

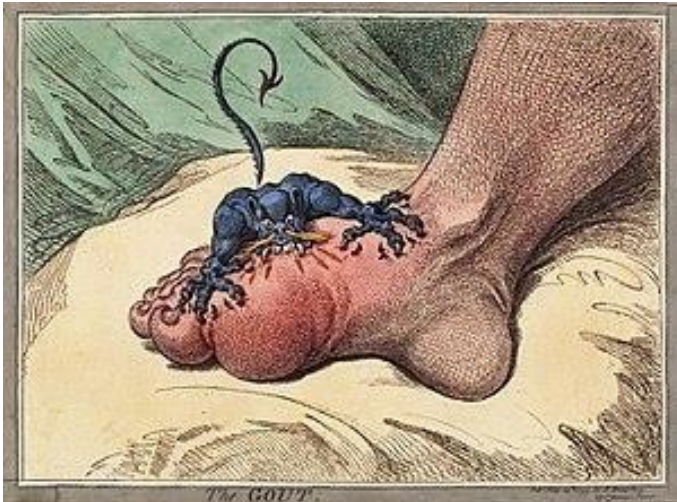
Gout Diagnosis and Management in 2022

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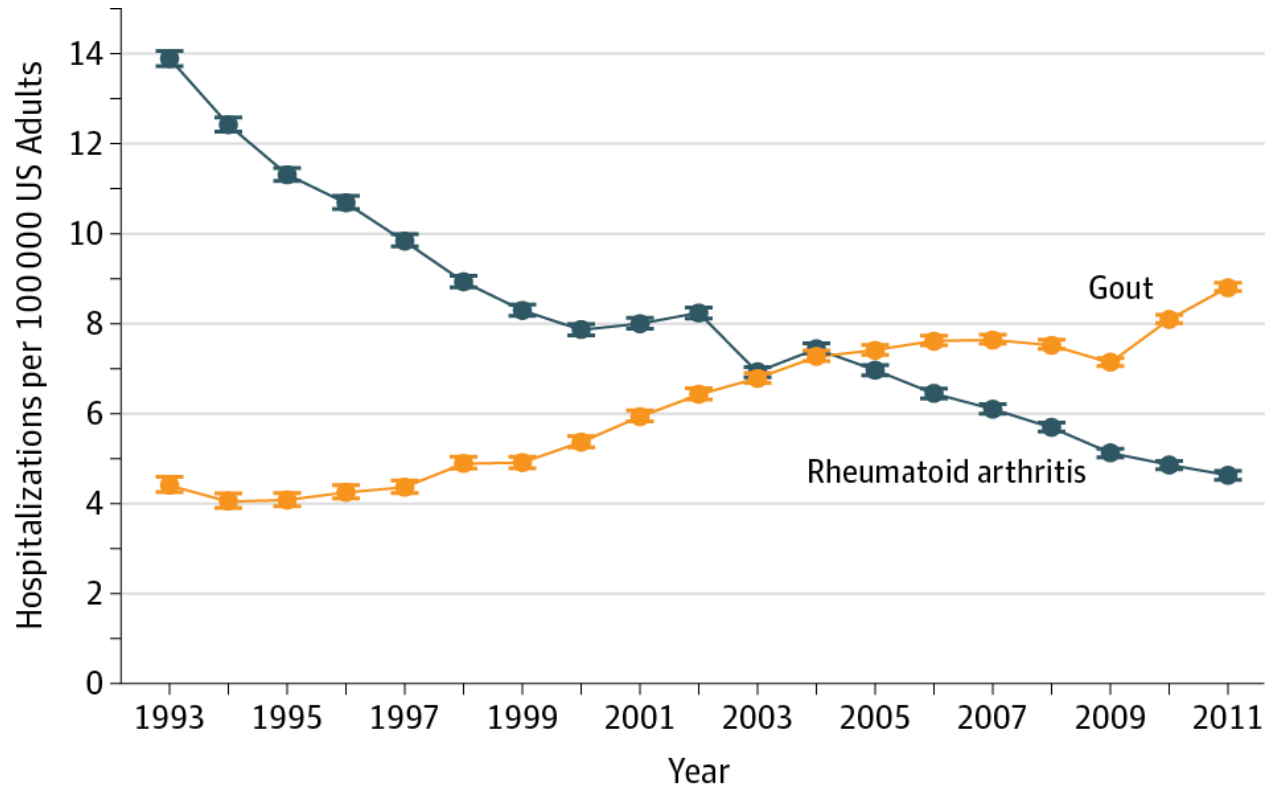
Disclosures

