Urolithiasis (1 of 11)

1. Patient presents with lower urinary tract symptoms (LUTS) suggestive of urolithiasis

2. DIAGNOSIS
   - Is urolithiasis confirmed?
   - No → ALTERNATIVE DIAGNOSIS

3. CLASSIFY THE TYPE OF KIDNEY STONES
   - Calcium oxalate stones
   - Cystine stones
   - Struvite or infection stones
   - Urate containing stones
   - Calcium phosphate stones

A. Non-pharmacological therapy
   - Watchful waiting
   - Diet therapy

B. Pharmacological therapy
   - Alkaline citrate
   - Allopurinol
   - Sodium bicarbonate
   - Thiazide diuretic (Hydrochlorothiazide)

C. Surgery
D. Follow-up

TREATMENT
See next page

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Urolithiasis (2 of 11)

TREATMENT OF KIDNEY STONES

CYSTINE STONES

A Non-pharmacological therapy
- Watchful waiting
- Diet therapy

B Pharmacologic therapy
- Alkaline citrate or
- Sodium bicarbonate
- Tiopronin

C Surgery

D Follow-up

STRUVITE OR INFECTION STONES

A Non-pharmacological therapy
- Watchful waiting
- Diet therapy

B Pharmacological therapy
- Acetohydroxamic acid
- Antibiotics
- Sodium bicarbonate

C Surgery

D Follow-up

urate-containing stones

A Non-pharmacological therapy
- Watchful waiting
- Diet therapy

B Pharmacological therapy
- Alkaline citrate
- Allopurinol
- Sodium bicarbonate

C Surgery

D Follow-up

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UROLITHIASIS

1. **UROLITHIASIS**

- The formation of urinary stones in the kidney, bladder &/or urethra
- The hallmark of obstruction in the ureter & renal pelvis is the sudden onset of excruciating, intermittent pain that radiates from the flank to the groin or to the genital area & inner thigh
- Painful urologic disorder that occurs in 12% of the global population & has a high recurrence rate of 71-80% among male patients
- Lower urinary tract symptoms associated w/ urolithiasis are:
  - Urgency
  - Frequency
  - Urge incontinence
  - Dysuria
  - Hematuria (gross or microscopic)
- Stone incidence depends on the following factors:
  - Geographical
  - Climatic
  - Ethnic
  - Dietary
  - Genetic

2. **DIAGNOSIS**

**History**

- A detailed history from the patient should be elicited
- Thorough review of medical records should include:
  - Number & frequency of episodes
  - Previous imaging studies, interventions, evaluations & treatments
- Family history that may reveal genetic predisposition:
  - Cystinuria (type A, B & AB)
  - 2,8 Dihydroxyadeninuria
  - Xanthinuria
  - Renal tubular acidosis (RTA type 1)
  - Primary hyperoxaluria
  - Lesch-Nyhan syndrome
  - Cystic fibrosis
- General factors:
  - Early onset of urolithiasis (especially in children & teenagers)
  - Familial stone formation
  - Brushite-containing stones (calcium hydrogen phosphate)
  - Uric acid & urate-containing stones
  - Infection stones
  - Solitary kidney
- Dietary history of the patient:
  - Average daily intake of fluids (amount & specific beverages)
  - Eating habits (meals & snacks)
  - Calcium, sodium, high oxalate-containing food
  - Fruits & vegetables
- Nutritional factors associated w/ stone diseases:
  - Calcium intake that is below or significantly above the recommended dietary allowance (RDA)
  - Low fluid intake
  - High sodium intake
  - Limited intake of fruits
  - Vegetables & high intake of animal-derived purines

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**History (Cont’d)**

- Complete list of current prescription & over-the-counter drugs, as well as vitamins & supplements should be obtained; stone-provoking medications include:
  - Probenecid
  - Some protease inhibitors
  - Lipase inhibitors
  - Triamterene
  - Chemotherapy
  - Vitamins C & D
  - Carbonic anhydrase inhibitors (eg Topiramate, Acetazolamide, Zonisamide)

- Conditions associated w/ stone disease:
  - Obesity
  - Gout
  - Hyperparathyroidism
  - Renal tubular acidosis type 1
  - Diabetes mellitus type 2
  - Bone disease
  - Primary hyperparathyroidism
  - Bariatric surgery
  - Bowel or pancreatic disease
  - Nephrocalcinosis
  - Sarcoidosis
  - Due to jejunoileal bypass & intestinal resection

