TEHRAN UNIVERSITY OF MEDICAL SCIENCES

# Kidney Stone Disease (Nephrolithiasis)

Dr. Simin Dashti-Khavidaki;
Professor of Pharmacotherapy;
Faculty of Pharmacy;
TUMS

# Objectives

- Signs & Symptoms
- Kidney stone types
- Risk factors
- Nutrition
- Pharmacotherapy
- Herbal medicines
- Drug-induced nephrolithiasis

# Case

- A 56 y/o gentleman (WT: 105Kg, Ht: 175Cm; BMI≈34.3kg/$m^2$) was admitted in ED with CC of severe renal colic. He denies any past medical history. He is a Taxi deriver who works from 9 to 17 outdoor.

- What tests should be requested for the patient? How the patient should be managed?

# Renal Stones Presentation

- Although stones may pass asymptomatically, symptoms may occur when stones pass:
- Pain (renal colic or flank pain that radiates to the groin)
- Gross or microscopic hematuria
- N/V
- Dysuria
- Urinary urgency

Uptodate. 2024; Applied Therapeutics 2023

# Signs & Symptoms

- Flank and lower abdominal pain suggest upper obstruction

- Urinary frequency, hesitancy (difficulty in beginning the flow of urine), dribbling, abdominal fullness indicate lower obstruction

# Warning

- Nephrolithiasis may lead to persistent kidney obstruction, which could cause permanent kidney damage if left untreated,

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# Work-up On Presentation

- Basic laboratory tests
- Imaging of kidneys and ureters and bladder
- For most non-pregnant patients, non-contrast, low-radiation dose CT scan of the abdomen and pelvic is preferred that accurately describes stone size and location.
- If CT is not available or concern for it, ultrasound of the kidneys and bladder± abdominopelvic radiography.

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# Acute Management

- Pain medication + hydration until the stone passes.
- NSAIDs rather than opioids or other therapies as initial therapy.
- Reserve opioids for:

➢Contraindication to NSAIDs

➢Severe kidney function impairment (eGFR<30mL/min/1.73m$^2$)

➢Inadequate pain relief with NSAIDs

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# Stone Passage

The likelihood that ureteral stones will pass depends upon the size and location of the stone.

stones >10 mm and/or in the proximal ureter: usually require intervention and should be referred to urology.

stones >5 & ≤10 mm: treatment with tamsulosin for up to 4 weeks to facilitate stone passage.

If tamsulosin is not available, use another alpha blocker such as terazosin, doxazosin, alfuzosin, silodosin.

Stones ≤5 mm (in renal tubules, calyces, ureter or bladder) do not require specific treatment; most will pass spontaneously.

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# Confirmation of Stone Passage

- Confirm stone passage as resolution of pain is not necessarily consistent with stone passage.
- Patients are instructed to strain their urine for several days and bring in any passed stone for analysis.
- Patients who have not passed a stone after four weeks should have an imaging study to confirm stone passage.
- If the stone has not passed, patients are referred to urology.

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# Treatment of UTI

- All patients should be monitored for symptoms of UTI.

- UTI is a medical emergency in this setting.

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# Subsequent Evaluation

- a focused history
  - Identifying risk factors such family history and dietary habit
- radiologic imaging
  - Non-contrast low-dose CT to find residual stones at 1 year then Q2-4 y
- stone analysis (if available)
  - For stone analysis, although novel CT imaging techniques may permit noninvasive discrimination among main subtypes of urinary calculi
- laboratory evaluation
  - Blood, UA, and at least two 24h urine tests;
  - In 24hurine: Cr, Ca, Na, K, Mg, Ox, Citate, Uric acid, pH;
  - Urinary supersaturation should be calculated; 24 h urine test should not be performed if current obstruction due to stone or UTI is present.

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# Risk Factors


## Urinary

- Low urine volume
- Hypercalciuria
- Hyperoxaluria
- Hyperuricosuria
- Hypocitraturia
- Chronically low or high urinary pH

## Diet

- Low fluid intake or high fluid loss (sweating, GI loss)V
- Very high animal Pr which can lead to higher Ca-uria and uricosuria and hypocitraturia
- Low dietary calcium which increases Ox absorption
- Higher oxalate intake
- Lower K intake
- Higher Na intake
- Higher sugar (sucrose & fructose); increases Ca and Ox excretion
- Lower phytate
- Higher Vit C & D

## Other medical conditions

- Primary hyperparathyroidism
- Gout
- Obesity
- DM
- Distal RTA
- IBD
- Malabsorptive bariatric surgery
- Short bowel syndrome

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# Back to the Case

- A 56 y/o gentleman (WT: 105Kg, Ht: 175Cm) was admitted in ED with CC of severe renal colic. He denies any past medical history. He is a Taxi deriver who works from 9 to 17 outdoor.