- Grants from Bristol-Myers Squibb and Principia/Sanofi unrelated to gout
- Consulting for Zenas, Sanofi, Horizon, Viela Bio, and MedPace

Learning Objectives

1. To review the epidemiology of gout
2. To discuss options for diagnosing gout
3. To review the treatment of acute gout (brief)
4. To discuss the management of gout to prevent flares

The Modern Gout Epidemic



- Lifestyle
 - Increasingly sedentary
 - Increasing sugary consumption
- Rising rates of related conditions
 - Obesity and metabolic syndrome
 - Hypertension
 - Chronic kidney disease
- Changes in medications associated with hyperuricemia
 - Diuretics
 - Aspirin
 - Transplant-related immunosuppression

Arthritis Rheum. 2004;50:2400-2414.

Arthritis Res Ther. 2006;8(suppl):S2

JAMA. 2016;315(21):2345-2347

Arthritis Rheum. 2020;72(1):157

A Common Case

55 year old Asian man

Acute right knee pain, warmth, redness, swelling

Podagra one year ago and similar knee pain 4 months ago

Prior episodes treated with naproxen at urgent care

PMH

- Hypertension
- Diabetes

Meds

- HCTZ
- Metformin

Case Continued

Afebrile
Pain with ambulating
but non-toxic
appearing



Labs

- Creatinine 0.8
(GFR >60)
- Uric acid 8.9

What is the most likely diagnosis?

- a) Rheumatoid arthritis
- b) Gout
- c) ACL tear
- d) Pseudogout
- e) Septic arthritis

What is the diagnosis?

a) Rheumatoid arthritis

b) Gout



c) ACL tear

d) Pseudogout

e) Septic arthritis

- Demographics & risk factors
- Recurrent monoarticular inflammatory arthritis
- Podagra
- Tophi on exam
- Elevated uric acid

How can you confirm the diagnosis?

- a) You don't need to, it's most likely gout
- b) X-ray of the right foot (site of podagra before) and the right knee
- c) Arthrocentesis
- d) Dual energy CT scan of the right knee or right foot
- e) Musculoskeletal ultrasound

Calculators to Diagnose / Classify Gout

- Acute Gout Diagnosis Rule
 - <https://www.mdcalc.com/acute-gout-diagnosis-rule#evidence>
- ACR/EULAR Gout Classification Criteria
 - <https://www.mdcalc.com/acr-eular-gout-classification-criteria#next-steps>

Male sex	No 0	Yes +2
Previous patient-reported arthritis attack	No 0	Yes +2
Onset within 1 day	No 0	Yes +0.5
Joint redness	No 0	Yes +1
1st metatarsophalangeal joint involvement	No 0	Yes +2.5
Hypertension or ≥1 cardiac diseases Angina, MI, CHF, Stroke/TIA, PVD	No 0	Yes +1.5
Serum uric acid > 5.88 mg/dL (0.35 mmol/L)	No 0	Yes +3.5

10.5 points
82.5% prevalence of gout in original study.
Gout is very likely.

