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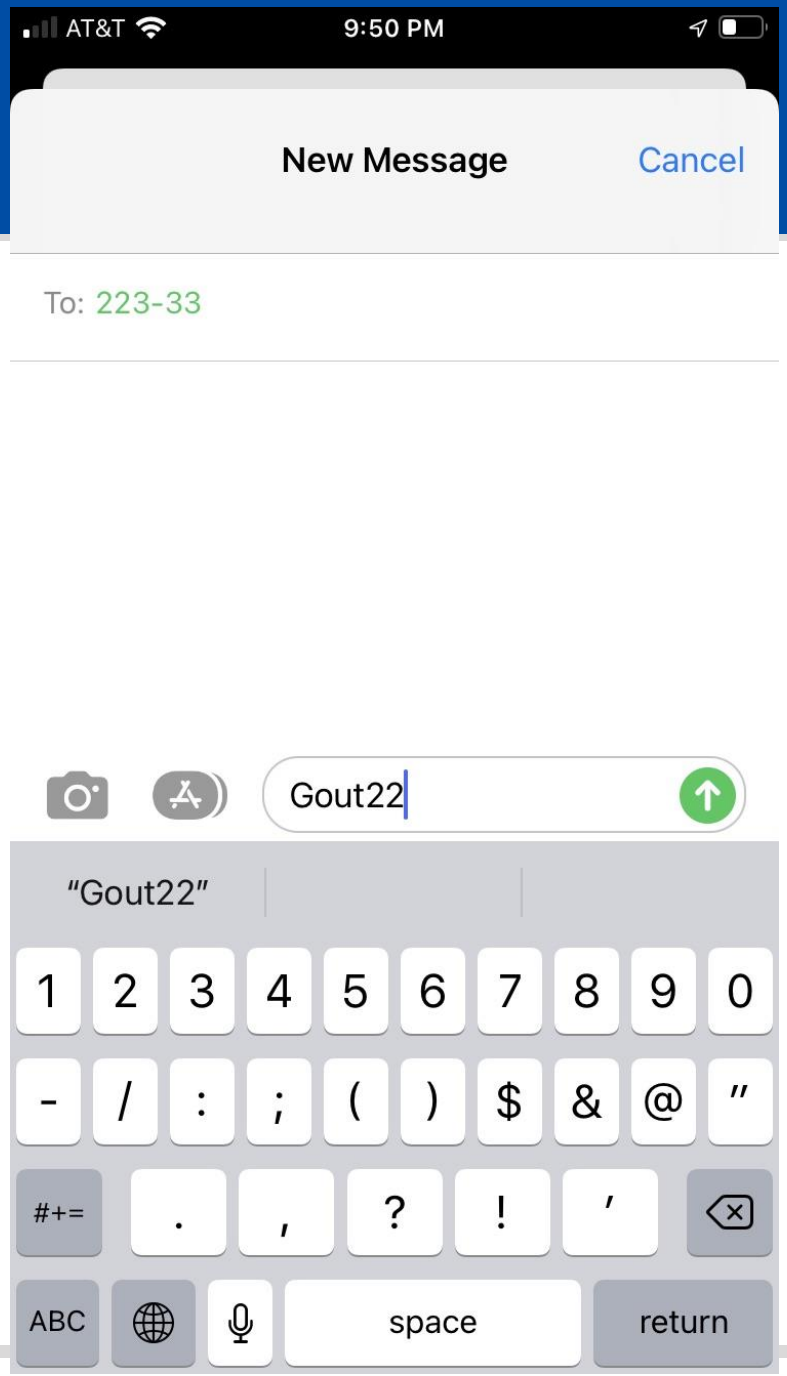

Gout for the Family Physician

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Disclosures

Research Grant- Novartis, Lilly
Member- ACR 2020 Gout guideline committee
Advisory board- Abbvie, Janssen, Medscape, Amgen
Speaker bureau- Abbvie, Novartis

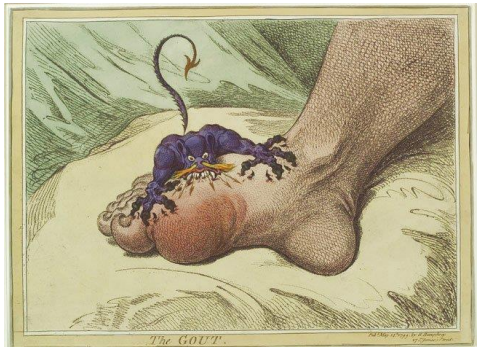
Objectives

- Discuss the epidemiology and global burden of gout
- Learn about pathophysiology of urate metabolism and risk factors of gout
- Understand the comorbidities of the gout
- Learn management of gout as per ACR 2020 guidelines

Gout- an ancient disease

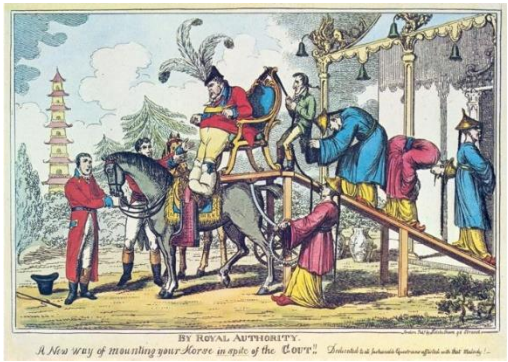
- Acute episodic arthritis characterized by intense inflammatory reaction in response to articular/periarticular deposits of monosodium urate crystals

- 2640 BC: podagra first identified by the Egyptians
- Hippocrates described gout as “the king of diseases and the disease of kings



The Gout, cartoon by James Gillray (1799).

