Rolling Stones: Primer on Nephrolithiasis for PAs in Primary Care

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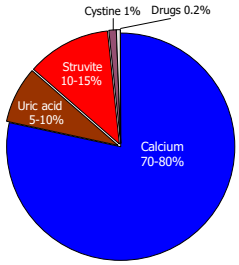
Prevalence of Types of Stones



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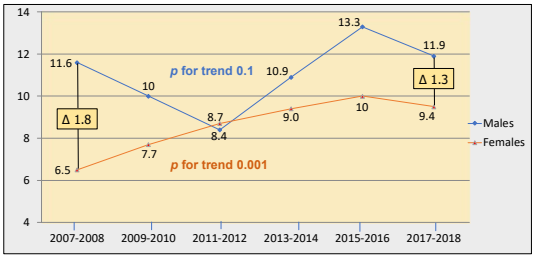
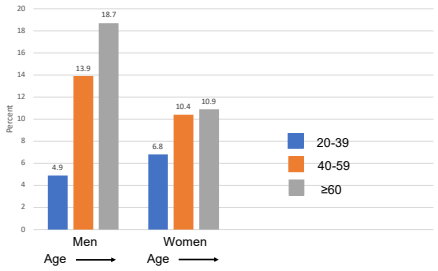
Prevalence of Nephrolithiasis based on NHANES Data 2007-2018



Abufaraz M et al. Eur Urol Focus 2021;7:1468-1475

3

Age-based Prevalence of Nephrolithiasis, NHANES Data 2017-2018



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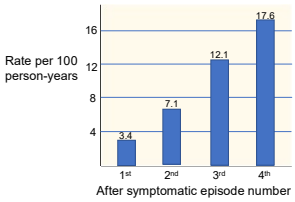
FAST FACTS

- Lifetime prevalence: 11% for men, 7% for women
- Symptomatic recurrence rates (%): 20, 31, and 39 at 5, 10, and 15 years
- Chance of a new stone increases with the number of preceding stones



~ 35% of stone formers will have a second episode
~ 25% will have a third episode

Tundo G et al. J Urol 2021;205:1704-09
Rule AD et al. J Am Soc Nephrol 2014;25:2878-86
Vaughn LE et al. Mayo Clin Proc 2019;94:202-10

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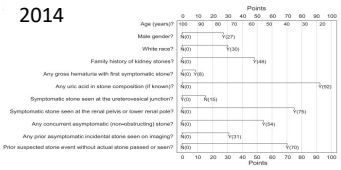
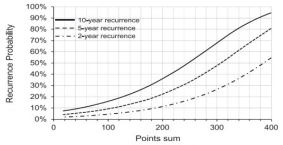
Recurrence of Kidney Stone (ROKS) Nomogram to Predict a Second Symptomatic Stone **after a first episode**

2014





2018 ROKS2 predicts recurrence in people who have had **2 or more symptomatic episodes.**

https://qxcalc.app.link/ROKS2

Not intended for rare stone types or genetic disorders.

The ROKS calculator is free at the **QxMD** Calculate app (iOS: qx.md/qx, Android: qx.md/android, or web based qxmd.com/ROKS).

Rule AD et al. J Am Soc Nephrol 2014;25:2878-86
Vaughn LE et al. Mayo Clin Proc 2019;94:202-10

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It's not just about acute renal colic…..
Long-term renal and systemic risks of nephrolithiasis

- Renal/urologic
  - Pyelonephritis– acute and chronic (infected stones, obstruction)[1]
  - Chronic kidney disease and kidney failure[2,3,4]
  - Renal cell carcinoma and upper tract urothelial carcinoma[5]
  - Ureteral stricture[6]
- Systemic
  - Osteoporosis and increased fracture risk[7]
  - Metabolic syndrome (diabetes, hypertension, dyslipidemia)[8-11]
  - Cardiovascular disease (CAD, stroke)[12-14]
  - Opioid abuse/dependency (with multiple stone-related encounters)[15]