- Anatomical abnormalities associated w/ stone formation:
  - Medullary sponge kidney (tubular ectasia)
  - Ureteropelvic junction (UPJ) obstruction
  - Calyceal diverticulum, calyceal cyst
  - Ureteral stricture
  - Vesico-uretero-renal-reflux
  - Horseshoe kidney
  - Ureterocele

**Physical examination**

- Should include the weight, blood pressure, costovertebral angle tenderness & lower extremity edema, as well as signs of primary hyperparathyroidism (HPT) & gout in the assessment

**Diagnostic tests**

- Serum chemistries should include electrolytes (eg sodium, potassium, chloride, bicarbonate, calcium, creatinine, & uric acid) to uncover hypokalemia or renal tubular acidosis (RTA)
- Parathyroid hormone (PTH) level should be measured if there is high normal or elevated serum & urine calcium concentration
- Level of 25-hydroxy vitamin D should also be investigated to rule out the possibility of vitamin D deficiency in patients w/ elevated PTH
- Urinalysis should include dipstick, microscopic evaluation (urinary pH, indicators of infection & identification of crystals that are pathognomonic of stone type)
- 24-hour urine collection/metabolic testing
  - The cornerstone for which the therapeutic recommendations are based
  - At least two samples are collected, while consuming their usual diet & volume of fluid
  - Metabolic testing should analyze total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium & creatinine
  - Urinary potassium measured at baseline can be compared to urinary potassium obtained during follow-up, to gauge compliance w/ medication regimens
  - Urinary cystine should additionally be measured in stone formers w/ known cystine stones or a family history of cystinuria or for those in whom cystinuria is suspected
  - Primary hyperoxaluria should be suspected when urinary oxalate excretion exceeds 75 mg/day in adults w/o bowel dysfunction
  - These patients should be considered for referral for genetic testing &/or specialized urine testing

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**Diagnostic tests (Cont’d)**

**Basic laboratory analysis in emergency cases**
- Urine (e.g., dipstick test of spot urine sample, urine microscopy &/or culture)
- Serum blood sample (e.g., creatinine, uric acid, ionized calcium, sodium & potassium)
- Blood cell count
- Coagulation test, if intervention is likely or planned

**Basic laboratory analysis in non-emergency cases**
- Biochemical work-up is similar for all patients but if there is no planned intervention, then sodium, potassium, & blood coagulation time can be omitted

**Imaging**
- Choice of imaging modality will depend on the clinical situation of the patient
- Indicated for patients w/ fever or solitary kidney & when diagnosis is doubtful
- Used to differentiate ureteral stones from renal stones

**Ultrasound (UTZ)**
- Used as the primary diagnostic tool
- Identifies presence of stones in the calices, pelvis, pyeloureteric & vesicoureteric junctions, & in patients w/ upper urinary tract dilatation

**Kidneys, Ureter & Bladder (KUB) radiography**
- Helpful in differentiating radiolucent & radiopaque stones
- Used for comparison during follow-up
- Should not be performed if non-contrast CT scan (NCCT) is being considered

**Evaluation of patient w/ acute flank pain**

**NCCT**
- First choice in confirming stone diagnosis in patients w/ acute flank pain
- Significantly more accurate than intravenous urography (IVU)/intravenous pyelogram (IVP) in evaluating patients w/ acute urolithiasis
- Used to determine the diameter, density, inner structure & skin-to-stone distance that affects the outcome of extracorporeal shockwave lithotripsy (SWL)
- Can detect uric acid & xanthine stone that are radiolucent on plain films

**Low-Dose CT Scan**
- Can reduce radiation risk
- Used to detect ureteral stones in patients w/ a BMI of <30

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**Classification & Analysis of Stones**

**Classification of urinary stones**

**Size**
- Usually given in one or two dimensions & is stratified to those measuring up to 5, 5-10, 10-20 & 20 mm in largest diameter

**Location**
- Classified according to anatomical position: upper, middle or lower calyx, renal pelvis, upper, middle or distal ureters & urinary bladder

**X-ray characteristics**
- Classified according to plain X-ray appearance (e.g., kidney-ureters-bladder (KUB) radiography), according to mineral composition
- NCCT is used to classify stones according to density, structure & composition