X-rays

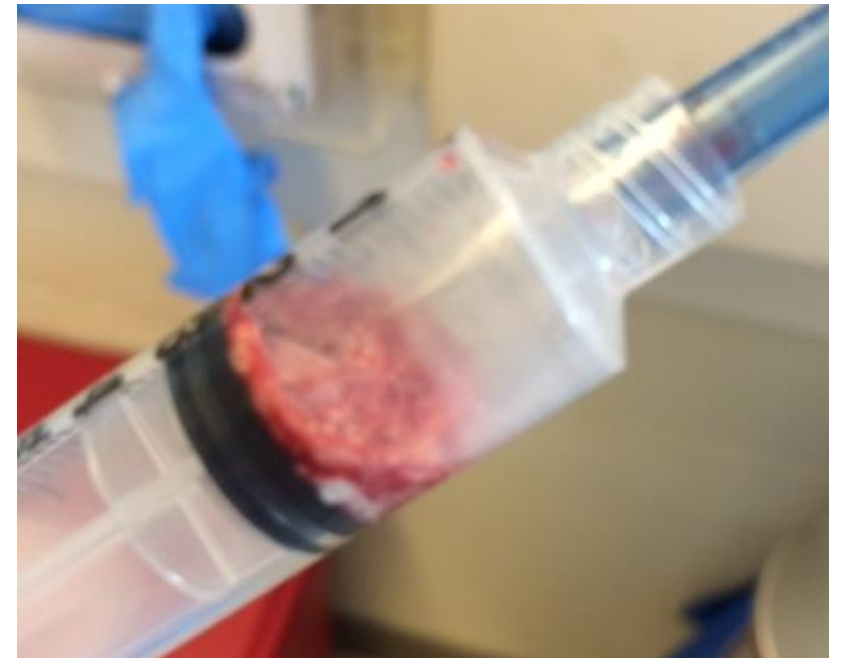


- Overhanging edges
- Punched out erosions
- Typically juxta-articular
- Soft-tissue density
- Notable absence of:
 - Periarticular osteopenia
 - Chondrocalcinosis
- Changes are often absent early in disease course so not sensitive



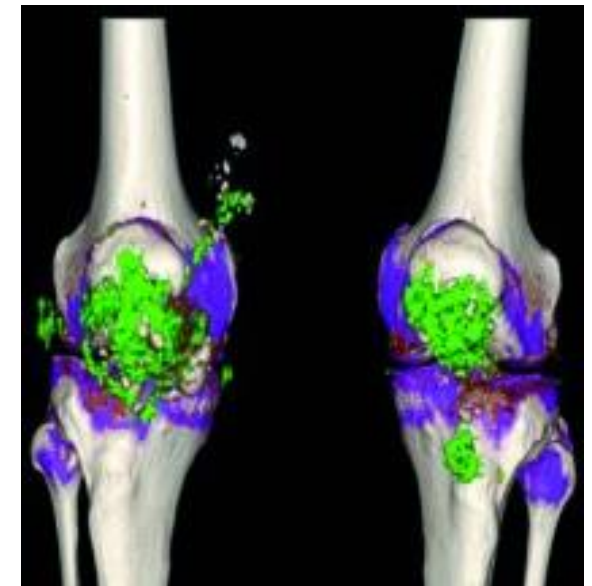
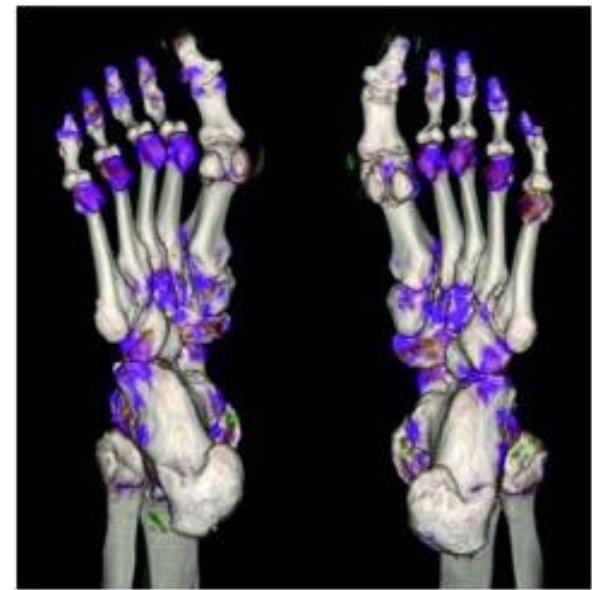
Arthrocentesis

