GOUT

BOTTOM LINE

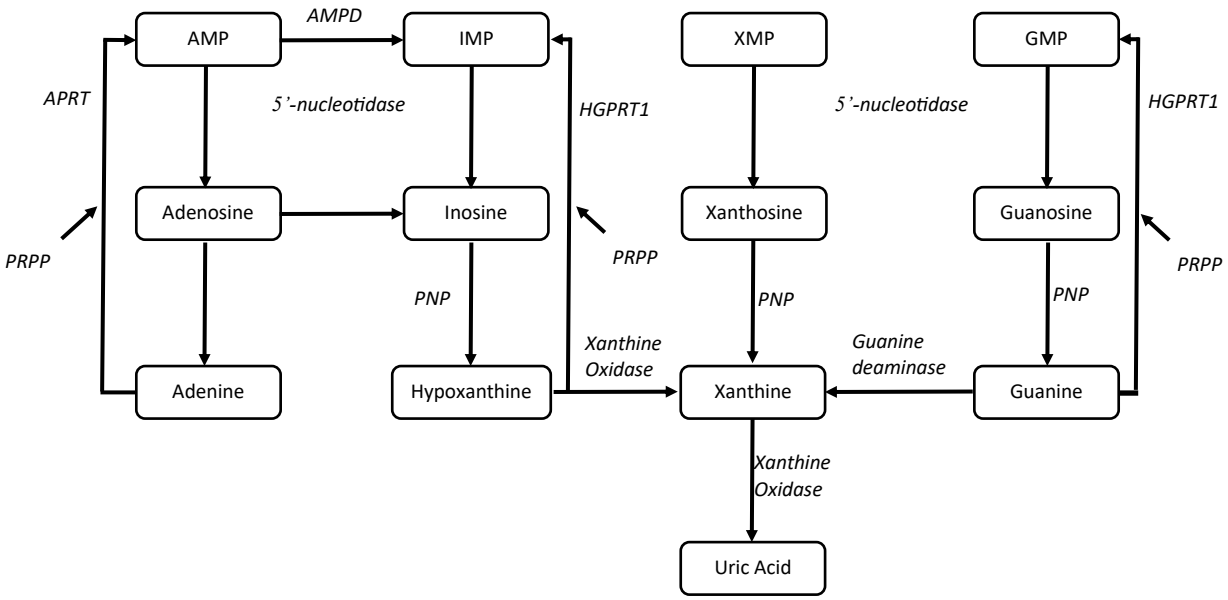
Gout is a crystalline arthritis caused by accumulation of uric acid. Precipitation of uric acid in the joint causes characteristic acute red/warm/swollen mono/oligoarticular lower-extremity predominant erosive inflammatory arthritis in patients with hyperuricemia and often male sex. Acutely treated with NSAIDs, colchicine, or corticosteroids. Urate-lowering therapies (allopurinol is first line) used if indicated (most commonly: >1 flare/year).

EPIDEMIOLOGY

- Prevalence 2.4%; most common inflammatory arthritis
- Annual Incidence: 1.9/1000 people;
- Prevalence and incidence increases with age; highest in 85-89 year olds (Canada)

Age at onset		• Men 40-50 years; women 60-70 years. Pre-menopausal women unlikely to get gout • 90% of cases due to under-excreting uric acid, causing 10 years of hyperuricemia until first gout attack • Women have higher urinary fractional excretion of urate, mediated by estrogen, and thus typically only develop hyperuricemia post-menopause • 10% of cases due to over-production of uric acid (consider in young patients, pre-menopausal women)
Ethnicity		• More prevalent in Oceania (includes Australasia, Melanesia, Micronesia, and Polynesia)
Hyper-uricemia	Acquired	• Urate Underexcretion (90%): Chronic renal failure, impaired urate secretion (keto/lactic/respiratory acidosis), hyperparathyroidism, hypothyroidism, diuretic use. • Urate Overproduction (10%): Urate consumption (beer, high-fructose drinks), Urate synthesis via hepatic degradation of ATP: (alcohol increases urate synthesis, fructose is converted to ATP), urate synthesis from increased cell turnover (myelo/lymphoproliferative disease).
	Inherited	• PRPP overactivity (phosphoribosylpyrophosphate synthetase) • HGPRT deficiency (hypoxanthine–guanine phosphoribosyltransferase): Kelley-Seegmiller syndrome (partial HGPRT deficiency), Lesch-Nyhan syndrome (complete HGPRT deficiency) • G6PD deficiency: von Gierke's disease (glucose-6-phosphatase deficiency) • Fructose-1-phosphadate aldolase deficiency

