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MEDICAL MANAGEMENT OF KIDNEY STONES: AUA GUIDELINE

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Purpose: The purpose of this guideline is to provide a clinical framework for the diagnosis, prevention and follow-up of adult patients with kidney stones based on the best available published literature.

Methods: The primary source of evidence for this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review titled *Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventative Medical Strategies* (2012). That report included rigorous searches of MEDLINE, the Cochrane Database of Systematic Reviews, Google Scholar and ClinicalTrials.gov for English-language studies published from 1948 through November 2011 relevant to recurrent nephrolithiasis in adults. To augment and broaden the body of evidence provided in the original AHRQ report, the American Urological Association (AUA) conducted additional supplementary searches of PubMed and EMBASE for relevant articles published between January 2007 and November 2012 that were systematically reviewed using a methodology developed *a priori*. In total, these sources yielded 46 studies that were used to inform the statements presented in the guideline as Standards, Recommendations or Options. When sufficient evidence existed, the body of evidence for a particular clinical action was assigned a strength rating of A (high), B (moderate) or C (low). In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions. While some of the statements in this guideline may be applicable to the pediatric population, this patient group was not the focus of our systematic review due to the limited number of relevant studies available.

GUIDELINE STATEMENTS

Evaluation

1. A clinician should perform a screening evaluation consisting of a detailed medical and dietary history, serum chemistries and urinalysis on a patient newly diagnosed with kidney or ureteral stones. (Clinical Principle)
2. Clinicians should obtain serum intact parathyroid hormone (PTH) level as part of the screening evaluation if primary hyperparathyroidism is suspected. (Clinical Principle)
3. When a stone is available, clinicians should obtain a stone analysis at least once. (Clinical Principle)
4. Clinicians should obtain or review available imaging studies to quantify stone burden. (Clinical Principle)
5. Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers. (Standard; Evidence Strength: Grade B)
6. Metabolic testing should consist of one or two 24-hour urine collections obtained on a random diet and analyzed at minimum for total volume, pH,

calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine. (Expert Opinion)

7. Clinicians should not routinely perform "fast and calcium load" testing to distinguish among types of hypercalciuria. (Recommendation; Evidence Strength: Grade C)

Diet Therapies

8. Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5 liters daily. (Standard; Evidence Strength: Grade B)

9. Clinicians should counsel patients with calcium stones and relatively high urinary calcium to limit sodium intake and consume 1,000-1,200 mg per day of dietary calcium. (Standard; Evidence Strength Grade: B)

10. Clinicians should counsel patients with calcium oxalate stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal calcium consumption. (Expert Opinion)

11. Clinicians should encourage patients with calcium stones and relatively low urinary citrate to increase their intake of fruits and vegetables and limit non-dairy animal protein. (Expert Opinion)

12. Clinicians should counsel patients with uric acid stones or calcium stones and relatively high urinary uric acid to limit intake of non-dairy animal protein. (Expert Opinion)

13. Clinicians should counsel patients with cystine stones to limit sodium and protein intake. (Expert Opinion)

Pharmacologic Therapies

14. Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones. (Standard; Evidence Strength Grade B)

15. Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate. (Standard; Evidence Strength Grade B)

16. Clinicians should offer allopurinol to patients with recurrent calcium oxalate stones who have hyperuricosuria and normal urinary calcium. (Standard; Evidence Strength Grade B)

17. Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists. (Standard; Evidence Strength Grade B)

18. Clinicians should offer potassium citrate to patients with uric acid and cystine stones to raise urinary pH to an optimal level. (Expert Opinion)

19. Clinicians should not routinely offer allopurinol as first-line therapy to patients with uric acid stones. (Expert Opinion)

20. Clinicians should offer cystine-binding thiol drugs, such as alpha-mercaptopropionylglycine (tiopronin), to patients with cystine stones who are unresponsive to dietary modifications and urinary alkalinization, or have large recurrent stone burdens. (Expert Opinion)

21. Clinicians may offer acetohydroxamic acid (AHA) to patients with residual or recurrent struvite stones only after surgical options have been exhausted. (Option; Evidence Strength Grade B)

Follow-up

22. Clinicians should obtain a single 24-hour urine specimen for stone risk factors within six months of the initiation of treatment to assess response to dietary and/or medical therapy. (Expert Opinion)

23. After the initial follow-up, clinicians should obtain a single 24-hour urine specimen annually or with greater frequency, depending on stone activity, to assess patient adherence and metabolic response. (Expert Opinion)

24. Clinicians should obtain periodic blood testing to assess for adverse effects in patients on pharmacological therapy. (Standard; Evidence Strength Grade: A)
25. Clinicians should obtain a repeat stone analysis, when available, especially in patients not responding to treatment. (Expert Opinion)
26. Clinicians should monitor patients with struvite stones for reinfection with urease-producing organisms and utilize strategies to prevent such occurrences. (Expert Opinion)
27. Clinicians should periodically obtain follow-up imaging studies to assess for stone growth or new stone formation based on stone activity (plain abdominal imaging, renal ultrasonography or low dose computed tomography [CT]). (Expert Opinion)

INTRODUCTION

Purpose

Kidney stone disease is a common malady, affecting nearly 1 in 11 individuals in the United States at some point in their lives, and there is evidence that the number of those who have had a stone is rising.[1] Unlike appendicitis and other surgical conditions, surgical treatment of stones is not the endpoint of the disease process, as stones are likely to recur, with at least 50% of individuals experiencing another stone within 10 years of the first occurrence.[2] For those who have experienced a stone or undergone surgical intervention for a stone, there is strong motivation to avoid a repeat episode. Consequently, these patients often seek advice from a variety of practitioners on how to prevent recurrent stones. However, misinformation abounds in the lay community and on the internet, and even medical providers often promulgate recommendations that are contrary to evidence-based medicine.[3] This Guideline is aimed at practitioners from a variety of disciplines who are confronted with patients afflicted with stone disease, and it is based on a systematic review of the literature with respect to the evaluation, treatment and follow-up of first-time and recurrent stone formers. Patient preferences and goals must be taken into account by the practitioner when considering these guidelines, as the cost, inconvenience and side effects of drugs and dietary measures to prevent stone disease must be weighed against the benefit of preventing a recurrent stone.

Methodology

The primary source of evidence for this guideline was the systematic review and data extraction conducted as part of the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review Number 61 titled *Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventative Medical Strategies* (2012). That report, prepared by the University of Minnesota Evidence-Based Practice Center (EPC), included searches of MEDLINE, the Cochrane Database of Systematic Reviews, Google Scholar, ClinicalTrials.gov and Web of Science for English-language studies published from 1948 through November 2011 relevant to the treatment of recurrent nephrolithiasis in adults.

Eligible studies included RCTs and large prospective observational trials of patient populations limited to adults aged 18 years or older with a history of one or more past kidney stone episodes. Studies addressing acute pain management and treatment to promote expulsion of stones were excluded. Full details of the AHRQ search strategies and inclusion/exclusion criteria can be found in the original report.