- Can be challenging to aspirate the MTP
- Large knee effusion more amenable to arthrocentesis
- Send for:
 - Cell count (inflammatory, $> 2,000$ PMN)
 - Crystal analysis (intracellular MSU crystals)
 - Gram stain and culture (negative)



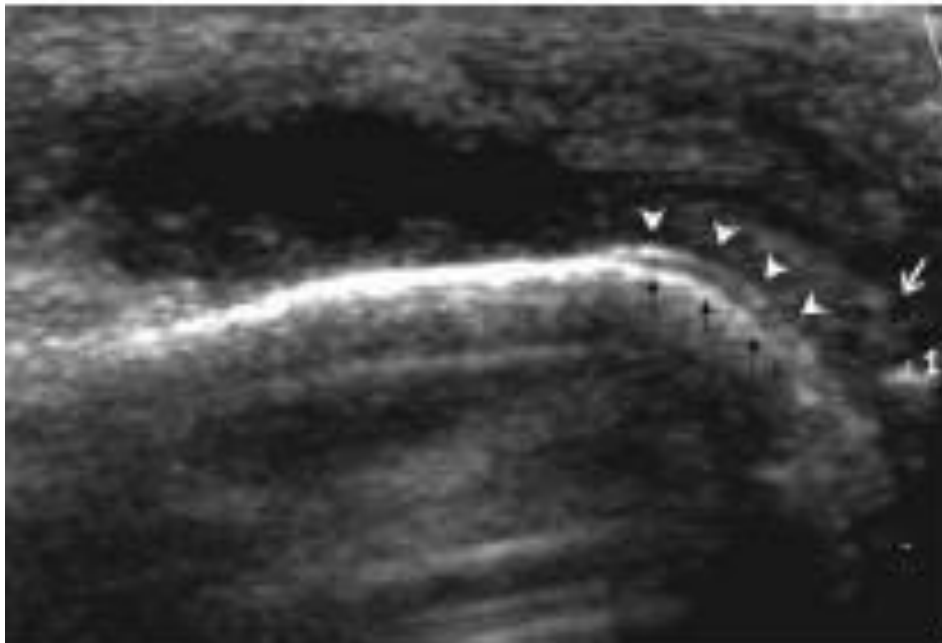
Dual Energy CT Scan

- CT uses 2 different energies to differentiate material on the same image (e.g., iodine/bone)
 - Used in some CT-PE protocols
- Protocols allow for identification of monosodium urate crystals
- Good test performance
 - Sensitivity = 87%
 - Specificity = 84%
- Most studies have been performed in patients with long-standing gout



Musculoskeletal Ultrasound

1st MTP Joint



- Requires trained radiologist or rheumatologist
 - Performance is user-dependent
- “Double contour sign”
 - May have comparable sensitivity/specificity to DECT
- Identify tophi and typical appearance of monosodium urate crystals
- Can aspirate and inject at point of care

How can you confirm the diagnosis?

- a) You don't need to, it's definitely gout
- b) X-ray of the right foot (site of podagra before) and the right knee
- c) Arthrocentesis – “gold standard”
- d) Dual energy CT scan of the right knee or right foot
- e) Musculoskeletal ultrasound

How do you treat this patient's acute gout?

- a) Colchicine
- b) NSAIDs
- c) Intra-articular steroid injection
- d) Oral steroid taper
- e) Any of the above

Labs	
-	Creatinine 0.8
-	Uric acid 8.9

How do you treat this patient's acute gout?

a) Colchicine

1.2mg followed by
0.6mg 1 hr later then
0.6 BID

b) NSAIDs

c) Intra-articular steroid injection

d) Oral steroid taper

e) Any of the above

Labs

- Creatinine 0.8
- Uric acid 8.9

Should this patient be on urate lowering therapy (e.g., allopurinol)?

- a) Yes
- b) No
- c) I don't know



Should this patient be on urate lowering therapy (e.g., allopurinol)?