- Three months later his 24h urine exam is as follows:

Volume: 1600CC; pH: 5.6; Cr: 1100mg; Ca: 280mg; oxalate: 90mg; uric acid:900mg; citrate:300mg

# 24h Urine Test

*Ca<200mg/d in females and <250mg/d in males

*Uric acid <750mg/d in females and <800mg/d in males

*Oxalate <40mg/d in females and males

*Citrate>450mg/d in females and males

*Cystine ≈30mg/d

Uptodate. 2024

# Types of Kidney Stones

- Calcium salts (oxalate (70-80%) or phosphate (15%))
- Uric acid (≈8%)
- Magnesium ammonium phosphate (struvite) (≈1%)
- Cystine (1-2%)
- Individual stones may contain more than one type.

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# Back to the Case

- A 56 y/o gentleman (WT: 105Kg, Ht: 175Cm) was admitted in ED with CC of severe renal colic. He denies any past medical history. He is a Taxi deriver who works from 9 to 17 outdoor.

- How he should be managed?

# Preventive Therapy

❖Goal:

- prevention of future kidney stones recurrence &
- preventing the growth of existing kidney stones.

❖Preventive therapy generally consists of:

- lifestyle changes,
- drug therapy,
- or a combination of two above.

❖For calcium oxalate and calcium phosphate stones, dietary modification begins before initiating drug therapy. However, for uric acid or cystine stones, drug therapy is frequently initiated at the same time as dietary changes.

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# Preventive Measures For All Stone Types

| | |
|---|---|
| Fluid intake | • Fluid intake to produce at least 2L urine/day<br>• Water is an ideal choice, but other non-calorie-containing beverages are also effective. |
| Na intake | • Na intake below 100 mEq (2300mg)/d |
| Fruit and vegetable intake | • Due to high K and citrate contents |
| Weight loss | |

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# Preventive Measures For Ca- Ox and Phosphate Stones

- Ca intake
- Animal protein intake
- Oxalate intake
- Sucrose and fructose intake

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# Preventive Measures For Ca- Ox and Phosphate Stones

## Ca Intake

Avoid low-Ca diet since it increases stone formation, develops negative Ca balance and exacerbates the already diminished bone density in some patients with hypercalciuria

Taking several serving of dairy or other Ca-rich foods to reach 800 to 1000 mg/day

Some plant-based milk alternatives are calcium enriched and low in oxalate and may be options in place of traditional dairy offerings

Ca supplements should not be routinely used, as they are not effective in preventing recurrent stones and may even slightly increase risk.

If taking Ca supplement, measure urinary Ca at baseline and 1-month after supplement initiation. If hypercalciuria, decrease Ca dose or add thiazides

Take Ca supplement with food

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## Preventive Measures For Ca- Ox and Phosphate Stones

# Animal Protein Intake

Reduce nondairy animal protein

Adverse changes in urinary Ca and citrate excretion can be induced by a high-protein diet since the metabolism of sulfur containing amino acids increases the daily acid load by generating sulfuric acid

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# Preventive Measures For Ca- Ox and Phosphate Stones

# Oxalate Intake

For all patients with calcium oxalate stones, limit taking of high oxalate foods and high-dose supplemental vitamin C.

However, excessive restriction of oxalate is not likely to be helpful; patients should continue to consume a wide variety of fruits and vegetables while avoiding those very high in oxalate.

Some foods contain very large amounts of oxalate and should be avoided (spinach, rhubarb (ریواس), potatoes).

Some nuts and legumes are also high (almonds) or moderate (peanuts, cashews (بادام هندی)) in oxalate, and their intake should be limited.

High-oxalate foods should be avoided regardless of urine oxalate since there may be a period of very high urinary oxalate excretion soon after the food is consumed.

Tea traditionally believed to be high in oxalate, however, do not increase the risk of stone formation.

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## Preventive Measures For Ca- Ox and Phosphate Stones

# Sugar Intake

For all patients with calcium oxalate stones, limit intaking sucrose and fructose.