Origin of the gout, cartoon by HenryBunbury (1786)



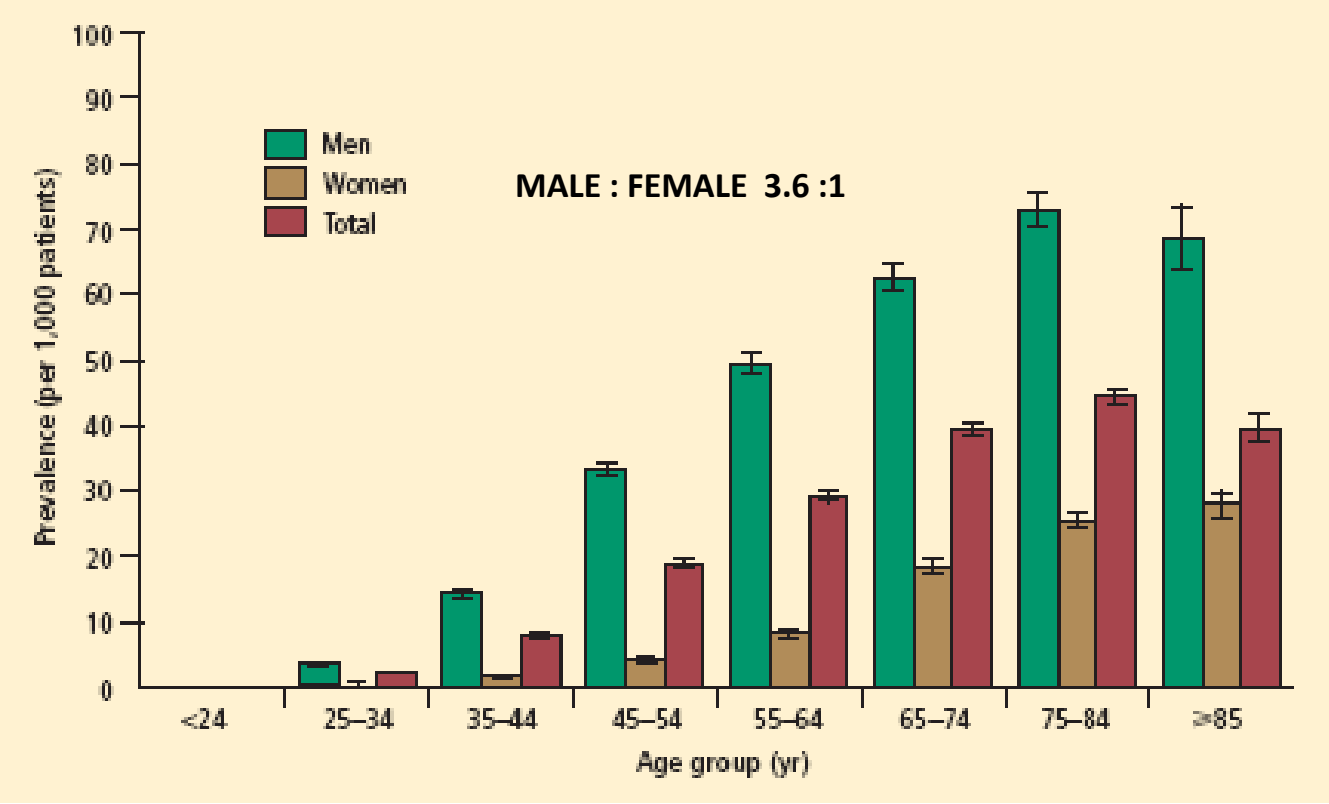
Epidemiology

- Most common inflammatory arthritis,~9.2 million adults (3.9%) in US, 42 million adults in world
- Gout is twice as common as RA.
- Associated with comorbidities including hypertension (75%), CKD (70%), obesity (53%) and CVD (10% to 14%)
- Despite available and inexpensive medications, 70% patients continue to have flares.
- Over the past 2 decades there has been no increase in ULT utilization

Danve and Neogi; Rising Global Burden of Gout: Time to Act; Arthritis Rheumatol. 2020 Nov;72(11):1786-1788.

