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CLINICAL GUIDELINE

# Dietary and Pharmacologic Management to Prevent Recurrent Nephrolithiasis in Adults: A Clinical Practice Guideline From the American College of Physicians

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**Description:** The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the comparative effectiveness and safety of preventive dietary and pharmacologic management of recurrent nephrolithiasis in adults.

**Methods:** This guideline is based on published literature on this topic that was identified using MEDLINE, the Cochrane Database of Systematic Reviews (through March 2014), Google Scholar, ClinicalTrials.gov, and Web of Science. Searches were limited to English-language publications. The clinical outcomes evaluated for this guideline include symptomatic stone recurrence, pain, urinary tract obstruction with acute renal impairment, infection, procedure-related illness, emergency department visits, hospitalizations, quality of life, and end-stage renal disease. This guideline grades the quality of evidence and strength of recommendations using ACP's clinical practice guidelines grading system. The target audience for this guideline is all clinicians, and the target patient population is all adults with recurrent nephrolithiasis (≥1 prior kidney stone episode).

**Recommendation 1:** ACP recommends management with increased fluid intake spread throughout the day to achieve at least 2 L of urine per day to prevent recurrent nephrolithiasis. (Grade: weak recommendation, low-quality evidence)

**Recommendation 2:** ACP recommends pharmacologic monotherapy with a thiazide diuretic, citrate, or allopurinol to prevent recurrent nephrolithiasis in patients with active disease in which increased fluid intake fails to reduce the formation of stones. (Grade: weak recommendation, moderate-quality evidence)

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Nephrolithiasis is a condition in which kidney stones, formed from crystals precipitating from the urine, develop within the urinary tract when the urinary concentration of crystal-forming substances is high or that of substances that inhibit stone formation is low. Approximately 80% of adults with kidney stones have stones consisting primarily of calcium oxalate, calcium phosphate, or both. Other stones consist of struvite, uric acid, or cystine. The lifetime prevalence of nephrolithiasis is 13% for men and 7% for women (1, 2), with a 5-year recurrence rate after an initial event of 35% to 50% without treatment (3). Stones are caused by an interaction between genetics and environmental exposure (4).

Efforts to prevent the recurrence of nephrolithiasis target decreasing concentrations of the lithogenic factors (for example, calcium and oxalate) and increasing the concentrations of inhibitors of stone formation (for example, citrate). This is achieved by both dietary changes and appropriate pharmacologic approaches for preventing recurrent kidney stones. Dietary changes include increasing water intake, reducing dietary oxalate, reducing dietary animal protein and other purines, and maintaining normal dietary calcium.

The purpose of this American College of Physicians (ACP) guideline is to present the available evidence on the comparative effectiveness and safety of preventive dietary and pharmacologic management for recurrent nephrolithiasis. The target audience for this guideline is all clinicians, and the target patient population is all adults with recurrent nephrolithiasis (≥1 prior kidney stone episode). This guideline is based on a systematic evidence review (5) and an evidence report sponsored by the Agency for Healthcare Research and Quality (6).

## METHODS

This guideline is based on a systematic evidence review (5) that addressed the following key questions in adults with a history of nephrolithiasis:

1. Do results of baseline stone composition and blood and urine chemistries predict the effectiveness of diet

*See also:*

Summary for Patients . . . . . I-24
Related article: Ann Intern Med. 2013;158:535-43.

* This paper, written by Amir Qaseem, MD, PhD; Paul Dallas, MD; Mary Ann Forciea, MD; Melissa Starkey, PhD; and Thomas D. Denberg, MD, PhD, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were: Thomas D. Denberg, MD, PhD (*Chair*); Michael J. Barry, MD; Molly Cooke, MD; Paul Dallas, MD; Nick Fitterman, MD; Mary Ann Forciea, MD; Russell P. Harris, MD, MPH; Linda L. Humphrey, MD, MPH; Tanveer P. Mir, MD; Holger J. Schünemann, MD, PhD; J. Sanford Schwartz, MD; Paul Shekelle, MD, PhD; and Timothy Wilt, MD, MPH. Approved by the ACP Board of Regents on 23 November 2013.