[1]Kidney Int. 2011;79(4):393
[2]BMC Nephrol 2015;16:149
[3]Curr Opin Nephrol Hypertens 2013;22:390
[4]BMJ 2012 Aug 29;345:e5287
[5]*Br J Cancer.* 2019;120(3):368
[6]Arch Ital Urol Androl 2011;83:141
[7]Osteoporos Int 2016;27:3155
[8]Am J Kidney Dis 2013;61:923
[9]Curr Opin Nephrol Hypertens 2008;17(3):304
[10]Clin J Am Soc Nephrol 2017;12:476
[11]Am J Kidney Dis 1998;32:802
[12]Am J Kidney Dis 2014;64:402
[13]J Am Soc Nephrol 2010;21:1641
[14]Clin Sci (Lond). 2018;132:615
[15]Urology 2021 Oct 13;[EPub]

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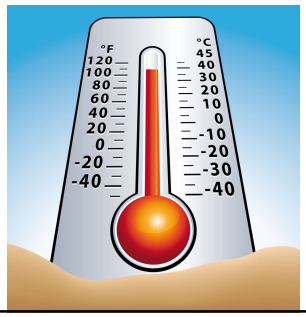
Ambient Temperature



Stone Belt

Southeastern U.S.

Mediterranean

Middle East

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How does ambient temperature contribute to kidney stones?

- Fluid loss from sweating with inadequate replacement
- Sunlight exposure
- Humidity
- Migration to urban areas
- Regional dietary variations
- Regional genetic variations

Fakheri RJ and Goldfarb D. Kidney Int 2011; 79:1178-1185

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Evidence for a genetic component of nephrolithiasis

- **Family clustering of stones**
  - 25-40% of stone patients have a family history of stones
  - Men with a family history of stones are 3X more likely to have stones cf. to men without a family history of stones
- **Ethnic differences in stone rates**
- **Monozygotic vs. dizygotic twin studies**

Goldfarb D et al. Kidney Int 2005;67:1053–1061

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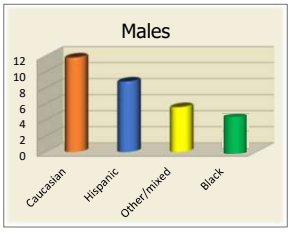
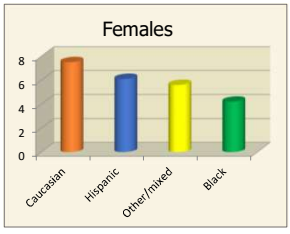
Racial Differences in Kidney Stone Prevalence





Scales CD et al. Europ Urol 2012;62:160–165, 2007-2010 NHANES Data

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Evidence for a genetic role in nephrolithiasis rates in blacks vs. whites

Data from Nurses' Health Study
postmenopausal non-stone formers

Differences in 24-hour urinary excretion*	
Blacks higher (n = 146)	Whites higher (n = 330)
pH Citrate	Calcium Phosphorus Rel. supersaturation of CaOx Rel. supersaturation of brushite

*Results adjusted for age, BMI, thiazide use, other urinary factors, and dietary factors (vitamin D intake and excretion of sodium and urinary markers of protein intake)

Taylor EN and Curhan GC. J Am Soc Nephrol 2007;18:654-659

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Rates of Kidney Stones in Monozygotic vs. Dizygotic Twins

Twin concordance rates for kidney stones

	Total number of pairs	Pairs concordant for kidney stones	Pairs discordant for kidney stones	Proband concordance*
Monozygotic	1928	29	163	**32.4**
Dizygotic	1463	17	162	**17.3**

***P* <0.001**

Heritability of risk = 56%

Goldfarb D et al. Kidney Int 2005;67:1053–1061

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The New England
Journal of Medicine

VOLUME 346 JANUARY 10, 2002 NUMBER 2

COMPARISON OF TWO DIETS FOR THE PREVENTION OF RECURRENT STONES IN IDIOPATHIC HYPERCALCIURIA

LORIS BORGHI, M.D., TANIA SCHIANCHI, M.D., TIZIANA MESCHI, M.D., ANGELA GUERRA, PH.D., FRANCA ALLEGRI, M.D., UMBERTO MAGGIORE, M.D., AND ALMERICO NOVARINI, M.D.