Gout is more common in men and the elderly

Prevalence of gout from a UK General Practice Research Database



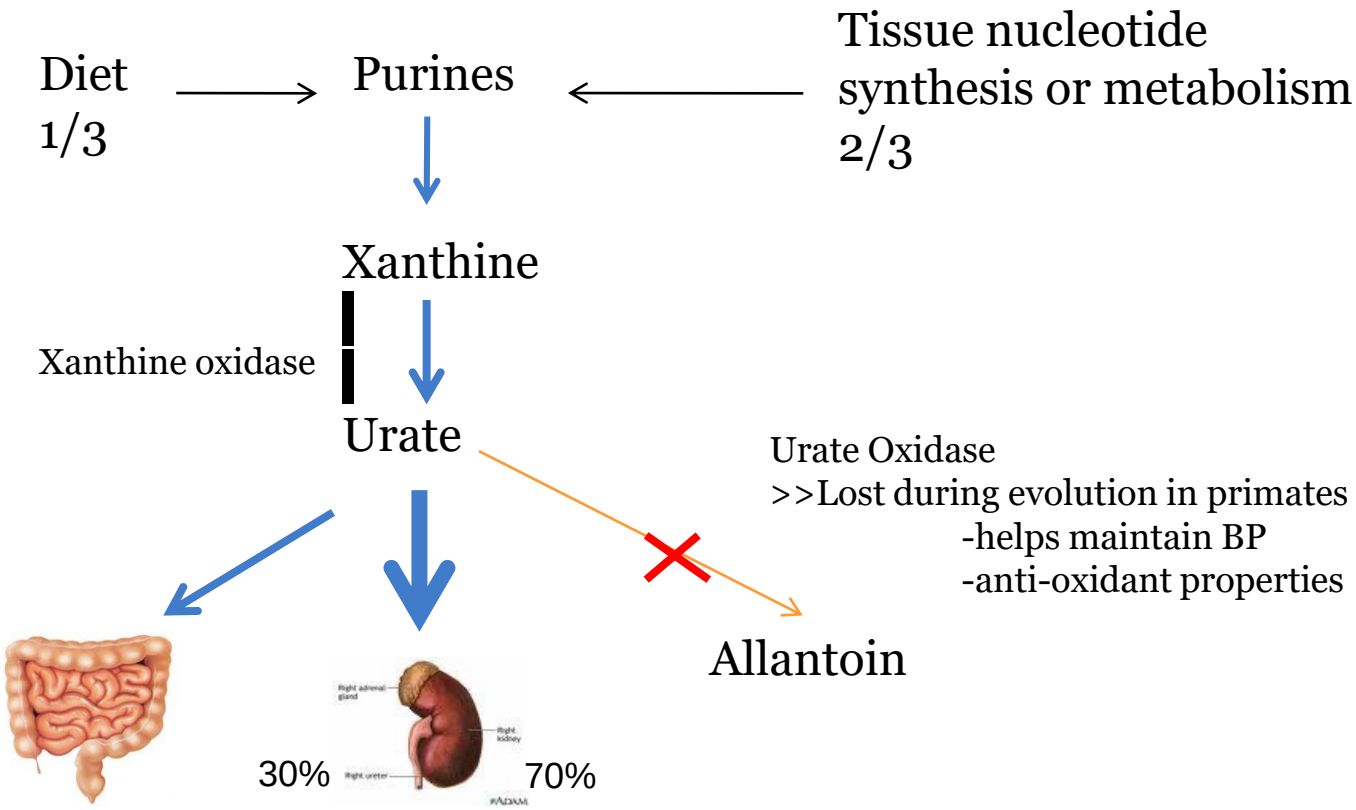
Mikuls et al Ann Rheum Dis 2005; 64:267
Weaver A. Clev Clin J Med 2008 ; 75:S5

Hyperuricemia

- Pathological hyperuricemia has been defined as the serum urate concentration (6·8 mg/dL) above which monosodium urate crystals form in vitro at physiological pH and temperature.