 

*Table 1.* **The American College of Physicians' Guideline Grading System***

| Quality of Evidence | Strength of Recommendation | |
|---|---|---|
| | Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits | Benefits Finely Balanced With Risks and Burden |
| High | Strong | Weak |
| Moderate | Strong | Weak |
| Low | Strong | Weak |
| Insufficient evidence to determine net benefits or risks | | |

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

and/or pharmacologic treatment on final health outcomes and intermediate stone outcomes, as well as reduce adverse effects?

2. Do results of follow-up blood and urine biochemistry measurements predict final health outcomes and intermediate stone outcomes in adults being treated to prevent recurrence?

3. What is the effectiveness and comparative effectiveness of different dietary therapies on final health outcomes and intermediate stone outcomes?

4. What is the evidence that dietary therapies to reduce risk for recurrent stone episodes are associated with adverse effects?

5. What is the effectiveness and comparative effectiveness of different pharmacologic therapies on final health outcomes and intermediate stone outcomes?

6. What is the evidence that pharmacologic therapies to reduce risk for recurrent stone episodes are associated with adverse effects?

The literature search included English-language trials identified by using MEDLINE, the Cochrane Database of Systematic Reviews (January 1948 to September 2012), Google Scholar, ClinicalTrials.gov, and Web of Science. The literature search was updated in March 2014, and no additional studies met the inclusion or exclusion criteria. Dietary interventions that were evaluated included intake of fluids, calcium, animal protein, sodium, fruit and fiber, purine, oxalate, potassium, soft drinks, citrus, or multicomponent diets. We also included empirical dietary interventions and those tailored according to patient demographics, comorbid conditions, baseline diet, baseline urine or blood biochemical testing, and/or stone type. Pharmacologic agents evaluated include medications approved by the U.S. Food and Drug Administration and available in the United States for prescription (for example, hydrochlorothiazide, chlorthalidone, indapamide, potassium citrate, potassium–magnesium citrate, sodium citrate, allopurinol, magnesium hydroxide, or acetohydroxamic acid [AHA]). For key questions 1, 2, 4, and 6, we considered final clinical health outcomes as the most important measures of treatment benefit, including symptomatic stone recurrence, pain, urinary tract obstruction with acute renal failure, infection, morbidity related to treatment of a recurrent stone, emergency department visits or hospitalizations for treatment of recurrent stones (for example, for renal colic or acute renal failure), quality of life (general or urologic), and end-stage renal disease. The next most important measures of treatment considered for key questions 1, 2, 4, and 6 were intermediate stone outcomes, including composite recurrence (combination of symptomatic or radiographically detected recurrence), recurrence detected only by scheduled radiographic imaging, and change in stone size. Evidence suggests that stones identified with imaging are associated with symptomatic recurrence. For key questions 3 and 5, adverse effects included any reported by eligible trials (for example, nausea, diarrhea, hypokalemia, weight change, hyperlipidemia, and hyperglycemia). Measures of treatment adherence were those reported by the individual trials (for example, self-report questionnaire, pill count, or as estimated by follow-up urine biochemical measures). Further details about the methods and inclusion and exclusion criteria applied in the evidence review are available in the full Agency for Healthcare Research and Quality report (6).

This guideline rates the quality of evidence and strength of recommendations using ACP's guideline grading system (**Table 1**). Details of the ACP guideline development process can be found in ACP's methods paper (7).

## Relationship Between Baseline (Pretreatment) Stone Composition and Biochemistry (Blood and Urine) and Treatment Efficacy to Prevent Stone Recurrence

Results from 1 good-quality (8) and 28 fair-quality trials (9–35) showed that current evidence is insufficient to conclude that assessing baseline stone composition, blood chemistry, or urine chemistry before initiating pharmacologic or dietary interventions reduces stone recurrence.

## Relationship Between Monitoring (In-Treatment) Stone Composition and Biochemistry (Blood and Urine) and Treatment Efficacy to Prevent Stone Recurrence

Evidence is insufficient from 1 good-quality (8) and 15 fair-quality trials (9, 11–14, 18–21, 27, 28, 30, 32–34) to conclude that monitoring stone composition, blood chemistry, or urine chemistry once pharmacologic or dietary interventions have been initiated reduces stone recurrence.