Sucrose intake increases urine calcium independent of calcium intake and has been associated with an increased risk of stones.

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## Preventive Measures For Ca- Ox and Phosphate Stones

# Drug Therapy

❖Drug therapy is indicated if the stone disease remains active (as evidenced by the formation of new stones, enlargement of old stones, or the ongoing passage of gravel) or if there is insufficient improvement in the urine chemistries despite attempted dietary modification over a 3-6 months period.

- Thiazides
- K citrate or bicarbonate
- Allopurinol

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## Preventive Measures For CaOx and Phosphate Stones

# Drug Therapy: Thiazides

For patients with recurrent caOx stones & high urine Ca: thiazide diuretic.

Long-acting thiazides (chlorthalidone, indapamide) is preferred over short-acting thiazides (HCTZ).

Chlorthalidone 12.5 to 25 mg/d, indapamide 2.5 mg/d, HCTZ 25 mg/d to ↓ diuretic-induced ADRs.

Many patients require 50 -100 mg/d of chlorthalidone or HCTZ to achieve adequate ↓the urine Ca.

Patients who do not respond to 50 mg/d are unlikely to respond to higher doses.

Chlorthalidone is given QD, but HCTZ at doses above 25 mg/day is given BD.

Amiloride (5 -10 mg/d) can be added: may increase ca absorption in the cortical collecting tubule, further ↓ Ca excretion, and may also prevent hypokalemia, which could lead to lower citrate

Avoid triamterene

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## Preventive Measures For CaOx and Phosphate Stones

# Drug Therapy: K citrate or bicarbonate

For patients with recurrent CaOx stones who have low urine citrate, potassium citrate or potassium bicarbonate is administered to increase urinary citrate excretion.

30 to 60 mEq of alkali per day in 2-3 divided doses.

Each 1g potassium citrate is equivalent to 10 mEq citrate

Via an unknown mechanism, raising the plasma bicarbonate concentration increases calcium reabsorption and lowers calcium excretion.

Although orange juice is a good source of K and citrate, it does not lower Ca excretion, modestly raises Ox excretion, ↑caloric intake could lead to weight gain.

By comparison, lemon juice has been proposed to be an effective source of citrate

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# Potassium Citrate/Bicarbonate

Keep urine pH≈6.5.

Monitor urine pH at baseline, with dose change and every 4 months thereafter.

keeping in mind that very high urine pH in some individuals may predispose to calcium phosphate stone.

Monitor serum electrolyte, CBC and Cr every 4 months and more frequently in patients with cardiac or renal diseases.

Given the data on diurnal variation in uric acid excretion and pH, dosing should probably be done intermittently (2-3times daily) rather than QD to maintain a higher urinary pH more consistently.

Dosing is also altered based on GI intolerance.

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## Preventive Measures For CaOx and Phosphate Stones

# Drug Therapy: Ca, B6, Allopurinol

Treatment in individuals with enteric hyperoxaluria is directed toward diminishing intestinal oxalate absorption. The initial regimen consists of oral calcium carbonate or citrate (1 to 4 g/day) with meals to bind oxalate in the intestinal lumen.

Treatment in individuals with primary hyperoxaluria is directed at reducing endogenous oxalate production, which is increased in patients with primary hyperoxaluria. The role of Vit B6?

For patients with recurrent calcium oxalate stones who do not respond to dietary modification and other drug therapies and who have high urine uric acid, treatment with allopurinol is suggested. Oral: 300 mg/day, usually given in a single daily dose but may be given in 2 or 3 divided doses, if needed, to improve GI tolerability

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# Pyridoxine

- B6 is a coenzyme of alanine-glyoxylate aminotransferase (AGT) that promotes the conversion of glyoxylate to glycine, rather than to oxalate.

- Approximately 10-30% of patients with primary hyperoxaluria type 1 will respond to pyridoxine therapy with a significant reduction of urinary oxalate excretion.

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# Struvite Stones

- Magnesium ammonium phosphate or triple phosphate nephrolithiasis
- High morbidity and mortality because they tend to recur and can result in irreversible kidney damage
- “Staghron appearance” in collecting duct
- Generally, result when existing stones are colonized with urease producing bacteria (e.g., *Proteus mirabilis, Klebsiella pneumoniae, Corynebacterium sp., Ureaplasma urealyticum).* Urease enzyme hydrolyzes urea and alkalinize the urine.