	Low calcium diet	Normal calcium, low sodium, low animal protein diet
Calcium	400 mg/day	1200 mg/day
Sodium	----------	50 mmol/day (~1250 mg/day)
Animal protein	----------	52 g/day (total protein 93 g/day)

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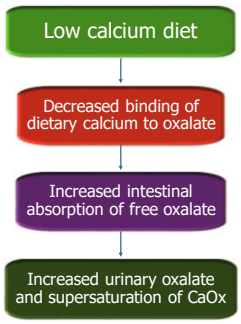
Low dietary calcium causes CaOx stones



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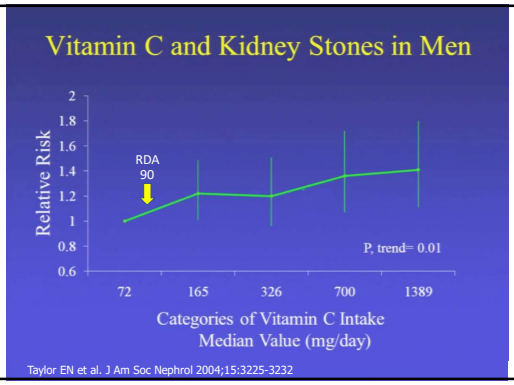
Vitamin C and Kidney Stones in Men



Taylor EN et al. J Am Soc Nephrol 2004;15:3225-3232

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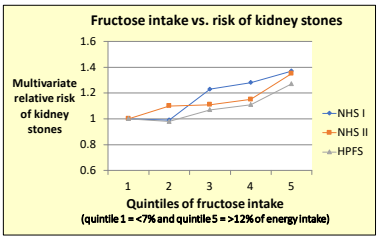
High-fructose corn syrup



Taylor EN and Curhan GC. Kidney Int 2008;73:207-212

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How does fructose cause kidney stones?

- Mechanisms aren't completely known, but fructose causes…
  - Increased excretion of calcium
  - Increased excretion of oxalate
  - Increased production and excretion of uric acid
  - Low urine pH
    - Insulin resistance

Taylor EN and Curhan GC. Kidney Int 2008;73:207-212

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Systemic Disorders Associated with Nephrolithiasis

Increased calcium excretion

- Hyperparathyroidism
- Sarcoidosis
- Vitamin D intoxication
- Paget's disease
- Cushing's syndrome
- Hyperthyroidism
- Malignant tumors
- Distal renal tubular acidosis

Renal anatomical abnormalities

- Polycystic kidney disease
- Medullary sponge kidney
- Horseshoe kidney
- UPJ obstruction

CaOx and uric acid stones

- Inflammatory bowel disease and other malabsorptive states
- Obesity, metabolic syndrome, diabetes

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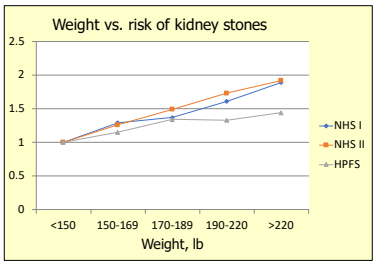
Obesity Increases Risk of Kidney Stones



Taylor EN et al. JAMA 2005;293:455-462

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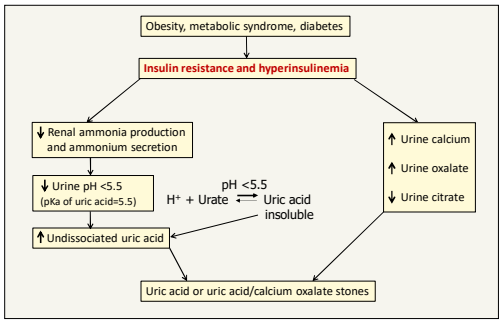
The path from obesity to kidney stones



