Gout and its Cousins: Crystal Arthritis 2024

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Disclosures

- *Non-Declaration Statement: I have no relevant relationships with ineligible companies to disclose within the past 24 months. (Note: Ineligible companies are defined as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.)*

Objectives

At the end of this session, participants will be able to:

- recognize the risk factors and triggers for gout and other forms of crystal arthritis.
- distinguish gout from other forms of inflammatory arthritis.
- preform the appropriate work-up for gout and other forms of crystal arthritis.
- recommend appropriate treatment regimens for crystal arthritides.

Thomas Sydenham

"The patient goes to bed and sleeps quietly until about two in the morning when he is awakened by a pain which usually seizes the great toe, but sometimes the heel, the calf of the leg or the ankle. The pain resembles that of a dislocated bone ... and this is immediately succeeded by a chillness, shivering and a slight fever ... the pain ..., which is mild in the beginning ..., grows gradually more violent every hour ... so exquisitely painful as not to endure the weight of the clothes nor the shaking of the room from a person walking briskly therein."

Gout in Art

https://commons.wikimedia.org/wiki/File:The_gouty_George_IV_using_tongs_to_pass_his_discarded_wig_to_Wellcome_V0011363.jpg

https://upload.wikimedia.org/wikipedia/commons/9/9d/A_man_with_gout_seated_at_a_table_drinking_with_a_parson_and_Wellcome_V0010857.jpg

https://commons.wikimedia.org/wiki/File:The_gouty_George_IV_relaxing_before_nine_portraits_chronicli_Wellcome_V0011336.jpg

Uricase

https://en.wikipedia.org/wiki/File:Fish_-_Puntius_sarana_from_Kerala_(India).png

https://commons.wikimedia.org/wiki/File:Triceratops-vs-T-Rex001.jpg

http://sargentanimalsystems.wikispaces.com/Reproduction

Sue (*Tyrannosaurus rex*)

Rothschild BM, et al.
Tyrannosaurs
suffered from gout.
Nature **volume387,**
page357.

Gout sufferer…

No uricase

Gout

- Hyperuricemia (SUA >7.0 mg/dL in males, >6.0 mg/dL in females) leads to tissue deposition of monosodium urate crystals
  - Gouty arthropathy
  - Tophi (articular, osseous, cartilaginous or soft tissue)
  - Gouty nephropathy
  - Uric acid nephrolithiasis

Gout

- Peak age of onset
  - Male: 40 – 50 years old
    - If under age 25, consider
      - Inherited defect of purine degradation
      - EtOH
      - Renal Insufficiency (familial juvenile hyperuricemic nephropathy, medullary cystic kidney disease)
  - Female: after 60 years old (post menopausal)
    - Osteoarthritis
    - Hypertension (diuretics)
    - Mild chronic renal insufficiency
    - Tophi at sites with arthritic changes (Heberdeen nodes, finger pads)

Gout

- Prevalence increasing due to
  - Diet
  - Obesity
  - Metabolic syndrome
  - Medications (low dose aspirin, diuretics)
- Male:female ratio- 2:1 to 7:1
- Increases with age and serum uric acid
  - >2% in males age over 30 and females over 50
  - Over age 80: men-9%, women-6%
  - 30-50% increase if serum uric acid >10 mg/dL

2018

Gout

- Overproduction of urate
- Underexcretion of urate
- Combination of overproducer/underexcreter

- 24 Hour urine collection
  - ❖Uric acid
  - ❖Creatinine excretion

  - ❖Urate >800mg=overproduction
  - ❖Urate <800mg=underexcreter

2018

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Comorbidity checklist for gout patients

- Obesity, dietary factors
- Excessive EtOH intake
- Metabolic syndrome
- Type II diabetes
- Hypertension
- Hyperlipidemia
- Serum urate elevating drugs
- History of urolithiasis
- Chronic kidney disease
- Lead toxicity
- Potential genetic or acquired causes of uric acid overproduction
  - Inborn error of uric acid metabolism
  - Psoriasis
  - Myeloproliferative or lymphoproliferative disease