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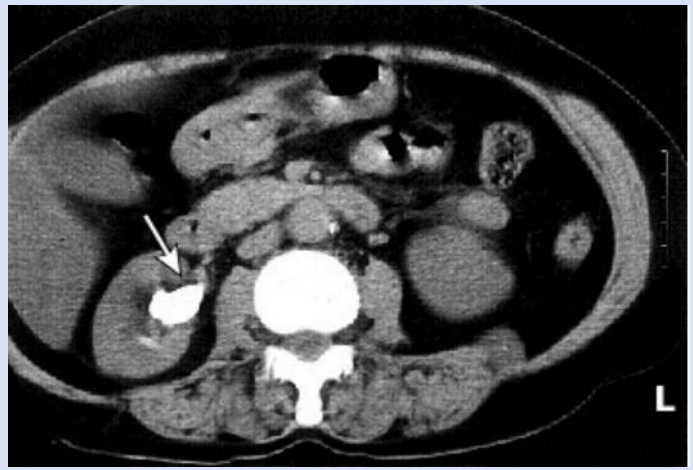
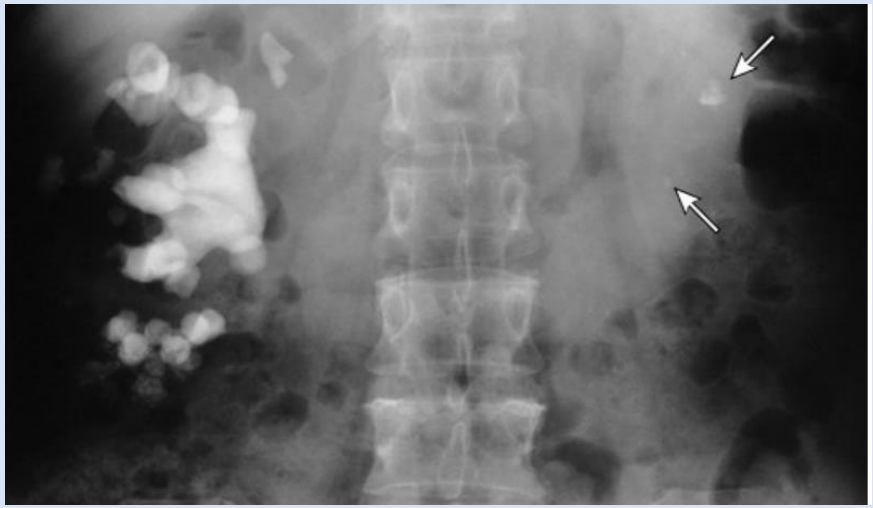
# Struvite stone

CT scan




Radiography



Urine crystal microscopic picture

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# Struvite Stones

Population at risk:

1. obese women,
2. pts with frequent UTI,
3. pts with GU tract abnormalities that promote bacterial colonization or make eradication of infection difficult

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# Struvite Stones

Tx consist of

- surgical intervention or shock-wave lithotripsy

- prolonged course of antibiotics (at the time of surgery to six month after complete stone removal),

- administration of acetohydroxamic acid which inhibit bacterial urease,

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# Uric acid Stones

- **In pts with gout and those receiving chemotherapy**
- **Administer allopurinol 200mg/d**

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# Cystine Stones

Cystinuria is a rare genetic cause of kidney stones that is caused by inactivating mutations in either SLC3A1 or SLC7A9.

Cystine is a homodimer of the amino acid cysteine with disulfide bond.

Patients with cystinuria have impairment of renal cystine transport, with ↓ proximal tubular reabsorption of filtered cystine resulting in ↑ urinary cystine excretion.

Cystine stones are found in 1-2% of all stone formers and ≈ 5% percent of children who form stones.

Cystinuria is not the same as cystinosis.

Median age at presentation is 12 years, may occasionally present in infancy or late adulthood.

Can be visualized with non-contrast CT &ultrasound.