**Etiology of formation**
- Non-infectious (e.g., calcium oxalate, calcium phosphate, uric acid)
- Infectious (e.g., magnesium, ammonium phosphate, carbonate apatite, ammonium urate)
- Genetic causes (e.g., cystine, xanthine, 2,8 dihydroxyadenine)
- Further diagnostic tests & management depends on the composition of the stone
- Risk status of the stone formers should be assessed because it will define the probability of recurrence or regrowth & is imperative for the choice of pharmacological treatment
Analysis of stone composition
- Preferred analytical procedures are infrared spectroscopy (IRS) & X-ray diffraction analysis of urinary stones
- Repeat stone analysis is needed in cases of:
  - Recurrence after pharmacological intervention
  - Early recurrence after interventional therapy w/ complete stone clearance
  - Late recurrence after a prolonged stone-free period since stone composition may change overtime

Stone types
Calcium stones (oxalate & phosphate)
- Most common type of kidney stone
- Formed when there is high level of calcium in the urine
- Characterized as either large & smooth or rough & spiky

Calcium stones (oxalate & phosphate)
- Diseases & disorders related to calcium stones:
  - Hypercalciuria (inherited condition)
  - Renal tubular acidosis
  - Nephrocalcinosis
  - Primary hyperparathyroidism
  - Kidney disease
  - Sarcoidosis (granulomatous disease)
  - Primary hyperoxaluria
  - Enteric hyperoxaluria

Struvite or infection stones
- May originate de novo or grow on pre-existing stones infected w/urea-splitting bacteria
- Predisposing factors for stone formation:
  - Neurogenic bladder
  - Spinal cord injury or paralysis
  - Continent urinary diversion
  - Ileal conduit
  - Foreign body
  - Stone disease
  - Indwelling urinary catheter
  - Urethral stricture
  - Benign prostatic hyperplasia
  - Bladder diverticulum
  - Cystocele
  - Caliceal diverticulum
  - Uteropelvic junction (UPJ) obstruction

Uric acid & ammonium urate stones
- Associated w/ hyperuricosuria or low urinary pH
- Hyperuricosuria may be due to dietary excess, endogenous overproduction (enzyme defects), myeloproliferative disorders, tumor lysis syndrome, drugs, gout & catabolism
  - Ammonium urate stones are rare & are associated w/ inflammatory bowel disease (IBD), ileostomy diversion, laxative abuse, potassium deficiency, hypokalemia & malnutrition
  - Forms in the urine at pH <6.5 (ammonium urate crystals) & <5.5 (uric acid stones)

Cystine stones
- Poorly soluble in urine & crystallizes spontaneously w/in the physiological urinary pH at 6.0
- Clinical manifestations are the same for patients who are genotypic or phenotypic type of cystinuria

Other stone types
2,8-Dihydroxyadenine stones & xanthine stones
- Both stone types were rare & the diagnosis is similar to that of uric acid
- Genetically determined defect of adenine phosphoribosyl transferase that causes high urinary excretion
- Decreased levels of serum uric acid are seen in patients who forms xanthine stones

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### 3 Classification & Analysis of Stones (Cont’d)

#### Other stone types (Cont’d)

**Drug stones**
- These are induced by pharmacological treatment & exists as:
  - Stones formed due to unfavorable changes in urine composition under drug therapy & by the crystallized compounds of the drug
- Compounds that causes drug stones:
  - Allopurinol/oxypurinol
  - Amoxicillin/ampicillin
  - Ceftriaxone
  - Quinolones
  - Ephedrine
  - Indinavir
  - Magnesium trisilicate
  - Sulphonamides
  - Triamterene
  - Zonisamide
- Substances impairing urine composition:
  - Acetazolamide
  - Allopurinol
  - Aluminium magnesium hydroxide
  - Ascorbic acid
  - Calcium
  - Furosemide
  - Laxatives
  - Methoxyflurane
  - Vitamin D
  - Topiramate

**Matrix stones**
- Pure matrix stones are extremely rare
- More prevalent among females
- Main risk factors are:
  - Urinary tract infections (UTIs) due to *Proteus mirabilis* or *Escherichia coli*
  - Previous surgery for stone disease
  - Chronic renal failure
  - Hemodialysis

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### A NON-PHARMACOLOGICAL THERAPY

**Watchful Waiting**
- Since most stones are small, about 5 mm in size, the patient is advised for the passage of stones through normal urination, that usually happens w/in 2-3 days
- A collection kit is provided w/ filter & the patient is instructed to collect the passed stone for testing & analysis

