In the name of God

Metabolic Approach to Diagnosis & Management of Nephrolithiasis

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Outline

1. A case report
2. Introduction
3. Epidemiology
4. Diagnosis
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7. Take-Home Message

Roedel *et al. BMC Urol* (2021) 21:133
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BMC Urology

CASE REPORT

Open Access

Sulfamethoxazole-induced sulfamethoxazole urolithiasis: a case report

Megan M. Roedel[1], Stephen Y. Nakada[2,3] and Kristina L. Penniston[2*]

Abstract

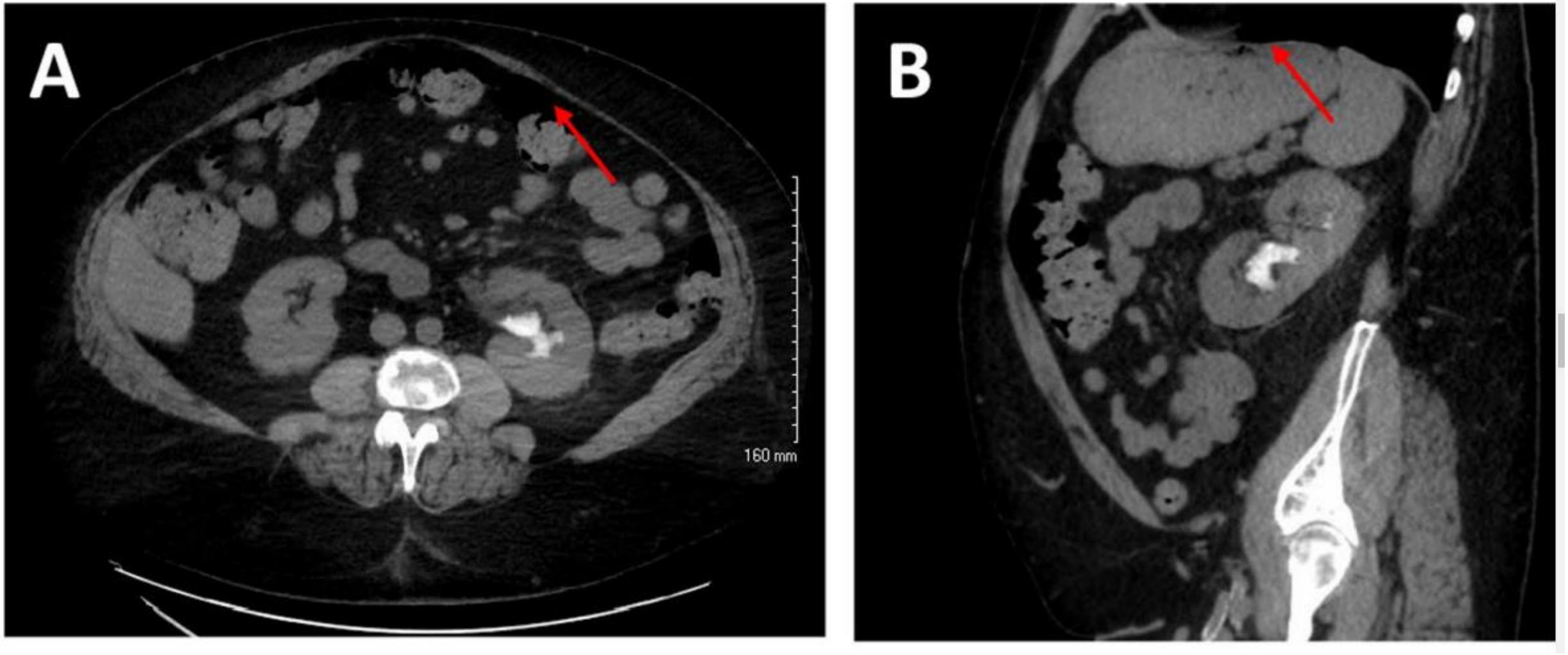
Background: Drug-induced urolithiasis falls into two categories: drug-induced and metabolically-induced. Certain antimicrobials are associated with each; sulfonamides are associated with drug- or metabolite-containing calculi

Case report

- ✓A patient with a brief history of recurrent Ca Ox nephrolithiasis requiring 2 ureteroscopic procedures whose existing 6 mm lower pole renal stone more than quadrupled in size to form a 4 cm renal staghorn after 4 months of high-dose treatment for Nocardia pneumonia with TMP/SMX.
- ✓After ureteroscopy with laser lithotripsy & basketing of fragments, the stone was found to be predominantly composed of N4 -acetyl-sulfamethoxazole, a metabolite of sulfamethoxazole

Roedel MM. BMC Urology. 2021

Radiographic images of left renal pelvis stone



Roedel MM. BMC Urology. 2021

AJKD

Kidney Stone Pathophysiology, Evaluation and Management: Core Curriculum 2023

Shani Shastri, Jiten Patel,* Kamalanathan K. Sambandam, and Eleanor D. Lederer*

Kidney stone disease, also known as nephrolithiasis or urolithiasis, is a disorder in which urinary solutes precipitate to form aggregates of crystalline material in the urinary space. The incidence of nephrolithiasis has been increasing, and the demographics have been evolving. Once viewed as a limited disease with intermittent exacerbations that are simply managed by urologists, nephrolithiasis is now recognized as a complex condition requiring thorough evaluation and multifaceted care. Kidney stones are frequently manifestations of underlying systemic medical conditions such as the metabolic syndrome, genetic disorders, or endocrinopathies. Analysis of urine chemistries and stone composition provide a window into pathogenesis and direct ancillary studies to uncover underlying diseases. These studies allow providers to devise individualized strategies to limit future stone events. Given its complexity, kidney stone disease is best addressed by a team led by nephrologists and urologists with input from multiple other health professionals including dietitians, endocrinologists, interventional radiologists, and endocrine surgeons. In this installment of *AJKD*'s Core Curriculum in Nephrology, we provide a case-based overview of nephrolithiasis, divided by the individual stone types. The reader will gain a pragmatic understanding of the pathophysiology, evaluation, and management of this condition.

Complete author and article information provided at end of article.

**S.S. and J.P. contributed equally to this work.*

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Shastri S. AJKI. 2023

Introduction

- ✓ Nephrolithiasis describes a **syndrome** characterized by the development of solid crystalline masses within the urinary space of the kidney.
- ✓ Predisposing factors can be genetic, metabolic, & environmental.
- ✓ Nephrolithiasis is now recognized as a marker for **systemic disease** & a predictor of metabolic & CV complications.

Shastri S. AJKI. 2023

The Medical Community's Perspective on Nephrolithiasis

Primarily urologic illness

→ Chronic medical condition requiring long-term surveillance & management

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Epidemiology

- ✓Nephrolithiasis is common, affecting approximately 1 in 11 people in the US.
- ✓By age 70, 19.1% of men & 9.4% of women report ever having a kidney stone.

Shastri S. AJKI. 2023

Epidemiology

- ✓The M/F ratio has decreased from 3:1 to about 2:1 in the past 2 decades, attributed to an increasing prevalence of obesity.
- ✓Obesity & DM are strongly associated with a history of kidney stones in multivariate models, particularly for women.

Shastri S. AJKI. 2023

Epidemiology

- ✓Nephrolithiasis has been associated with significant morbidity beyond the urologic system including:
  - CKD
  - Cardiovascular disease
    - HTN
    - Possibly increased carotid wall thickness
    - MI
  - Reduced BMD & fractures

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Epidemiology

✓The risk of stone recurrence: 50% in 5-10 ys & 75% in 20 ys.

✓Risk factors for recurrent stones:

- Multiple prior stone episodes
- Younger age of onset
- Male gender
- FH of kidney stones
- Higher BMI
- Presence of ≥ 2 stones across both kidneys, the presence of stones in the renal pelvis or lower kidney pole
- A stone composition consisting of uric acid, struvite, or brushite

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Diagnosis

Focused Hx for Stone Risk Factors

✓Adverse dietary habits include:

1. Low fluid intake or a high fluid loss
2. A very high animal protein diet
3. Higher Na diet
4. Increased intake of higher oxalate-containing foods, (spinach)
5. Lower Ca intake
6. Excessive Vit C & D supplementation
7. Excessive sugar (sucrose & fructose)
8. Certain medications (Atazanavir, Sulfadiazine, & Triamterene)