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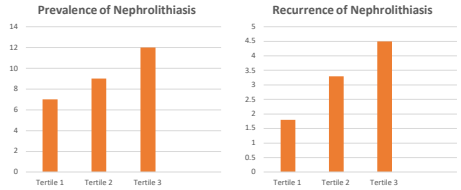
Higher Triglyceride-Glucose Index* Is Associated With Increased Likelihood of Kidney Stones

21,000 participants in NHANES 2007-2014 survey
*TG-Glucose Index is a reliable indicator of **insulin resistance**
Results are independent of BMI, diabetes, HTN, gender, and age



Qin Z et al. Front. Endocrinol. 2021;12:774567.
doi: 10.3389/fendo.2021.774567

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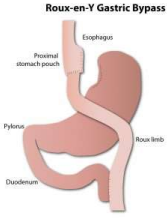
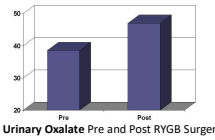
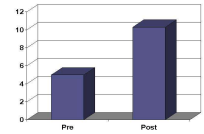
Gastric Bypass and Oxalate Excretion





Urinary Oxalate Pre and Post RYGB Surgery



Supersaturation of Calcium Oxalate
Pre and Post RYGB Surgery

Wu JN et al. Surg Obes Relat Dis 2013;9:83-87

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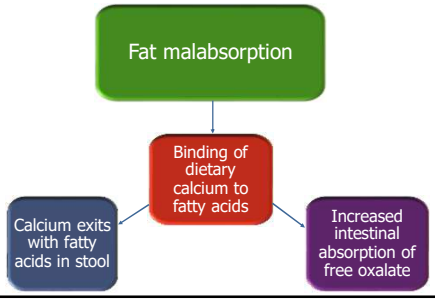
Mechanism of Bariatric Surgery-Induced Hyperoxaluria



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Urinary Factors

Promoters of stones	Stone type
Low urine volume	All
Low urine citrate	CaOx
Hypercalciuria	CaOx, CaPhos
Hyperoxaluria	CaOx
pH	
Low (<5.5)	Uric acid
High (>6.2)	CaPhos
Infection with urease-producing bacteria (e.g. Proteus mirabilis)	Struvite
Inhibitors of stones	
Citrate, **magnesium, potassium**, glycosaminoglycans, Tamm-Horsfall protein, osteopontin, pyrophosphate, fetuin-A, nephrocalcin, etc.	

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Drugs Associated with Nephrolithiasis

Urinary factor	Drug
Hypercalciuria	Excessive calcium/vitamin D supplements, Loop diuretics, glucocorticoids
Hyperoxaluria	Frequent use of antibacterials, excess vitamin C
Hypocitraturia, high pH	Carbonic anhydrase inhibitors (acetazolamide, topiramate)
Hyperuricosuria	Uricosuric agents (probenecid, losartan)
Drugs that crystallize and form stones	
Antibiotics: sulfadiazine, sulfamethoxazole, amoxicillin, ampicillin, ciprofloxacin, ceftriaxone Others: triamterine, allopurinol, guaifenesin	

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Urinary Factors
"Abnormal values"

- Hypercalciuria
  - –Males: >300 mg/d
  - –Females: >250 mg/d
  - –Either: >4 mg/kg/d
- Hyperoxaluria: >45 mg/d
- Hypocitraturia: <320 mg/d
- Hyperuricosuria
  - –Males: >800 mg/d
  - –Females: >750 mg/d

Fuhgeddaboutit!

These are continuous variables, not dichotomous. Published cutoffs are arbitrary.