- a) Yes
- b) No
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Urate Lowering Therapy

1. Xanthine Oxidase Inhibitor Options: Allopurinol or febuxostat
2. Uricosuric Agents: Probenecid
3. Uricase: Pegloticase

➤ Indications:

- ≥ 2 gout attacks / year
- tophaceous gout (clinical or imaging) 
- joint damage from gout 
- Consider in > 1 gout attack with CKD \geq stage 3;
- Consider in > 1 gout attack with uric acid > 9 mg/dL;
- Consider in > 1 gout attack with urolithiasis

➤ Targets:

- Uric acid: ≤ 6 mg/dL (can consider ≤ 5 mg/dL in advanced/tophaceous gout or persistent flares)
- Resolution of tophi (it will take time once you get to target uric acid)
- No additional gout attacks

Myths and Pearls Regarding Gout Management Common in Day-to-Day Practice

Pearl: Allopurinol can be started during an acute flare

- Contrasts with previous recommendations
- Delaying initiation leads to missed opportunities to start urate lowering therapy
- Allopurinol and febuxostat do NOT treat a flare so you need to use treatments specific for acute flares
- Consider prophylaxis for subsequent gout flares during allopurinol uptitration
 - Low dose prednisone
 - Colchicine (monitor for diarrhea)
 - NSAIDs

Pearl: Allopurinol should be slowly uptitrated

- Starting Dose:
 - Normal renal function: start at 100mg/d
 - CKD Stage \geq 4: start at 50mg/d
- Every 2-5 weeks:
 - Check Uric Acid, CBC, LFT
 - Assess if uric acid at goal (<6mg/dL or <5mg/dL)
 - Yes \rightarrow Stay at current dose and recheck in 2-5 weeks
 - No \rightarrow Increase dose by 50mg/d or 100mg/d depending on renal function
- Dose may be > 300mg/d, even with renal impairment, and dose may need to be as high as 800mg/d
- Dose escalation leads to structural benefits (less damage and lower crystal deposition in joints)

Pearl: HLA-B5801 is associated with allopurinol hypersensitivity syndrome (AHS)

- Allopurinol hypersensitivity syndrome (AHS)
 - Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
 - High mortality rate (~25%)
- Slow up-titration significantly reduces the risk of AHS
- HLA-B5801+ is associated with AHS
 - ~7% Asian subjects (esp Han Chinese) → 3x higher risk of AHS (vs White)
 - ~4% Black subjects → 3x higher risk of AHS (vs White)
 - ~6% Hawaiian / Pacific Islander → 7x higher risk of AHS (vs White)
- Screening for HLA-B5801 and treating + subjects with alternative approach (e.g., febuxostat) dramatically reduces the risk of AHS