To augment and broaden the body of evidence provided in the AHRQ report, AUA conducted additional supplementary searches of PubMed and EMBASE for relevant articles published between January 2007 and November 2012, which were systematically reviewed using a methodology developed *a priori*. Study populations were limited to adults 18 years or older with one or more past kidney stone episodes. No limitations on study design were set, however the search protocol prioritized RCTs, CCTs and prospective studies with a comparison group. A total of 3,760 abstracts were obtained, from which 24 articles were selected for full-text review. All dietary and pharmacologic therapies were acceptable, with the exception of interventions addressing acute pain management for urolithiasis, treatment to promote expulsion of ureteral stones, pharmacological agents not approved by the FDA for use in the United States, and finally imaging for suspected acute renal colic. Outcomes of interest included stone recurrence (symptomatic/asymptomatic detection through imaging) and other clinical outcomes relevant to kidney stones: changes in stone size, residual stone clearance, intermediate biochemical changes in urine or blood, quality of life, morbidity related to treatment of recurrent stones as well as adverse event outcomes.

Overall, this supplementary review identified 18 studies to complement the 28 RCTs identified by the AHRQ report. Data on study design, treatment parameters (e.g., dose, administration protocols, follow-up durations), patient characteristics (i.e., age, gender, race, stone composition), adverse events, and primary outcomes (as defined by study authors) were extracted to evidence tables for analysis and synthesis by the methodologist.

Quality of Studies and Determination of Evidence Strength. Quality of individual studies was rated as high, moderate, or low based on instruments tailored to specific study designs. Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias instrument.[4] Conventional diagnostic cohort studies, diagnostic case-control studies, or diagnostic case series that presented data on diagnostic test characteristics were evaluated using the QUADAS-2 tool[5] that evaluates the quality of diagnostic accuracy studies. Cohort studies with a comparison of interest were evaluated with the Newcastle-Ottawa scale.[6]

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes consideration of study design, individual study quality, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings and treatments for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted

RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies) or Grade C (observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data).

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens.[7] ***Standards*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. ***Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. ***Options*** are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears relatively equal or appears unclear; the decision is based on full consideration of the patient's prior clinical history, current quality of life, preferences and values. ***Options*** may be supported by Grade A, B or C evidence.

In some instances, the review revealed insufficient publications to address certain questions from an evidence basis; therefore, some statements are provided as *Clinical Principles* or as *Expert Opinions* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[8] A ***Clinical Principle*** is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. ***Expert Opinion*** refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge and judgment for which there is no evidence.

Limitations of the Literature. The Panel proceeded with full awareness of the limitations of the kidney stone literature. These limitations include heterogeneous patient groups, small sample sizes, lack of studies with diagnostic accuracy data, lack of RCTs or controlled studies with patient outcome data, and use of a variety of outcome measures. Overall, these difficulties precluded use of meta-analytic procedures or other quantitative analyses. Instead, narrative syntheses were used to summarize the evidence for the questions of interest.

Panel Selection and Peer Review Process. The Panel was created by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the additional panel members, all of whom have specific expertise with regard to the guideline subject. Once nominated, panel members are asked to record their conflict of interest (COI) statements, providing specific details on the AUA interactive web site. These details are first reviewed by the Guidelines Oversight Committee (GOC), a member sub-committee from the PGC consisting of the Vice Chair of the PGC and two other members. The GOC determines whether the individual has potential conflicts related to the guideline. If there are no conflicts, then the nominee's COI is reviewed and approved by the AUA Judicial and Ethics (J&E) committee. A majority of panel members may not have relationships relevant to the guideline topic.

The AUA conducted an extensive peer review process. The initial draft of this Guideline was distributed to 107 peer reviewers of varying backgrounds; 40 responded with comments. The panel reviewed and discussed all submitted comments and revised the draft as needed.

Once finalized, the Guideline was submitted for approval to the PGC. It was then submitted to the AUA Board of Directors for final approval. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work.

Background

Although calculi can form *de novo* anywhere within the urinary tract, including the kidneys, bladder and prostate, the pathophysiology related to stone formation differs according to the site of origin. The focus of this Guideline is on renal calculi as these stones are the main source of morbidity, cost and resource utilization associated with urinary tract calculi.

Kidney stone disease is a common condition. According to the most recent National Health and Nutrition Examination Survey (NHANES), the overall prevalence of self-reported kidney stones in the period 2007-2010 was 8.8%, with a higher prevalence among men (10.6%) than among women (7.1%).[1] This prevalence represents a 70% increase over the last reported prevalence (5.2%) derived from an NHANES sample (1988-1994), and the increased prevalence was observed across all age groups and in both sexes. However, prevalence data pose some problems. Unlike other conditions, like appendicitis, for which the diagnosis is readily apparent and can be confirmed by a pathology report, stone disease can be asymptomatic and occurs intermittently and repeatedly. Some individuals harbor undiagnosed stones and require no medical attention, while others necessitate repeated

medical encounters for a single stone. Consequently, stone prevalence depends on the metric used as a surrogate for stone disease (e.g., hospital discharges for a diagnosis of stones, self-reported stones, stones identified on autopsy studies, stones identified on unrelated imaging studies as well as the sensitivity of the imaging modality used to diagnose stones). Most of these surrogates likely underestimate stone prevalence because of failure to detect asymptomatic stones, because of spontaneously passed stones that never involve health care resources, or because a stone was not substantiated by imaging studies or by the documentation of a passed stone despite a history of classic stone symptoms. As such, true stone prevalence is difficult to determine, and the best we can do is to define the parameter measured to determine prevalence.

Historically, kidney stones have occurred more commonly in men than in women. However, by any number of metrics, the gender gap in stone disease is closing.[9-11] Administrative data from the Nationwide Inpatient Sample showed a decline in the male-to-female ratio among hospital discharges with a primary diagnosis of kidney or ureteral stone from 1.7:1 in 1997 to 1.3:1 in 2002.[11] The change in the male-to-female ratio is thought to reflect a disproportionate increase in stone disease among women, rather than a decline among men.[9] The reasons for the observed rise in stone disease among women are not certain, but the impact of obesity, a known risk factor for kidney stones, was found to be greater in women than in men.[12]

Stone disease has been linked to systemic conditions, although it is not clear if stone disease is a cause of these disorders or if it is a consequence of the same conditions that lead to these disorders. Overweight/ obesity,[1,12] hypertension[13] and diabetes[14] have all been shown to be associated with an increased risk of stone disease.

With the increase in the prevalence of stone disease, the cost associated with diagnosis, treatment and follow -up of individuals with stones has risen accordingly. Using claims data from 25 large employers as part of the Urologic Disease in America Project, Saigal and colleagues estimated that the annual incremental health care cost per individual associated with a diagnosis of nephrolithiasis in year 2000 was $3,494, thereby resulting in a total direct cost of nephrolithiasis among the employed population of $4.5 billion.[15] Additionally, since stone disease primarily affects the working-age population, the total direct and indirect costs associated with nephrolithiasis, taking into account the cost of lost workdays, was estimated at $5.3 billion that year.

Diet and lifestyle likely impact the risk of developing stones. The beneficial effect of dietary moderation in reducing the risk of recurrent stones was demonstrated by Hoskings and co-workers, who found a reduction in stone recurrence rate among 108 idiopathic calcium oxalate stone formers who were encouraged to maintain a high fluid intake and avoid "dietary excess".[16] At a mean follow-up of 63 months, 58% of patients showed no new stone formation. Although there was no control group in this study, the favorable effect of dietary modification on stone formation was termed the "stone clinic effect," and it comprises the standard against which pharmacologic therapy is measured.