URIC ACID PATHWAY



- Main source of uric acid is degradation of purines from cell turnover, dietary intake, and de novo synthesis.
- Purines like adenosine monophosphate (AMP), inosine monophosphate (IMP), Xanthine monophosphate (XMP), and guanosine monophosphate (GMP) are metabolized to via common substrate Xanthine to Uric Acid.
- Purine salvage via hypoxanthine guanine phosphoribosyl transferase 1 (HGPRT1) returns hypoxanthine and guanine to IMP and GMP, respectively. HGPRT1 deficiency results in increased Hypoxanthine and urate production as well as decreased feedback inhibition on purine synthesis.
- AMPD, AMP deaminase; APRT, adenine phosphoribosyl transferase; PNP, purine nucleotide phosphorylase; PRPP, phosphoribosyl pyrophosphate.

CLINICAL MANIFESTATIONS		
Articular	Asymptomatic	• 10-20 years of asymptomatic hyperuricemia, slow accumulation of total body urate until precipitation of urate into joint causing the first flare

	Flares	• Triggers: anything that can alter extracellular urate or proinflammatory state
		  • Changes in urate serum urate: new allopurinol, new thiazide/loop diuretic, high-purine foods
		  • Surgery, trauma, illness
		• Initial flare most commonly lower extremity and often at night
		  • MTP1 (podagra) in >50% of initial flares; knee also common for first flare; can also affect periarticular sites like Achilles enthesitis, olecranon/prepatellar bursitis, and dactylitis.
		  • Lower extremity joints are cooler and body temperature decreases normally at night, therefore making crystal precipitation more likely
		• Stereotypical presentation: acute, red, warm, monoarticular (85-90%) joint swelling that resolves within a few days to several weeks.
		• Can be followed by desquamating skin rash over joint.

	Inter-critical	• Asymptomatic hyperuricemia between flares; most will experience another flare within 2 years • Can develop tophi and erosions during inter-critical period.
	Chronic	• Inter-critical periods become shorter and flares become more frequent and polyarticular; can develop chronic polyarticular erosive inflammatory arthritis
	Atypical presentations	• Tophi without inflammatory arthritis, oligo/polyarticular flares, upper extremity flares occur after very high sustained hyperuricemia, rare but reported in large joints other than knee or in spine

Non-articular	• Metabolic syndrome association (hypertension, type 2 diabetes, hyperlipidemia, obesity)
	• Tophi:
	  • Deposits of MSU crystals and chronic granulomatous inflammatory tissue
	  • Often MTP1, Achilles tendon, other joint/tendon of foot, prepatellar bursa, olecranon bursa, helix of ear
	  • Can be mistaken for purulent infection if ulcerated—can get superinfected too
	• Nephrolithiasis
	• Chronic urate nephropathy (deposit of urate in the medullary interstitium of kidney, leading to local inflammation and interstitial fibrosis)
	• Associated diseases causing hyperuricemia
	  • Psoriasis (increased cell turn-over means more purines to metabolise); differentiating psoriatic arthritis and gout can sometimes be a challenge. Patients can indeed have both.
	  • Hematologic diseases (increased cell turn-over): myeloproliferative, lymphoproliferative, hemolytic anemias, polycythemia vera, sickle cell
	  • Endocrinological: hypothyroidism, hyperparathyroidism, diabetic ketoacidosis, diabetes insipidus, Barter's syndrome
	  • Renal: autosomal dominant medullary cystic kidney disease, familial hyperuricemic nephropathy, lead nephropathy	