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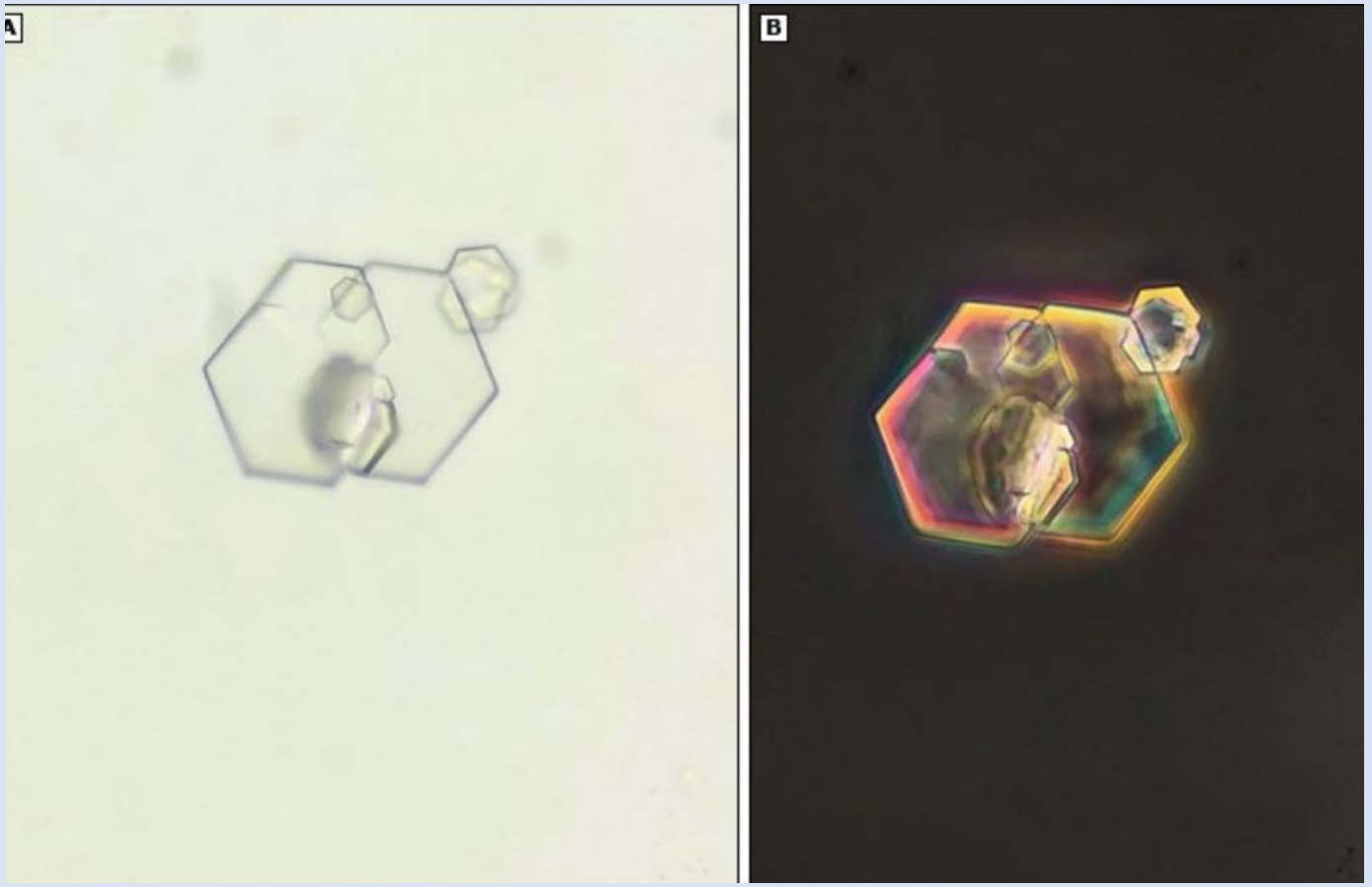
# Cystine Stones

Hexagonal crystal

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# Treatment of Cystine Stones

Goal: maintain urine cystine concentration below its solubility level (≈250 mg/L and urine pH is ≥7).

If not responded to conservative measures after 3 months (↑fluid intake, ↓Na, modest ↓(0.8-1 g/kg) animal protein, urinary alkalinization) or if urine cystine concentration is very high or in patients with prior large stones, pharmacotherapy with tiopronin.

If tiopronin is not available, D- penicillamine.

Have sulfhydryl groups that can reduce disulfide bond, producing mixed drug-cysteine disulfides that are more soluble than the homodimer cystine.

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# Thiol Containing Drugs

Tiopronin: Tab 100mg ; Dose 600-800mg in adults or 15mg/kg in children in 3 divided doses.

D-Penicillamibe 0.5 -2g/d in 3-4 divided doses; 20-40mg/kg/d max: 1.2g/d in children.