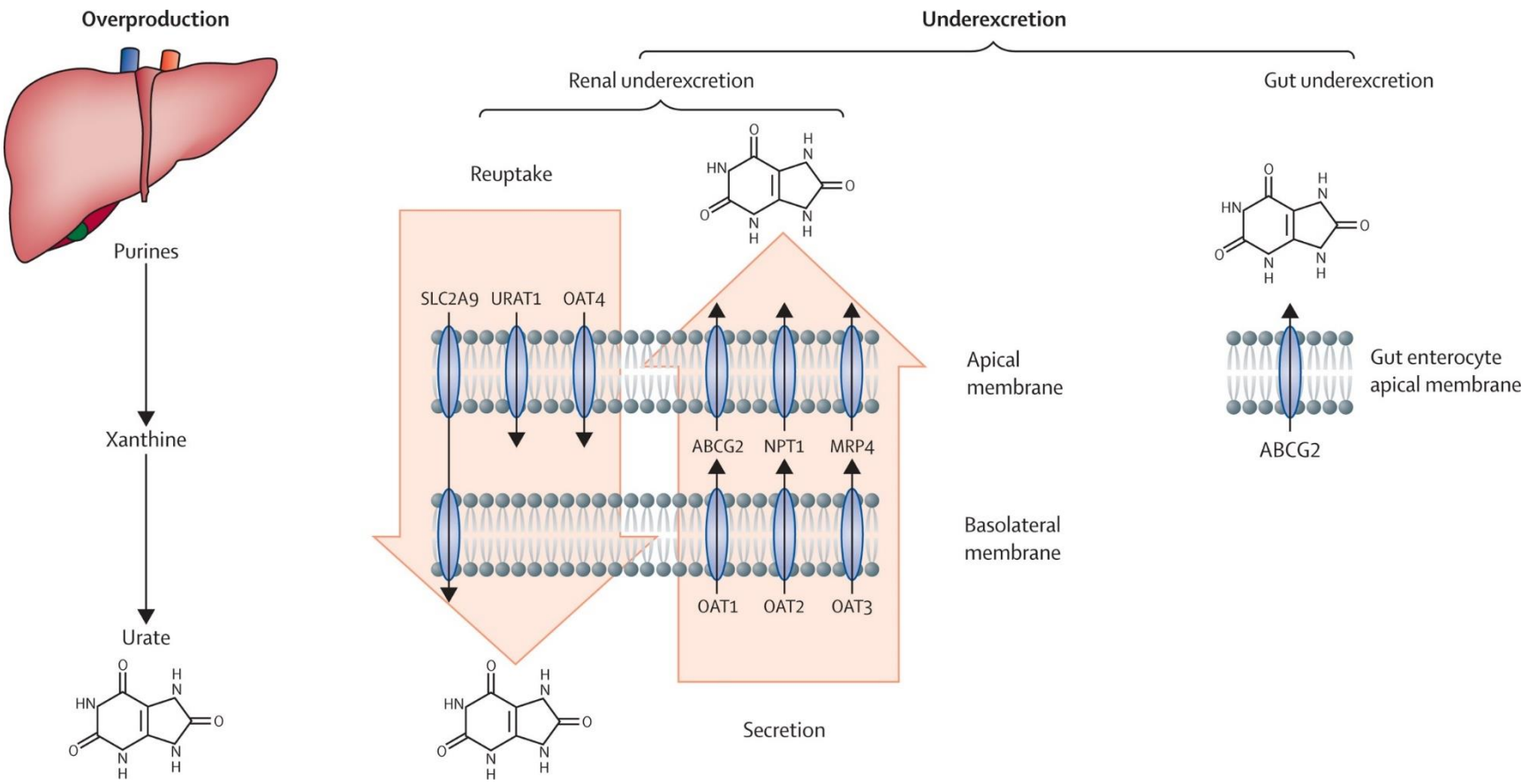
Urate Metabolism

End product of purine metabolic pathway



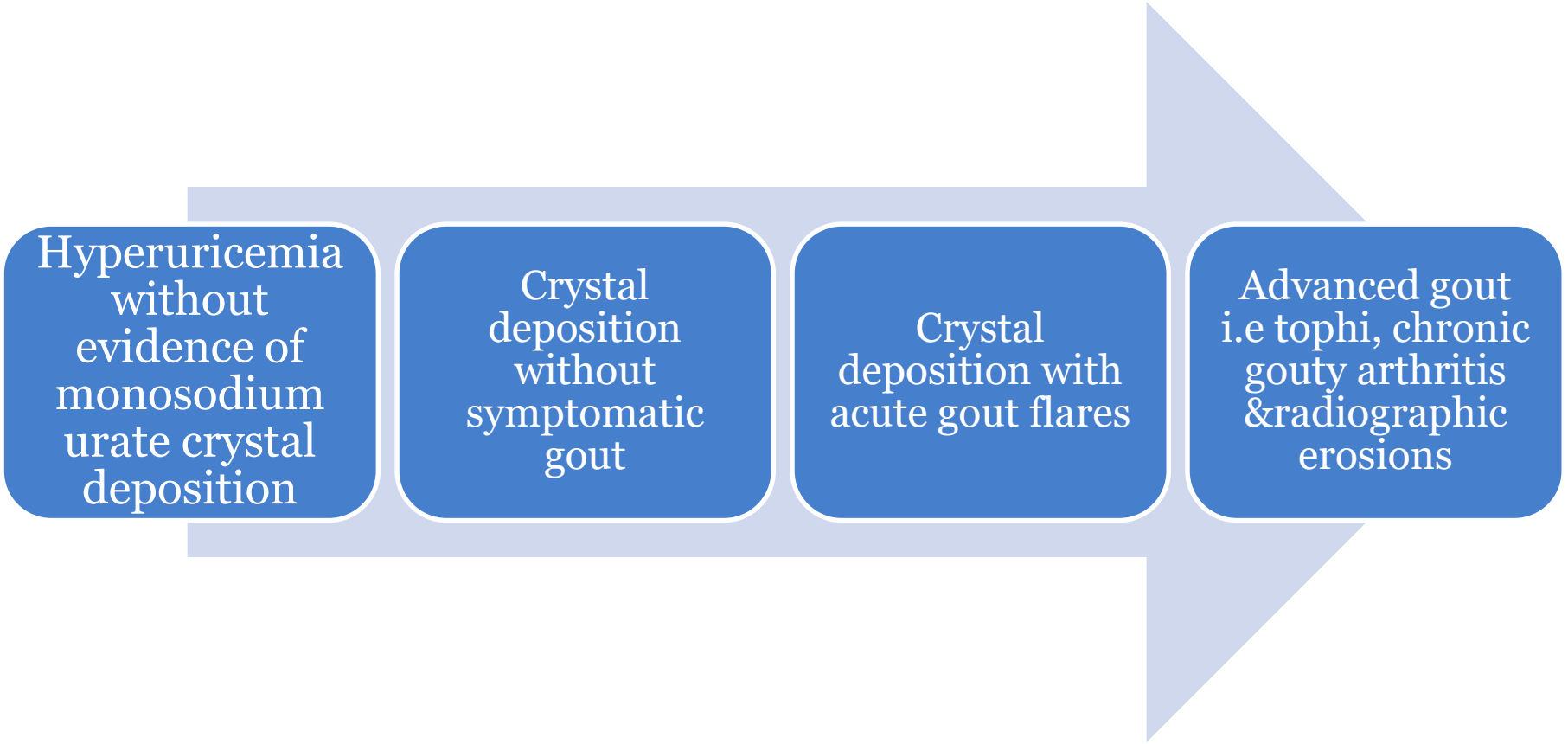
Roddy et al. *Nature Rheum* 2007; 3(8):443

Urate Metabolism



The Lancet DOI: (10.1016/S0140-6736(16)00346-9)

Four Pathophysiological Stages



Hyperuricaemia and gout: time for a new staging system?
Ann Rheum Dis, 73 (2014), pp. 1598–1600

