage likely results in improved physiologic parameters and less adverse effects.[23,24]

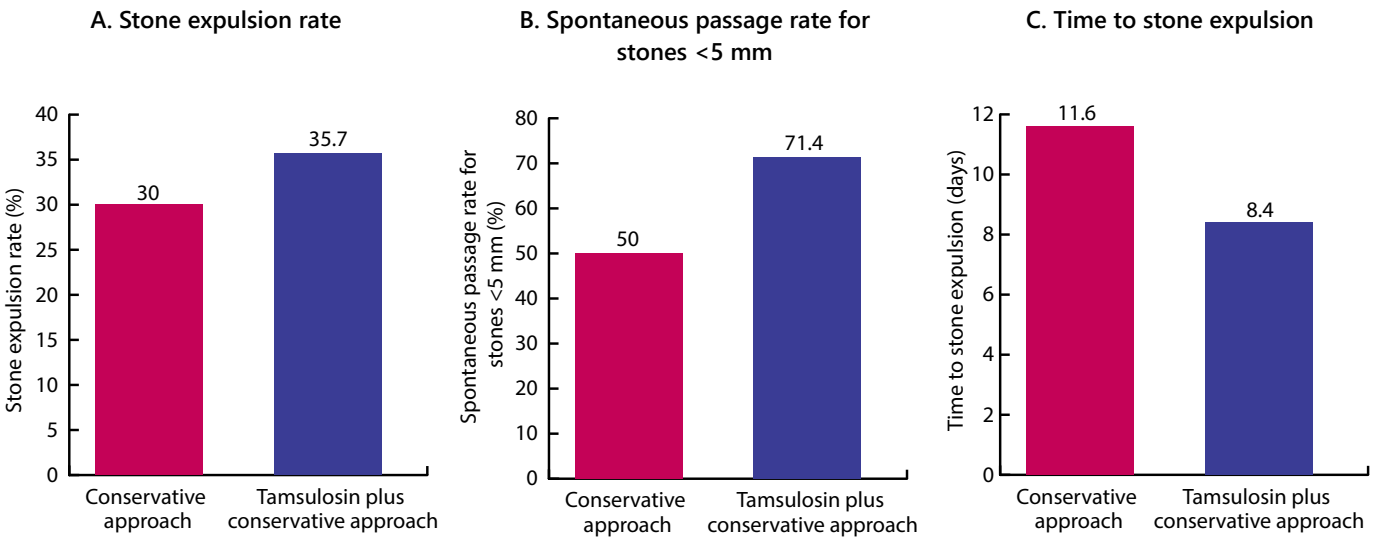
**Box 1: Pharmacological and clinical benefits of tamsulosin with ADS technology[23, 24]**

- 24 hours consistent drug release
- Lesser $C_{max}$ related side effects
- Favorable efficacy/tolerability ratio
- Lower incidence of treatment emergent adverse events
- No dependence on food intake
- Flexible dosing time; can be given anytime during the day
- Decreased risk of postural hypotension, especially in patients with cardiovascular comorbidities; thereby reducing the risk of falls and fractures.

## Additional considerations for urolithiasis management

Since pain is the prominent symptom in patients with symptomatic urolithiasis, analgesics like non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used in the management of patients with renal colic. However, the use of NSAIDs is not without limitations; while they may alleviate some degree of pain, there seems no impact on the stone passage rate.[25] Besides, chronic use of NSAIDs is often associated with a variety of adverse effects.[26] Herein, drotaverine, a well-established directly acting, smooth muscle antispasmodic agent, could be a possible alternative analgesic for pain related to urinary stone disease. Drotaverine is a phosphodiesterase inhibitor that brings about quick and effective pain relief in renal colic as

**Figure 2: Efficacy of tamsulosin in MET for proximal ureteral stones[22]**



> **"Tamsulosin is effective for the conservative management of uncomplicated distal-ureteral stones"**

a result of its potent spasmolytic effect. The drug is without any serious side-effects, and has been shown to have non-inferior efficacy and safety as compared to diclofenac.[27-29]