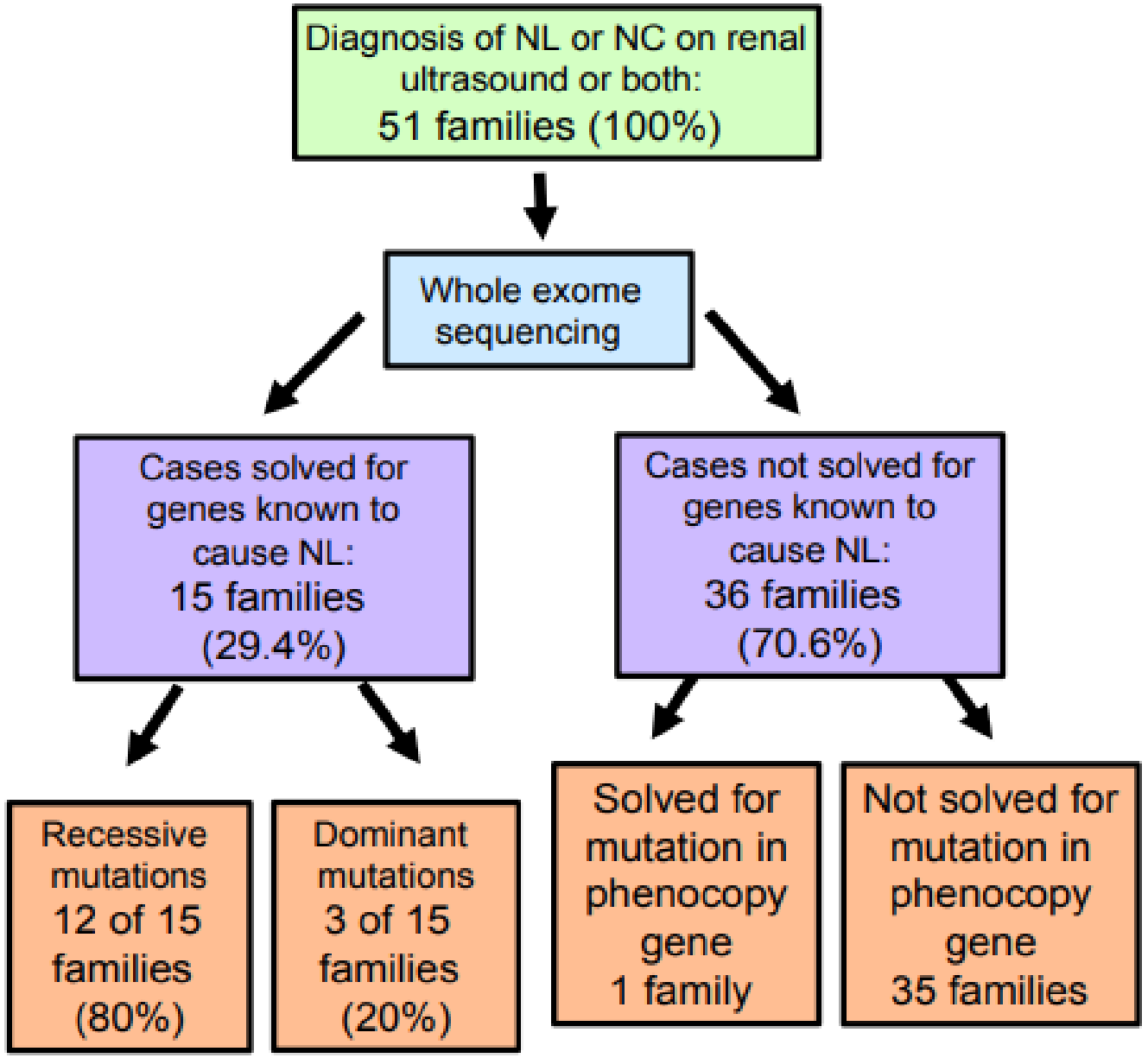
clinical investigation www.kidney-international.org

2018

Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis

see commentary on page 15

Ankana Daga[1,20], Amar J. Majmundar[1,20], Daniela A. Braun[1], Heon Yung Gee[2], Jennifer A. Lawson[1], Shirlee Shril[1], Tilman Jobst-Schwan[1], Asaf Vivante[1], David Schapiro[1], Weizhen Tan[1], Jillian K. Warejko[1], Eugen Widmeier[1], Caleb P. Nelson[3], Hanan M. Fathy[4], Zoran Gucev[5], Neveen A. Soliman[6,7], Seema Hashmi[8], Jan Halbritter[9], Margarita Halty[10], Jameela A. Kari[11], Sherif El-Desoky[11], Michael A. Ferguson[1], Michael J.G. Somers[1], Avram Z. Traum[1], Deborah R. Stein[1], Ghaleb H. Daouk[1], Nancy M. Rodig[1], Avi Katz[12], Christian Hanna[12], Andrew L. Schwaderer[13], John A. Sayer[14], Ari J. Wassner[15], Shrikant Mane[16,17,18], Richard P. Lifton[16,17,18], Danko Milosevic[19], Velibor Tasic[5], Michelle A. Baum[1] and Friedhelm Hildebrandt[1]



Flow diagram on detection by whole exome sequencing of causative monogenic mutations in 30% nephrolithiasis or nephrocalcinosis or both (NL/NC) genes in 51 families with NL/NC

Daga A. KI.2018

Conclusion

We established WES as an efficient approach toward a molecular genetic diagnosis in individuals with nephrolithiasis/nephrocalcinosis who manifest before age **25** years.

Daga A. KI.2018

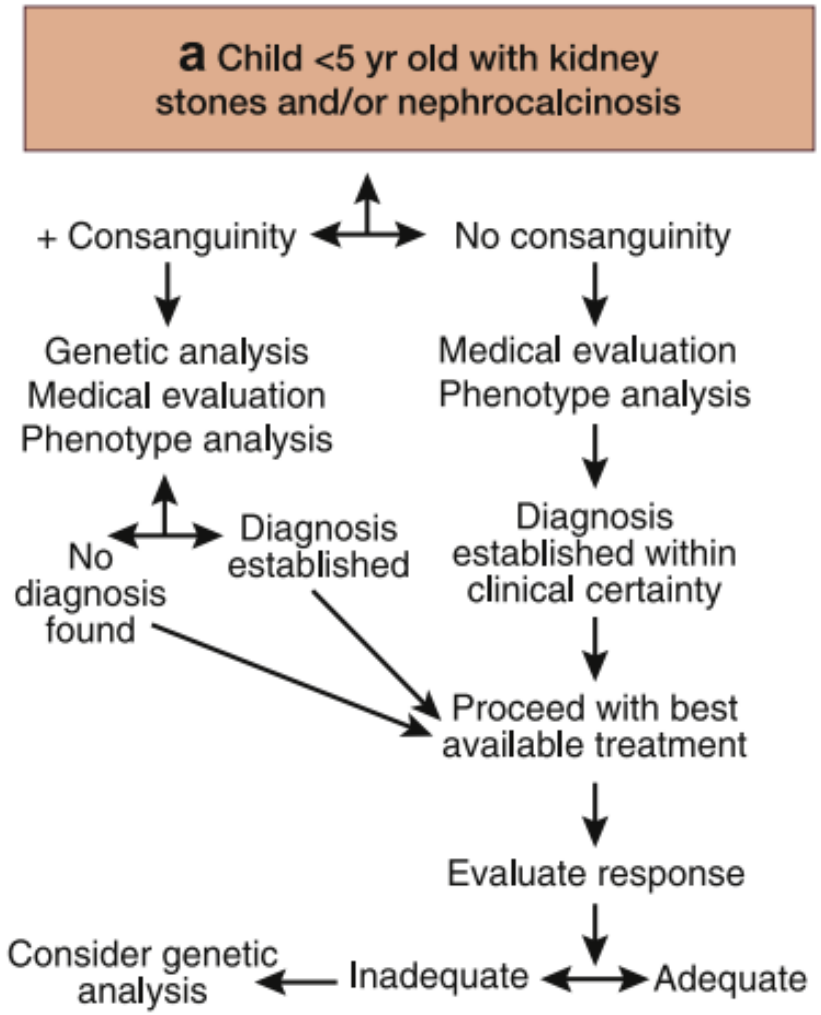
A rational approach to the use of sophisticated genetic analyses of pediatric stone disease

Craig B. Langman[1]

Kidney stone disease in the childhood years has a genetic underpinning in some. The relationships between clinical phenotype, medical evaluation, and genetic etiologies were investigated using whole-exome sequencing by the Hildebrandt laboratory. At this time, a genetic evaluation of pediatric nephrolithiasis should be reserved for specific circumstances when clinical uncertainty of the reason for the presence of the stone or therapy is not satisfactory.