## Benefits of Dietary Therapies

Eight fair-quality trials were identified that assessed the effectiveness of dietary therapies on recurrent kidney stones

*Table 2.* **Evidence for Prevention of Stone Recurrence With Dietary and Pharmacologic Interventions***

| Intervention | Type of Stone Recurrence (Reference) | RR for Stone Recurrence (95% CI) | Quality of Evidence | Adverse Events | RR for Withdrawal (95% CI) |
|---|---|---|---|---|---|
| **Dietary intervention** | | | | | |
| Increased fluid intake vs. control | Composite (33)<br>Radiographic (29) | 0.45 (0.24–0.84)<br>0.15 (0.02–1.07) | Low<br>Insufficient‡ | None reported | 1.11 (0.49–2.50) |
| Increased mineral water intake vs. increased tap water intake | Radiographic (31) | 0.73 (0.48–1.09) | Low | None reported | None reported |
| Reduced soft drink intake vs. control | Symptomatic (35) | 0.83 (0.71–0.98); subgroup of soda acidified by phosphoric acid: 0.65 (0.49–0.87) | Low | None reported | 1.57 (1.00–2.49) |
| Decreased animal protein intake vs. control | Composite (28, 30, 32, 34) | 1.00 (0.52–1.91) | Low | None reported | 0.94 (0.70–1.27) |
| Increased dietary fiber intake vs. control | Composite (28) | 1.18 (0.66–2.12) | Low | None reported | 0.89 (0.66–1.21) |
| Multicomponent diet (high calcium, low protein, and low sodium) vs. control diet | Composite (30) | 0.52 (0.29–0.95) | Low | Hypertension, gout, and stroke | 0.89 (0.37–2.15); withdrawal due to adverse events, 0.43 (0.12–1.58) |
| Multicomponent diet (low animal protein and high fiber) vs. control diet | Composite (34) | 5.88 (1.39–24.92) | Low | None reported | 0.60 (0.29–1.24) |
| Tailored diet vs. empirical diet | Composite (32) | 0.32 (0.14–0.74) | Low | None reported | NA |
| **Pharmacologic intervention** | | | | | |
| Thiazide diuretic vs. placebo or control | Symptomatic (14)<br>Composite (9–11, 13, 27) | 1.04 (0.39–2.80)<br>0.53 (0.41–0.68) | Insufficient‡<br>Moderate | Orthostatic reactions, gastrointestinal upset, erectile dysfunction, fatigue, and muscle symptoms | 1.77 (1.12–2.82); withdrawal due to adverse events, 5.15 (1.51–17.57) |
| Citrate vs. placebo or control | Composite (8, 15, 16, 19)<br>Radiographic (18) | 0.25 (0.14–0.44)<br>0.95 (0.62–1.44) | Moderate<br>Low | Gastrointestinal symptoms | 1.76 (1.12–2.75); withdrawal due to adverse events, 5.18 (1.51–17.79) |
| Allopurinol vs. placebo or control | Symptomatic (20)<br>Composite (20, 23)<br>Radiographic (20) | 0.36 (0.11–1.19)<br>0.59 (0.42–0.84)<br>1.07 (0.16–7.10) | Low<br>Moderate<br>Insufficient‡ | Rash, acute gout, and leukopenia | 0.81 (0.41–1.62); withdrawal due to adverse events, 0.53 (0.16–1.77) |
| AHA vs. placebo or control | Radiographic (24, 25) | 0.81 (0.18–3.66) | Insufficient‡ | Anemia (RR, 2.18 [CI, 1.13–4.21]), headache (RR, 2.18 [CI, 0.42–11.32]), alopecia (RR, 4.36 [CI, 0.51–37.53]), tremor, and deep venous thrombosis | 1.31 (0.56–3.05); withdrawal due to adverse events, 4.39 (2.02–9.55) |
| Magnesium vs. placebo | Composite (27) | 0.65 (0.37–1.16) | Low | Diarrhea | 1.09 (0.40–2.97); withdrawal due to adverse events, 1.82 (0.20–16.77) |
| Thiazide diuretic plus citrate vs. thiazide diuretic | Composite (9) | 0.94 (0.52–1.68) | Low | None reported | None reported |
| Thiazide diuretic plus allopurinol vs. thiazide diuretic | Composite (11) | 0.79 (0.18–3.49) | Insufficient‡ | None reported for combination group; both hypokalemia and hypotension reported in 1 participant receiving thiazide monotherapy | 0.17 (0.02–1.29); withdrawal due to adverse events, 0.20 (0.01–3.97) |