Drugs contributing to decreased urate excretion

- **C**yclosporine
- **A**lcohol
- **N**icotinic Acid
- **T**hiazides

CAN'T LEAP

- **L**asix
- **E**thambutol
- **A**spirin
- **P**yrazinamide

Renal disease associated with hyperuricemia

- Urate nephropathy
  - MSU crystals in renal interstitial tissue
  - May be associated with intermittent proteinuria and rarely renal dysfunction
- Uric acid nephropathy
  - Uric acid crystals in collecting ducts and ureters
  - Can result in acute renal failure
  - Most common after chemotherapy for lymphoma, leukemia, medulloblastoma
- Uric acid nephrolithiasis
  - 10-25% of 1° gout patients
  - Uric acid stones are radiolucent
  - Calcium stones are more prevalent in gout patients (hyperuricosuria)
  - 10-40% of gout patients have renal colic episode before 1st gout flare

When gout goes to the heart: does gout equal a cardiovascular disease risk factor?

Jasvinder A Singh[1,2,3]

"…considerable data show an increased risk of cardiac disease in patients with gout, above and beyond that contributed by the traditional risk factors for heart disease. It is not known whether gout is an equivalent risk factor for cardiovascular disease to conditions such as diabetes or not."

Singh JA. Ann Rheum Dis April 2015 Vol 74 No 4

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SPECIAL ARTICLE

2015 Gout Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

Tuhina Neogi,[1] Tim L. Th. A. Jansen,[2] Nicola Dalbeth,[3] Jaap Fransen,[4] H. Ralph Schumacher,[5] Dianne Berendsen,[4] Melanie Brown,[6] Hyon Choi,[1] N. Lawrence Edwards,[7] Hein J. E. M. Janssens,[4] Frédéric Lioté,[8] Raymond P. Naden,[9] George Nuki,[10] Alexis Ogdie,[5] Fernando Perez-Ruiz,[11] Kenneth Saag,[12] Jasvinder A. Singh,[13] John S. Sundy,[14] Anne-Kathrin Tausche,[15] Janitzia Vaquez-Mellado,[16] Steven A. Yarows,[17] and William J. Taylor[6]

AMERICAN COLLEGE OF RHEUMATOLOGY
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Criteria

2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative

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2015 ACR-EULAR Gout Classification Criteria (1)

Criteria (to be used if Sufficient Criterion not met): *Score ≥8 required for classification as gout*		Categories	Score
CLINICAL	**Pattern of joint/bursa involvement during symptomatic* episode(s) ever**	Joint(s) or bursa(e) other than ankle, midfoot or 1st MTP (or their involvement only as part of a polyarticular presentation)	0
		Ankle OR midfoot (as part of monoarticular or oligoarticular episode without MTP1 involvement)	1
		MTP1 (as part of monoarticular or oligoarticular episode)	2
	Characteristics of symptomatic episode(s) ever: i) Erythema overlying affected joint (patient-reported or physician-observed) ii) can't bear touch or pressure to affected joint **iii)** great difficulty with walking or inability to use affected joint	No characteristics	0
		One characteristic	1
		Two characteristics	2
		Three characteristics	3
	Time-course of episode(s) ever: Presence (ever) of ≥2, irrespective of anti-inflammatory treatment: i) Time to maximal pain <24 hours ii) Resolution of symptoms in ≤14 days **iii)** Complete resolution (to baseline level) between symptomatic episodes	No typical episodes	0
		One typical episode	1
		Recurrent typical episodes	2
	Clinical evidence of tophus: Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles).	Absent	0
		Present	4