**Diet therapy**
- All stone formers are advised to have a fluid intake that will achieve a urine volume of at least 2.5 liters daily
- Limit sodium intake & consume 1,000-1,200 mg per day
  - Lower calcium diet in the absence of other specific dietary measures increases the risk of stone formation
- Limit the intake of oxalate-rich foods & maintain normal calcium consumption
- Increase the intake of fruits & vegetables
  - Hypocitruria is common among patients w/ stone disease, w/ a prevalence of 20-60%
  - Promoted by RTA, chronic diarrhea & carbonic anhydrase inhibitor
- Limiting the intake of non-dairy animal protein may help reduce stone recurrence
  - Patients w/ a history of uric acid stones should be counseled to:
    - Increase the intake of alkali & decrease the intake of acids
    - Increase the urine pH
    - Reduce the urinary acidity

### B PHARMACOLOGICAL THERAPY

**Alkaline citrate (Sodium & Potassium)**
- A urinary alkalinizer used to prevent uric acid or cystine calculi formation
- Also used as an adjuvant w/ uricosuric agents in gout therapy
- Effective in correcting the acidosis of certain renal tubular disorders
- Contraindicated in patients w/ severe renal impairment w/ oliguria or azotemia, untreated Addison’s disease & severe myocardial damage

**Allopurinol**
- Inhibits xanthine oxidase & reduces the production of uric acid w/o disrupting the biosynthesis of vital purines
- Used in the prevention of gout, renal calculi due to uric acid or calcium oxalate, prophylaxis & treatment of uric acid nephropathy
- Contraindicated in patients w/ idiopathic hemochromatosis & asymptomatic hyperuricemia

**Chlorthalidone**
- A long-acting antihypertensive/diuretic that enhances the excretion of sodium, chloride ions & water by interfering w/ the transport of sodium ions across the renal tubular epithelium
- Contraindicated in patients w/ known anuria & hypersensitivity to other sulfonamide-derived drugs

**Thiazide diuretics (Hydrochlorothiazide)**
- Inhibits the sodium reabsorption in the distal tubules & as a result, the excretion of sodium, water, potassium & hydrogen ions increases
- Used as treatment for hypercalciuria & calcium stone recurrence
- Contraindicated in patients w/ known anuria & hypersensitivity to other sulfonamide-derived drugs

**Sodium bicarbonate**
- Raises blood & urinary pH by dissociation to provide bicarbonate ions, which neutralizes the hydrogen ion concentration
- Used to alkalize the urine & to titrate the dose to achieve the desired urinary pH
- Contraindicated in patients w/ alkalosis, hypernatremia, severe pulmonary edema, hypocalcemia & unknown abdominal pain

**Tiopronin**
- An active reducing agent that undergoes a thiol-disulfide exchange w/ cystine & forms a tiopronin-cystine disulfide
- It decreases the amount of soluble cystine in the urine & reduces the formation of cystine calculi
- Contraindicated in patients w/ prior history of developing agranulocytosis, aplastic anemia or thrombocytopenia

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Indications for active removal of stones:
- Choice of treatment or patient preference
- Comorbidity (e.g., hypertension, diabetes, obesity, dyslipidemia & gout)
- Infection (e.g., pyelonephritis)
- Obstruction caused by stones
- Patients who are high-risk stone formers
- Stone size of ≥6 mm after a period of watchful waiting
- Symptomatic stones (e.g., presence of pain & hematuria)

Special problems encountered in stone removal:
- Presence of caliceal diverticulum stones
- Patient has horseshoe kidneys
- Patients with UPJ obstruction

**Extracorporeal Shockwave Lithotripsy (SWL)**
- A non-invasive & non-aesthetic procedure, & the first choice of treatment for stone size <1.5 cm
- Success depends on the efficacy of the lithotriper & some factors:
  - Size, composition & location of the stones
  - Patient’s habitus
  - Performance of SWL
- Contraindications include:
  - Arterial aneurysms
  - Anatomical destruction distal to the stones
  - Bleeding diathesis
  - Infection
  - Severe skeletal malformations
  - Severe obesity
  - Uncontrolled UTIs

**Percutaneous Nephrolithotomy (PNL)**
- Standard procedure for large renal calculi
- Different rigid & flexible endoscopes are used in this procedure & it depends on the preference of the surgeon
- Contraindications include:
  - Patients on anticoagulant therapy
  - Untreated UTI
  - Tumour in the presumptive access tract area
  - Potential malignant kidney tumour
  - Pregnancy
- Complications associated w/ PNL:
  - Fever
  - Bleeding
  - Urinary leakage
  - Problems due to residual stones
  - Steinstrasse
    - Accumulation of stone fragments or stone gravel in the ureters
    - Major factor for its formation is the size of the stone
    - If asymptomatic, then conservative treatment is the initial option
    - For steinstrasse associated w/ UTI & fever, percutaneous nephrostomy is indicated
    - When large stones fragments are present, shockwave lithotripsy is indicated