A number of dietary measures have been evaluated for their effect on stone formation. Unfortunately, few RCTs have compared the incorporation of specific dietary measures with no recommendations on recurrence rates in groups of well-defined stone formers. Those that have made such comparisons typically utilized multicomponent diets such that the independent effects of individual components cannot be determined.[17-19] However, a single RCT found reduced stone recurrence rates among recurrent calcium oxalate stone formers randomized to a high fluid intake compared to a comparable group given no specific recommendations (12% versus 27%, respectively, at 5 years), validating the long held notion that high fluid intake reduces the likelihood of stone recurrence.[20] The only specific beverage that has been evaluated for an effect on stone recurrence in an RCT is soft drinks, for which a group of 1,009 stone formers with a baseline soft drink consumption exceeding 160 ml daily were randomized to avoid soft drinks or continue their typical beverage consumption.[21] The group avoiding soft drinks demonstrated a marginally lower rate of stone recurrence at the end of the three-year trial (58.2% versus 64.6%, respectively, p=0.023), but the effect appeared to be limited to those consuming primarily phosphoric acid-based (e.g. colas) rather than citric acid-based soft drinks.

Multicomponent diets have been evaluated for their effect on stone recurrence by combining dietary measures thought to individually reduce stone recurrence rates. A multicomponent diet consisting of normal calcium, low sodium, low animal protein intake was shown to be superior to a low calcium diet in preventing stone recurrence in hypercalciuric, recurrent calcium oxalate stone-forming men (20% versus 38% recurrence rate at 5 years, respectively).[17] However, the independent effects of calcium, sodium and animal protein could not be assessed. Another multicomponent diet comprised of high fluid, high fiber, low animal protein intake surprisingly was *not* shown to be superior to a high fluid diet in preventing stone recurrence in a group of 102 first-time calcium oxalate

stone formers.[19] However, the control group was found to have higher urine volumes than the study group at two out of three visits, confounding the results. Another RCT also found no benefit of a low animal protein diet in reducing stone recurrence rates among 175 idiopathic calcium stone formers randomized to one of three groups: low animal protein diet, high fiber diet or a control group with no recommendations.[22] There was no significant difference in recurrence rates among the three groups at the conclusion of the four-year trial. Consequently, only the combined effect of low sodium, low animal protein, normal calcium intake has been shown to reduce the likelihood of stone recurrence compared to low calcium intake. It remains unclear how much each of the dietary components contributes to the beneficial effect of the diet. Furthermore, the benefit of these diets was only definitively demonstrated in recurrent calcium stone-forming men.

In the absence of large numbers of well-designed RCTs for the evaluation of dietary measures on stone recurrence, three large cohort studies have been extensively analyzed to determine the independent effect of a variety of foods and supplements on incident stone formation: the Nurses' Health Study I (NHS I) comprised of 121,700 female registered nurses age 30-55, the Nurses' Health Study II (NHS II) comprised of a slightly younger cohort of 116,671 female registered nurses age 25-42 and the Health Professionals Follow-up Study (HPFS) comprised of 51,529 male health professionals age 40-75 years. In all three cohorts, subjects completed food frequency questionnaires and biennial surveys inquiring about different aspects of their health, including whether they had ever been diagnosed with a kidney stone.[23-32] These epidemiologic studies have implicated low calcium intake[23,24,28,29] (women and younger men), low fluid intake,[23,24,28,29] sugar-sweetened beverages[33] and animal protein[23,24,28,29] (men with a BMI >25 mg/kg^2) as risk factors for the development of a first-time stone.

Other dietary measures have been evaluated in small metabolic trials, which in some cases validate the findings of large epidemiologic studies and RCTs, but sometimes do not. The endpoint of these studies is the effect of therapy on urinary stone risk factors, rather than actual stone formation, despite a clear lack of validation of these parameters as proxies for stone formation. Consequently, this Guideline focused primarily on RCTs using actual stone formation rate as the primary outcome, although the benefit of some therapies was inferred from the effect on urinary stone risk factors; the later treatment recommendations were made with a lower strength of evidence.

Drug therapies, primarily directed against specific metabolic abnormalities, have been shown to be superior to placebo, or no-treatment control groups, in randomized trials.[34] Unfortunately, RCTs in stone disease are relatively sparse, likely because the relative infrequency of the event requires long periods of observation. However, for the purposes of this guideline we focused on published RCTs to derive recommendations regarding pharmacologic therapy aimed at preventing stone recurrence. Interestingly, the benefit of directed medical therapy aimed at specific underlying metabolic abnormalities over empiric therapy administered without regard to metabolic background, has never been proven. Indeed, several RCTs have demonstrated a benefit of therapy in unselected groups of patients despite drug therapy targeted to address a specific metabolic abnormality, e.g., thiazides[35,36] or potassium magnesium citrate.[37] Thiazide diuretics, the best-studied drug therapy for stone prevention, along with high fluid intake, have been shown to reduce stone recurrence rates in recurrent calcium stone formers.[38] The effect is not necessarily limited to hypercalciuric stone formers, although even in trials in which patients were not selected on the basis of hypercalciuria, hypercalciuria was likely the most common metabolic abnormality. Along with high fluid intake, alkali citrate[37,39] and allopurinol[40,41] have each been shown to be effective in reducing the risk of calcium stones, although the effect of allopurinol is limited to hyperuricosuric and/or hyperuricemic patients. Thus, to be strictly accurate, recommendations by the Panel would have to be restricted to the specific groups of stone formers studied in the limited RCTs (i.e., hypercalciuric, recurrent calcium stone-forming men) to recommend a normal calcium, low animal protein, low sodium diet.[17] However, in some cases, recommendations were broadened to include the larger stone-forming population, although the recommendation was supported with lower strength of evidence. Further study will be necessary to determine if these recommendations hold for women or for normocalciuric stone formers.

Diet therapy has never been compared head-to-head with pharmacologic therapy. As such, recommendations by the Panel incorporate drugs and/or diet therapy in select circumstances, until the superiority of one over the other can be demonstrated and to allow individualization for particular patients.

GUIDELINE STATEMENTS

Evaluation

Guideline Statement 1.

A clinician should perform a screening evaluation consisting of a detailed medical and dietary history, serum chemistries and urinalysis on a patient newly diagnosed with kidney or ureteral stones. (Clinical Principle)

A detailed history should elicit from the patient any medical conditions, dietary habits or medications that predispose to stone disease. Conditions associated with stone disease include obesity, hyperthyroidism, gout, renal tubular acidosis (RTA) type 1, diabetes mellitus type 2, bone disease, primary hyperparathyroidism and malabsorptive gastrointestinal states due to bowel resection, bariatric surgery or bowel or pancreatic disease. Nutritional factors associated with stone disease, depending on stone type and risk factors, include calcium intake below or significantly above the recommended dietary allowance (RDA), low fluid intake, high sodium intake, limited intake of fruits and vegetables and high intake of animal-derived purines. Patients should be queried regarding their regular use of any stone-provoking medications or supplements (probenecid, some protease inhibitors, lipase inhibitors, triamterene, chemotherapy, vitamin C, vitamin D, calcium and carbonic anhydrase inhibitors such as topiramate, acetazolamide, zonisamide).

Dietary history should elicit from the patient their average daily intake of fluids (amount and specific beverages), protein (types and amounts), calcium, sodium, high oxalate-containing foods, fruits and vegetables and over-the-counter supplements.