2015 ACR-EULAR Gout Classification Criteria (2)

LAB	**Serum urate:** Measured by uricase method. Ideally should be scored at a time when the patient was not taking urate-lowering treatment and patient was beyond 4 weeks of the start of an episode (i.e., during intercritical period); ***if*** practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4mg/dL [<0.24mM] †	**-4**
		4-<6mg/dL [0.24-<0.36mM]	0
		6-<8mg/dL [0.36-<0.48mM]	2
		8-<10mg/dL [0.48-<0.60mM]	3
		≥10mg/dL [≥0.60mM]	4
	Synovial fluid analysis of a symptomatic (ever) joint or bursa:** Should be assessed by a trained observer.	Not done	0
		MSU negative	**-2**
IMAGING‡	**Imaging evidence of urate deposition in symptomatic (ever) joint or bursa:** Ultrasound evidence of double-contour sign¶ ***or*** DECT demonstrating urate deposition§.	Absent OR Not done	0
		Present (either modality)	4
	Imaging evidence of gout-related joint damage: Conventional radiography of the hands and/or feet demonstrate at least one erosion.‡‡	Absent OR Not done	0
		Present	4
		TOTAL SCORE	

Maximum score is 23. **Threshold to classify as gout is ≥8.**

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ABBREVIATED VERSION

Criteria		Categories	Score
CLINICAL	Pattern of joint/bursa involvement	Ankle OR midfoot (mono-/oligo-)	1
		MTP1 (mono-/oligo-)	2
	Characteristics of episode(s) ever	One characteristic	1
		Two characteristics	2
		Three characteristics	3
	Time-course of episode(s) ever	One typical episode	1
		Recurrent typical episodes	2
	Clinical evidence of tophus	Present	4
LAB	Serum Urate	<4mg/dL [<0.24mM]	-4
		6-<8mg/dL [0.36-<0.48mM]	2
		8-<10mg/dL [0.48-<0.60mM]	3
		≥10mg/dL [≥0.60mM]	4
	Synovial Fluid examination for MSU crystals	negative	-2
IMAGE	Imaging evidence of urate deposition	Present	4
	Imaging evidence of gout-related joint damage	Present	4
		Maximum Possible Total Score	**23**

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Olecranon bursitis

- Trauma
- Rheumatoid arthritis
- Septic arthritis
- Gout

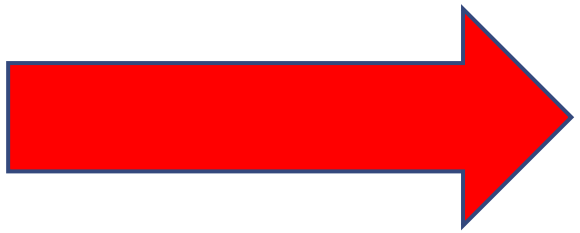
Pseudogout

- Calcium pyrophosphate crystal deposition
  - Pseudogout-flare
  - Chondrocalcinosis-radiographic finding
  - Pyrophosphate arthropathy-joint disease or radiographic abnormality
- Affects 4-7% of adult populations in Europe and US
- Average age at diagnosis-72 years old
  - 65-74 years: 15%
  - 75-84 years: 36%
  - >84 years: approximately 50%

Pseudogout

- Radiographic findings
  - Chondrocalcinosis
  - Hook osteophytes, particularly 2nd and 3rd MCP (R/O hemochromatosis)
  - Osteoarthritic changes in joints not expected to have these changes
- Treatment
  - Intraarticular glucocorticoid injection (after septic joint R/O)
  - NSAIDs
  - Colchicine
  - Oral glucocorticoid
  - Analgesic
  - IL-1 inhibitors (investigational)

Chondocalcinosis



Chondocalcinosis

Chondocalcinosis

Calcium oxalate crystals

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Four stages of gouty arthritis

- Asymptomatic hyperuricemia
  - 15% develop gout
  - May have 20 years before first gout flare
- Acute gouty arthritis
  - First attack: 85-90% monoarticular, 15% polyarticular
- Intercritical gout
  - Asymptomatic interval between gout attacks
  - 60% will have 2nd attack within 1-2 years
  - 5-10% will have no additional attack
- Chronic tophaceous gout