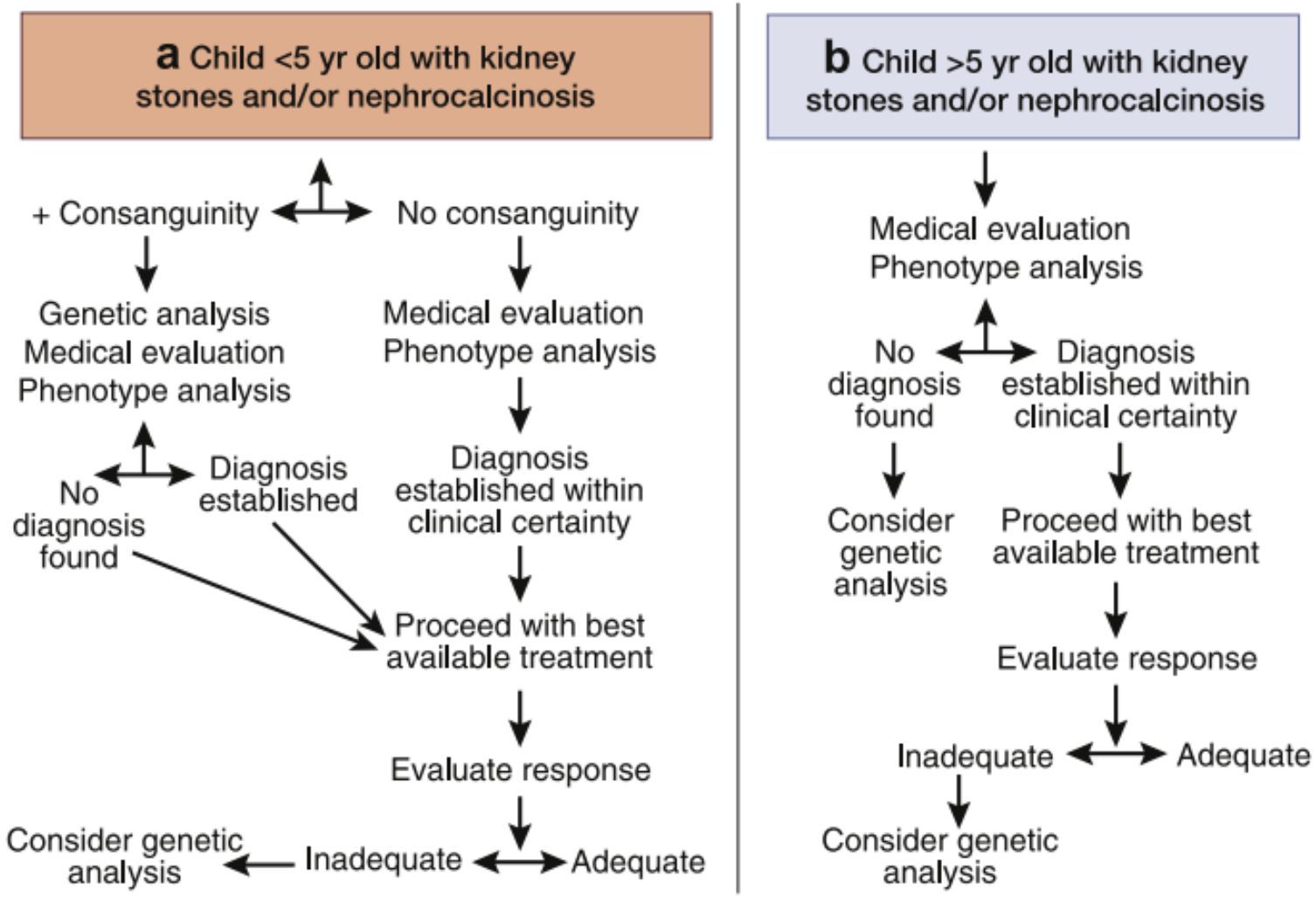
Kidney International (2018) **93,** 15–18; https://doi.org/10.1016/j.kint.2017.08.023

see clinical investigation on page 204



Diagnostic approach to the care of the pediatric patient with nephrolithiasis &/or nephrocalcinosis

Langman CB. KI. 2018



Diagnostic approach to the care of the pediatric patient with nephrolithiasis &/or nephrocalcinosis

Langman CB. KI. 2018

Patient Work Up

- ✓ Low risk patient (first single stone, no F. HX, no bowel disease)
  - Abbreviated study
- ✓ High risk patient (second stone, multiple stones, increasing size, + F. HX, bowel dis., children)
  - Comprehensive study

Kidney Stones 2012: Pathogenesis, Diagnosis, and Management

Khashayar Sakhaee, Naim M. Maalouf, and Bridget Sinnott

Department of Internal Medicine, Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, Texas 75390

Context: The pathogenetic mechanisms of kidney stone formation are complex and involve both metabolic and environmental risk factors. Over the past decade, major advances have been made in the understanding of the pathogenesis, diagnosis, and treatment of kidney stone disease.

Evidence Acquisition and Synthesis: Both original and review articles were found via PubMed search reporting on pathophysiology, diagnosis, and management of kidney stones. These resources were integrated with the authors' knowledge of the field.

Conclusion: Nephrolithiasis remains a major economic and health burden worldwide. Nephrolithiasis is considered a systemic disorder associated with chronic kidney disease, bone loss and fractures, increased risk of coronary artery disease, hypertension, type 2 diabetes mellitus, and the metabolic syndrome. Further understanding of the pathophysiological link between nephrolithiasis and these systemic disorders is necessary for the development of new therapeutic options.
(*J Clin Endocrinol Metab* 97: 1847–1860, 2012)

Diagnostic evaluation & interpretation of laboratory profiles

Simplified ambulatory metabolic evaluation	Extensive ambulatory metabolic evaluation	Expected daily values	Results interpretation
Random 24-h urinary profile	Random 24-h urine profile and 24-h urine profile after 1 wk of dietary restrictions		
Total volume	Total volume	≥2.5 liter	Indicative of daily fluid intake. This value diminishes with low fluid intake, sweating, and diarrhea
pH	pH	5.9–6.2	Values < 5.5 increase UA precipitation. Commonly found in UA stone patients, subjects with intestinal disease and diarrhea, and in those with intestinal bypass surgery. Values > 6.7 increase CaP precipitation. Commonly found in patients with dRTA, primary hyperparathyroidism, alkali overtreatment, and carbonic anhydrase treatment. Values > 7.0–7.5 indicate a urinary tract infection as a result of urease-producing bacteria
Creatinine	Creatinine	15–25 mg/kg body weight	15–20 mg/kg body weight in females; 20–25 mg/kg body weight in males
Sodium	Sodium	100 mEq	Reflective of dietary sodium intake, given a lack of excessive sweating and/or diarrhea
Potassium	Potassium	40–60 mEq	Reflective of dietary potassium intake, given a lack of diarrhea
Calcium	Calcium	≤250–300 mg	There may be differences in male and female subjects. A higher value is expected in males

Sakhaee K. J Clin Endoc Metab. 2012

Diagnostic evaluation & interpretation of laboratory profiles

Magnesium	Magnesium	30–120 mg	Low urinary magnesium is detected with low magnesium intake, intestinal malabsorption (small bowel disease), and after bariatric surgery
Oxalate	Oxalate	≤45 mg	Commonly encountered with intestinal fat malabsorption and after bariatric surgery. Values > 100 mg/d may indicate primary hyperoxaluria
Phosphorus	Phosphorus	≤1100 mg	Indicative of dietary phosphorus intake and absorption. A higher excretion may increase the risk of CaP stone formation
UA	UA	600–800 mg	Hyperuricosuria is encountered with the overindulgence of purine-rich foods such as red meat, poultry, and fish
Sulfate	Sulfate	≤25–30 mmol	Sulfate is a marker of an acid-rich diet that occurs as a result of increased oxidation of sulfur-rich amino acids (methionine) found in meat and meat products
Citrate	Citrate	≥320 mg	An inhibitor of calcium stone formation. Hypocitraturia is commonly encountered in metabolic acidosis, dRTA, chronic diarrhea, excessive protein ingestion, strenuous physical exercise, hypokalemia, intracellular acidosis, with carbonic

Sakhaee K. J Clin Endoc Metab. 2012

Ammonium	Ammonium	30–40 mEq	Ammonium is a major buffer that neutralizes hydrogen protons secreted by the kidney. Its excretion corresponds with urinary sulfate (acid load). A higher ammonium:sulfate ratio indicates gastrointestinal alkali loss
Chloride	Chloride	100 mEq	Chloride values also correspond with sodium intake
Cystine	Cystine	<30–60 mg	Cystine has a limited urinary solubility at 250 mg/liter
	2-h fasting Ca:Cr ratio	<0.11 mg/100 ml glomerular filtrate	Elevated fasting Ca:Cr, high serum calcium, and elevated PTH are suggestive of primary hyperparathyroidism. Elevated fasting Ca:Cr, normal serum calcium, and normal or suppressed PTH are suggestive of resorptive hypercalciuria. Elevated fasting Ca:Cr, normal serum calcium, and elevated PTH are suggestive of renal hypercalciuria
	4-h Ca:Cr ratio after a 1-g oral calcium load	≤0.20 mg/mg Cr	Elevated Ca:Cr after a 1-g oral calcium load is suggestive of absorptive hypercalciuria
Simplified fasting blood chemistries	Extensive fasting blood chemistries		
Complete metabolic panel	Complete metabolic panel	Variable[a]	Low serum potassium, high serum chloride, and low serum total CO_2 content are suggestive of a diarrheal state of dRTA
PTH	PTH	10–65 pg/ml[a]	High serum calcium, low serum phosphorus, and high PTH are suggestive of primary hyperparathyroidism
	$1,25(OH)_2D$	Variable[a]	Normal serum calcium, normal PTH, and elevated $1,25(OH)_2D$ are suggestive of absorptive hypercalciuria. Normal serum calcium, normal PTH, low serum phosphorus, and elevated $1,25(OH)_2D$ are suggestive of renal phosphorus leak
	Other evaluations		
	Bone mineral density measurements (DXA)	Z-score > −2; T-score > −2.5	Z-score < −2 or T-score < −2.5 indicates bone loss. This finding may be more prevalent in hypercalciuric kidney stone formers