Serum chemistries should include electrolytes (sodium, potassium, chloride, bicarbonate), calcium, creatinine and uric acid that may suggest underlying medical conditions associated with stone disease (e.g., primary hyperparathyroidism [42,43], gout, RTA type 1). Urinalysis should include both dipstick and microscopic evaluation to assess urine pH and indicators of infection and to identify crystals pathognomonic of stone type. Urine culture should be obtained in patients with a urinalysis suggestive of urinary tract infection (UTI) or in patients with recurrent UTIs. The presence of high urine pH (>7.0) or urea-splitting organisms, such as *Proteus* species, raises the possibility of struvite stones.

Guideline Statement 2.

Clinicians should obtain serum intact parathyroid hormone (PTH) level as part of the screening evaluation if primary hyperparathyroidism is suspected. (Clinical Principle)

Primary hyperparathyroidism should be suspected when serum calcium is high or high normal. Predominantly calcium phosphate stone composition, elevated urinary calcium or mid-range PTH in the face of higher serum calcium may additionally lead to a suspicion of primary hyperparathyroidism. Measurement of vitamin D levels may additionally be helpful as low vitamin D levels may mask primary hyperparathyroidism, or contribute to secondary hyperparathyroidism. A high or high normal intact PTH in these settings should prompt further endocrine evaluation, imaging or referral for consideration of parathyroidectomy.

Guideline Statement 3.

When a stone is available, clinicians should obtain a stone analysis at least once. (Clinical Principle)

Stone composition of uric acid, cystine or struvite implicates specific metabolic or genetic abnormalities, and knowledge of stone composition may help direct preventive measures.[44,45] Calcium phosphate stone composition is more likely to be associated with certain medical conditions or medications, such as RTA Type 1, primary hyperparathyroidism, medullary sponge kidney and the use of carbonic anhydrase inhibitors. [44,45]

Guideline Statement 4.

Clinicians should obtain and review available imaging studies to quantify stone burden. (Clinical Principle)

Multiple or bilateral renal calculi at initial presentation may place a stone former at greater risk of recurrence. Nephrocalcinosis implies an underlying metabolic disorder (e.g., RTA type 1, primary hyperparathyroidism, primary hyperoxaluria) or anatomic condition (medullary sponge kidney) predisposing to stone formation.

Guideline Statement 5.

Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers. (Standard; Evidence Strength: Grade B)

Urinary saturation of stone-forming salts has been shown to correlate with stone composition, suggesting that 24-hour urine testing can be used to inform and monitor treatment protocols.[46,47] High-risk and/or recurrent stone formers are likely to benefit from metabolic testing and medical therapy and include those with a family history of stone disease, malabsorptive intestinal disease or resection, recurrent urinary tract infections, obesity or medical conditions predisposing to stones (e.g., RTA Type 1, primary hyperparathyroidism, gout, diabetes mellitus type 2). Patients with a solitary kidney are considered "high-risk" because of the serious implications of stone passage/obstruction in a solitary kidney. Recurrent stone formers include patients with repeated stone episodes as well as those with multiple stones at initial

presentation. Additionally, interested first-time stone formers might be offered metabolic testing to help direct dietary recommendations or potentially initiate medication.

Identification of metabolic and environmental risk factors can help direct dietary and medical therapy. Specific nutritional therapy, informed by both diet assessment and metabolic testing, has been shown to be more effective than general dietary measures in preventing recurrent stones.[18] Although the benefit of directed medical therapy over empiric treatment has not been definitively proven, observational studies support the effectiveness of a targeted approach.[48,49] RCTs, however, have shown benefits associated with both empiric and directed medical therapy.[38]

Guideline Statement 6.

Metabolic testing should consist of one or two 24-hour urine collections obtained on a random diet and analyzed at minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine. (Expert Opinion)

There are conflicting opinions in the literature regarding the adequacy of a single 24-hour urine in reliably identifying urinary abnormalities.[50-54] In the absence of clear consensus, either one or two 24-hour urines may be obtained, although two collections are preferred by the Panel. The accuracy of a 24-hour urine collection should be assessed prior to interpretation of results. To assess the adequacy of the 24-hour urine collection, 24 -hour urinary creatinine excretion, taking into account patient gender and body weight, as well as patient recall of the start and end times of his or her collection, should be considered.

Other urinary parameters may be helpful in the initial and follow-up evaluation of stone formers. Urinary supersaturation of stone-forming salts is provided as part of the 24-hour urine analysis panel from many commercially available laboratories, or it can be calculated using a computer program. Supersaturation can guide and monitor effectiveness of treatment and as such, is useful as part of the initial 24-hour urine evaluation.[46,47,55] Likewise, markers of protein intake, such as urine urea nitrogen or urinary sulfate, are reflective of animal protein intake and can be used to assess dietary adherence. Finally, urinary potassium measured at baseline can be compared to urinary potassium obtained during follow-up to gauge compliance with medication regimens.

In stone formers with known cystine stones or a family history of cystinuria or for those in whom cystinuria is suspected, urinary cystine should additionally be measured.

Primary hyperoxaluria should be suspected when urinary oxalate excretion exceeds 75 mg/day in adults without bowel dysfunction. These patients should be considered for referral for genetic testing and/or specialized urine testing.[56]

Guideline Statement 7.

Clinicians should not routinely perform "fast and calcium load" testing to distinguish among types of hypercalciuria. (Recommendation; Evidence Strength: Grade C)

Use of the fast and oral calcium load test to distinguish among types of hypercalciuria has not been shown to change clinical practice.[57,58]

Diet Therapies

Guideline Statement 8.

Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5 liters daily. (Standard; Evidence Strength: Grade B)

Nephrolithiasis is a disease of increased urinary concentration of stone-forming salts, and urine volume is a major determinant of the concentration of lithogenic factors. Fluid intake is the main determinant of urine volume, and as such, high fluid intake is a critical component of stone prevention. Observational studies[23,24,29] and a randomized controlled trial[20] have demonstrated that higher fluid intake reduces the risk of stone formation. Although there is no definitive threshold for urine volume and increased risk (the relationship is continuous and may not be linear), an accepted goal is at least 2.5 liters of urine daily. Because of insensible losses and varying intake of fluid contained in food, a universal recommendation for total fluid intake is not appropriate. Instead, the recommendation should be tailored to the individual patient by using information on total volume derived from the 24-hour urine collections. There are no data to support the use of urine color as a guide, and the desire to have constantly dilute urine needs to be balanced against the need for sleep and competing activities of daily living, including work and school.

Observational studies have found that certain beverages may be associated with risk of stone formation beyond their impact on urine volume. Indeed, alcoholic beverages, coffee, decaffeinated coffee, tea and wine have been shown in observational studies to be associated with a lower risk of stone formation,[26,59,60] while sugar-sweetened beverages demonstrated an increased risk.[33] However, these beverages have not been evaluated in randomized trials. On the other hand, a single randomized trial showed a benefit of reduced soda consumption, although the benefit was largely due to reduced intake of phosphoric acid-based soda (e.g. cola), and the overall reduction in stone recurrence rate was only 6%

fewer stones at 3 years as compared with the control group which did not reduce soda consumption.[21]

Guideline Statement 9.