A Common Case

Check HLA-B5801 in our case prior to allopurinol initiation

55 year old Asian man

Acute right knee pain, warmth, redness, swelling

Podagra one year ago and similar knee pain 4 months ago

Prior episodes treated with naproxen at urgent care

PMH

- Hypertension
- Diabetes

Meds

- HCTZ
- Metformin

Myth: Allopurinol is nephrotoxic

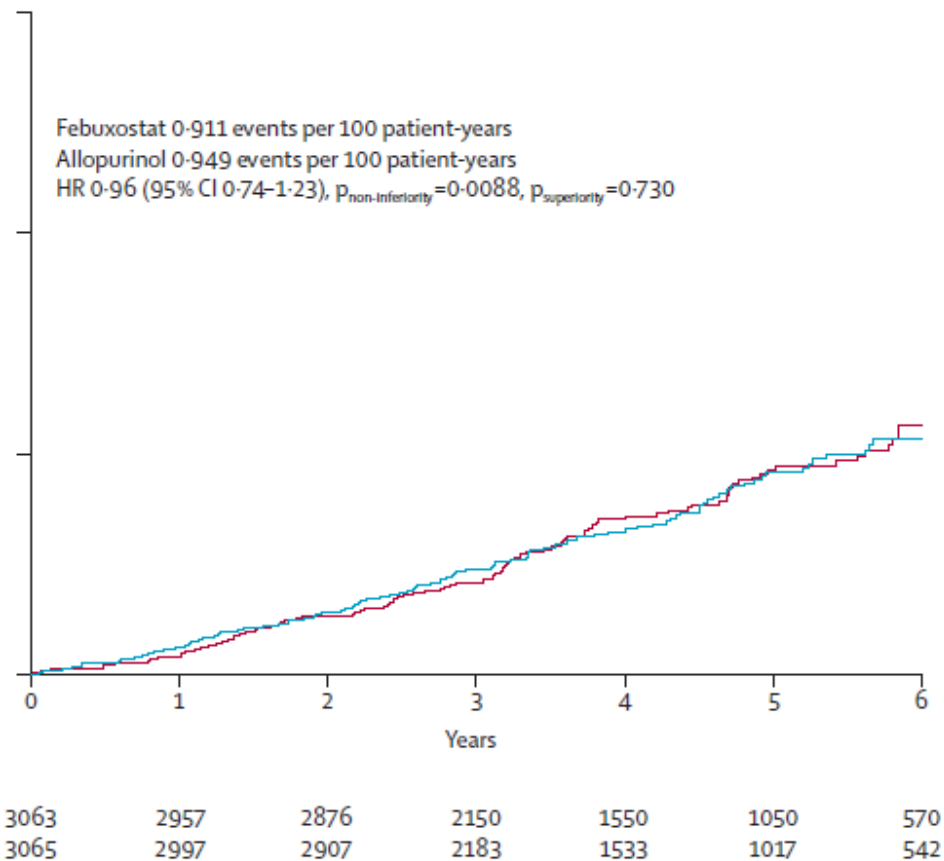
- Incident gout cases initiating allopurinol $\geq 300\text{mg/d}$
- Compared to non-initiators
- Allopurinol was not associated with renal function decline
- Actually associated with a lower risk of renal function decline
- When patients have acute kidney injury, consider alternative etiologies
- Allopurinol safe to use at all levels of renal function; limited data on febuxostat use $< 15\text{ml/min}$

Table 2. Risk of Developing Chronic Kidney Disease (Stage ≥ 3) Among Patients With Incident Gout and Incident Allopurinol Use (at Least 300 mg/d)

Main Results	Incident Allopurinol User	Non-Allopurinol User
Total, No.	4760	4760
Incident CKD stage ≥ 3 , No. (%)	579 (12.2)	623 (13.1)
Death, No. (%)	254 (5.3)	240 (5.0)
Mean follow-up time, y	4.9	4.5
Crude incidence rate (CKD stage ≥ 3) per 1000 person-years	24.9	29.4
Propensity score-matched hazard ratio (95% CI)	0.87 (0.77-0.97)	
Adjusted hazard ratio (95% CI) ^a	0.88 (0.79-0.99)	

Pearl: Febuxostat is not associated with increased risk of death due to CVD

D Cardiovascular death, intention-to-treat analysis



- The FAST trial (Lancet) demonstrated that there is no higher risk of CVD death with febuxostat
 - Contrast with prior controversial CARES trial in NEJM
- Allopurinol and febuxostat have similar clinical efficacy
 - Allopurinol needs to be dose-adjusted
 - Benefits seen in gout flare & uric acid
- Allopurinol is not associated with a higher risk of death in gout (contrast with recent RCTs in CKD)

Pearl: High uric acid / gout associated with future complications

	High Serum Uric Acid	Gout
MI	Yes	Yes
Stroke	Yes	Unknown
Hypertension	Yes	Unknown
Type 2 Diabetes	Yes	Yes
ESRD	Yes	Unknown
Kidney Stones	Unknown	Yes

Consider closely monitoring gout patients for these complications

Pearl: Medications, especially anti-hypertensives, can affect uric acid

- ↑ serum uric acid
 - Hydrochlorothiazide (HCTZ)
 - ACE inhibitors
 - Beta blockers
- ↓ serum uric acid (uricosuric)
 - Losartan
 - Calcium channel blockers
 - SGLT2 inhibitors
- Consider switching our case patient off of HCTZ