AHA = acetohydroxamic acid; NA = not applicable; RR = relative risk.
* Adapted from reference 6.
‡ Overall quality graded as insufficient because of the small number of recurrent stone events and imprecise risk estimates.

(28–35). Most studies assessed treatment in patients with calcium stones. Low-quality evidence showed that increased fluid intake; reduced soft drink intake (particularly soda acidified by phosphoric acid); and a high-calcium, low-protein, low-sodium multicomponent diet compared with a control diet reduced stone recurrence. Further, a tailored diet compared with an empirical diet reduced stone recurrence. A summary of the evidence is presented in **Table 2**.

### Increased Fluid Intake Versus No Treatment

Low-quality evidence from 1 study (33) showed that patients with calcium stones who increased fluid intake to achieve more than 2 L of urine per day had less composite

stone recurrence than the control group (12.1% vs. 27.0%; follow-up, 60 months). Another trial (29) of radiographic stone recurrence in patients with calcium stones showed a nonstatistically significant decrease in stone recurrence in patients with increased fluid intake compared with no treatment (8.0% vs. 55.6%; follow-up, 24 to 36 months).

### Increased Mineral Water Intake Versus Increased Tap Water Intake

Oligomineral water is a type of mineral water often marketed for diuretic properties. Low-quality evidence from 1 study (31) of radiographic stone recurrence showed that patients with calcium stones who were assigned to drink more than 2 L of a particular brand of mineral water each day (Fiuggi brand oligomineral water) that contained 15 mg of calcium per liter versus tap water with 55 to 130 mg of calcium per liter showed that 17.0% had recurring stones compared with 22.9%, respectively. No studies assessed the effect of other types of mineral or oligomineral waters on stone recurrence.

### Decreased Soft Drink Intake Versus No Intervention

Low-quality evidence from 1 study (35) showed that patients (any stone type) with baseline soft drink consumption of more than 160 mL per day who were instructed to abstain from drinking soda had a reduced risk for symptomatic stone recurrence compared with no treatment (33.7% vs. 40.6%). Subgroup analysis showed that the benefit was limited to patients who drank soda that was acidified by phosphoric acid (typically colas) rather than those acidified by citric acid (typically fruit-flavored sodas) (29.7% vs. 45.6%).

### Multicomponent Dietary Interventions Versus Control

Three RCTs (30, 32, 34) reported mixed results in comparing multicomponent diets with control diets in patients with calcium stones. One fair-quality study (34) showed that 24.0% of patients on a multicomponent diet (low animal protein, high fiber, increased bran, and low purine) had composite stone recurrence compared with 4.1% of those on a control diet. Patients on the multicomponent diet also had a higher rate of composite stone recurrence (7.1 vs. 1.2 per 100 person-years). One fair-quality trial (30) showed that 20.0% of patients on a diet that included normal to high calcium, low animal protein, and low sodium had composite stone recurrence compared with 38.3% of patients on a low-calcium control diet. A third fair-quality study (32) showed that fewer patients who received an extensive metabolic evaluation and subsequent dietary modification had increased composite stone recurrence than patients who received a limited biochemical evaluation with general dietary recommendations (6.2% vs. 19.1%).

### High Fiber Intake Versus Usual Diet

Low-quality evidence from 1 study (28) of patients with calcium stones showed no statistically significant difference between composite stone recurrence for those on a high-fiber diet (increase baseline fiber intake to 25 g per day through increased fruit, fiber, and whole grain consumption) compared with patients on their usual diet. Two other trials (32, 34) of patients assigned to high fiber intake as part of a multicomponent diet compared with a control diet reported conflicting results.