Clinicians should counsel patients with calcium stones and relatively high urinary calcium to limit sodium intake and consume 1,000-1,200 mg per day of dietary calcium. (Standard; Evidence Strength Grade: B)

There is substantial evidence demonstrating that a lower calcium diet in the absence of other specific dietary measures is associated with an increased risk of stone formation. In the case of calcium oxalate stones, a potential mechanism to explain this apparent paradox is that lower calcium intake results in insufficient calcium to bind dietary oxalate in the gut, thereby increasing oxalate absorption and urinary oxalate excretion. In contrast, the calcium RDA, defined as 1,000-1,200 mg/day for most individuals, was shown in large cohort studies of men and women to be associated with reduced risk. These prospective observational studies consistently showed an independent reduced risk of stone formation with higher dietary calcium intake.[23,24,28,29,61] These observational studies did not have information on stone composition or urine composition for the whole cohort, but in the subset of participants with medical records calcium oxalate was the most common stone type and 24-hour urine values were collected from a subset of participants.

Dietary salt (sodium chloride) is linked to urinary calcium excretion.[62] A randomized trial demonstrated that a lower salt diet, in conjunction with the recommended calcium intake and low animal protein consumption, reduced urinary calcium excretion in hypercalciuric stone formers.[17] The Panel supports a target of ≤100 mEq (2,300 mg) sodium intake daily. As this may be a difficult goal to achieve, especially at once, multi-tiered, progressive targets for reduction of sodium intake may be helpful.

A five-year randomized controlled clinical trial compared stone recurrence in men with a history of calcium oxalate nephrolithiasis and idiopathic hypercalciuria assigned to a diet lower in calcium (400 mg/day) or to a diet with normal calcium content (1,200 mg/day) and lower amounts of animal protein and sodium; both groups were advised to limit oxalate intake.[17] At the end of the study, the risk of developing a recurrent stone on the normal calcium diet was 51% lower than on the lower calcium diet. Although urinary calcium declined in both groups, urinary oxalate increased in the lower calcium group and decreased in the normal calcium group. Because dietary sodium and animal protein may both contribute to the formation of calcium stones, this trial did not directly address the independent role of dietary calcium in the pathogenesis of kidney stones.

Supplemental calcium, in contrast, may be associated with an increased risk of stone formation. In an observational study of older women, calcium supplement users were 20% more likely to form a stone than women who did not take supplements.[24] In younger women and men, there was no association between calcium supplement use and risk of stone formation.[29] The Women's Health Initiative clinical trial also demonstrated an increased risk of stones with calcium supplementation, but, notably, supplement users had a total calcium intake that exceeded the recommended daily upper limit.[63] The discrepancy between the risks associated with dietary calcium and calcium supplements may be due to the timing of calcium supplement intake and/or to overzealous calcium supplementation resulting in excessive total calcium (from both foods and supplements).

Many patients are able to obtain adequate daily calcium from foods and beverages, from traditional sources such as dairy, and also from calcium-fortified beverages and foods, many of which are non-dairy; calcium supplementation is not necessary in these patients. Total calcium intake should not exceed 1,000-1,200 mg daily. If a patient with calcium urolithiasis uses calcium supplements, he or she should collect 24-hour urine samples on and off the supplement. If urinary supersaturation of the calcium salt in question increases during the period of supplement use, the supplement should be discontinued.

Guideline Statement 10.

Clinicians should counsel patients with calcium oxalate stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal calcium consumption. (Expert Opinion)

Higher urinary oxalate levels are associated with increased risk of nephrolithiasis;[64] thus, restricting oxalate-rich foods has generally been recommended for calcium stone formers. An extensive list of the oxalate content of foods is available online from the Harvard School of Public Health (https://regepi.bwh.harvard.edu/health/Oxalate/files/Oxalate%20Content%20of%20Foods.xls, accessed 2/23/2014). As non-dietary factors have also been shown to influence urinary oxalate,[65] overly restrictive low oxalate diets should be avoided as some foods often considered "high" in oxalate may have other health benefits (e.g., various fruits and vegetables). For example, individuals in large cohort studies who consumed diets more consistent with the Dietary Approaches to Stop Hypertension (DASH) diet, not restricted in oxalate, were found to have a significantly reduced risk of developing kidney stones.[31] The DASH diet is high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein.

Urinary oxalate is also modulated by calcium intake, which influences intestinal oxalate absorption. Large cohort studies have demonstrated an increased risk of stone formation with lower calcium diets[24,28,29] and have also found that diets higher in calcium are associated with reduced oxalate excretion.[65] When the recommended daily quantity of dietary calcium was consumed, calcium oxalate stone risk was not significantly affected despite a relatively high intake of dietary oxalate.[66] A randomized controlled trial of recurrent hypercalciuric calcium oxalate stone formers found a reduced rate of stone recurrence in men who consumed a higher calcium, lower sodium, lower animal protein diet.[17] Consequently, patients with hyperoxaluria and a history of calcium oxalate stones, should be advised to consume calcium from foods and beverages primarily at meals to enhance gastrointestinal binding of oxalate, but total calcium intake should not exceed 1,000-1,200 mg daily.

Of note, however, patients with enteric hyperoxaluria and high levels of urinary oxalate, such as those with malabsorptive conditions (e.g., inflammatory bowel disease or Roux-en-Y gastric bypass) may benefit from more restrictive oxalate diets as well as from higher calcium intakes, which may include supplements, specifically timed with meals.[67-70] In such cases, calcium will serve as an oxalate binder so that a significant proportion will appear in the stool. However, 24h urine monitoring can be used to ensure that hypercalciuria does not result.

Other factors that may contribute to higher urinary oxalate include vitamin C and other over-the-counter nutrition supplements. Vitamin C, at dosages much higher than are obtained from foods and beverages alone, contributes to increased urine oxalate[71,72] as ascorbic acid is metabolized to oxalate. The ingestion of turmeric and cranberry tablets has also been linked to higher urine oxalate.[73,74] Therefore, vitamin C and other over-the-counter supplements should be avoided. Finally, a role for other nutritional supplements, such as vitamin B6 (pyridoxine), omega-3 fatty acids, and probiotics,[28,75-79] in reducing urinary oxalate excretion in idiopathic calcium oxalate stone formers has been suggested. However, the data are insufficient to guide recommendations. Pre- and post-intervention 24-hour urine collections may help assess whether there is benefit to any dietary measures incorporated.

Guideline Statement 11.

Clinicians should encourage patients with calcium stones and relatively low urinary citrate to increase their intake of fruits and vegetables and limit non-dairy animal protein. (Expert Opinion)

Urinary citrate is a potent inhibitor of calcium stone formation.[80] Although hypocitraturia is variably defined, most healthy individuals excrete at least 600 mg daily in the urine, and many believe this urinary level should constitute the minimum target output for stone formers. Hypocitraturia is a common risk factor for stone disease with an estimated prevalence of 20-60%.[81,82] Urinary citrate excretion is determined by acid-base status; metabolic acidosis or dietary acid loads enhance renal citrate reabsorption, thereby reducing urinary excretion. A number of medical conditions such as renal tubular acidosis and chronic diarrhea, and some medications, such as carbonic anhydrase inhibitors, may promote hypocitraturia.[82] Acidosis can arise from a diet that is inordinately rich in foods with a high potential renal acid load compared to low-acid (i.e., alkaline) foods.[83] Foods providing an acid load include meats, fish, poultry, cheese, eggs, and to a lesser extent, grains. Foods conferring an alkali load include nearly all fruits and vegetables. Milk and yogurt, as well as fats, are essentially neutral for acid load.[84]

If diet assessment suggests that the acid load of foods contributes to low urinary citrate, patients should be instructed to increase fruit and vegetable intake and reduce intake of high-acid foods. However, it may be sufficient to recommend a higher fruit and vegetable intake without attention to other aspects of the diet, as increased urinary citrate has been shown to occur with this intervention alone.[85] In most circumstances, and certainly when weight loss or maintenance are goals, a reduction in calories from other foods is required when consuming increased calories associated with recommended foods.