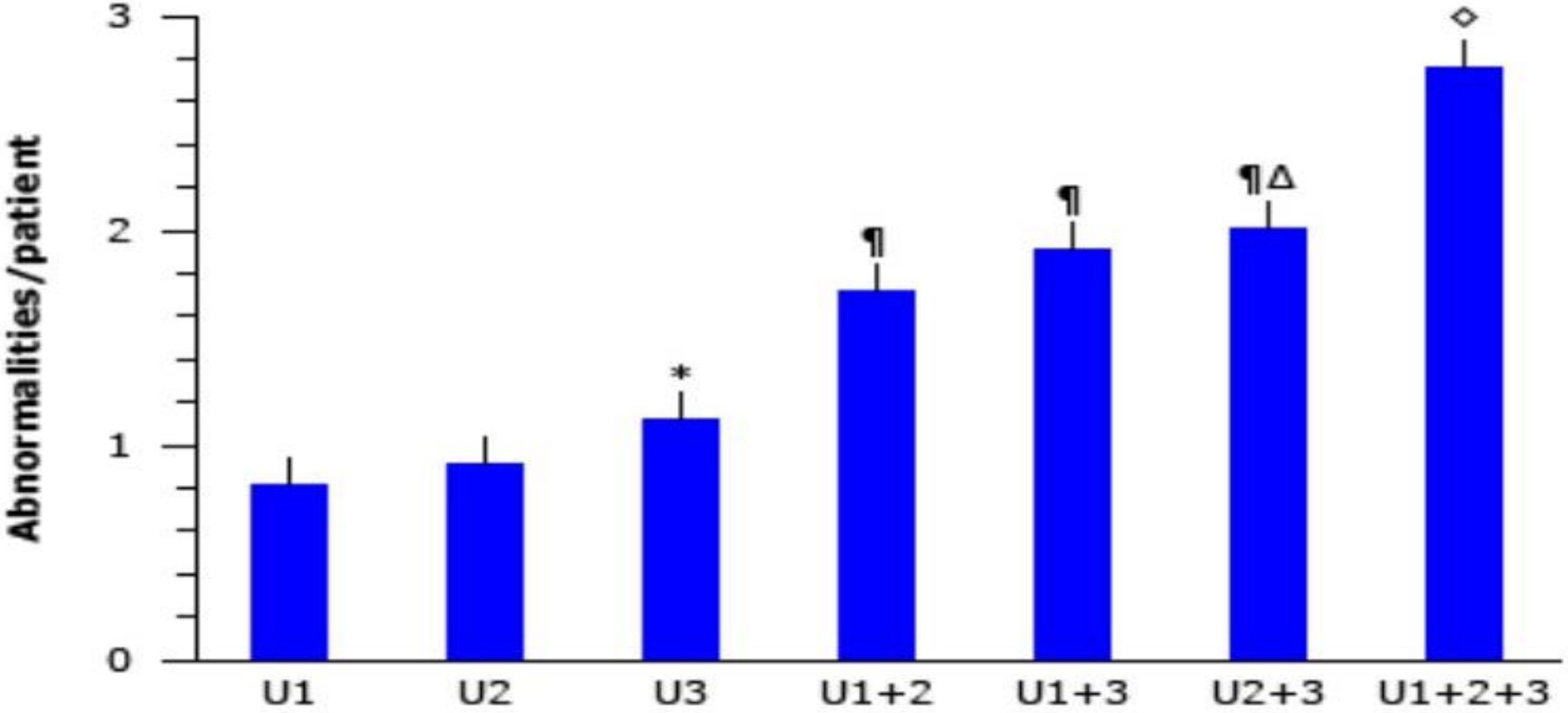
These limits are mean + 2 SD (for calcium, oxalate, UA, pH, sodium, sulfate, and phosphorus) or mean − 2 SD (for citrate, pH, and magnesium) from normal. ACE, Angiotensin-converting enzyme; DXA, dual-energy x-ray absorptiometry.

Sakhaee K. J Clin Endoc Metab. 2012

Timing of collections

- ✓While the patient is on their usual diet
- ✓Should **not** be measured immediately after the acute stone episode
- ✓To wait at least 1 - 2 months after a stone event to obtain the collections

Increased likelihood of detecting kidney stone risk factors with multiple 24-hour urine collection



Laboratory Evaluation

Comprehensive study:

- Not to be performed within 1-2 ms of an acute stone episode or during UTI
- CBC, FBS, BUN, Cr, Na, K, Cl, Ca, P, Mg, Uric acid, lipid profile, PTH, VBG
- 24 hr urine (on usual diet) X 2 : volume, pH, Ca, P, oxalate, U.A, citrate, Na, U.N. or sulfate, Cr.
- Urine screen for cystine X1
- Follow up 24 hr urine for response to dietary / drug interventions every 3-6 months

Laboratory Evaluation

- ✓ Specialized testing:
  - One 24 hr urine after 1 wk of restricted diet: Ca < 400 mg / day, Na < 100 mEq / day, low oxalate, low purine
  - Fasting urine: Ca / Cr ratio
  - Oral Ca load: urine Ca / Cr ratio

Interpreting 24-Hour Urine Studies to Address Risk for Recurrent Stones

Creatinine
- Allows an assessment of the completeness of 24-hour collection.
- Expect 15-20 mg/kg/d for females and 20-25 mg/kg/d for males.

Total Volume
- A goal of 2.5 L/d, sometimes more, is typical for reducing recurrence risk.

Calcium
- Though > 4 mg/kg is clearly excessive, a graded increase in stone risk is noted with levels > 150 mg/d.
- Correlate with urine sodium to determine of hypercalciuria is driven by excessive sodium intake.

Sodium
- A goal of <100 mg/d is sought if hypercalciuria is present.

Oxalate
- Values > 40 mg/d are excessive, though lower excretion rates may also increase risk.
- For values > 80 mg/d, consider primary hyperoxaluria.

Citrate
- Values > 400 mg/d may limit risk for calcareous stones, with even higher levels sometimes needed.

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pH
- Values < 6.0 may increase the risk of uric acid stones.
- Values > 6.0 with metabolic acidosis suggests renal tubular acidosis and a risk for calcium phosphate stones.
- Values > 7.0 may indicate urine infection by bacteria with urease and a risk for struvite stones.

Uric Acid
- Consider xanthine oxidase inhibitor or reduced purine intake if >750-800 mg/d and other measures for calcium oxalate stones or uric acid stones fail.

Ammonium
- Values of >45 mmol/d suggest excess acid production from diet, chronic diarrhea, or other cause.

Sulfate
- Values of >30 mmol/d suggest excessive dietary animal protein.

Cystine
- Normal individuals typically excrete < 30 mg/d.
- Patients with cystinuria generally excrete > 400 mg/d.
- For cystinuria patients, target a concentration < 250 mg/L to limit stone risk.

~~Mg, K, Cl, P~~

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Analysis of stone composition

✓Should be performed in all first-time stone formers.

✓Repeat stone analysis is needed in the case of:

1. Recurrence under pharmacological prevention
2. Early recurrence after interventional therapy with complete stone clearance
3. Late recurrence after a prolonged stone-free period

EAU Guideline. 2023

Radiological Evaluation of Acute Flank Pain

	Sensitivity	Specificity
Noncontrast Helical CT Scan	**96-100%**	**92-100%**
US	**24-61%**	**90-100%**
IVP	**64%**	**92%**
KUB	**46-54%**	

Helical CT and IVP are 100% sensitive to detect ureteral obstruction

***J Urol* 161:534, 1999**
***Radiology* 217:792, 2000**

X-ray Characteristics

Radiopaque	Poor radiopacity	Radiolucent
Calcium oxalate dehydrate	Magnesium ammonium phosphate	Uric acid
Calcium oxalate monohydrate	Apatite	Ammonium urate
Calcium phosphates	Cystine	Xanthine
		2,8-Dihydroxyadenine
		Drug-stones (Section 4.11)

GOAL OF EVALUATION

- ✓Is to identify, as efficiently & economically as possible, the particular behavioral & physiologic differences present in a given patient so that effective therapy to prevent recurrent stones can be established & the prognosis can be better defined.

Management

Lifestyle Modification

- ✓The **most important** lifestyle modification to prevent recurrent kidney stones is to increase fluid intake to guarantee diuresis of 2 to 2.5 L/d & a urine SG < 1.010.
- ✓Fluids should be consumed throughout the day & should consist of beverages with a neutral pH.
- ✓The diet should be with normal Ca content (1.0 to 1.2 g/d) & limited Na (4 to 5 g/d) & animal pr (0.8 to 1.0 g/kg/d).
- ✓Normal body weight through dietary modification & increased physical activity.

Fontenelle LF. Am Family Phys. 2019

Prevention of Further Stones

Dietary modification:

- High fluid intake (urine out put > 2.5 L) most important
- Low oxalate diet (hyperoxaluria)
- Low salt diet (< 6 g salt; hypercalciuria, cystinuria)
- Moderate Ca restriction (hypercalciuria)
- Low protein / purine diet (hyperuricosuria, hypercalciuria, hypocitraturia)

Tips to Reduce Your Sodium Intake

- ✓ Adults should aim to consume **< 2.3 gr/d**
- ✓ One teaspoon of table salt has 2.3 g of sodium
- ✓ Check the %DV for Na on the Nutrition Facts label found on many foods.
- ✓ Low in Na is ≤ 5%, & high in Na is ≥ 20%.