Take on empty stomach.

May cause Vit B6 deficiency, administer pyridoxine 50mg/d

ADRs are more common with D-penicillamine: fever, rash, abnormal taste, arthritis, leukopenia, aplastic anemia, hepatotoxicity, and pyridoxine deficiency. proteinuria (usually due to membranous nephropathy), typically within the first 6 -12 mo of therapy, or rarely, crescentic glomerulonephritis or minimal change disease. Remission of proteinuria typically follows months after discontinuation of the drugs.

# Sancol Oral Drop

عصاره هیدرو الکلی گیاهان زیر
۱- دانه رازیانه
۲-دانه زیره سبز
۳-برگ بو
٤-دم گیلاس
۵-کاکل ذرت
۶-میوه خارخاسک
۷-تخم خربزه

# سنکل (Sankol)

**مواد موثره:**

املاح پتاسیم ، اسیدهای چرب ، فلاوونوییدها ، روغن های فرار نظیرآنتول ،فنچون، سینئول و کاروون

**اثر دیورتیک:**

**میوه خارخاسک – کاکل ذرت – دم گیلاس- تخم خربزه**

**اثر ضد میکروبی و ضد اسپاسم:**

**دانه رازیانه – دانه زیره سبز – برگ بو**

**عصاره آبی خارخاسک روی متابولیسم اگزالا ت موثر بوده و ↓اگزالوری**

# سنکل (Sankol)

- **عوارض جانبی کاکل ذرت:** هایپوتانسیون، هایپو گلایسمی

- **مصرف در دوران بارداری و شیردهی:** هرچند بروشور قطره گیاهي سنکل مصرف این دارو در دوران بارداري را منع نکرده است وليکن کاکل ذرت با داشتن بعضي ترکيبات کلينرژيك در خرگوش باعث افزايش انقباضات رحمي گرديده است و مصرف بيش از دوزهاي خوراکي آن در اين دوران منع شده است.

- **تداخلات داروئی:** واکنش شبه دی سولفیرام با عصاره های هیدرو الکلی

# سنکل (Sankol)

- مقدار مصرف:
- بزرگسالان مبتلا به سنگ 50-60 قطره همراه با يك فنجان آب ، سه نوبت در روز به مدت يك ماه

- پیشگیری از تشکیل سنگهاي ادراري به صورت مزمن، 30 قطره 2-3 بار در روز سه بار در هفته

- در کودکان زیر 12 سال نیز 10-20 قطره سه بار در روز

# Rowatinex & Renanex

Components: A combination od 7 naturally available terpens (Pinene (α+β), Camphene, Cineole, Fenchone, Borneol, Anethole) and  Olive oil

Pharmacologic effects of these terpens: diuretic, spasmolytic, antibacterial, hyperemic.

Effects in urolithiasis: Based on 4 open-label and 5 RCT, compared to placebo, Rowatinex has the potential to promote and accelerate stone expulsion in primary management of urolithiasis and fragment discharge after SWL.

European Urology Supplements 9. 2010; 814-8.

# Cystone

- Is a polyherbal tablet.
- It has been FDA approved after extensive studies on each ingredient.
- It prevents the super-saturation of calcugenic substances and controls oxamide.
- It prevents urolithiasis formation via the reduction of stone formers.
- By acting on the mucin, leads to the disintegration of stones and crystals.
- Alsohas antimicrobial, antispasmodic, and anti-inflammatory properties that are helpful in the prevention of UTI associated with urolithiasis.
- A review article showed that compared to placebo, cystone significantly induces stone size decrement and clearance.

Jundishapur Journal of Natural Pharmaceutical ptoducts. 2018; 15(3): e69246

# Drug-Induced Renal Stones/Crystals

# Drug-induced renal calculi

- Drug-induced renal calculi represent 1-2% of the total number of kidney stones

# Risk Factors for Drug-Induced Renal Calculi

**Patient related**

**Drug related**

# Risk Factors for Drug-Induced Renal Calculi

**Patient related**

**personal or family Hx of nephrolithiasis;**

**Pre-existing calculi;**

**urinary stasis;**

**Underlying lithogenic metabolic abnormalities (hypercalciuria, hypocitraturia)**

**Detoxification enzyme pattern**
**Abnormally low or high urine pH**
**UTI**
**Low U/O**
**Environmental factors (e.g. hot temperature)**