Joints affect by gout

- Lower extremity>Upper extremity
- 1st MTP (>50% of initial attacks, 90% of patients over time)-podagra
  - Instep
    - Ankle
      - Heel
        - Knee
          - Wrist
            - Fingers
              - Elbow

Tophus

- May occur on average 10 years after 1st attack if gout untreated
- White chalky material consisting of dense concentrations of MSU crystals
- May occur at any site
  - Synovium
  - Subchondral bone
  - Digits of hands and feet
  - Olecranon bursa
  - Extensor forearm
  - Achilles tendon
  - Antihelix of ear

CPPD considerations

- Hemochromatosis
- Hyperparathyroidism
- Hypomagnesemia
- Hypophosphatasia
- Familial hypcalciuric hypercalcemia

Lab work-up

- Calcium
- Phosphorus
- Magnesium
- Alkaline phosphatase
- Ferritin, iron, transferrin

Monosodium Urate crystals

Strongly negatively birefringent

Perpendicular=blue

Parallel=bright yellow

Calcium Pyrophosphate Dihydrate crystals

Weakly positive birefringence

Perpendicular=yellow

Parallel=blue

Radiographic features of gout

- Acute: Soft tissue swelling around affected joint
- Chronic: tophi-irregular soft tissue densities, occasionally calcified
- Bony erosions-"punched out" w/ sclerotic margins, overhanging edges ("rat bite erosions")
- Joint space typically maintained until late disease
- No juxtaarticular osteopenia

Radiographic changes of gout

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Strategy for gout patients

- Establish diagnosis of gout
- Baseline recommendations for patient with diagnosis of gout
- Indications for Pharmacologic urate lowering therapy (ULT)
- Treat to target
- Long-term management of Gout

Baseline recommendations for patient with diagnosis of gout

- Patient education (diet, lifestyle)
- Consider 2° causes of hyperuricemia
- Consider elimination of non-essential prescription medications that induce hyperuricemia
- Clinically evaluate gout burden
  - Palpable tophi
  - Frequency of acute and chronic symptoms and signs
  - Severity of acute and chronic symptoms and signs

General health, diet, and lifestyle measures for gout patients

- Weight loss for obese patients
- Healthy overall diet
- Exercise
- Smoking cessation
- Stay well hydrated

General health, diet, and lifestyle measures for gout patients

Avoid	Limit	Encourage
Organ meats high in purine content (sweetbreads, liver, kidney)	Serving sizes of beef, lamb, pork, seafood with high purine content (sardines, shellfish)	Low-fat or non-fat dairy products
High Fructose corn syrup-sweetened sodas, other beverages or foods	Servings of naturally sweet fruit juices, table sugar, sweetened beverages and desserts, table salt including sauces and gravies	Vegetables
EtOH overuse (male-≤2 servings/day, female-≤1 serving/day) Any EtOH during frequent gout attacks or advanced, poorly controlled gout	EtOH (beer, wine, all spirits) in all gout patients	

To treat or not to treat… asymptomatic hyperuricemia

- No prior gouty arthritis
- No tophaceous deposits
- No nephrolithiasis

- Acute overproduction
- Uric acid excretion >1100 mg/d

- Nonpharmacologic recommendations encouraged
  - Weight loss
  - Diet modifications
  - Decrease EtOH

Treatment of acute gout

- Nonsteroidal anti-inflammatory drugs
- Oral colchicine
  - 1.2 mg, then 0.6 mg 1 hour later, then 0.6 mg q day or bid
- Corticosteroid
  - Oral, IV, intramuscular or intraarticular
- Ice
- Others
  - Adrenocorticotropic hormone, IL-1 inhibitors, Chinese herbs (simiao pill, danggui-nian-tong-tang (DGNTT)

Indications for Pharmacologic urate lowering therapy (ULT)

- Treat those with established diagnosis of gout and …
  - Tophus or tophi (clinical exam or imaging)
  - Frequent, acute attacks (≥2/year)
  - CKD stage 2 or worse
  - Past urolithiasis

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When should urate lowering therapy be initiated?

