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	>6 mg/dL
Hyperuricemia does *not* 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 *final* step in the degradation of_____	**Purines**
The two common abnormalitites in enzymes that lead to *increased uric acid*	- Increased levels of PRPP (Phsphoribosyl 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 Propphylaxis **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 XOI is contraindicated or ineffective
Probenecid initial dosing	250 mg PO BID x1 week
Probenecid maintenance dosing	500 mg PO BID

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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 (*over 120min*) 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 Pegloticas	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 visi
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, *Erythema*, 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 *inflammation* and can *INCREASE* white blood cell count
Diagnostic Testing for Gout	*Arthrocentesis* and *Radiography*
Arthrocentsis	Removal of synovial fluid from the affected joint, microscopic examination, can give a definitive diagnosis of gout.

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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*
Contraindications	CVD history or recent CV event
Genotype contraindication	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*

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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?	24-48 hours
Celecoxib should be avoided if significant history of what?	CAD
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 cycloxygenase 1 and 2 enzymes
Corticosteroids can be initiated when for an acute gout attack?	24-48 hours
Corticosteroids for Acute Gout attack:	Prednisone, Methylprednisolone, Triamcinolone, ACTH
ACR guidelines recommend this as an option for acute gout flare:	Corticosteroids
Corticotropin's 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 amoutn 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 *mainenance* dosing: (Day 2)	12 hours after Day one, 0.6 mg PO daily or BID

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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 Contraindicated when:	Blood dyscrasias, severe renal disease (CrCl <10 ml/min)
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

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