**Uteroscopic Lithotripsy - Rigid & Flexible (URS)**
- A minimally invasive procedure that is used for both ureteric & renal stones as an alternative treatment to SWL
- Can be performed under a local, intravenous or general anesthesia
- URS may be used in patients who had failed previous treatment attempts, stones too large for ESWL, strictures, tumors, stones in children, those w/ bleeding disorders & obese
- Stone-free rate status w/ larger stones is achieved earlier w/ URS
**Dosage Guidelines**

### HYPERURICEMIA & GOUT PREPARATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>200-300 mg PO 12-24 hrly</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Reactions**

- Dermatological effects (exfoliative dermatitis, pruritus, maculopapular rash);
- GI effects (N/V);
- CNS effects (headache, vertigo, drowsiness);
- Hematological effects (leucopenia, thrombocytopenia, hemolytic & aplastic anemia);
- Other effects (arthralgia, fever, visual & taste disturbances)

**Special Instructions**

- Use w/ caution in patients w/ known hepatic/renal disease & those w/ poor uric acid clearance
- Contraindicated in patients w/ liver disease, bone marrow suppression, idiopathic hemochromatosis & asymptomatic hyperuricemia

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All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.

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### OTHER DRUGS ACTING ON THE GENITO-URINARY SYSTEM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Adverse Reactions</th>
<th>Special Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potassium citrate</strong></td>
<td><strong>Patients w/ mild hypocitraturia:</strong> 30 mEq PO 8 hrly</td>
<td>• GI effects (abdominal discomfort, N/V, diarrhea)</td>
<td>• Should follow a diet low in salt &amp; is advised to increase intake of fluids</td>
</tr>
<tr>
<td></td>
<td><strong>Patients w/ severe hypocitraturia:</strong> 60 mEq PO 8 hrly</td>
<td></td>
<td>• Use w/ caution in patients w/ altered potassium excretion mechanism &amp; renal insufficiency</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Contraindicated in patients w/ renal insufficiency, persistent alkaline urinary infections, obstruction of the urinary tract, hyperpotassemia, adrenal insufficiency, respiratory or metabolic alkalosis, active peptic ulcer, intestinal obstruction, patients who have submitted to anticholinergic therapy &amp; w/ slow gastric emptying</td>
</tr>
<tr>
<td><strong>Sambong</strong> (Blumea balsamifera Leaf)</td>
<td>1,000 mg PO 8 hrly</td>
<td>• GI effects (abdominal discomfort, N/V, diarrhea)</td>
<td>• Use w/ caution in patients w/ excretory urogram that shows signs of renal obstruction</td>
</tr>
<tr>
<td><strong>Tiopronin</strong></td>
<td><strong>Initial dose:</strong> 800 mg PO 8 hrly</td>
<td>• CNS effects (chills, fatigue, fever); Dermatological effects (bruising, pemphigus, pruritus, rash, skin friability/ wrinking, iritis, warts); GI effects (abdominal pain, anorexia, bloating, diarrhea, flatulence, loss of taste perception, oral ulceration, N/V); Hematological effects (anemia, bleeding, eosinophilia, leukopenia, thrombocytopenia); Hepatic effects (jaundice, abnormal liver function tests); Neuromuscular &amp; skeletal effects (arthritis, myalgia, myasthenia gravis, weakness); Renal effects (Goodpasture's syndrome, hematuria, nephrotic syndrome, proteinuria); Respiratory effects (bronchiolitis, dyspnea, hemoptyisis, laryngeal edema, pharyngitis, pulmonary infiltrates, respiratory distress); Others (elastosis perforans serpiginosa, hypersensitivity, loss of smell, lupus-like syndrome, lymphadenopathy, positive ANA test)</td>
<td>• Patient should continue drinking at least 3 liters of fluid while taking this medication</td>
</tr>
<tr>
<td></td>
<td><strong>Average dose:</strong> 1000 mg PO 24 hrly</td>
<td></td>
<td>• Contraindicated in patients w/ known agranulocytosis, aplastic anemia or thrombocytopenia that has developed from this medication</td>
</tr>
</tbody>
</table>

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