NIH National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

Nutrition Facts

8 servings per container

Serving size **2/3 cup (55g)**

Amount per serving

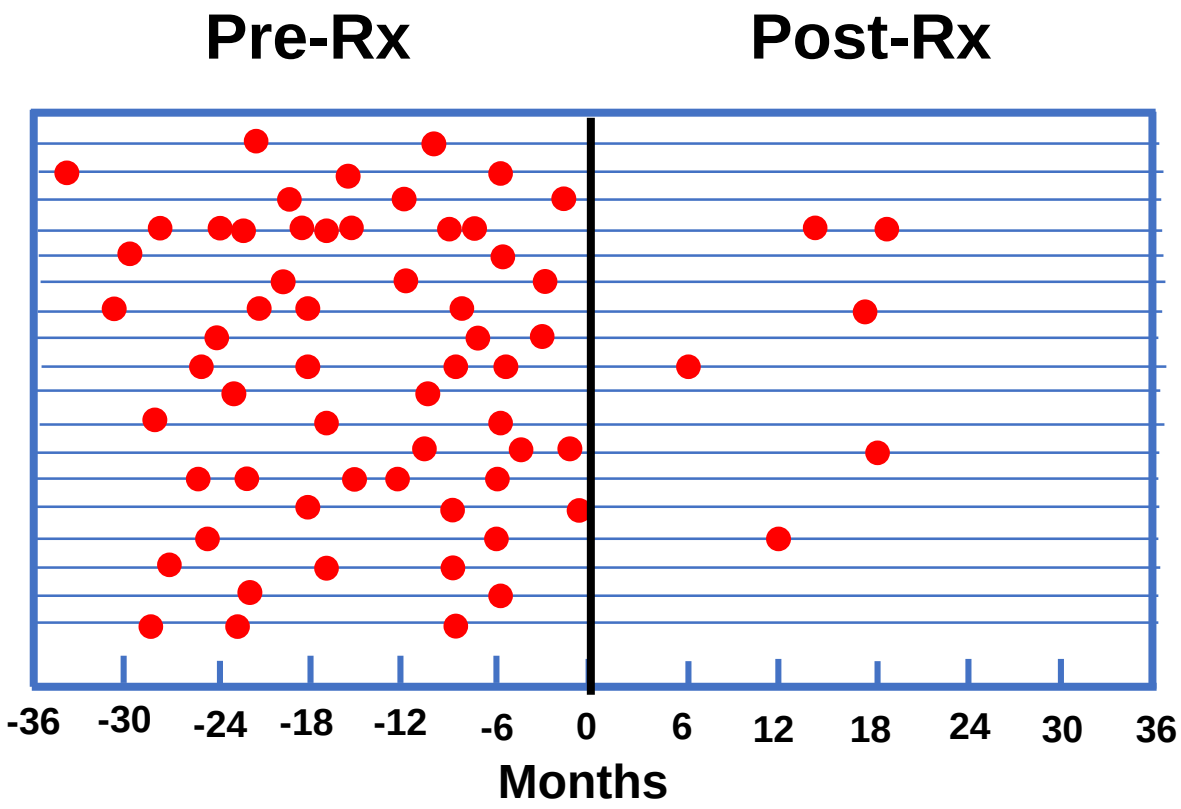
Calories **230**

	% Daily Value*
Total Fat 8g	**10%**
Saturated Fat 1g	**5%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 160mg	**7%**
Total Carbohydrate 37g	**13%**
Dietary Fiber 4g	**14%**
Total Sugars 12g	
Includes 10g Added Sugars	**20%**
Protein 3g	
Vitamin D 2mcg	10%
Calcium 260mg	20%
Iron 8mg	45%
Potassium 235mg	6%

Prevention of Further Stones

- ✓ Pharmacological Rx:
  - K- citrate (Urocit - K, Polycitra,)
    - Corrects acidosis
    - Alkalinizes urine
    - Increases urine citrate
    - Dose:10 - 20 mEq bid - tid
  - Thiazide diuretics (+ salt restriction)
    - Reduce hypercalciuria
    - Cause hypokalemia → hypocitraturia
    - Add K - citrate ± Amiloride

The Effect of K-citrate on Hypocitraturic Ca-oxalate Stone Disease



J Urol. 150:176, 1993

K citrate in Iran

تولید کننده
قرص اوروسیترا 5 میلی اکی والان
قرص پتاسیترال 5 میلی اکی والان
قرص پتاسیم سیترات مهر دارو 10 میلی اکی والان
قرص یورکا 10 میلی اکی والان
قرص آلکانف 10 میلی اکی والان
قرص آلیترال 5 میلی اکی والان - آلیتورال
قرص آلیترال 10 میلی اکی والان - آلیتورال

تولید کننده
قرص اوروسیترا 15 میلی اکی والان
قرص سیی سیترا 10 میلی اکی والان
قرص کی سیتب 5 میلی اکی والان
قرص اوروسیترا 10 میلی اکی والان
قرص پتاسیم سیترات زهراوی 10 میلی اکی والان
قرص کی سیتب 10 اکی والان
قرص آلیترال 10 میلی اکی والان - آلیتورال

Prevention of Further Stones

Pharmacological Rx:

- Allopurinol (hyperuricosuria)
- Mg supplement (hypomagnesuria)
- Ca supplement (enteric hyperoxaluria)
- Pyridoxine (B6) (PH - Type I)
- Lumasiran (siRNA) FDA approved in November 2020 for PH1 in all ages
- Captopril, D-penicillamine, Tiopronin (cystinuria)
- Acetohydroxamic acid (Lithostat) (urease inhibitor)

Treatment of Cystinuric Patients

Pharmacological Rx:

- Mercaptopropionyl glycine (Tiopronin = Thiola)
  - A complexing, reducing thiol compound
  - Forms soluble disulfide complex with cystine
  - Less side effects than D - penicillamine
  - More effective in alkaline urine
  - Given with K - Citrate
  - Keep urine cystine concentration < 250 mg / L
  - Side effects:
    - B6, Zn, Fe deficiency

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Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence

Nasser A. Dhayat, M.D., Olivier Bonny, M.D., Ph.D., Beat Roth, M.D., Andreas Christe, M.D., Alexander Ritter, M.D., Nilufar Mohebbi, M.D., Nicolas Faller, M.D., Ph.D., Lisa Pellegrini, M.D., Giulia Bedino, M.D., Reto M. Venzin, M.D., Philipp Grosse, M.D., Carina Hüsler, M.D., Irene Koneth, M.D., Christian Bucher, M.D., Rosaria Del Giorno, M.D., Luca Gabutti, M.D., Michael Mayr, M.D., Urs Odermatt, M.D., Florian Buchkremer, M.D., Thomas Ernandez, M.D., Catherine Stoermann-Chopard, M.D., Daniel Teta, M.D., Bruno Vogt, M.D., Marie Roumet, Ph.D., Luca Tamò, Ph.D., Grazia M. Cereghetti, Ph.D., Sven Trelle, M.D., and Daniel G. Fuster, M.D.

