

Pathophysiology

Gout	Inflammatory condition.
What makes Gout painful?	Build up of uric acid crystals in the joints, bones, or soft tissues. Usually affects one joint at a time and is most often the metatarsal phalangeal joint (MPJ)
What in the blood can lead to Gout?	Elevated uric acid levels
Hyperuricemia for males is what level?	>7 mg/dL
Hyperuricemia for females is what level?	>6 mg/dL
Hyperuricemia does <i>not</i> always lead to...	does not always lead to gout.
At 37 degrees C, serum urate concentrations >7 mg/dL begin to limit...	solubility for monosodium urate.
Higher concentrations of serum urate will lead to more what?	monosodium urate crystals (MSU)
Gout is more prevalent societies with__.	Lifestyles of overindulgence

Pathophysiology (cont)

Uric acid is the <i>final</i> step in the degradation of_____	Purines
The two common abnormalities in enzymes that lead to <i>increased uric acid</i>	- Increased levels of PRPP (Phosphoribosyl pyrophosphate synthetase) -Deficiency of HGPRT (HYPOxanthine-guanine phosphoribosyltransferase)
Tophi is created by	Uric acid binding to sodium and creating monosodium urate (msu) crystals that get deposited in tissues/joints
Tophi is	the build up of uric acid crystals in the synovial fluid
Non-Modifiable Risk factors of Gout	Age, Sex, Race, Genetic Variants
Modifiable Risk Factors of Gout	Obesity, HTN, CKD, Diabetes, Medications altering urate balance
Medications that alter urate balance:	Diuretics, Ethanol, Salicylates (<2g/day), Nicotinic Acid, Pyrazinamide, Cyclosporin

Gout Prophylaxis

First line for Gout Prophylaxis	NSAIDs, Colchicine
Colchicine	0.6 mg PO daily or BID (QD>BID)
NSAID	Naproxen is an example (250 mg PO BID). May use a PPI if NSAID prolonged or increased GI bleeding risk.
Alternative/- First line contraindicated Prophylaxis dosing	Low dose corticosteroids (like prednisone 10 mg/day)
Duration of Prophylaxis without tophi	3-6 months
Duration of Prophylaxis with >1 tophi or radiographic evidence	6-12 months
Uricosuric	
2nd line Therapy for Gout Management	Probenecid
Rarely used monotherapy...	but can be XO1 is contraindicated or ineffective
Probenecid initial dosing	250 mg PO BID x1 week
Probenecid maintenance dosing	500 mg PO BID

Uricosuric (cont)	
Mainly for patients that...	underexcrete uric acid
MOA	Competitively inhibits the reabsorption of uric acid at the proximal convoluted tubule, thereby promoting its excretion and reducing serum uric acid levels
Works where?	RENALLY
Contraindicated	Nephrolithiasis, moderate--severe renal impairment (CKD 3)
Effect of Salicylates on Probenecid	may impact the concentrations

Recombinant Uricase	
Pegloticase	8 mg IV infusion (<i>over 120min</i>) q2weeks
MOA	Pegylated recombinant form of urate-oxidase enzyme, also known as uricase; which converts uric acid to allantoin (an inactive and water soluble metabolite of uric acid)
ethicacy:	4-6 months

Recombinant Uricase (cont)	
MONOTHERAPY	Can only be used as monotherapy
Used for	Refractory gout when failed conventional therapies.
Produced from modified strain of	E. coli (Escherichia coli)
Start prophylactic therapy	1 week PRIOR to initiation (high risk of flares)
Duration of prophylaxis while on Pegloticase	6 months
Requires...	Pre-treatment with antihistamines and corticosteroids to mitigate infusion reaction
Immunogenicity	develops antibodies against itself
Discontinue therapy:	serum urate >6 mg/dL on more than one clinic visit
Contraindicated:	G6PD-deficiency
G6PD-deficiency	Increase risk of Hemolysis and methemoglobinemia

Diagnosis, Signs, Symptoms, Classification	
Diagnosis of Gout	Symptoms are used for diagnosis
Signs and Symptoms of Gout	Intense pain, <i>Erythema</i> , warmth, Fever, Tophi, Inflammation of Joint
Where can inflammation of the joint be in Gout?	Toes, Knees, Fingers, Elbows, Ankles
Uric Acid Levels	High uric acid levels do NOT always mean Gout!
Leukocytosis in Gout	MSU crystals induce <i>inflammation</i> and can INCREASE white blood cell count
Diagnostic Testing for Gout	<i>Arthrocentesis</i> and <i>Radiography</i>
Arthrocentesis	Removal of synovial fluid from the affected joint, microscopic examination, can give a definitive diagnosis of gout.

Diagnosis, Signs, Symptoms, Classification (cont)

Radiography X-ray that can be used for more advanced gout, will be *unremarkable for first acute gout attacks, can help rule out other causes of arthritis.