Dietary citrate increases urinary citrate excretion by conversion to bicarbonate *in vivo*, while a small amount may be circulated and filtered by the kidneys.[86] Dietary alkali citrate has been proposed as an alternative to pharmacologic citrate to increase citrate excretion.[60,87] Although a number of fruits and juices have been evaluated for their effect on urinary stone risk factors,[88-93] none have been prospectively evaluated in a randomized clinical trial assessing actual stone formation. Consequently, there is insufficient data on which to make specific dietary recommendations.

Guideline Statement 12.

Clinicians should counsel patients with uric acid stones or calcium stones and relatively high urinary uric acid that limitation of intake of non-dairy animal protein may help reduce stone recurrence. (Expert Opinion)

Urinary uric acid is derived from both endogenous and exogenous sources. Diet-derived purines account for an estimated 30% of urinary uric acid.[94] Nearly all foods have purines, but they may have differential biological effects depending on the food source. The typical intake of purines in the United States averages 500-1,500 mg/day, including both animal and plant sources, although the latter may account for only 20% of the total in most

cases.[95]

No relevant studies were identified to either refute or confirm the use of diet to manage high urinary uric acid in uric acid or calcium stone formers. Nonetheless, if diet assessment suggests that purine intake is contributory to high urinary uric acid, patients may benefit from limiting high- and moderately-high purine containing foods. Although the reported purine content of foods varies, "high purine" foods are generally considered those containing more than 150 mg/3-ounce serving. These include specific fish and seafood (anchovies, sardines, herring, mackerel, scallops and mussels), water fowl, organ meats, glandular tissue, gravies and meat extracts. "Moderately-high" sources of purines include other shellfish and fish, game meats, mutton, beef, pork, poultry and meat-based soups and broths.[96,97] Note that an individual may never or only rarely consume "high purine" foods but may habitually consume large portions of foods in the "moderately-high" category. Additionally, the recommendation to reduce "red meat" intake without also addressing fish and poultry is not advised as all of these foods are associated with higher urinary uric acid excretion.[98]

Finally, uric acid crystal formation and growth occur in more acidic urine.[94] Thus, patients with a history of uric acid stones should be counseled to increase the alkali load and decrease the acid load of their diet in an effort to increase urine pH and reduce urinary acidity. Foods conferring an alkali renal load include most fruits and vegetables, while milk and yogurt are acid-neutral, and meats, fish, seafood, poultry, cheese, eggs, and grains all confer an acid load.[99]

Guideline Statement 13.

Clinicians should counsel patients with cystine stones to limit sodium and protein intake. (Expert Opinion)

Patients with cystinuria have high rates of stone recurrence often necessitating urological procedures, despite medical management.[100] Dietary therapy should be offered in combination with pharmacological therapy. Because cystine stone formation is largely driven by cystine concentration, high fluid intake is particularly important in cystine stone formers. The target for urine volume is typically higher than that recommended to other stone formers because of the need to decrease urinary cystine concentration below 250 mg/L.[100] Oral intake of at least four liters per day is often required to meet this goal. Dietary sodium restriction should also be advised as lower sodium intake has been shown to reduce cystine excretion.[101-103] A reasonable goal for sodium intake in individuals with cystinuria is 100 mEq (2,300 mg) or less daily.

Limiting animal protein intake has been suggested as a means to decrease cystine substrate load, as all foods of animal origin are rich in cystine and methionine, which is metabolized to cystine. Limited animal protein diets may also promote increased intake of fruits and vegetables that promote urinary alkalinization and favor cystine solubility. Urinary cystine excretion was significantly decreased in homozygous cystinuric patients who were maintained on a low protein diet (9% of total calories) compared to those on a diet in which protein constituted 27% of total calories.[104] However, protein restriction should be recommended with caution as methionine is an essential amino acid for growth and is limited in plant foods.

Pharmacologic Therapies

Guideline Statement 14.

Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones. (Standard; Evidence Strength Grade B)

A number of RCTs have shown that thiazide diuretics reduce the formation of recurrent calcium kidney stones.[35,36,105-108] Specific drugs and dosages associated with a hypocalciuric effect include hydrochlorothiazide (25mg orally, twice daily; 50mg orally, once daily), chlorthalidone (25mg orally, once daily), and indapamide (2.5mg orally, once daily). Dietary prescription, especially restriction of sodium intake, should be continued when thiazides are prescribed, in order to maximize the hypocalciuric effect and limit potassium losses. Potassium supplementation (either potassium citrate or potassium chloride) may be needed when thiazide therapy is employed because of the hypokalemic effects of these medications. Dietary sources of potassium, such as certain fruits and vegetables low in oxalate content, should also be encouraged. The addition of amiloride or spironolactone may avoid the need for potassium supplementation. Triamterene, although it is potassium -sparing, should be avoided as stones of this compound have been reported.

Although no randomized trials have specifically targeted calcium phosphate stone formers, these individuals were included among the subjects in some of the aforementioned studies. Therefore, thiazide therapy should be considered appropriate for both calcium oxalate and calcium phosphate stone formers. Likewise, although the studies were performed exclusively on patients with recurrent stone formation, the Panel believes that some high-risk first-time stone formers might also benefit from thiazide therapy, such as those with a solitary kidney, hypertension or a large stone burden, or individuals who are refractory to other risk-mitigating maneuvers.

Guideline Statement 15.

Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate. (Standard; Evidence Strength Grade B)

Prospective, randomized controlled trials have demonstrated that potassium citrate therapy is associated with reduced risk of recurrent calcium stones.[37,39,109,110] Patients in these trials had 24-hour urinary citrate excretion that was either low or at the lower end of the normal range. Calcium stone-forming patients with normal citrate excretion but low urinary pH may also benefit from citrate therapy. Finally, potassium citrate therapy should be offered to calcium phosphate stone formers with hypocitraturia because citrate is a known potent inhibitor of calcium phosphate crystallization. However, there is also a risk that higher urine pH can promote calcium phosphate stone formation, or change calcium oxalate stone formers to calcium phosphate stone formers. No randomized controlled trials have assessed the benefit or risk of potassium citrate therapy in calcium phosphate stone formers, although non-randomized observational studies in patients with renal tubular acidosis, who typically produce calcium phosphate stones, suggest that citrate does have a net beneficial effect.[111] Increased fluid intake, sodium restriction, ample fruits and vegetables to counterbalance foods that confer an acid load (see Guideline Statement 11), and thiazides to lower urinary calcium excretion may increase the safety and efficacy of citrate therapy.

Potassium citrate is preferred over sodium citrate, as the sodium load in the latter may increase urine calcium excretion.[112] However, other agents such as sodium bicarbonate or sodium citrate should be considered if the patient is at risk for hyperkalemia.