ABSTRACT

Dhayat NA. NEJM. 2023

Methods

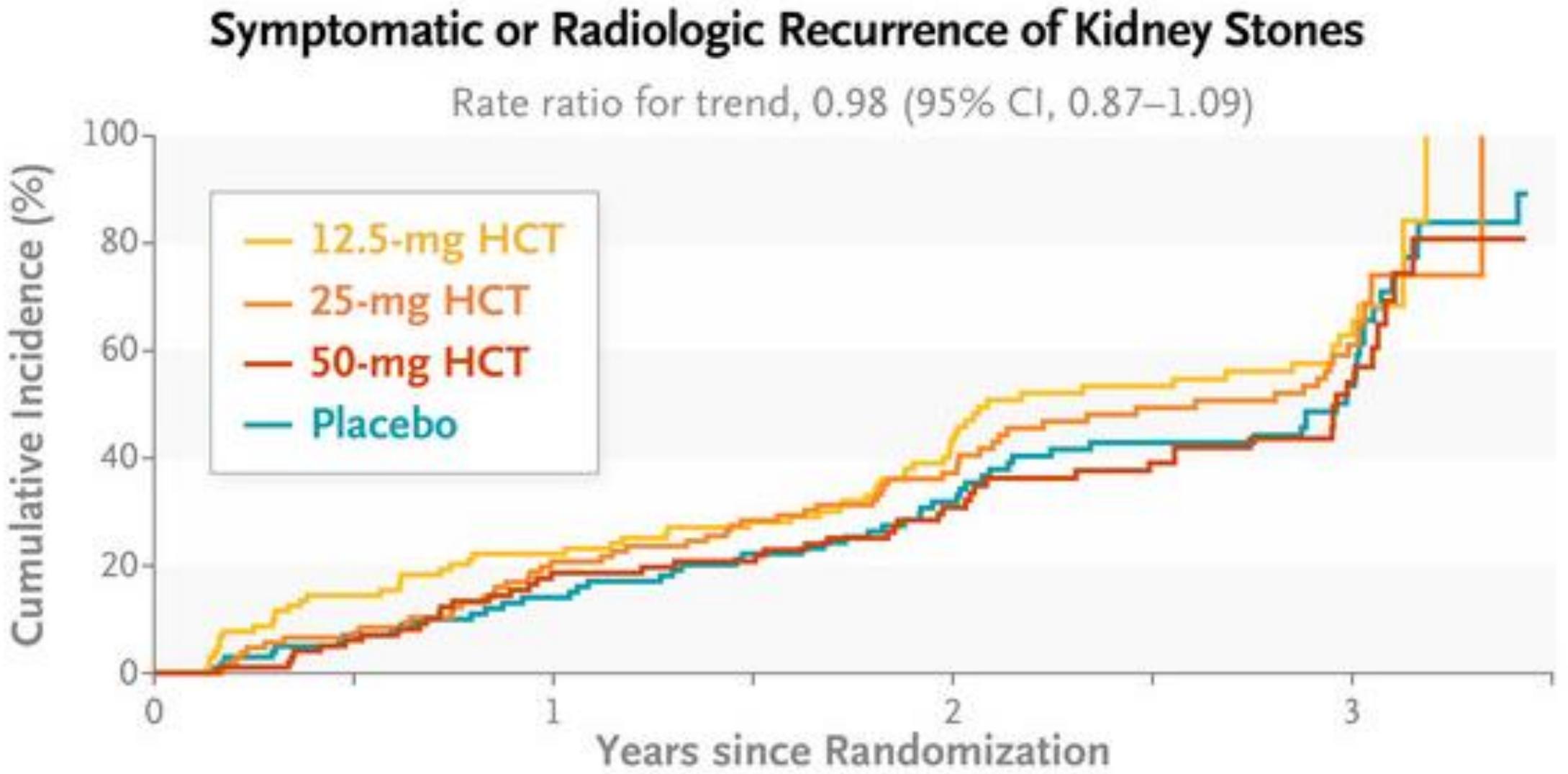
- ✓In this double-blind trial, we randomly assigned patients with recurrent ca containing kidney stones to receive hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg once daily or placebo once daily.
- ✓The main objective was to investigate the dose–response effect for the primary end point, a composite of symptomatic or radiologic recurrence of kidney stones.
- ✓Safety was also assessed.

Dhayat NA. NEJM. 2023

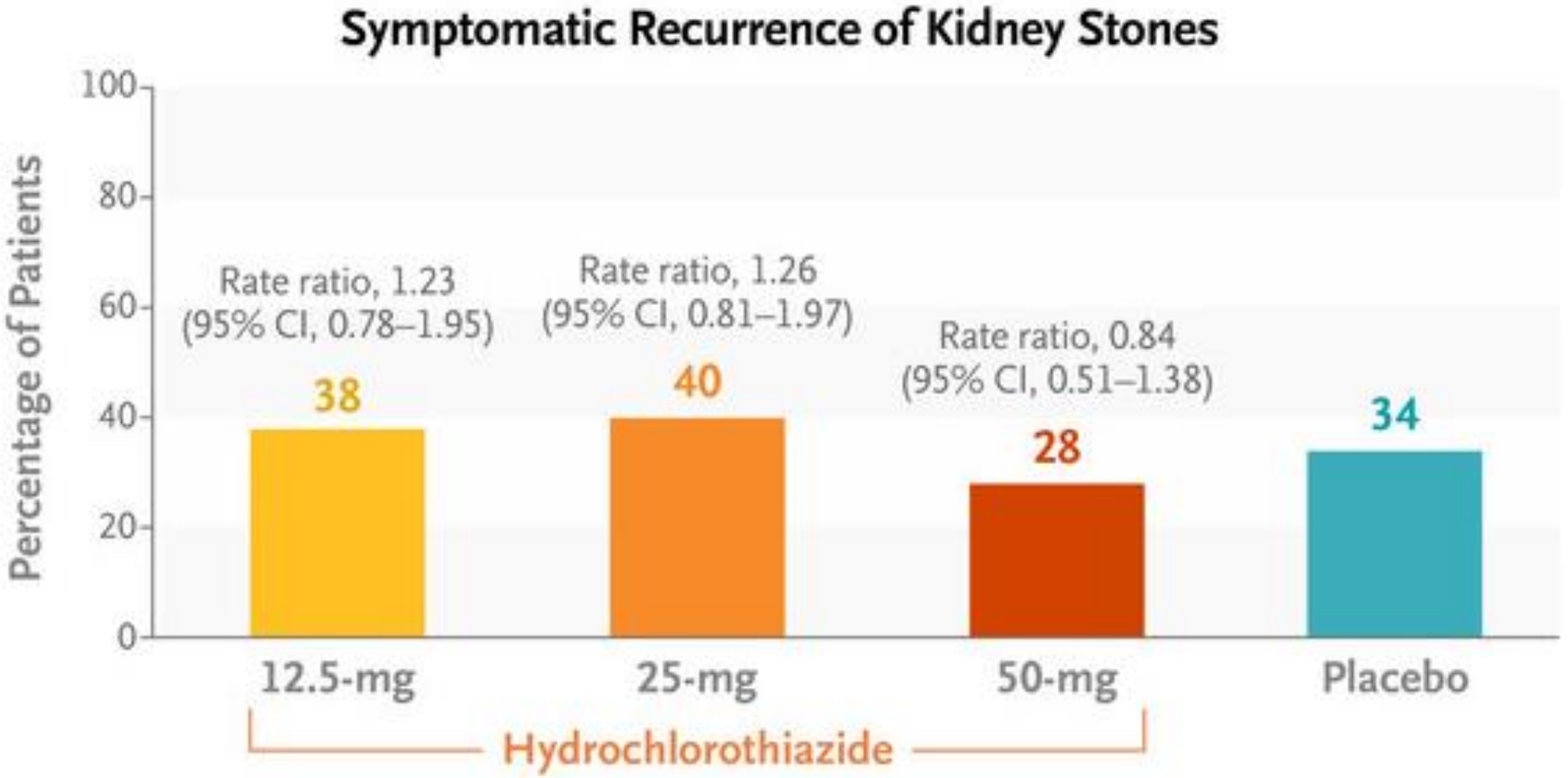
Results

- ✓In all, **416** patients underwent randomization and were followed for a median of **2.9** ys.
- ✓A primary end-point event occurred in:
  - 60 of 102 patients (59%) in the placebo group
  - 62 of 105 patients (59%) in the 12.5-mg hydrochlorothiazide group
  - 61 of 108 patients (56%) in the 25-mg hyd. group
  - 49 of 101 patients (49%) in the 50-mg hyd. group.
- ✓There was no relation between the hydrochlorothiazide dose & the occurrence of a primary end-point event (P=0.66).