Conditions that precipitate Gout Attack Most can't identify a *trigger*. Dehydration, Stress, excessive alcohol intake, excessive intake of purine-rich foods, increased physical activity, uric acid lowering agents, medications that increase uric acid levels

What are the 4 Gout Classifications Asymptomatic, Acute Gouty Arthritis, Intercritical Gout, Chronic recurrent Gout

Asymptomatic Hyperuricemia

Intercritical Gout Intervals between attacks

Diagnosis, Signs, Symptoms, Classification (cont)

Severity of Chronic Tophaceous Gouty Arthritis (CTGA) Mild, Moderate, Severe

CTGA Mild One joint, *stable* disease

CTGA Moderate 2-4 joints, *stable* disease

CTGA Severe 4+ OR Unstable, complicated, severe articular tophi

Large Joints: Knee, ankle, wrist, elbow, hip, shoulder

Medium Joints: Ankle, Wrist, Elbow

Small Joints: Interphalangeal

Xanthine Oxidase Inhibitors (XOI)

What are the Two XOI for Gout? Allopurinol, Febuxostat

Allopurinol Initial dose 100 mg PO daily

Allopurinol Maintenance dosing 100-800 mg daily (average is 300 mg/day)

Allopurinol Renal adjustment 50 mg/day for CKD stage 4+

Febuxostat initial dose 40 mg PO daily

Febuxostat Maintenance dosing 40-80 mg daily

Xanthine Oxidase Inhibitors (XOI) (cont)

First line agent for *Chronic management of gout*

Contra-indications CVD history or recent CV event

Genotype contra-indication HLC-B*5801 haplotype

Genotype is conditionally recommended for what race? Southeast Asian descent, African Americans

XOI MOA Inhibits xanthine oxidase, an enzyme responsible for the conversion of hypoxanthine to xanthine to development of uric acid. Acts on purine metabolism, thereby reducing uric acid production without disrupting biosynthesis of vital purines

Black Box Warning **Febuxostat**

Gout Management

Non-Pharmacological Dietary Modifications, Promote Weight Loss, Adjuvant ice therapy, *Avoid heat*

Gout Management (cont)

Pharmacotherapy of Acute Gout Terminate acute attacks, Prevent Recurrent Attacks of gouty arthritis, Prevent complications associated with deposition of urate crystals in tissues, Prevent/reverse comorbidities associated with gout (Obesity, HTN)

Dietary Modifications for Gout Limit: Purine (meats, seafood), alcohol (beer, fortified wines/-liquours), high-fructose corn syrup, maintain adequate hydration

Acute Gout Treatment NSAIDS, Corticosteroids, Colchicine

NSAIDS can be initiated when for a Acute attack?

Celecoxib should be avoided if significant history of what?

NSAIDS with Acute Gout Attack FDA indication: Indomethacin, Naproxen, Sulindac

Gout Management (cont)

NSAIDs are contraindicated for *Decompensated* heart failure.

NSAIDs MOA Inhibit *prostaglandins* for anti-inflammatory, analgesic and antipyretic effects via inhibition of cyclooxygenase 1 and 2 enzymes

Corticosteroids can be initiated when for an acute gout attack?

Corticosteroids for Acute Gout attack: Prednisone, Methylprednisolone, Triamcinolone, ACTH

ACR guidelines recommend this as an option for acute gout flare:

Corticosteroids' anti-inflammatory properties work through: melanocortin type-3 receptor

Gout Management (cont)

Corticosteroids are contraindicated when? Active systemic infections (can worsen them), IA injections if septic arthritis, long term use decreases amount of physiological steroids so there can be rebound which is why we taper

Adverse event of corticosteroid use: HPA axis suppression

When can *Colchicine* be initiated for Acute Gout attack? 12-24 hours of symptom onset. if >36 hours, consider alternative therapies

Colchicine for acute gout attack initial dosing: Day 1: 1.2 mg PO *once*, then 0.6 mg PO 1-6 hour later

Colchicine for acute gout attack *maintenance* dosing: (Day 2) 12 hours after Day one, 0.6 mg PO daily or BID

Gout Management (cont)

Colchicine MOA Decreases inflammation during gout flare by decreasing activation, degranulation and migration of neutrophils through inhibiting betatubulin polymerization into microtubules

Colchicine is Contra-indicated when:

If gout is seen on an x-ray, it's immediately classified as Severe

Initiate Monotherapy Mild/Moderate Pain intensity

Initiate Combination Therapy Severe, X-ray

Combination therapy includes Colchicine + NSAID, Colchicine + Oral Corticosteroid, NSAID + IA injection, Colchicine + IA, Oral Corticosteroid + IA

Goal Serum Urate level to maintain <6 mg/dL

Gout Management (cont)

When using a ULT, what should also be used? Anti-inflammatory to overlap

High level of evidence/- Strong recommendation for Initiation of ULT 1 or more subcutaneous tophi, evidence of radiographic damage from gout, >2 gout flares per year

Moderate Evidence, Conditional recommendation ULT is recommended for patients who have previously experienced >1 flare but have infrequent flares (<2 per year)

ULT options for Gout Xanthine Oxidase Inhibitors (XOI), Recombinant Uricase, Probenecid

Fenofibrate Increase clearance of hypoxanthine and xanthine. Consider if concomitant Hypertriglyceridemia

Losartan Inhibits tubular reabsorption of uric acid and increases excretion. Alkalinizes urine to reduce risk of calculi

Gout Management (cont)

Asymptomatic Hyperuricemia treatment **No pharmacotherapy required**, Target lifestyle modifications