INVESTIGATIONS		
Blood-work	CBC	Neutrophilia or thrombocytosis during acute flare
	ALT	Normal, can be elevated if co-morbid fatty liver disease
	Creatinine	May be elevated if comorbid chronic renal failure
	CRP, ESR	Elevated during acute flare
	Uric acid	• During flare, urate measurement can pseudo-normalize in up to ~40% of patients • High uric acid can be supportive of clinical diagnosis of gout
Fluids	• Synovial fluid is inflammatory (usually 10e9 to 100e9/L total neutrophil count) during acute flare • Monosodium urate (MSU) crystals may be visualized if aspirated during flare • "Paraye***ll***ow": yellow needle shaped crystals when oriented para***ll***el to a polarized light source under microscope • "Gold standard" for diagnosis is visualization of MSU crystals; however, this is not always possible (ex: difficult to aspirate from MTP1) or completely sensitive. Lack of MSU crystals does not exclude gout.	

Imaging	X-ray	• Soft tissue swelling • Tophi • "Punched-out" "rate bite" erosions with sclerotic margins and overhanging edges
	Ultrasound	• Urate deposition: superficial hyperechoic band on articular cartilage surface ("double contour sign")
	DECT	• Dual-energy computed tomography: can identify articular/periarticular urate deposits and can distinguish from calcium deposition. Not routinely done.

DIAGNOSIS

Gout should be suspected in a patient (males or post-menopausal females) with risk factors (including hyper-uricemia, metabolic syndrome, renal failure) presenting with a history of self-limited acute/red/warm mono/oligoarticular lower-extremity inflammatory arthritis — usually first presenting at MTP1. Serum hyperuricemia is supportive, but can be falsely normal if measured during acute flare. Definitive diagnosis can be made when monosodium urate crystals are visualized in synovial fluid aspirated during a flare, but aspiration is often not possible and lack of visualized crystals does not exclude gout. Screen for co-morbidities including alcohol abuse, renal insufficiency, and metabolic syndrome.

Validated diagnostic criteria for patients presenting with monoarthritis in primary care settings with unavailable synovial fluid

Criteria	**Point**	**Interpretation**
Male	2.0	• Score ≤4: Low probability gout • Score 4-8: Intermediate probability of gout • Score ≥8: High probability gout
Previous patient-reported inflammatory arthritis flares	2.0	
Onset within one day	0.5	
Joint redness	1.0	
MTP involvement	2.5	
Hypertension or last least one cardiovascular disease	1.5	
Serum urate >360 mmol/mL	3.5	

DIFFERENTIAL DIAGNOSIS

Infection	• Cellulitis • Septic bursitis, arthritis, osteomyelitis	• *Gout and infection can co-exist in the same joint*
Crystalline	• Calcium pyrophosphate deposition disease (CPPD) • Basic calcium phosphate periarthritis	• *Joint involvement patterns can help differentiate* • *Chondrocalcinosis may support CPPD*
Spondylo-arthritis	• Psoriatic arthritis	• *Does not onset so acutely, flares may last >weeks, and may still have symptoms of inflammatory arthritis between flares*
Rheumatoid	• RA vs. advanced polyarticular gout	• *Advanced polyarticular gout can involve hand joints and tophi may be confused with RA nodules; however patients likely have long history of preceding gout and are RF/CCP-*

CLASSIFICATION CRITERIA: 2015 ACR/EULAR CRITERIA.

Gout is a clinical diagnosis. Classification criteria are not meant as diagnostic criteria to diagnose disease in a single specific patient. Classification criteria are a standardized way of recruiting a well-defined homogenous population of patients in research studies in order to ensure comparability across studies of a heterogenous disease. Gout Classification Criteria described out of interest only.

Step 1	**Entry criterion**: only apply criteria below if meeting this entry criterion)		At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2	**Sufficient criterion**: if met, can classify as gout without applying criteria below		Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	
Step 3	**Criteria: used if sufficient criterion not met**		**Categories**	**Score**
	Clinical	Joint pattern during flare	Ankle or midfoot (without MTP1)	1
			MTP1	2
		Characteristics of symptomatic episode • Erythema over affected joint • Cannot bear touch of pressure to joint • Great difficulty to walk or use joint	One characteristic	1
			Two characteristics	2
			Three characteristics	3
		Time course of flare • Time to maximal pain <24h • Resolution of symptoms in ≤14 days • Complete resolution between flares	One typical flare	1
			Recurrent typical flares	2
		Tophus Draining/chalk-like subcutaneous nodule typically over joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Present	4
	Laboratory	Serum Urate Ideally measured off urate-lowering meds and >4 weeks from the start of a flare (i.e., during intercritical period);	<240 umol/L	-4
			360-480 umol/L	2
			480-600 umol/L	3
			>600 umol/L	4
		Synovial fluid from symptomatic joint	No MSU crystals	-2
	Imaging	Imaging evidence of urate deposition in symptomatic joint/bursa: ultrasound evidence of double-contour sign or DECT demonstrating urate deposition	Present (either modality)	4
		Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion	Present	4

