Guidelines Being Compared:

1 American College of Physicians (ACP)

Dietary and pharmacologic management to prevent recurrent nephrolithiasis in adults: a clinical practice guideline from the American College of Physicians.

2014 Nov 04

View Summary >

2 American Urological Association Education and Research, Inc. (Am Urol Assoc Edu Res)

Medical management of kidney stones: AUA guideline.

2014 Mar 01

View Summary >

Areas of Agreement and Difference

A direct comparison of recommendations presented in the above guidelines for dietary and pharmacologic management of adults with recurrent nephrolithiasis (≥1 prior kidney stone episode) is provided in the tables. The AUA guideline also provides recommendations for the diagnosis and follow-up of patients with kidney stones, which are beyond the scope of this synthesis.

Both developers recommend that stone formers maintain a fluid intake that will achieve at least 2 (ACP) or 2.5 liters (AUA) of urine daily in order to prevent stone recurrence. ACP notes that 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. According to AUA, 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, AUA adds, 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.

AUA also addresses dietary management strategies other than increased fluid intake, recommending the following interventions according to stone type and clinical circumstances: calcium stones and relatively high urinary calcium (limit sodium intake and consume 1,000-1,200 mg/day of dietary calcium); calcium oxalate stones and relatively high urinary oxalate (limit intake of oxalate-rich foods and maintain normal calcium consumption); calcium stones and relatively low urinary citrate (increase intake of fruits and vegetables and limit non-dairy animal protein); uric acid stones or calcium stones and relatively high urinary acid (limit intake of non-dairy animal protein); cystine stones (limit sodium and protein intake).

Pharmacologic Management

The guideline developers are in agreement that the primary pharmacologic interventions used to reduce the risk of stone recurrence are thiazide diuretics, potassium citrate (AUA), citrate (ACP) and allopurinol. The scope of the guidance differs, however. The ACP recommendation applies specifically to prevention of composite calcium stones, whereas AUA makes recommendations for the prevention of recurrent calcium, cystine, uric acid and struvite stones. See **Areas of Difference** below for more information.

Areas of Difference

interventions used to reduce the risk of stone recurrence are thiazide diuretics, potassium citrate, and allopurinol, the scope of the guidance differs. ACP recommends monotherapy with one of these agents in patients with active disease in which increased fluid intake fails to reduce the formation of stones. The evidence for this recommendation came primarily from calcium stone formers. According to ACP, 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, notes ACP, and evidence showed that thiazide diuretics, citrates, and allopurinol all effectively reduced recurrence of this stone type.

In contrast, AUA makes pharmacologic treatment recommendations according to stone type/composition and urinary abnormalities detected on 24-hour urine collections. For the prevention of recurrent calcium stones, AUA recommends thiazide diuretics for patients with increased urine calcium, and potassium citrate for patients with decreased urinary citrate. AUA also recommends thiazide diuretics and/or potassium citrate for patients in whom other metabolic abnormalities are absent or have been appropriately addressed and stone formation persists. Allopurinol is recommended by AUA for patients with recurrent calcium oxalate stones who have hyperuricosuria and normal urinary calcium. With regard to treatment of other stone types, AUA recommends cystine-binding thiol drugs (e.g., alpha-mercaptopropionylglycine [tiopronin]) for patients with cystine stones who are unresponsive to dietary modifications and urinary alkalinization, or have large recurrent stone burdens. For patients with residual or recurrent struvite stones in whom surgical options have been exhausted, AUA cites acetohydroxamic acid as a treatment option. AUA recommends potassium citrate for patients with uric acid and cystine stones in order to raise urinary pH to an optimal level.

Comparison of Recommendations

Prevention of Recurrent Kidney Stones

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.

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

	2 in the original guideline document.
AUA (2014)	<u>Diet Therapies</u> • 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**) • 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**) • 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**) • 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**) • 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**) • Clinicians should counsel patients with cystine stones to limit sodium and protein intake. (**Expert Opinion**) <u>Pharmacologic Therapies</u> • Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones. (**Standard; Evidence Strength Grade B**) • Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate. (**Standard; Evidence Strength Grade B**) • Clinicians should offer allopurinol to patients with recurrent calcium oxalate stones who have hyperuricosuria and normal urinary calcium. (**Standard;**

	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**) • Clinicians should offer potassium citrate to patients with uric acid and cystine stones to raise urinary pH to an optimal level. (**Expert Opinion**) • Clinicians should not routinely offer allopurinol as first-line therapy to patients with uric acid stones. (**Expert Opinion**) • 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**) • 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**) **NGC Note**: Refer to the NGC summary for recommendations from AUA on the evaluation and follow-up of kidney stones, which are beyond the scope of this synthesis.