Guideline Statement 16.

Clinicians should offer allopurinol to patients with recurrent calcium oxalate stones who have hyperuricosuria and normal urinary calcium. (Standard; Evidence Strength Grade B)

A prospective randomized controlled trial demonstrated that allopurinol reduced the risk of recurrent calcium oxalate stones in the setting of hyperuricosuria (urinary uric acid excretion >800 mg/day) and normocalciuria.[40] Whether the drug is effective in patients with hypercalciuria has not been established. Hyperuricemia is not a required criterion for allopurinol therapy. In addition to medication, specific recommendations about limiting non-dairy animal protein (see Guideline Statement 12) may maximize the efficacy of allopurinol.

Guideline Statement 17.

Clinicians should offer thiazide diuretics and/or potassium citrate to patients with recurrent calcium stones in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists. (Standard; Evidence Strength Grade B)

Some patients have no demonstrable abnormalities on 24-hour urine evaluation, and yet continue to form stones. Both thiazides and potassium citrate therapy have been shown to prevent recurrent stones in patients with normal range urinary calcium and citrate, respectively.[35-37,113] Therefore, it may be appropriate to utilize these therapies for patients with recurrent stones who do not demonstrate specific urinary abnormalities. For patients with no identified risk factors for nephrolithiasis, potassium citrate may be the preferred first-line therapy, given its relatively low side effect profile. Patients with either calcium oxalate or calcium phosphate stones may benefit from thiazide and/or potassium citrate therapy.

Guideline Statement 18.

Clinicians should offer potassium citrate to patients with uric acid and cystine stones to raise urinary pH to an optimal level. (Expert Opinion)

The solubility of uric acid and cystine is increased at higher urinary pH values.[114] Potassium citrate therapy provides an alkali load that leads to increased urine pH. For uric acid stone formers, urine pH should be increased to 6.0, and for cystine stone formers, a urine pH of 7.0 should be achieved. Persistent alkalinization of the urine may dissolve existing uric acid and cystine stones and requires administration of therapy throughout the day to maintain consistently higher urine pH values. However, the success of dissolution is variable.

Guideline Statement 19.

Clinicians should not routinely offer allopurinol as first-line therapy to patients with uric acid stones. (Expert Opinion)

Most patients with uric acid stones have low urinary pH rather than hyperuricosuria as the predominant risk factor.[115] Reduction of urinary uric acid excretion with the use of allopurinol in patients with uric acid stones will not prevent stones in those with unduly acidic urine. Therefore, first-line therapy for patients with uric acid stones is alkalinization of the urine with potassium citrate. Allopurinol may be considered as an adjunct when alkalinization is not successful (e.g., patients with inflammatory bowel disease, chronic diarrhea and ileostomies) or for patients who continue to form uric acid stones despite adequate alkalinization of the urine.

Guideline Statement 20.

Clinicians should offer cystine-binding thiol drugs, such as alpha-mercaptopropionylglycine (tiopronin), to patients with cystine stones who are unresponsive to dietary modifications and urinary alkalinization, or have large recurrent stone burdens. (Expert Opinion)

First-line therapy for patients with cystine stones is increased fluid intake, restriction of sodium and protein intake, and urinary alkalinization. If these modifications are not sufficient, cystine-binding thiol drugs constitute the next line of therapy.[116] Tiopronin is possibly more effective and associated with fewer adverse events than d-penicillamine and should be considered first.[117] Captopril, another thiol agent, has not been shown to be effective for the prevention of recurrent cystine stones.[118] Its excretion in the urine at maximal doses is not sufficient to have a stoichiometrically important effect in binding cystine. Studies that suggest a benefit of captopril have had methodological problems with cystine assays.

Guideline Statement 21.

Clinicians may offer acetohydroxamic acid (AHA) to patients with residual or recurrent struvite stones only after surgical options have been exhausted. (Option; Evidence Strength Grade B)

Struvite stones occur as a consequence of urinary infection with a urease-producing organism. Patients treated for struvite stones may still be at risk for recurrent urinary tract infections after stone removal, and in some patients surgical stone removal is not feasible. These patients are at increased risk for stone recurrence or progression, and an aggressive medical approach is required to mitigate this risk.[119] The use of a urease inhibitor, AHA, may be beneficial in these patients, although the extensive side effect profile may limit its use.[120] In particular, patients taking this medication should be closely monitored for phlebitis and hypercoagulable phenomena.[121]

Follow-up

Guideline Statement 22.

Clinicians should obtain a single 24-hour urine specimen for stone risk factors within six months of the initiation of treatment to assess response to dietary and/or medical therapy. (Expert Opinion)

The aim of dietary/medical therapy of nephrolithiasis is to promote changes in the urinary environment that reduce stone recurrence or growth. These changes may include decreases in urinary calcium, oxalate, uric acid and cystine excretion, alterations in urine pH and increases in urinary volume and citrate excretion, ultimately leading to decreases in the supersaturation or concentration of relevant stone-forming salts. Although not clearly demonstrated in prospective randomized trial form, there are a number of observational and case-control studies demonstrating that such changes are associated with a reduction in stone activity.[122-124] Thus, monitoring of urinary parameters may assess patient adherence and guide the clinician in making adjustments in therapy. Rather than obtaining a standard chemistry panel from every 24-hour urine collection, tailored urinary testing may be considered. For example, in patients with pure uric acid stones, urine pH, uric acid, and creatinine could comprise the parameters assessed while an expanded panel should be obtained in those with calcium stones.

Guideline Statement 23.

After the initial follow-up, clinicians should obtain a single 24-hour urine specimen annually or with greater frequency, depending on stone activity, to assess patient adherence and metabolic response. (Expert Opinion)

Longitudinal monitoring of urinary parameters allows for the assessment of patient adherence, the identification of patients who become refractory to therapy and more timely adjustments in therapy for those individuals with active stone formation.[125,126] If patients remain stone free on their treatment regimen for an extended period of time, discontinuation of follow-up testing may be considered.

Guideline Statement 24.

Clinicians should obtain periodic blood testing to assess for adverse effects in patients on pharmacological therapy. (Standard; Evidence Strength Grade: A)

The majority of medications prescribed for stone prevention are associated with potential adverse effects, some of which can be detected with blood testing. For example, thiazide therapy may promote hypokalemia and glucose intolerance; allopurinol and tiopronin may cause an elevation in liver enzymes; AHA and tiopronin may induce anemia and other hematologic abnormalities; potassium citrate may result in hyperkalemia. Such monitoring may also allow the clinician to detect other metabolic abnormalities; for example patients with undiagnosed primary hyperparathyroidism may develop hypercalcemia after initiation of thiazide therapy.[100,120,127-133] The type and frequency of testing should be tailored to the patient's comorbidities and medications.

Guideline Statement 25.

Clinicians should obtain a repeat stone analysis, when available, especially in patients not responding to treatment. (Expert Opinion)

A change in stone composition may account for the lack

of response to dietary/medical therapy. Therefore, repeat stone analysis is justified in this setting. Changes in stone composition have been reported in calcium oxalate stone formers who have converted to forming calcium phosphate stones, while cystine and uric acid stone formers may have additional metabolic abnormalities that predispose them to form other types of stones.[134-143]

Guideline Statement 26.