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Four Steps in Diagnostic Evaluation of Kidney Stones

1. H&P to identify systemic disease, genetic and dietary risk factors
2. Imaging to quantify stone burden (non-contrast CT, ultrasound, KUB)
3. Analyze stone composition
4. Metabolic Testing (blood and urine)

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Imaging Modalities for Diagnosing Kidney Stones

Modality	Cost	Ionizing Radiation	Advantages	Drawbacks
Unenhanced CT Scan	Moderate	High	- Detects extrarenal pathology - No contrast; has replaced IVP - Identifies uric acid stones	- Radiation - Cost
Ultrasound	Moderate	None	- Portable US available - Useful in children and pregnancy	- Does not visualize ureteral stones - Large body size limits visualization
Plain X-ray (KUB)	Low	Low	- Useful in follow-up of known radiopaque stones	- Cannot detect radiolucent stones - Overlying bowel gas and extrarenal calcification impact interpretation
MRI	High	None	- Useful in children and pregnancy	- Contrast risk in CKD - Cannot distinguish stone for blood clot

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Stone Composition Analysis

- Indications
  - All first-time stone formers
  - Repeat stone analysis – stone composition may change over time
    - Recurrences despite optimal treatment (dietary, pharmacologic)
    - Early recurrence after complete stone clearance
    - Late recurrence after a long stone-free interval
- Rationale
  - Identify underlying metabolic abnormalities
  - Determine medical interventions to prevent recurrences
  - Direct appropriate choice of urological procedures
- Limitation
  - Accuracy good for pure stones but not as good for mixed stones

AUA guideline. Medical management of kidney stones. J Urol. 2014;192(2):316-24.

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Blood Tests

Measurement	Purpose
Calcium	Detect hypercalcemia (primary hyperparathyroidism, sarcoidosis, vitamin D excess, etc.)
Phosphorus	Detect primary hyperparathyroidism
Bicarbonate	Detect renal tubular acidosis
Chloride	Detect renal tubular acidosis
Potassium	Detect renal tubular acidosis, gastrointestinal disease
Creatinine	Detect chronic kidney disease
Uric acid	Detect hyperuricemia
PTH	Obtain only if hyperparathyroidism is suspected
CBC	Detect leukocytosis as an indicator of infection

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Urinalysis

- Specific gravity
- pH
- Crystals
- WBCs (UTI)
  - Urine culture if UTI suspected

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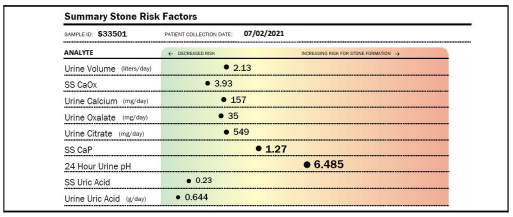
24-hour Stone Risk Analysis

- Indications
  - Recurrent stones or high risk for recurrent stones
  - First-time interested stone formers



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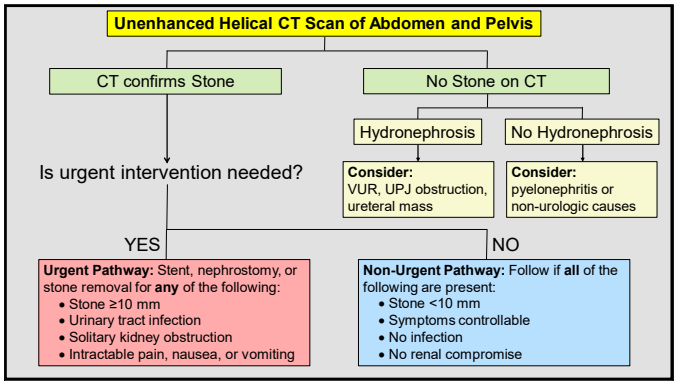

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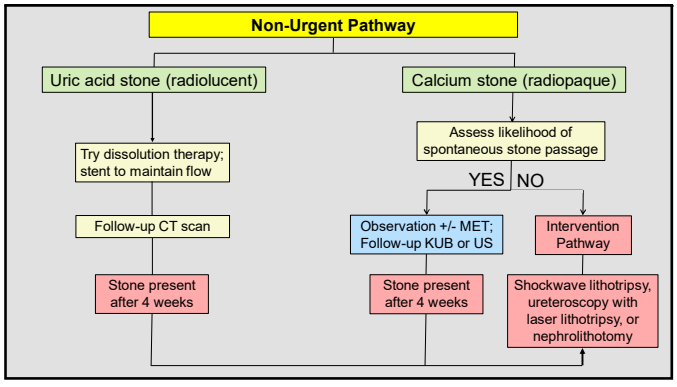

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What is the likelihood of a ureteral stone passing spontaneously?