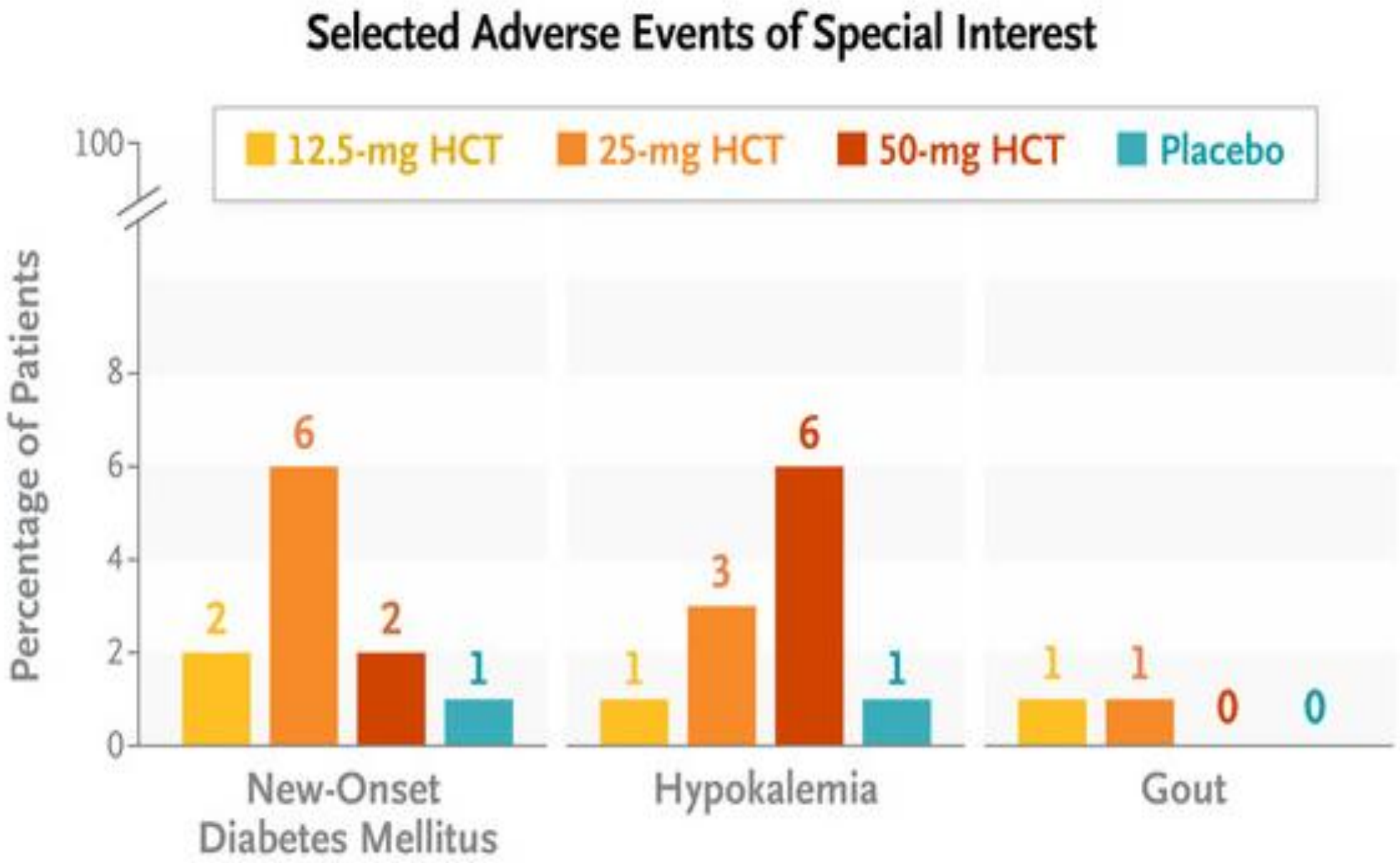
Dhayat NA. NEJM. 2023



Dhayat NA. NEJM. 2023



Dhayat NA. NEJM. 2023



Dhayat NA. NEJM. 2023

Conclusion

- ✓ Among patients with recurrent kidney stones, the incidence of recurrence **did not appear** to differ substantially among patients receiving hydrochlorothiazide once daily at a dose of 12.5 mg, 25 mg, or 50 mg or placebo once daily.

Dhayat NA. NEJM. 2023

Leave NOSTONE unturned: are thiazides useless in preventing kidney stone recurrence?

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KEYWORDS: diuretics; kidney stones; nephrolithiasis; urolithiasis

Nephrolithiasis, or kidney stone disease, is the second most frequent kidney disease after hypertension, affecting up to approximately 20% of men and approximately 10% of women in industrialized countries. The prevalence of nephrolithiasis has consistently increased over the last 50 years.[1] Nephrolithiasis represents a considerable burden for health care systems, with the total health care expenditure for kidney stones exceeding US $10 billion in 2006 in the United States alone.[2]

Kidney stones are commonly recurrent, with up to 15%, 30%, and 50% of individuals experiencing a second episode within 3, 5, or 10 years of their initial presentation,

Brazier F. KI. 2023

Are thiazides useless in preventing kidney stone recurrence?

1. At randomization, half of the participants in NOSTONE exhibited a urine Na output 168 mmol/24 hs (equivalent to daily NaCl intake of approximately 9 g/24 hs), indicating very poor dietary control.
2. Poor dietary control persisted throughout F/U with mean urine output remaining < 2.15 liters/24 hs & mean urine Na excretion >181 mmol/24 hs.
3. Urine oxalate excretion was also relatively high during the F/U period.

Brazier F. KI. 2023

Are thiazides useless in preventing kidney stone recurrence?

✓Indeed, thiazide diuretics are generally recommended as second-line therapy after dietary control which includes:

- Increased water intake of > 2.5 liters/d
- The reduction of salt

Brazier F. KI. 2023

Conclusion

✓The NOSTONE trial provides:

- Hydrochlorothiazide is ineffective at reducing the recurrence of symptomatic kidney stones at 3 ys in the absence of dietary control including abundant water intake & reduced dietary Na.
- However, additional studies are required to conclude that hydrochlorothiazide is a useless therapy for kidney stone recurrence

Brazier F. KI. 2023

Medical Expulsive Therapy

- ✓MET is probably most useful for stones 3-10 mm in size.
- ✓MET with 0.4 mg tamsulosin once daily or 4 mg of terazosin once daily is recommended dosing.
- ✓Limit MET to a 10-14 day course, as most stones that pass during this regimen do so in that time frame.
- ✓If outpatient treatment fails, promptly consult a urologist.

Dave CN. Medscape. 2023

MET

Recommendation	Strength rating
Consider α-blockers as medical expulsive therapy as one of the treatment options for (distal) ureteral stones > 5 mm.	Strong

Chemolysis

- ✓Percutaneous irrigation chemolysis may be an option for **infection-stones** & theoretically also for **uric acid** stones.
- ✓For dissolution of struvite stones, Suby's G solution (10% hemiacidrin; pH 3.5-4) can be used.
- ✓Oral chemolitholysis is based on **alkalinisation** of urine by application of alkaline citrate or sodium bicarbonate.
- ✓The pH should be adjusted to **7.0-7.2**.

EAU Guideline. 2023

Clinical Follow-up

- ✓ Annual clinical visit

1. Medical history
2. PE
3. Laboratory examination for full serum chemistries & urine profiles
4. Ultrasonography

Sakhaee K. J Clin Endoc Metab. 2012

An Epidemiological Survey on Kidney Stones and Related Risk Factors in the Iranian Community

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Abstract- Increasing number of patients with kidney stones is a major worldwide concern that needs more attention for recognizing the disease in order to set up suitable prevention systems. In this study, we aimed to assess the prevalence and related risk factors of kidney stones in our local area (Isfahan, Iran). In 2011, we celebrated World Kidney Day (WKD) with several training programs for informing people about kidney diseases. A questionnaire containing demographic data, past medical history, and familial and self-history of kidney disease was fulfilled by each individual who participated in WKD. Blood pressure and body mass index (BMI) were also measured using standard methods. Statistical analysis with SPSS-20 software was done. 556 participants with a mean age of 44.69±15.32 were included in the study, of which 107 cases (19.2%) with a mean age of 50.24±12.33 had a kidney stone, and 449 cases (80.8%) with a mean age of 44.69±15.32 had no

Variables		History of kidney stone		Total	*P*
		Yes	No		
Daily work	High activity	16(21%)	60(13.4%)	76(13.7%)	0.91
	Low activity	91(85%)	389(86.6%)	480(86.3%)	
Place of living	Isfahan (Urban area)	64(59.8%)	271(60.3%)	335(60.3%)	0.92
	Rural area near Isfahan	37(34.6%)	157(35%)	194(34.9%)	
	Other cities	6(5.6%)	21(4.7%)	27(4.8%)	
Diabetes Mellitus	Present	23(21.5%)	64(14.2%)	87(15.6%)	0.64
	Absent	84(78.5%)	385(85.8%)	469(84.4%)	
Cardiovascular diseases	Present	13(12.1%)	26(5.8%)	39(7%)	0.02
	absent	94(87.9%)	423(94.2%)	517(93%)	
Hypertension	Present	36(33.6%)	86(19.1%)	122(21.9%)	0.001
	Absent	71(66.4%)	363(80.9%)	434(78.1%)	
Vitamin C consumption	Yes	2 (1.9%)	9(2.1%)	11(1.9%)	0.21
	No	105 (98.1%)	440(97.9%)	545(98.1%)	
Vitamin D consumption	Yes	2(1.9%)	11(2.5%)	13(2.3%)	0.13
	no	105(98.1%)	438(97.5%)	543(97.7%)	
Familial history of kidney stone	No	57(53.3%)	343(76.4%)	400(71.9%)	<0.001
	First degree	46(43%)	93(20.7%)	139(25%)	
	Second degree	4(3.7%)	13(2.9%)	17(3.1%)	
Total		107(19.2%)	449(80.8%)	556(100%)	-

Probable risk factors of kidney stone

KIDNEY DISEASES IJKD

Review

Metabolic Disorders in Patients with Nephrolithiasis in Iran

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Keywords. Nephrolithiasis, Urolithiasis, Kidney Stone, Renal Calculi, Metabolic Disease, Etiology, Iran

Nephrolithiasis is a common disease entity around the world, with an increasing prevalence and incidence. There is no consolidated information available on the cause of kidney stones in Iranian patients. As a result, we decided to review the etiology of kidney stones in Iran. PubMed, Scopus, Web of Science, Google scholar, and Scientific Information Database (SID) were searched with the following keywords "Nephrolithiasis", "Renal stone", "Kidney stone", "Urolithiasis", "Etiology", "Metabolic abnormalities", and "Iran". There was no time period limit for selection of the papers. The inclusion criteria included any paper on evaluation of urine biochemistry regarding stone formation in Iranian adult patients (with or without children) with nephrolithiasis. We found 217 articles, of which 9 were eventually included. In conclusion, 1896 patients with nephrolithiasis from 6 provinces and 7 cities of Iran with different climates from 2000 to 2019 were evaluated collectively. The results showed that in contrast to western countries, hypercalciuria was not the most common biochemical disorder of patients with nephrolithiasis (18.2% vs. 30 to 60%). Low urine volume (49.6%) and hypocitraturia (27%) were the most frequent urine abnormalities in our country.