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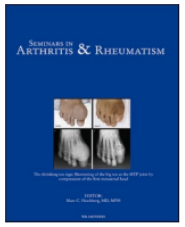

Participants with renal impairment were excluded from most studies. There were no differences in patient-rated pain scores at baseline, days 3–4, days 7–8, day 10 or days 14–15 ($p \geq 0.42$). Additionally, there was no significant difference in time to resolution of gout flare (standardised mean difference 0.77 days; 95 % CI -0.26 to 1.79; $p = 0.14$) or the risk of recurrent gout flare in the subsequent 28 to 30 days (RR 1.06; 95 % CI 0.59 to 1.92; $p = 0.84$). Adverse events were similar between groups. The included studies did not report time to achieve target serum urate, long-term adherence to ULT, or patient satisfaction with treatment.

Conclusion: There appears to be no evidence for harm or for benefit to initiating ULT during a gout flare. These findings have limited applicability to patients with tophaceous gout, or those with renal impairment.

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Treat to target

The magic number is…

6 or 5

Tophaceous gout

Tophaceous gout

Treat to target

allopurinol or febuxostat

probenecid, fenofibrate or losartan

Single agent XOI

Uricosuric

Pegloticase

Xanthine Oxidase Inhibitor

Allopurinol

- Starting dose not greater than 100 mg/day (50 mg/day in CKD ≥ stage 4)
- Titrate q 2-5 weeks until target serum urate level
- Maximum allopurinol dose-800 mg/day
- CrCl 10-20 mL/min-200 mg/day

  CrCl 3-10 mL/min-<100 mg/day

  CrCl <3mL/min-dosing interval may need to be extended, <100 mg/day
- Hepatic function-no dosing adjustments per manufacture
- HLA-B*5801 genetic testing for populations at risk of allopurinol hypersensitivity reaction
  - Koreans with CKD ≥stage 3
  - Han Chinese or Thai

Xanthine Oxidase Inhibitor

Febuxostat

- Starting dose-40 mg/day
- Titrate to 80 mg/day if target serum urate acid level not met
- CrCl <30mL/min-40 mg/day
- Child-Pugh class C-use caution
- 11/2017 FDA warning

Uricosurics

- Probenecid only potent uricosuric in US
  - Probenecid contraindicated in uric acid overproducers, history of nephrolithiasis, GFR <50
  - Probenecid starting dose: 250 mg bid
  - Probenecid usual maintenance dose: ≤2 g/day, in divided doses
- Other agents: fenofibrates, losartan
- Measure serum uric acid prior to starting uric sic

Pegloticase

- Uricase (urate oxidase): converts urate to allantoin
  - Recombinant uricase with covalent polyethylene glycol to prolong enzyme activity and reduce immunogenicity
- Used in advanced gout or when other therapies have failed or are contraindicated
  - 40% effective in those who did not respond to previous therapies
- Not used with other urate lowering therapies
- Contraindicated in G6PD deficiency
- IV administration over 2 hours q 2 weeks
  - D/C if loss of urate lowering effectiveness (serum uric acid >6 mg/dL) on one occasion with infusion reaction or on two successive occasions

Long-term management of Gout

- Continue gout attack prophylaxis for approximately 6 months after starting ULT or if ongoing symptoms and/or signs
- Continue to regularly monitor serum urate levels and ULT side effects
- Continue ULT to maintain serum urate levels below 6 mg/dL (or 5 mg/dL in tophaceous gout patients)

When to refer…

- Unclear etiology of hyperuricemia
- Refractory signs or symptoms of gout
- Difficulty reaching target serum urate
  - Renal impairment
  - After XOI trial
- Multiple and/or serious adverse events to pharmacologic ULT

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Lessons for practice

- Gout is the most common inflammatory arthritis in men over 40 years old.
- Synovial fluid analysis using polarized light microscopy is the gold standard for diagnosing gout and other forms of crystal arthritis.
- Doses of allopurinol can exceed 300 mg per day in appropriate patients.

Evidence Based Medicine

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