Clinicians should monitor patients with struvite stones for reinfection with urease-producing organisms and utilize strategies to prevent such occurrences. (Expert Opinion)

Due to the infected nature of struvite stones, patients may continue to be at risk for persistent or recurrent urinary tract infections even after stone removal. Therefore, close monitoring of these patients is recommended in order to identify and treat recurrent infection. Patients with altered lower urinary tract anatomy may be at particular risk for re-infection and recurrence. Monitoring should include surveillance urine culture testing on a periodic basis. In some cases, recurrences may be reduced with long-term, prophylactic antibiotic therapy.[119]

Guideline Statement 27.

Clinicians should periodically obtain follow-up imaging studies to assess for stone growth or new stone formation based on stone activity (plain abdominal imaging, renal ultrasonography or low dose computed tomography [CT]). (Expert Opinion)

Other than stone passage, imaging is the most sensitive way to detect stone activity, defined as either existing stone growth or new stone formation. Plain abdominal imaging has the advantages of being readily available and associated with limited radiation exposure and lower cost compared to other modalities. While the sensitivity and specificity of plain abdominal radiographs and tomograms do not approach those of CT, plain radiography provides an acceptable method of assessment of stone activity in most patients with radiopaque stones. Recent reports on the use of digital tomograms suggest that it may provide enhanced detection of radiopaque stones.[144]

Other studies may be utilized if plain imaging does not adequately delineate stones. Renal ultrasonography is the preferred imaging modality for most patients with radiolucent stones, as there is no exposure to ionizing radiation, and it typically is less costly than CT. However, specificity and sensitivity of ultrasound are inferior to CT. Ultimately, unenhanced CT imaging remains the most sensitive imaging modality, and if needed, can be performed effectively using a low dose protocol in many patients. A one-year imaging interval is recommended for stable patients, but this may be tailored based on stone activity or clinical signs.[145-150]

FUTURE RESEARCH

For a disease with relatively high incidence and prevalence, research in the prevention of kidney stone disease is surprisingly sparse. The reasons for the paucity of work have not been investigated but may relate to the facts that kidney stones are sporadic; that the associated pain and discomfort are transient; that recurrence rates in individuals may be high but episodes of renal colic may be separated by years; by a perception, right or wrong, that the pharmaceutical industry is not likely to find substantial profit in stone prevention. The recent AHRQ-sponsored review of medical management identified only 28 RCTs performed through 2012.[38]

The interest in kidney stones has grown in recent years in two important respects, and we hope that these factors will stimulate further interest in understanding and treating stone disease. First, kidney stones appear to be increasing in prevalence.[1] Hypotheses regarding this phenomenon range from changes in diet (more salt and less dairy); the growing epidemics of metabolic syndrome, diabetes and obesity; the effects of global warming and the elimination of *Oxalobacter formigenes* by widespread exposure to antibiotics in the food supply and elsewhere. Prospective monitoring of kidney stone development in populations for whom these sorts of exposures are recorded would be most critical for learning more about the etiologies and root causes of stone disease.

Second, stones have consistently been shown to be associated with more morbidity than previously expected. Associations with coronary artery disease[151], hypertension[13] and diabetes[14] have led to questions about which of these factors are simply associations, and which, if any, are actually in the causal pathways. If stones precede these co-morbidities, we need to understand that relationship; if stones are another indicator of a metabolic alteration resulting from weight gain, we need to advance our efforts to intervene in our patients' diet and exercise regimens. The impression that stones may have more lasting effects or arise from factors that themselves are cardiovascular risk factors may help patients understand that renal colic is perhaps a sentinel event.

With those newsworthy trends in mind, perhaps the effort to prevent stones needs to be broadened to other populations of practitioners. Many patients never see a urologist, most never see a nephrologist, and few are evaluated and personally counseled regarding individualized regimens to address stone prevention. Primary care practitioners and physician extenders are experts at counseling weight loss, exercise and smoking

cessation. If research regarding implementation of stone prevention regimens in emergency rooms and primary care offices advanced, stone recurrence could be the purview of a vastly larger pool of practitioners. Along with the potential to prevent and relieve human suffering, there is ample reason to believe that kidney stone prevention research could have economic impact as well.[15] A wide range of healthcare providers are capable of implementing such strategies without a very sophisticated view of urine chemistry.

We note that although both dietary manipulation[17] and medications such as thiazides, allopurinol and citrate[38] have all been shown to have efficacy in kidney stone prevention, the relative merits of diet and medications have never been compared head-to-head. There may be important patient-centered variables that determine which stone formers are best able to adhere to a medication and respond favorably and which prefer dietary manipulation. Determination of the characteristics of patients who do well incorporating one or the other or both would provide an important aid to practitioners interested in prescribing successful preventive strategies. Whether modifying these exposures will change stone prevalence must be examined.

Furthermore, it is hopeful that the revolution in genetics will lend power to the diagnosis and prevention of disease, and progress is indeed being made slowly. The recent discovery of mutations in CYP24A1, the gene encoding the 24-hydroxylase that inactivates 1,25 -dihydroxy vitamin D, as a cause of hypercalcemia and kidney stones,[152-154] serves as an example that genetics can uncover important genotype-phenotype correlations. Rare genetic causes of kidney stones are being thoroughly investigated and may yield insights into the mechanisms and treatments of more common idiopathic disease affecting wider populations.[155] However the genetic basis for the widespread prevalence of kidney stones in the United States remains relatively unsolved.

Finally, we are only just beginning to understand the potential importance of the intestinal microbiome in the determination of urinary chemistry. Clearly dietary intake is not the sole variable influencing urinary output; an appropriate complement of intestinal microbiota will serve an important role. We have been most familiar with *Oxalobacter formigenes*, an obligate metabolizer of its only substrate, oxalate; its presence is associated with prevention of stones and its absence with increased urinary oxalate and more stones.[156] How the microbiome influences urinary lithogenicity and whether we can safely and productively manage the human microbiome using probiotics, prebiotics, fecal transplants and other strategies will be examined in the coming years.

In summary, there is no dearth of important kidney stone research questions to be raised. Kidney stones now appear to be related to chronic conditions that require a long-term view by a broad range of physicians, physician extenders and patients. They may be associated with adverse effects that either precede or follow stones; the directionality of those relationships needs to be understood. Strong evidence from an admittedly low number of clinical trials demonstrates that stones are indeed preventable.[35] There is now not only a need for new research into the causative and exacerbating factors associated with stones, but also a need to ensure that the acquired knowledge to prevent stones is shared with every stone former in a clinical setting.

LIST OF ABBREVIATIONS

AHA	Acetohydroxamic acid
AHRQ	Agency for Healthcare Research and Quality
AUA	American Urological Association
CT	Computed tomography
DASH	Dietary Approaches to Stop Hypertension
HPFS	Health Professionals Follow-up Study
NHANES	National Health and Nutrition Examination Survey
NHS I	Nurses' Health Study I
NHS II	Nurses' Health Study II
PTH	Parathyroid hormone
RCT	Randomized controlled trial
RDA	Recommended dietary allowance
RTA	Renal tubular acidosis
UTI	Urinary tract infection

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CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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DISCLAIMER

This document was written by the Medical Management of Kidney Stones Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2013. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists and other clinicians with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus -based, depending on Panel processes and available data, for optimal clinical practices in the treatment kidney stones.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.