### Low Animal Protein Intake Versus Control Diet

Low-quality evidence from 1 study (28) showed no difference between a diet low in animal protein (<3 servings of meat or fish per week and <100 g of milk products per day) and a control diet for risk for composite recurrent stones (47.8% for both groups) in patients with calcium stones. Three other trials included low animal protein as part of a multicomponent diet compared with a control diet; 2 of these found a lower risk for recurrent stones (30, 32), whereas the other (34) found a higher risk for recurrent stones with the multicomponent diet.

### Other Dietary Interventions

One trial (30) in patients with calcium oxalate stones found that fewer patients treated with a multicomponent diet including normal or high calcium intake (1200 mg/d) had recurrent stones than those on a low-calcium diet (400 mg/d); further, patients on a multicomponent diet including low sodium intake (50 mmol/d) were less likely to experience stone recurrence than those on the control diet. Multicomponent diets including low purine intake were assessed in 2 trials (32, 34) with mixed results. No included studies addressed a low-oxalate diet.

## Harms of Dietary Therapies

Evidence showed that withdrawals from studies for any cause were low because of increased fluid intake. However, withdrawals were high in long-term trials evaluating soft drink intake, high fiber intake, low animal protein intake, and multicomponent dietary interventions. Most trials had poor reporting of adverse events.

### Increased Fluid Intake Versus No Treatment

Average withdrawals from the 2 trials (29, 33) were 9.5% (range 0% to 10.0%) and were similar between increased fluid intake and no treatment. One trial (29) reported no withdrawals due to adverse events.

### Increased Mineral Water Intake Versus Increased Tap Water Intake

One study (31) reported no withdrawals from either group, and they did not report adverse events.

### Decreased Soft Drink Intake Versus No Intervention

One study (35) reported that 8.7% of patients instructed to abstain from soft drinks withdrew compared with 5.5% of patients given no treatment (relative risk, 1.57 [95% CI, 1.00 to 2.49]).

### Multicomponent Dietary Interventions Versus Control

No increased risk for withdrawals for multicomponent dietary interventions compared with control was found,

and the average from 3 trials was 16.4%. One trial reported that 5.0% of withdrawals were due to adverse events for the multicomponent diet compared with 11.7% for the control diet, including hypertension (2.0% vs. 12.0%; relative risk, 0.14 [CI, 0.02 to 1.13]), stroke (2.0% vs. 0%), and gout (2.0% vs. 0%) (30). Another trial reported an 18% withdrawal rate for the multicomponent diet compared with 29% for the control diet and no adverse events were reported (34).

### High Fiber Intake Versus Control Diet

One study (28) reported no increase in withdrawals for patients on the high-fiber diet compared with the control diet (55.0% vs. 61.7%).

### Low Animal Protein Intake Versus Control Diet

One study (28) reported no increase in withdrawals for a low-protein diet compared with a control diet (58.2% vs. 61.7%).

## Benefits of Pharmacologic Therapies

A total of 20 (1 good-quality and 19 fair-quality) trials (8–27) assessed pharmacologic therapy for reducing stones. Both control and therapy groups were instructed to increase fluid intake. Most studies assessed treatment in patients with calcium stones. Thiazide, citrate, and allopurinol treatment decreased stone recurrence.

### Monotherapy

#### *Thiazide Diuretic Monotherapy Versus Placebo or Control*

Moderate-quality evidence from 6 fair-quality trials compared thiazide diuretic with placebo (13, 14, 27) or control (9–11) in patients with recurrent calcium stones. The results showed that the risk for composite stone recurrence was lower in persons treated with thiazide than placebo or control (24.9% vs. 48.5%) (9–13, 27). No significant differences were found in the risk for recurrence between the different types of thiazides studied or varying dosages.

#### *Citrate Monotherapy Versus Placebo or Control*

Moderate-quality evidence was derived from 6 trials comparing citrate monotherapy with placebo (8, 19) or control (15–18) in patients with nephrolithiasis (calcium stones in 5 of 6 studies; stone type not specified for 1 study). Pooled data from 4 trials (8, 15, 16, 19) showed that composite stone recurrence was lower in patients treated with citrate than placebo or control (11.1% vs. 52.3%). Results were similar for different types of citrate used, including potassium citrate (16, 19), potassium–magnesium citrate (8), and potassium–sodium citrate (15). One fair-quality trial (18) showed no difference between citrate and control for risk for radiographic stone recurrence.