BMJ. 2012;12;344:d8190
Ann Intern Med. 2020;172:186

Pearl: Dietary changes can help with gout management but typically insufficient

- Low purine approach:
 - Low palatability
 - Low efficacy
 - Not very sustainable
 - Increased carbohydrate and trans fats consumption
- The **DASH** diet may be a great alternative
 - High intake of fruits, vegetables, nuts and legumes, low fat dairy products, and whole grains
 - Low intake of sodium, sweetened beverages, and red and processed meats

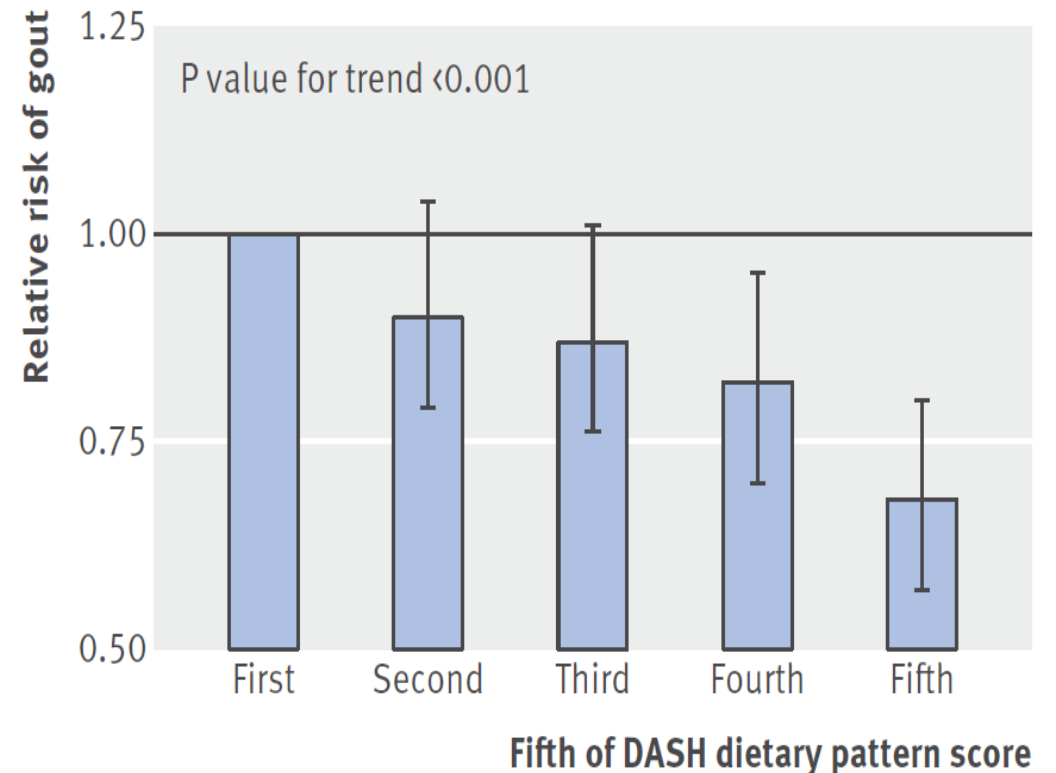


Fig 1 | Multivariable relative risk of incident gout and 95% confidence interval according to fifth of DASH dietary pattern score

Conclusions

- Gout is a treatable condition, arthrocentesis not always necessary
- Appropriately selected patients can benefit from urate lowering therapy
- When using allopurinol, start low and go slow
- Allopurinol doses can exceed 300mg/d, even in renal insufficiency
- Check HLA-B5801 in appropriate populations to minimize risk of allopurinol hypersensitivity
- Allopurinol does not cause nephrotoxicity and may be used in CKD
- Observational studies and a recent well-designed RCT suggest that febuxostat is safe compared with allopurinol

Thank you!