Risk Factors for Gout

Genetic*

- Male sex
- Ancestry
- *SLC2A9*
- *ABCG2*
- *SLC17A1/SLC17A3*
- *GCKR*

Dietary

- Red meat
- Seafood
- Beer
- Spirits
- Sugar-sweetened beve

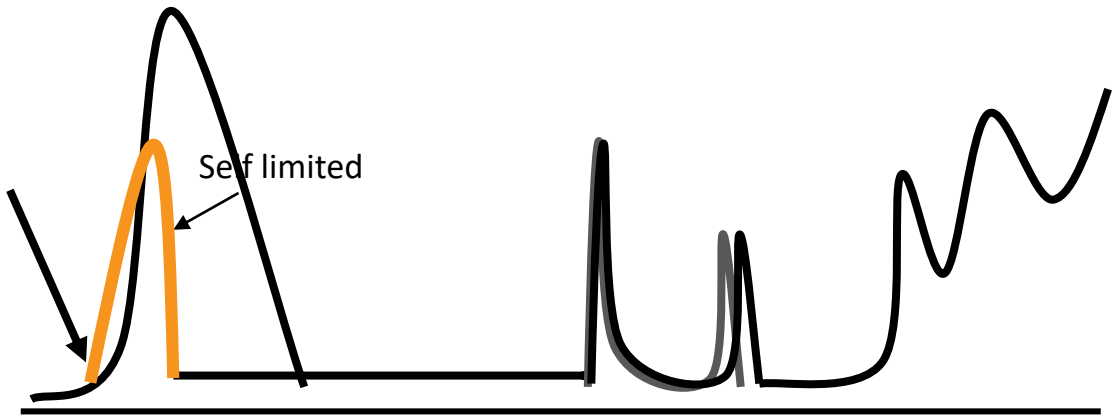
Drugs

- Diuretics
- Cyclosporin
- Tacrolimus
- Angiotensin-converting-enzyme inhibitors
- Non-losartan angiotensin II receptor blockers
- β blockers
- Pyrazinamide
- Ritonavir

Other

- Increasing age
- Menopause
- Chronic kidney disease
- Overweight, obesity, or weight gain
- Hypertension
- Hyperlipidaemia
- Hypertriglyceridaemia
- Congestive cardiac failure
- Obstructive sleep apnoea
- Anaemia
- Psoriasis
- Sickle cell anaemia
- Haematological malignancy
- Lead exposure

Clinical Syndrome of Gout



Acute gout	Intercritical	Chronic gout
Monoarthritis		Polyarticular
Lower ext		Soft tissue
		Tophi
		Erosions

Modified - Courtesy of Steve Campbell, MD

Comorbid disorders

- NHANES 2008-74% of gout pt w/ HTN, 71% W/ CKD Stage ≥2, 53% obese, 26% w/ diabetes, 14% w/ Hx of MI, and 10% w/ hx of stroke
- Gout is associated with increased risk of death, primarily due to cardiovascular disease.
- The cause–effect relation between comorbid disorders is difficult to assess because of the confounding
- Increased body-mass index is causally associated with increased urate levels
- Some evidence that hyperuricemia might causally contribute to worse outcomes in cardiovascular and kidney disease

Am J Med, 125 (2012), pp. 679–687
Circulation, 116 (2007), pp. 894–900
Am J Kidney Dis, 65 (2015), pp. 294–302
J Am Soc Nephrol, 26 (2015), pp. 2831–2838

Arthritis Care & Research
Vol. 0, No. 0, Month 2020, pp 1–17
DOI 10.1002/acr.24180

American College of Rheumatology
Empowering Rheumatology Professionals

ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

John D. FitzGerald,[1] Nicola Dalbeth,[2] Ted Mikuls,[3] Romina Brignardello-Petersen,[4] Gordon Guyatt,[4] A. M. Abeles,[5] Allan C. Gelber,[6] Leslie R. Harrold,[7] Dinesh Khanna,[8] Charles King,[9] Gerald Levy,[10] Caryn Libbey,[11] David Mount,[12] Michael H. Pillinger,[5] Ann Rosenthal,[13] Jasvinder A. Singh,[14] James Edward Sims,[15] Benjamin J. Smith,[16] Neil S. Wenger,[17] Sangmee Sharon Bae,[17] Abhijeet Danve,[18] Puja P. Khanna,[19] Seoyoung C. Kim,[20] Aleksander Lenert,[21] Samuel Poon,[22] Anila Qasim,[4] Shiv T. Sehra,[23] Tarun Sudhir Kumar Sharma,[24] Michael Toprover,[5] Marat Turgunbaev,[25] Linan Zeng,[4] Mary Ann Zhang,[20] Amy S. Turner,[25] and Tuhina Neogi[11]

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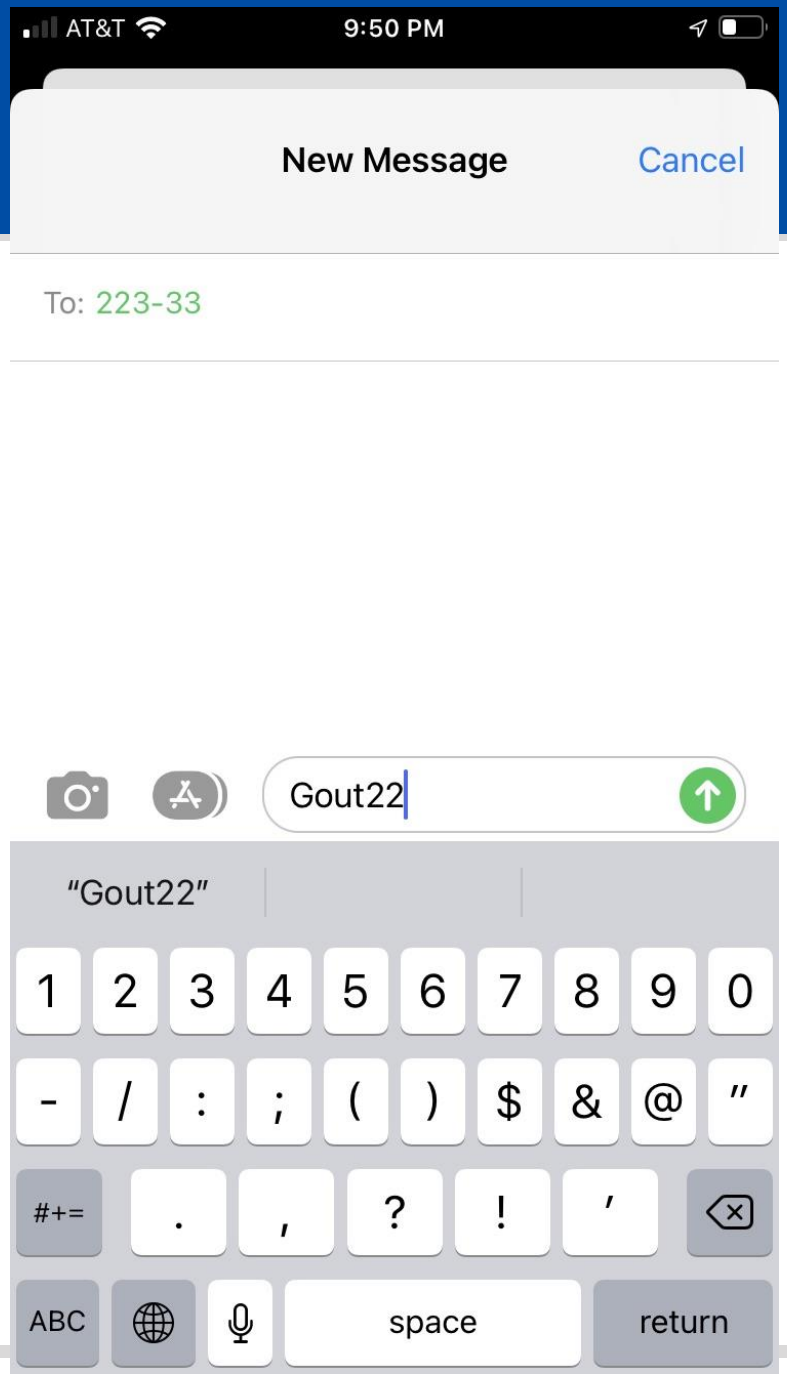