#### *Allopurinol Monotherapy Versus Placebo or Control*

Moderate-quality evidence from 4 trials that compared allopurinol monotherapy with placebo (20, 21) or control (22, 23) in patients with calcium oxalate stones showed a reduced risk for composite stone recurrence with allopurinol. Two trials (20, 23) reporting on composite stone recurrence showed that risk for recurrence was lower in patients treated with allopurinol than placebo (33.3% vs. 55.4%). One fair-quality study (20) showed a reduction in symptomatic stone recurrence (10.3% vs. 29.0%), although they found no difference in recurrence of radiographic stones between the treatments.

#### *AHA Monotherapy Versus Control*

Evidence from 2 fair-quality trials showed no statistically significant difference in symptomatic or radiographic stone recurrence between AHA treatment compared with placebo or control group (24, 25) in patients with struvite stones. The overall quality of evidence for this outcome was graded as insufficient because of the small number of recurrent stone events and imprecise risk estimates.

#### *Magnesium Monotherapy Versus Placebo or Thiazide Diuretic*

Low-quality evidence from 1 fair-quality study (27) showed that risk for composite stone recurrence in patients with calcium stones treated with magnesium was nonstatistically significantly lower than placebo (29.4% vs. 45.2%) and nonstatistically significantly higher than thiazide diuretic (29.4% vs. 14.3%).

### Combination Therapy

#### *Thiazide Diuretic Plus Citrate Combination Therapy Versus Thiazide Diuretic Monotherapy*

Evidence from 1 trial (9) showed no difference in risk for composite stone recurrence between treatment with thiazide plus citrate compared with thiazide monotherapy (30.0% vs. 32.0%). The overall quality of evidence for this outcome was graded as insufficient because of the small number of recurrent stone events and imprecise risk estimates.

#### *Thiazide Diuretic Plus Allopurinol Combination Therapy Versus Thiazide Diuretic Monotherapy*

Low-quality evidence from 1 study (11) showed that the risk for composite stone recurrence was similar in patients with recurrent calcium oxalate treated with thiazide plus allopurinol compared with thiazide monotherapy (12.5% vs. 15.8%).

## Harms of Pharmacologic Therapies

Evidence related to harms of pharmacologic therapies were derived largely from trials reporting on withdrawals from the studies or withdrawals due to adverse events, and trials were variable. Specific adverse event reporting was poor.

### Monotherapy

#### *Thiazide Diuretic Monotherapy Versus Placebo or Control*

Pooled data from 7 fair-quality trials (9–14, 27) showed an increase in withdrawals for thiazides compared with placebo or control (17.0% vs. 8.0%; relative risk, 1.77 [CI, 1.12 to 2.82]), and more withdrawals due to adverse events were in the thiazide treatment group (8.0% vs. 1.0%). Four trials (10, 13, 14, 27) reported adverse events as a composite outcome, including orthostasis, gastrointestinal upset, erectile dysfunction, fatigue, and muscle symptoms, although the list of adverse events was different for each study. One of two trials reporting risk for composite adverse events according to treatment group found an increase with thiazide treatment (27, 34). No adverse events were reported for more than 1 patient in any of the other trials.

#### *Citrate Monotherapy Versus Placebo or Control*

Data from 4 trials (1 good and 3 fair quality) showed an increased risk for withdrawal for citrate therapy compared with placebo or control (36.0% vs. 20.0%) (8, 17–19) and an increased risk for withdrawals due to adverse events (15.0% vs. 2.0%).

#### *Allopurinol Monotherapy Versus Placebo or Control*

Two fair-quality trials showed no increased risk for withdrawals (31.0% vs. 42.0%) and no increased risk for withdrawals due to adverse events (4.0% vs. 8.0%) when comparing allopurinol with placebo (20, 23).