- Gout Classification Criteria described out of interest only; not routinely used in clinic
- A threshold score of ≥8 classifies an individual as having gout; 92% Sensitive, 89% Specific

TREATMENT		
NON-PHARMACOLOGIC		
• Low purine diet; avoid: meat, seafood, alcohol, sugary drinks • Exercise, weight loss		
PHARMACOLOGIC		
• Consider removing/substituting offending medications (diuretics) if feasible and treating underlying disorders/comorbidities • Losartan metabolites can increase renal urate excretion and could be used supplementally if an ARB required for hypertension		
Acute flare	NSAIDs	Any NSAID, regular dosing, until flare resolves.
	Colchicine	1.2mg at first sign of flare, followed by 0.6mg 1-hour later, and then 0.6mg daily until flare resolves
	Steroids	Intra-articular steroids: Systemic steroids (oral, intramuscular)
	IL-1	IL-1 inhibition (ex: anakinra, canakinumab) rarely used for gout flare if unable to above therapies
	• CKD: consider avoiding NSAIDs if comorbid CKD, colchicine more likely to give diarrhea in CKD • Bleeding risk: older patients or patients on anticoagulants may require PPI to decrease ulcer risk on NSAID/steroid	

Chronic urate lowering	Indications:
	• Tophi
	• Radiographic erosions
	• >1 gout flare/year
	• Consider treating if:
	  • >1 flare in lifetime but <2/year
	  • First gout flare but CKD Stage ≥3, urate >535umol/L, or Urolithiasis
	Target: 356 umol/L	

	Allopurinol	• Inhibits Xanthine Oxidase
		• First-line agent; **it is okay to start allopurinol during a flare**
		• Allopurinol 100mg/day
		  • Uptitrate 100mg each week until 300mg/day or at target urate level
		  • Start at 50mg/day if treating patient with CKD Stage ≥3
		  • Flare risk higher first 3-6 months after starting allopurinol; start concomitant prophylactic daily colchicine, NSAIDs, or steroids for 3-6 months after starting allopurinol
		  • If serum urate not falling within 4 weeks of allopurinol initiation, review medication compliance

		Allopurinol Hypersensitivity Syndrome (AHS) • Presents as rash (TENS, Stevens-Johnson, erythema multiforme, generalized maculopapular exanthem, generalized exfoliative dermatitis), fever, eosinophilia, acute hepatocellular injury, worsening renal function • Monitor CBC, ALT, Creatinine after starting allopurinol, especially in patients of southeast Asian or African descent • HLA-B*5801 allele associated with AHS; consider testing in southeast Asian or African patients
	Febuxostat	• Inhibits Xanthine Oxidase • Switch allopurinol for febuxostat if allergy/hypersensitivity to allopurinol • Febuxostat 40mg/day, uptitrate to 80mg/day in 2-3 weeks if below target urate • Avoid Febuxostat in patients with high cardiovascular risk
	Avoid allopurinol and febuxostat in patients on azathioprine or 6-mercaptopurine	
	Probenecid	• Increases urinary excretion of urate • Contraindicated in uric acid overproducers or have history of nephrolithiasis • Avoid probenecid for those with CKD stage >3. • 250mg BID, uptitrated to usual dose of 500-1000mg BID/TID to target urate • Rarely used; patients often are fine up increasing doses of allopurinol.
	Other	• Pegloticase: intravenous recombinant porcine-like uricase, metabolizes uric acid to allantoin. Rarely used in patients failing allopurinol/febuxostat/probenecid (consider medication compliance)

FURTHER READING

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