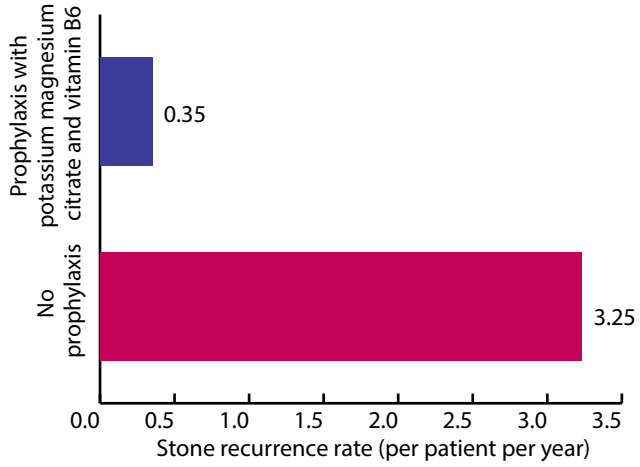
## Urinary alkalization for dissolution of urinary stones

Another significant adjunctive approach in the approach to stones' dissolution is the use of alkali for urinary alkalization. The method has been clinically established as an important treatment for urolithiasis;[30-32] with potassium citrate being a preferred alkalizing agent as it avoids a high sodium load.[33] In addition to its effect of urinary alkalization, potassium citrate offers an additional benefit of increasing the urinary citrate - an inhibitor of stone formation. The treatment thereby proves useful in patients with Ca-oxalate, cystine, and uric acid stones.[34,35] A retrospective cohort study conducted in patients with urolithiasis demonstrated a significant change in urinary metabolic profiles with potassium citrate therapy.[36] Within 6 months after treatment onset, there were increases in urinary pH (5.90 to 6.46) and urinary citrate (470 to 700 mg/day). In addition, a significant decrease in stone formation rate was observed following initiation of potassium citrate; from 1.89 to 0.46 stones per year. Overall, a 68% remission rate and a 93% decrease in stone formation rate were noted. Changes in urinary metabolic profiles were sustained for as long as 14 years of treatment, substantiating the long-term effectiveness of potassium citrate therapy in patients with recurrent urinary stone disease.[36]

## Combination therapy with potassium citrate, magnesium citrate and vitamin B6

The effectiveness and benefits of potassium citrate therapy may be further accentuated by combining it with other agents like magnesium citrate and Vitamin B6. In vitro data show that magnesium can increase the solubility of calcium oxalate; hence, by enriching urine with magnesium, it might be possible that the rate of calcium oxalate crystal growth is slowed. Thus, magnesium therapy may be used to prevent stone recurrence.[37,38] Similarly, while vitamin B6 deficiency has been linked to an increase in oxalate production and excretion; intake of vitamin B6 has been shown to have an inverse association with the risk of stone formation.[39] The

**Figure 3: Stone recurrence rate in recurrent calcium oxalate and calcium phosphate stones: Reduction with potassium magnesium citrate and vitamin B6 prophylaxis[40]**




rationale thus makes both magnesium citrate and Vitamin B6 suitable agents for combination therapy with potassium citrate. In fact, clinical data also seems to validate the efficacy of a combination of potassium citrate, magnesium citrate and Vitamin B6. An Indian study exploring the effects of long-term treatment with potassium magnesium citrate and vitamin B6 prophylaxis in recurrent stone formers prospectively followed 247 patients with hypocitraturia- and hyperuricosuria-induced recurrent calcium oxalate and calcium phosphate stones for 3 years;[40] and observed that prophylaxis with potassium magnesium citrate resulted in a sustained increase in 24-hour urinary citrate excretion from initially low values (221.79±13.39 mg/dL) to within normal to high limits (604.04±5.00 mg/dL) at the 6-months follow-up. The urinary pH also increased significantly from 5.62±0.2 to 6.87±0.01. Importantly, the stone recurrence rate reduced from 3.23±1.04 per patient per year to 0.35±0.47 per patient per year (Figure 3) following prophylaxis with potassium citrate, magnesium citrate and Vitamin B6 combination.

## Conclusion

Urolithiasis is a common disease seen in urology clinics, burdened by a high recurrence rates and associated morbidity. While the diagnosis of stone disease is mostly clinical – based on clinical history and examination – imaging test are often confirmatory. The management of urolithiasis is dependent on the acute condition of the patient and stone characteristics, mainly the size and location, and includes both conservative approach and surgical interventions. Generally, conservative approach is used for stones with size up to 10 mm. Herein, MET is a significant facilitator that can be used in a large subset of population with urinary stones. Several studies have substantiated the

effectiveness of tamsulosin, an alpha blocker and the most studied drug in MET in increasing the stone passage rate in patients with urolithiasis. Furthermore, urine alkalization, with use of potassium magnesium citrate, can be used as an adjunctive measure to enhance the effect of MET and prevent recurrence. Overall, tamsulosin and potassium magnesium citrate along with Vitamin B6 therapy holds significant promise in the treatment and prevention of urinary stones.

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