IJKD 2022;16:1-5
www.ijkd.org
DOI: 10.52547/ijkd.7055

Author	Year	Design	Population	Place	Laboratory Tests	First Author Specialty	Most Common Abnormality
Mahmoudi H.[8]	2000-2001	Cross-sectional	79	Kashan	Blood: [5]Cr, [9]Na, [7]K, Ca, uric acid 24-hour urine: Cr, Ca, uric acid	Urologist	1. Low urine volume 2. Hypercalciuria 3. Hyperuricosuria
Hosseini MM, et al.[9]	2010	Cross-sectional	376	Shiraz	Blood: [3]CBC, Bun, Cr, Na, K, [2]Ca, [10]Ph, uric acid U/A, U/C 24-hour urine: volume, Ca, Ph, [8]Mg, oxalate, citrate, uric acid	Urologist	1. Low urine volume 2. Hypercalciuria 3. Hyperuricosuria
Nouri-Majalan N, et al.[10]	2010	Cross-sectional	150	Yazd	Blood: Cr, K, Ca, Ph, Uric acid 24-hour urine: volume, pH, Cr, Na, K, Ca, uric acid	Nephrologist	1. Hypercalciuria 2. Hyperuricemia
Goodarzi MT, et al.[11]	2012	Case-control	28	Hamadan	U/A 24-hour urine: Cr, citrate, uric acid	-	Hypocitraturia
Emami-Naini A, et al.[12]	2012	Cross-sectional	437	Isfahan	Blood: [1]BUN, Cr, Na, K, Ca, Ph, albumin, uric acid 24-hour urine: volume, Cr, Na, Ca, citrate, oxalate, uric acid, cystine	Nephrologist	1. Hypocitraturia 2. Hyperoxaluria
Ghorbani A, et al.[13]	2012	Case-control	140	Ahwaz	Blood: [6]FBS, Cr, uric acid, [4]Chol, bicarbonate, Ph, [11]PTH [13]U/A: [12]SG, pH [14]U/C 24-hour urine: Na, Ca, Ph, Mg, citrate, oxalate, uric acid, cystine	Nephrologist	1. Hypocitraturia 2. Hyperuricosuria 3. Hyperuricemia
Hadian B, et al.[14]	2018	Cross-sectional	232	Lorestan	Blood: Ca, Ph, uric acid 24-hour urine: Ca, citrate, oxalate, uric acid	Nephrologist	Hyperoxaluria
Pakfetrat M, et al.[15]	2019	Cross-sectional	376	Shiraz	Blood: BUN, Cr, Ca, albumin, uric acid, PTH 24-hour urine: volume, Cr, Na, Ca, Ph, citrate, oxalate, uric acid	Nephrologist	1. Low urine volume 2. Hypercalciuria 3. Hyperoxaluria
Mohammadi Sichani M, et al.[16]	2019	Cross-sectional	78	Isfahan	Blood: BUN, Cr, Ca, Ph, Mg, uric acid, PTH 24-hour urine: volume, Cr, Na, Ca, Ph, citrate, oxalate, uric acid, cystine	Urologist	1. Cystinuria 2. Hyperoxaluria 3. Hypernatriuria

Characteristics of the Included Studies

Summary of Biochemical Disorders in the Included Studies

	Low Urine Volume	Hypercalcuria	Hyperuricosuria	Hypocitraturia	Hyperoxaluria	Hypernatriuria	Hyperphosphaturia	Cystinuria
Mahmoudi H. et al (n = 79)	62	22	9	Not available	Not available	Not available	Not available	Not available
Hosseini MM, et al. (n = 376)	219	67	57	7	9	Not available	Not available	Not available
Nouri-Majalan N, et al. (n = 150)	Not available	36	21	Not available	Not available	Not available	Not available	Not available
Goodarzi MT, et al. (n = 28)	Not available	Not available	Not available	12	Not available	Not available	Not available	Not available
Emami-Naini A, et al. (n = 437)	71	40	58	177	126	139	Not available	8
Ghorbani A, et al. (n = 140)	Not available	Not available	30	83	Not available	Not available	Not available	Not available
Hadian B, et al. (n = 232)	Not available	55	33	58	93	Not available	Not available	Not available
Pakfetrat M, et al. (n = 376)	277	90	17	69	73	57	12	Not available
Mohammadi Sichani M, et al. (n = 78)	Not available	5	10	10	13	13	0	15
Total (%)	629 (49.6)	315 (18.2)	235 (12.6)	416 (27)	314 (20.9)	209 (23.4)	12 (3.2)	23 (4.5)

Take-Home Message

1. Nephrolithiasis is a common problem that is increasing in prevalence & is associated with significant morbidity.
2. Although urinary supersaturation is a necessary substrate for stone formation, it is not sufficient.
3. Local & systemic factors interact with supersaturated solutes to cause stones.
4. These systemic factors can have important consequences beyond the urologic system, including adverse effects on bone & cardiovascular health.

Take-Home Message

5. Lowering supersaturation is a fundamental principal in management.

6. Additional interventions are tailored to the type of stone formed as well as the clinical context.

7. Often a multidisciplinary approach led by nephrologists & urologists is needed for optimal management.

Thanks for Your Attention

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ENDOUROLOGY

Guideline of guidelines

Guideline of guidelines for kidney and bladder stones

Thomas Hughes, Hui Ching Ho, Amelia Pietropaolo, Bhaskar K. Somani

Cite this article as: Hughes T, Ho HC, Pietropaolo A, Somani BK. Guideline of guidelines for kidney and bladder stones. Turk J Urol 2020; 46(Supp. 1): S104-S112.

ABSTRACT

Urological organizations publish detailed evidence-based guidelines to support the urologists in the management of urolithiasis. Our objective was to provide clear guidance on the management of urolithiasis, compare the American Urological Association (AUA) and European Association of Urologists (EAU) guidelines, and present an algorithm for different clinical scenarios. The latest AUA and EAU guidelines on urolithiasis were evaluated for the level of evidence and grade of recommendation. All recommendations on management of urolithiasis (surgical and medical management) were reviewed and included. Both the organizations provide guidance for initial patient assessment, imaging requirements, and therapeutic options, including surgical intervention and medical therapy. In addition, these guidelines provide advice for managing specific patient groups, including pediatric patients and pregnant patients. Although there is a general concordance between both the groups, differences exist particularly for recommended modality

Stone type	Metabolic status	AUA recommended interventions	AUA strength of recommendation	EAU recommended interventions	EAU strength of recommendation
Calcium oxalate	Hypercaluria	Limit sodium and calcium intake	Standard	Thiazide and alkaline citrates	Strong
		Thiazide	Standard		
	Hyperoxaluria	Avoid oxalate-rich foods but	Expert opinion	Oxalate intake restriction	Weak
		maintain normal calcium intake		Enteric - Alkaline citrates	Weak
				Calcium and magnesium	Weak
				Primary-Pyridoxine	Strong
	Hyperuricosuria	Limit non-dairy animal protein	Expert opinion	Avoid excessive intake of animal protein	Strong
		Allopurinol	Standard	Allopurinol (first-line)	Strong
				Febuxostat (second-line)	Strong

Hughes T. Turk J Urol. 2020

Summary of medical management depending on stone composition

Stone type	Metabolic status	AUA recommended interventions	EAU recommended interventions
Calcium oxalate	Hypercaluria	Limit Na & Ca intake	Thiazide & alkaline citrates
		Thiazide	
	Hyperoxaluria	Avoid oxalate-rich foods but maintain normal Ca intake	Oxalate intake restriction
			Enteric - Alkaline citrates
			Ca & Mg
			Primary-Pyridoxine
	Hyperuricosuria	Limit non-dairy animal protein	Avoid excessive intake of animal protein
		Allopurinol	Allopurinol (first-line)
			Febuxostat (second-line)

Hughes T. Turk J Urol. 2020

Summary of medical management depending on stone composition

Stone type	Metabolic status	AUA recommended interventions	EAU recommended interventions
	Hypomagnesuria		Magnesium
	Hypocitraturia	Increase the intake of fruit, vegetables & limit non-dairy animal intake.	Alkaline citrates & sodium bicarbonate
		Potassium citrate	
	Hypernaturia		Restricted salt intake
Ca Phosphate	Hypercaluria		Thiazide
	Acidic urine		L-methionine
Uric Acid	Alkaline urine	Potassium citrate	Alkaline citrates
	Hyperuricouria		Allopurinol

Hughes T. Turk J Urol. 2020

Summary of medical management depending on stone composition

Stone type	Metabolic status	AUA recommended interventions	EAU recommended interventions
Cystine		Increase fluid intake	Increase fluid intake
		Limit Na & protein intake	Alkaline citrates
		Potassium citrate	Tiopronin (added if above treatments are insufficient)
		Tiopronin (second-line, if unresponsive to above)	
Struvite		Surgical intervention (first-line)	Surgical intervention (first-line)
		AHA (second-line)	AHA (second-line)
	Acidic urine		Ammonium chloride or methionine
	Persistent bacteriuria		Antibiotics

Hughes T. Turk J Urol. 2020

Shock Wave Lithotriptor Trauma