Both **size** and **location** matter

Stone size (mm)	Passage (%)
1-4	**78**
5-7	60
8	56
9	33
≥10	25

Location in ureter	Passage (%) Av. all stones
Proximal	48
Mid	60
Distal	75
UV junction	**79**

Coll DM et al. Amer J Roentgen 2002;178:101-103

- Most stone ≤5 mm in diameter are likely to pass
- Two-thirds of stones that pass do so within 4 weeks
- Symptomatic stones remaining after 4 weeks have a complication rate of 20% (ureteral stricture, sepsis, renal deterioration)

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When is Medical Expulsion Therapy Beneficial?

- Best data: alpha blockers (**tamsulosin**, silodosin).
- Less data: calcium channel blockers (nifedipine)
- Stone passage rate vs. placebo
  - Overall, for stones <10 mm diameter: **No benefit**[1,2,3]
  - Stones ≤5 mm: **No benefit**[1-5]
  - Mid to proximal ureteral stones 5-10 mm diameter: **Limited data**[4]
  - **Distal ureteral stones >5 mm to 7 mm (? 8-10 mm): Benefit**[2,5]
- When MET works, other benefits have been found[4]
  - Faster expulsion time
  - Lower incidence of renal colic and use of analgesics
  - Less need for subsequent intervention
- Tamsulosin reduces discomfort from ureteral stents[6]

[1]Pickard R et al. Lancet 2015;386(9991):341-349 [2]Furyk JS et al. Ann Emerg Med 2016;67(1):86-95.e2
[3]Meltzer AC et al. JAMA Intern Med 2018;178(8):1051-1057 [4]Cui Y et al. J Urol 2019;201(5):950-955
[5]Ye Z et al. Europ Urol 2017;73(3);385-391 [6]Dellis AE et al. J Endourol. 2017;31(1):100-109

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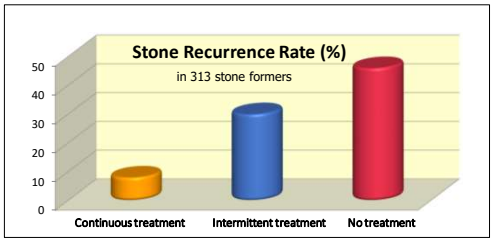
Medical Prophylaxis Matters



Lee YH et al. J Urol 1999; 161:1453-1457

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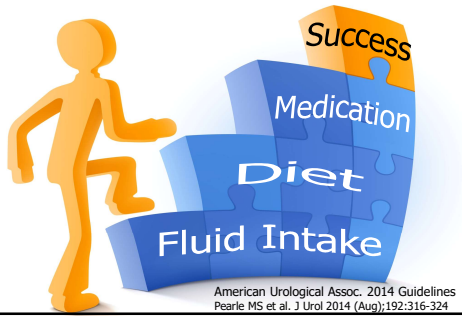
Three Steps Towards Fewer Kidney Stones



American Urological Assoc. 2014 Guidelines
Pearle MS et al. J Urol 2014 (Aug);192:316-324

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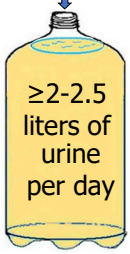
Fluid Intake