Strength of Evidence and Recommendation Grading Schemes

ACP (2014)	**Grading of Quality of Evidence** **High-Quality Evidence**: Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized, controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect. **Moderate-Quality Evidence**: Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with

or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

Low-Quality Evidence: Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

Insufficient Evidence to Determine Net Benefits or Risks: When the evidence is insufficient to determine for or against routinely providing a service, the recommendation was graded as "insufficient evidence to determine net benefits or risks." Evidence may be conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect that is very uncertain as evidence is either unavailable or does not permit a conclusion.

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**

	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.

AUA (2014)

<u>Body of Evidence Strength</u>

Grade A: Well-conducted and highly-generalizable randomized controlled trials (RCTs) or exceptionally strong observational studies with consistent findings

Grade B: RCTs with some weaknesses of procedure or generalizability or generally strong observational studies with consistent findings

Grade C: Observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data

Note: By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.

<u>American Urological Association (AUA) Nomenclature Linking Statement Type to Evidence Strength</u>

Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence

	on Grade C evidence **Option**: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B, or C evidence **Clinical Principle**: 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**: 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

Methodology

Click on the links below for details of guideline development methodology	
ACP **(2014)**	**AUA** **(2014)**
To collect the evidence, both ACP and AUA performed searches of electronic databases. ACP also performed hand-searches of published literature (primary and secondary sources). The guideline developers provide relevant details of their search strategies including databases searched and date ranges applied. ACP and AUA weighted the selected evidence according to a weighting scheme to assess its quality and strength; both provide the rating schemes used. Both guidelines are based in whole or in part on a 2012 Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review titled Recurrent Nephrolithiasis in Adults: Comparative Effectiveness of Preventive Medical Strategies. The ACP guideline is also based on a 2013 systematic review that was nominated to AHRQ by AUA. The review	

ACP Clinical Guidelines Committee helped to develop and refine the scope and reviewed the draft AHRQ report. Both developers reviewed published meta-analyses; ACP also conducted a meta-analysis.

Expert consensus was employed by both groups as a method of recommendation formulation (AUA specifies the Delphi method was used), and both provide a description of the formulation process. ACP and AUA rate the strength of the recommendations according to a scheme and provide the scheme. With regard to cost effectiveness, neither developer performed a cost analysis nor reviewed published cost analyses. A form of peer review (ACP specifies independent peer review through journal publication and internal review within the organization) was sought by both ACP and AUA as a method of guideline validation.

Benefits and Harms

Benefits

ACP (2014)	Decreased kidney stone recurrence Refer to the "Benefits of Dietary Therapies" and "Benefits of Pharmacologic Therapies" sections in the original guideline document for additional information concerning efficacy of specific interventions.
AUA (2014)	Appropriate management of patients with kidney stones

Harms

ACP (2014)	• Adverse effects associated with a multicomponent diet include hypertension, gout, and stroke. • Adverse effects associated with thiazides include orthostasis, gastrointestinal upset, erectile dysfunction, fatigue, and muscle symptoms.

	• Adverse effects associated with allopurinol include rash, acute gout, and leukopenia. Refer to the "Harms of Dietary Therapies" and "Harms of Pharmacologic Therapies" sections in the original guideline document for additional information on harms associated with specific interventions.
AUA (2014)	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; acetohydroxamic acid (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. The type and frequency of testing should be tailored to the patient's comorbidities and medications.

Contraindications

ACP (2014)	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.
AUA (2014)	Not stated

Abbreviations

ACP, American College of Physicians

AUA, American Urological Association Education and Research, Inc.

This synthesis was prepared by ECRI Institute on May 7, 2015. The information was verified by ACP on June 18, 2015 and by AUA on July 1, 2015.