John and Maggy's tale....

As John opened the 3rd bottle of red wine on a Friday evening, at dinner with his beloved wife Maggy who had prepared nice Omaha steak, Maggy requested John to go to Farmer's market next day to bring her favorite Rainier cherries. Of course, John agreed. At the Farmer's market John saw an ongoing health fair and decided to get free blood tests offered there, being now 64-year-old and having HTN. Results revealed sUA of 8.4 mg/dl, normal CBC and CKD stage II per the eGFR values. John never had history of gout flares.

Should John start ULT for his hyperuricemia?

A
Yes

B
No

Asymptomatic Hyperuricemia (ASH)

- *Initiating ULT is **conditionally recommended against** in patients with asymptomatic hyperuricemia*
- 16% US adult population has asymptomatic hyperuricemia
- RCT data- 24 patients would need to be treated with ULT for 3 years to prevent a single (incident) gout flare
- Among pts with ASH and sUA >9 mg/dl, only 20% develop gout in 5 yr
- Overall, the benefits of ULT do not outweigh potential treatment costs or risks for the large number of pts unlikely to progress to gout.

Maggy too!..

Maggy is now 63-year-old and is otherwise healthy with no history of HTN, CKD or CVD. One day she wakes up with painful, swollen and red R 1st MTP s/o podagra. She calls her PCP's office. To her surprise front desk scheduler picks up the phone immediately and schedules her for the same day appointment. PCP is sure that it is gout flare as Maggy also had asymptomatic hyperuricemia on one of the previous labs.

How should the PCP treat this flare?

A NSAIDs

B Colchicine

C Glucocroticoids (PO, IM or IV)

D IL-1 Inhibitors

E ACTH

F A, B, C or D based on patient factors

Gout flare management- recommendations

- *Colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first line therapy over IL-1 inhibitors or ACTH is **strongly recommended** for patients having gout flare.*

- *Given similar efficacy and lower risk of adverse effects, **low-dose over high-dose colchicine** is **strongly recommended** when colchicine is the chosen agent.*

- *Using **topical ice** as an adjuvant treatment over no adjuvant treatment is **conditionally recommended** for patients experiencing a gout flare.*

-

Gout flare management- recommendations

- *Using an IL-1 inhibitor over no therapy (beyond supportive/analgesic treatment) is **conditionally recommended** for patients experiencing a gout flare for whom the above anti-inflammatory therapies are either ineffective, poorly tolerated, or contraindicated.*

- *Treatment with glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH is **strongly recommended** for patients who are unable to take oral medications.*

Gout flare management- continued

- For colchicine, FDA-approved dosing should be followed (1.2 mg stat f/b 0.6 mg one hour later f/b anti-inflammatory Rx until the flare resolves

- Rx selection should be driven by patient factors (e.g., comorbidity, access, past experience) as part of shared decision making

- Patient Panel emphasized its preference for early intervention given the challenges of engaging a provider in timely manner, including an **at-home "medication-in-pocket" strategy** for patients who are able to identify the early signs of flare onset.

Maggy's gout flare….

Maggy's flare resolves completely with colchicine. But now she is scared of having future flares. Repeat sUA after 3 weeks is 8.2 mg/dl. She goes back to her PCP and expresses concerns about having the flare and wants to know if she can start ULT.

What should the PCP do next?

A Start Maggy on ULT for the gout

B Wait and watch as it is her first flare

C Not sure

D Send her to rheumatologist

Recommendation- ULT and First flare

*Initiating ULT is **conditionally recommended against** in patients with gout experiencing their first gout flare.*

- Voting panel recommends shared decision making here.

Maggy's worry continues....

Over the next 5 years, Maggy develops 3 flares of podagra and each time the flare resolves with colchicine, but never had 2 or more flare in a single year. She does not have tophi.

Should the PCP start her on ULT?