2.5 – 3 L/day



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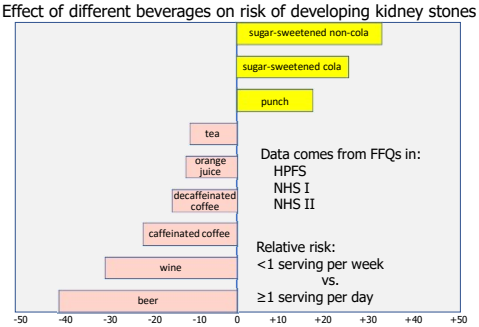
Effect of different beverages on risk of developing kidney stones



Ferraro PM et al. Clin J Am Soc Nephrol 2013;8:1389-1395

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Diet Modification

Diet Constitutent	Dose	Patient Selection
 Sodium	Less than 100 mmol/day (2300 mg)	Hypercalciuria Hyperuricosuria
 Animal protein	Less than 0.8-1.0 g/kg/day	Hypercalciuria Hyperuricosuria
 Calcium	1000-1200 mg/day (dietary, not as supplements)	All calcium stones
 Oxalate	Less than 100 mg/day	Hyperoxaluria

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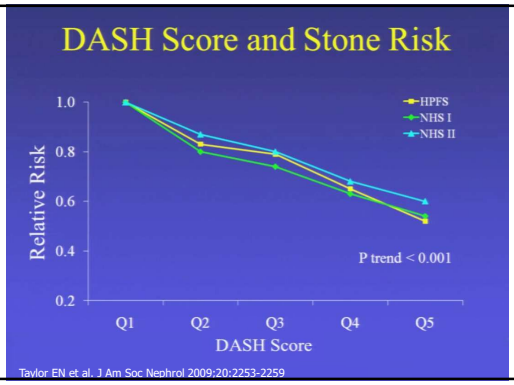
DASH Score and Stone Risk



Taylor EN et al. J Am Soc Nephrol 2009;20:2253-2259

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Medications

Drug	Dose	Patient Selection
 Thiazide diuretics	Chlorthalidone 25 mg/day Indapamide 2.5 mg/day HCTZ 25 mg bid or 50 mg od	Hypercalciuria and normocalciuria with calcium stones
 Potassium alkali	Potassium citrate 10-20 mmol bid or tid	Hypocitraturia with calcium stones; normocitraturia with low urine pH; uric acid stones
 Allopurinol	100-300 mg/day	Hyperuricosuria with calcium stones; hyperuricemia

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 Calcium	1000-1200 mg/day (dietary, not as supplements)	All calcium stones
 Oxalate	Less than 100 mg/day	Hyperoxaluria

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Benefit of Pharmacologic Treatments to Prevent Recurrent Nephrolithiasis

(American College of Physicians Systematic Review)

Pharmacologic treatment vs control for composite* stone recurrence in patients with ≥ 2 previous episodes of kidney stones†

Treatment	Number of trials (*n*)	Weighted event rates		At mean 1 to 5 y	
		Treatment	Control	RRR (95% CI)	NNT (CI)
Thiazide	5 (300)	29%	55%	48% (31 to 61)	4 (3 to 6)
Citrate	4 (197)	13%	52%	75% (56 to 86)	3 (3 to 4)
Allopurinol‡	2 (152)	33%	55%	41% (16 to 58)	5 (4 to 12)

**Composite of symptomatic or radiographic recurrence.*

†Abbreviations defined in Glossary. Weighted event rates, RRR, NNT, and CI calculated from control event rates and risk ratios in article using a random-effects model.

‡In patients with hyperuricosuria or hyperuricemia.

Fink HA et al. Ann Int Med 2013;158:535-543

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Summary of Stone Prevention

- **First-time or infrequent stone formers without family history of stones or other high-risk factors**
  - **Conservative management**
    - High fluid intake
    - Moderate dietary modification of sodium, animal protein and calcium intake; avoid supplemental vitamin C
    - Full metabolic profiling not necessary
- **Recurrent or first-time high-risk stone formers**
  - **Aggressive management**
    - Stricter dietary modification + high fluid intake
    - Full metabolic profiling
    - Targeted drug therapy

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