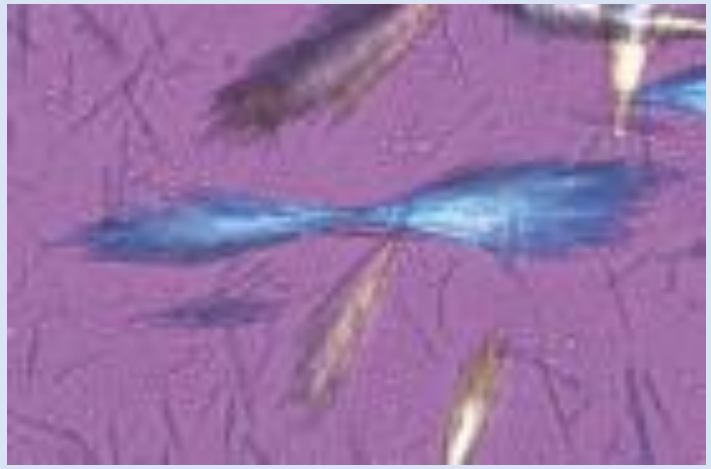
# Risk Factors for Drug-Induced Renal Calculi

- **Drug related**
  - High dose
  - Long-standing treatment
  - High urinary excretion of the drug/its metabolite
  - Low aqueous solubility of the drug/its metabolite
  - Short drug half-life, inducing concentration peaks in urine
  - Concomitant therapy that causes changes in the pharmacokinetics or metabolism of the drug
  - Size and morphology of drug crystals

# Drugs which may crystallise in urine

- **Antibacterials**
  - **Sulfonamides (sulfadiazine, sulfamethoxazole)(their N-acetyl metabolites)**
  - **Aminopenicillins (ampi, amoxi) (drugs trihydrate)(needle-shape crystals which may easily aggregates in acidic urine)**
  - **Cephalosporines (ceftriaxone) (calcium salt)**
  - **Quinolones (cipro (in alkaline pH))(magnesium salt)**
  - **Nitrofurantoin (with at least one report of calculi)**

# Amoxicillin Stone and Crystal



# Drugs which may crystallise in urine

- **Protease inhibitors** (indinavir, nelfinavir, atazanavir, kaletra (lopinavir+ ritonavir))
- **Other antivirals**(acyclovir, foscarnet)
- **Analgesics (Phenazopyridin)** (hydroxyphenazopyridin sulfate, other metabolites)
- **Antihypertensives (triamterene)** (hydroxy and glucoronide metabolites)
- **Antacids** (Mg tricilicate, Al hydroxide) (amorphus tricilicate, Al Mg K urate)
- **Primidone**
- **MTX** (drug and its hydroxyl metabolite in acidic urine)
- **Guaifenesin** (Ca salt of metabolite)
- **Allopurinol** (oxipurinol)
- **Sulfasalazin** (acetyl metabolite)

# Drug-Induced Renal Calculi

- **Drug Containing Renal Calculi** **(the drug or its metabolites are total or partial components of the calculi)**

- **Metabolically Induced Calculi** **(the drug induces the formation of calculi through its metabolic action by interfering with calcium oxalate or purine metabolism**)

# Drug-Induced Renal Calculi

## Drug Containing Renal Calculi

- **Triamterene**
- **Protease inhibitors**
- **Sulfonamides**
- **Other drugs :**
  - **Allopurinol**
  - **Antibacterial agents**
  - **Guaiafenesin and pseudoephedrine**

# Drug-Induced Renal Calculi
# Metabolically Induced Calculi

- Drug-Induced calcium-containing radio-opaque renal calculi

- Drug-Induced urate (purine)-containing radioleucent renal calculi

# Drug-Induced Renal Calculi
# Metabolically Induced Calculi

- Drug-Induced calcium-containing radio-opaque renal calculi
  - ❑Ca-Vit D supplements
  - ❑Carbonic anhydrase inhibitors (acetazolamide,, topiramate, zonisamide)
  - ❑Furosemide
  - ❑Antacids
  - ❑Phenytoin
  - ❑Corticosteroids
  - ❑Ascorbic acid

# Drug-Induced Renal Calculi
# Metabolically Induced Calculi

- **Drug-Induced purine-containing radioleucent renal calculi**
  - **Aluminium-containing drugs**
  - **Laxative drugs**
  - **Allopurinol**
  - **Urine pH modifiers**

# Thank You For Your Attention