#### *AHA Monotherapy Versus Placebo*

Two fair-quality trials reported withdrawal rates for 63% for patients receiving AHA therapy versus 46% for placebo (24, 25) and an increased risk for withdrawals due to adverse events for AHA compared with placebo (22.0% vs. 5.0%). An increased risk for any adverse event with AHA versus placebo (64.0% vs. 32.0%) was found, including anemia (18.0% vs. 8.0%) (24, 25), headache (9.0% vs. 4.0%) (25), and alopecia (9.0% vs. 2.0%) (25). Results for tremor (25.0%) and deep venous thrombosis (16.0%) each were reported only for the AHA group in 1 trial (26).

#### *Magnesium Monotherapy Versus Placebo*

One fair-quality trial (27) found no increased risk for withdrawal for magnesium compared with placebo (18.0% vs. 17.0%). Rates of withdrawal due to adverse events were 6.0% for the magnesium group and 3.0% for the placebo group.

### Combination Therapy

#### *Thiazide Diuretic Plus Citrate Combination Therapy Versus Thiazide Diuretic Monotherapy*

One fair-quality trial reported no withdrawals for either the thiazide plus citrate group or the thiazide treatment groups, and this study did not report adverse events (9).

#### *Thiazide Diuretic Plus Allopurinol Combination Therapy Versus Thiazide Diuretic Monotherapy*

One fair-quality trial (11) reported withdrawal rates of 4.0% in the thiazide plus allopurinol group, 24.0% in the thiazide-only group, and 16.0% in the control group. Withdrawals due to adverse events were reported in 8% of patients in the thiazide group and none for thiazide plus allopurinol or control groups.

## Summary

Increased fluid intake was shown to decrease stone recurrence by at least half with no reported side effects. Decreasing soft drink intake in men with a high baseline intake of soft drinks acidified by phosphoric acid also decreased stone recurrence. Other dietary interventions, including low-protein diets and multicomponent interventions, showed mixed results. Pharmacologic therapies plus increased fluid intake was effective, and thiazide, citrate, and allopurinol treatment resulted in a statistically significant decrease in stone recurrence. No trials were identified that directly compared these treatments with each other. Clinical outcomes and adverse events were sparsely reported, but they were more common for pharmacologic than nonpharmacologic therapies. Evidence was insufficient to determine the effect of dietary or pharmacologic therapy based on stone composition or blood and urine chemistries. Most studies included only patients with calcium stones, and no trials assessed treatment in patients with uric acid or cystine stones. See the **Figure** for a summary of the recommendations and clinical considerations.

## Recommendations

*Recommendation 1: ACP recommends management with increased fluid intake spread throughout the day to achieve at least 2 L of urine per day to prevent recurrent nephrolithiasis. (Grade: weak recommendation, low-quality evidence)*

Low-quality evidence showed that increased fluid intake is associated with a reduction in stone recurrence. Evidence also did not show any difference between tap water and a specific brand of mineral water (Fiuggi brand oligomineral water). People who already drink recommended amounts of liquids and those in whom increased fluid intake is contraindicated should not be directed to increase their fluid intake further. Although some low-quality evidence shows that a decrease in the consumption of soft drinks is associated with a reduced risk for stone recurrence, this benefit was limited to patients who drank soft drinks acidified by phosphoric acid, such as colas, but not for drinks acidified by citric acid, such as fruit-flavored sodas.

*Figure.* **Summary of the American College of Physicians guideline on dietary and pharmacologic management to prevent recurrent nephrolithiasis in adults.**

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## SUMMARY OF THE AMERICAN COLLEGE OF PHYSICIANS GUIDELINE ON DIETARY AND PHARMACOLOGIC MANAGEMENT TO PREVENT RECURRENT NEPHROLITHIASIS IN ADULTS