A Yes

B No

C Not sure

D Send her to rheumatologist

Patients with infrequent gout flares

*Initiating ULT is **conditionally recommended** for patients who have previously experienced >1 flare but have infrequent flares (<2/year)*

Patients with infrequent gout flares

- Why is this a conditional recommendation?- Potential clinical benefit of ULT would be lower than the ULT benefit for patients with more burdensome gout

- In a single RCT, patients with ≤2 previous flares (and no more than 1 gout flare in the preceding year) randomized to receive febuxostat (versus placebo) were less likely to experience a subsequent flare (30% versus 41%; $P < 0.05$)

- Specific characteristics for patients with infrequent flares (e.g., sUA >9 mg/dl, CKD, CVD) that might influence the risk-benefit assessment here

John now develops gout flare

John develops his first flare of the gout, involving the 1st MTP joint. By now PCP also finds him to have CKD Stage III and sUA 9.8 mg/dl.

Would you start John on ULT?

A
Yes

B
No

First flare a/w CKD ≥III, sUA > 9 mg/dl or urolithiasis

Initiating ULT even after the 1st flare is ***conditionally recommended*** *for patients with comorbid moderate to-severe CKD (stage ≥3), sUA >9 mg/ dl, or urolithiasis*

First flare and associated CKD ≥ III, sUA >9 and urolithiasis

- For patients with moderate- to- severe CKD (e.g., stage>3), there is a higher likelihood of gout progression and development of clinical tophi
- Options for gout flare are limited in this population, and there may be added benefit of using ULT to prevent progression of renal disease
- Patients with markedly elevated sUA levels (>9 mg/dl) are more likely to experience gout progression
- For patients with a history of urolithiasis, allopurinol and febuxostat reduce 24-hour urinary uric acid excretion
- Among patients with ca oxalate stones and hyperuricosuria, allopurinol (300 mg/day) is superior to placebo in reducing the 3-year incidence of stone-related events

Maggy is still struggling.....

Maggy develops progressively recurrent flares of the gout involving feet , 3 to 4 per year. She comes to you during a severe flare involving 3 joints at once. Feet x-ray shows gouty erosion at MTP. Should she be started on ULT?

- *Initiating ULT is **strongly recommended** for gout patients with any of the following: ≥1 subcutaneous tophi; evidence of radiographic damage (any modality) attributable to gout; OR frequent gout flares, with frequent being defined as ≥2 annually*

When should the PCP start ULT for Maggy?

A Four weeks after the flare resolves

B Two weeks after the flare resolves

C During the flare

Timing of the ULT

- *When the decision is made that ULT is indicated while the patient is experiencing a gout flare, starting ULT during the gout flare is* ***conditionally recommended*** *over starting ULT after the gout flare has resolved.*

- Benefits include the time efficiency offered by this strategy and avoiding the risk of patient not returning for ULT initiation.
- Patients are likely to be highly motivated to take ULT due to the symptoms related to the current flare
- Concerns include potential extension or worsening of a flare and possibility of information overload for patients, which may lead to conflating flare management and long-term ULT.
- Two small RCTs and an observational study support the hypothesis that starting ULT during flare does not significantly extend flare duration or severity.

Which of the following is correct sentence regarding ACR 2020 Gout guideline?

A Target sUA should be <6 mg/dl for patients without tophi and < 5 mg/dl for those with tophi

B Target sUA should be < 5 mg/dl

C Target sUA should be <6 mg/dl

D Do not reduce sUA below 3 mg/dl

What should be the target sUA?

- ***A T2T strategy*** *that includes ULT dose titration and subsequent dosing guided by serial sUA measurements to achieve a target sUA, over a fixed-dose ULT strategy, is* ***strongly recommended*** *for all patients .*

- *Achieving and maintaining sUA of* ***<6 mg/dl*** *over the use of no target is* ***strongly recommended*** *for all patients receiving ULT.*

- T2T is a/w greater ULT adherence, lower sUA, reduction in tophi, and a lower proportion of frequent (≥2) gout flares, compared with usual care.

- ULT titration should occur over a reasonable time frame (e.g., weeks to months, not years) to prevent "treatment inertia"

Recommendations for choice of initial ULT for patients with gout

- *Treatment with allopurinol as the preferred first-line agent, over all other ULTs, is **strongly recommended** for all patients, including those with moderate-to-severe CKD (stage ≥3).*

- *Choice of either allopurinol or febuxostat over probenecid is **strongly recommended** for patients with moderate-to-severe CKD (stage ≥3).*

- *Starting treatment with low-dose allopurinol (≤100 mg/day and lower in patients with CKD [stage ≥3]) and febuxostat (≤40 mg/day) with subsequent dose titration over starting at a higher dose is **strongly recommended.***

- *Starting treatment with low-dose probenecid (500 mg once to twice daily) with subsequent dose titration over starting at a higher dose is **conditionally recommended.***

Choice of initial ULT

- Lower starting dose of any ULT reduces the risk of flare a/w initiation
- Even lower initial allopurinol doses (e.g., ≤50 mg/day) should be considered in patients with CKD.
- Higher starting doses and CKD are associated with risk of Allopurinol Hypersensitivity Syndrome (AHS)
- Patients with CKD may still require dose titration above 300 mg/day to achieve the SU target
- Larger body size and diuretic use are a/w the need for higher allopurinol doses to achieve greater urate reduction.
- Renal function has only a modest impact on dose requirements and worse renal function only has a modest negative impact on urate reduction

Maggy's gout....

You decide to start Maggy on Allopurinol 100 mg daily during the flare along with colchicine. You also explain her about risk of recurrent flare in next few weeks to months and the need for prophylaxis with colchicine. Maggy is concerned about the high cost of colchicine in long run.

How long should the anti-inflammatory prophylaxis be continued?