| | |
|---|---|
| Disease/Condition | Recurrent nephrolithiasis |
| Target Audience | Internists, family physicians, and other clinicians |
| Target Patient Population | Adults with recurrent nephrolithiasis |
| Interventions Evaluated | Dietary: increased fluid intake, increased oligomineral water intake, decreased soft drink intake, multicomponent dietary interventions, high fiber intake, and low animal protein intake<br><br>Pharmacologic: thiazide diuretic, citrate, allopurinol, acetohydroxamic acid, and magnesium |
| Outcomes Evaluated | Symptomatic stone recurrence, radiographic and composite stone recurrence, pain, urinary tract obstruction with acute renal impairment, infection, procedure-related morbidity, emergency department visits, hospitalizations, quality of life, and ESRD |
| Benefits | Decreased stone recurrence |
| Harms | Adverse events associated with dietary interventions:<br>Multicomponent diet: hypertension, gout, and stroke<br><br>Adverse events associated with pharmacologic interventions:<br>Thiazides: orthostasis, gastrointestinal upset, erectile dysfunction, fatigue, and muscle symptoms<br>Citrates: gastrointestinal symptoms<br>Acetohydroxamic acid: anemia, headache, alopecia, tremor, and deep venous thrombosis<br>Allopurinol: rash, acute gout, and leukopenia<br>Magnesium: diarrhea |
| Recommendations | *Recommendation 1: ACP recommends management with increased fluid intake spread throughout the day to achieve at least 2 L of urine per day to prevent recurrent nephrolithiasis. (Grade: weak recommendation, low-quality evidence)*<br><br>*Recommendation 2: ACP recommends pharmacologic monotherapy with a thiazide diuretic, citrate, or allopurinol to prevent recurrent nephrolithiasis in patients with active disease in which increased fluid intake fails to reduce the formation of stones. (Grade: weak recommendation, moderate-quality evidence)* |
| Inconclusive Areas of Evidence | Relationship between pretreatment or in-treatment stone composition and biochemistry (blood and urine) with treatment efficacy to prevent stone recurrence |
| Clinical Considerations | Evidence is applicable primarily to calcium stones.<br><br>Evidence showed that patients who decreased intake of soda that was acidified by phosphoric acid had reduced kidney stone recurrence. Clinicians should encourage patients to avoid colas as opposed to fruit-flavored soft drinks, which are often acidified by citric acid. |

ESRD = end-stage renal disease.

*Recommendation 2: ACP recommends pharmacologic monotherapy with a thiazide diuretic, citrate, or allopurinol to prevent recurrent nephrolithiasis in patients with active disease in which increased fluid intake fails to reduce the formation of stones. (Grade: weak recommendation, moderate-quality evidence)*

Moderate-quality evidence showed that thiazide diuretics, citrates, and allopurinol reduce the risk for recurrence of composite calcium stones. Combination therapy with these agents was not more beneficial than monotherapy. Although biochemistry and some observational data on stone recurrence suggest that the choice of treatment could be based on the type of metabolic abnormality, evidence from randomized, controlled trials is lacking to correlate the drug of choice and stone type to the prevention of stone recurrence. Most patients have calcium stones, and evidence showed that thiazide diuretics, citrates, and allopurinol all effectively reduced recurrence of this stone type. Note that the available evidence evaluated higher doses of thiazides (hydrochlorothiazide, 50 mg; chlorthalidone, 25 or 50 mg; indapamide, 2.5 mg) to prevent recurrent nephrolithiasis. The use of lower doses of thiazides is associated with fewer adverse effects, but their effectiveness in preventing stone recurrence compared with higher doses is not known. All of the medications are associated with adverse events, which are summarized in **Table 2**.

## Inconclusive Areas of Evidence

The current evidence from randomized trials is insufficient to evaluate the benefits of knowing the stone composition, urine chemistry, and blood chemistry related to the effectiveness of treatment. The guidelines committee is aware that observational data show an association of stone composition and biochemistry with stone recurrence; moreover, physiologic knowledge suggests that interventions targeting stone composition, biochemistry, or both

can favorably alter biochemical composition that leads to stone formation. Clinicians often select pharmacologic therapy on the basis of method of action: Thiazide diuretics reduce urinary calcium and are often prescribed for patients with hypercalciuria, citrates bind to calcium and decrease urine acidity, and allopurinol decreases uric acid in urine. Almost all studies analyzed in the evidence review included only patients with calcium stones, which are the most common stone type. Although biochemistry suggests a relationship between pharmacologic method of action and stone type, no randomized, controlled trials link biochemical testing to outcomes. Our recommendations do not include patients with suspected hyperparathyroidism or other rare cases.

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**Note:** Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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