A 3 months

B 3 to 6 moths

C 6 to 12 months

D 3 to 6 months with assessment of ongoing need and continuation

Concomitant anti-inflammatory prophylaxis

- *Administering concomitant prophylactic therapy (e.g., colchicine, NSAIDs, prednisone/ prednisolone) over no anti-inflammatory prophylaxis therapy is* ***strongly recommended.***

- *Continuing concomitant prophylactic therapy for 3–6 months over <3 months, is* ***strongly recommended*** *with ongoing evaluation and continued prophylaxis as needed if the pt continues to experience gout flares.*

- Based on 8 RCTs and 2 observational studies there is moderate certainty of evidence to support the strong recommendations to use anti-inflammatory prophylaxis therapy when initiating ULT.
- Shorter durations were a/w flares upon cessation of prophylaxis.

Duration of ULT

- *Continuing ULT indefinitely over stopping ULT is* ***conditionally recommended.***

- In a single case series where ULT was withheld in pts in remission with years of well-controlled sUA, only 13% of pts (27 of 211) whose sUA remained at <7 mg/dl had no flares during a 5-year follow-up

- Furthermore, patients with higher sUA after withholding therapy had more frequent flares.

Testing for HLA B5801 before starting Allopurinol is indicated in which of the ethnicities below?

A South-east Asians (Han-Chinese, Thai, Koreans)

B African- American

C Hispanic

D A and B

E A, B and C

Recommendations for patients receiving Allopurinol

- *Testing for the HLA–B*5801 allele prior to starting allopurinol is **conditionally recommended** for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and for African American patients, over not testing for the HLA–B*5801 allele.*

- *Starting allopurinol in daily doses of ≤100 mg (and lower doses in patients with CKD) is **strongly recommended** over starting at a higher dose.*

Recommendations for patients receiving Allopurinol

- HLA–B*5801 allele is associated with a markedly elevated risk for AHS

- *Allopurinol desensitization is **conditionally recommended** for patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT agents.*

And John develops CVD.....

John was ultimately started on Febuxostat as allopurinol in maximal doses was not able to control the sUA and he continued having flares as well as had non-resolving tophi. With Febuxostat 80 mg/day, his uric acid and flare frequency are improving. Size of the tophi is decreasing as well. He also has HTN and CKD stage III. Since your last visit, John had ACS/ MI that required stenting and has mildly low EF.

What would you do with Febuxostat?

A Continue Febuxostat

B Switch back to Allopurinol

C Start Pegloticase

D Have in depth conversation about risks and benefits and involve shared decision making

Recommendations for patients receiving Febuxostat

- *Switching to an alternative oral ULT agent, if available and consistent with other recommendations in this guideline, is* ***conditionally recommended*** *for patients taking febuxostat with a history of CVD or a new CVD-related event.*
- Voting Panel considered CARES RCT and 2 observational studies.
- CARES- there was no difference between the 2 arms in the primary composite CVD end point. Febuxostat, however, was associated with a higher risk of CVD-related death and all-cause mortality (driven by CVD deaths) compared with allopurinol. but there was no association with the other 3 secondary CVD outcomes (nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina). Interpretation of these results is complicated by a high dropout rate (45%) with a majority of deaths occurring after ULT discontinuation

Recommendations for patients receiving Febuxostat

- A large observational study did not show an increased risk of CVD or all-cause mortality associated with febuxostat initiation compared with allopurinol using methods to address confounding by indication
- Another study using a managed care database demonstrated lower risk of any major CVD event among febuxostat initiators than allopurinol initiators
- The Patient Panel representative stated that members would be willing to accept “some” incremental CVD risk as long as the treatment adequately controlled their gout.
- Thus, as for many such decisions with conditional recommendations, providers and patients should engage in shared decision-making when considering febuxostat for patients at high risk for CVD

Recommendations for patients receiving uricosurics

- *Checking urinary uric acid is **conditionally recommend against** for patients considered for or receiving uricosuric treatment.*
- *Alkalinizing the urine is **conditionally recommended against** for patients receiving uricosuric treatment*
- Standard best practice is that patients with known renal calculi or moderate-to-severe CKD (stage >3) should not be treated with uricosurics
- Using uricosuric agent as add-on therapy to partially responsive XOI treatment can result in improved sUA control

Arthritis Rheumatol 2017;69:203–12.
Arthritis Rheumatol 2017;69:1903–13

When to consider changing ULT strategy

- *Switching to a second XOI over adding a uricosuric agent is **conditionally recommended** for patients taking their first XOI, who have persistently high sUA (>6 mg/dl) despite maximum-tolerated or FDA-indicated XOI dose, and who have continued frequent gout flares (>2 flares/year) OR who have nonresolving subcutaneous tophi.*

- *Switching to pegloticase over continuing current ULT is **strongly recommended** for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the sUA target, and who continue to have frequent gout flares (≥2 flares/year) OR who have nonresolving subcutaneous tophi.*

- *Switching to pegloticase over continuing current ULT is **strongly recommended against** for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the sUA target, but who have infrequent gout flares (costs and harms clearly outweigh the benefits)*

Maggy wants to change her lifestyle…

Maggy is committed to work on living a healthy lifestyle to prevent gout flares as well as improve her HTN, HLD and prediabetes. She is obese and her pattern of alcohol intake can be called excessive.

What would you advise her about the weight in relation to the gout?

A Try to lose weight as it may reduce the sUA as well as flare frequency

B Try to lose weight as it is a good thing to do, although it may not have any effect on gout control

What should the PCP advise patient about alcohol intake and gout?

A Studies have not confirmed beneficial effect of reducing or stopping alcohol on gout

B Advise her to reduce alcohol intake as alcohol can clearly increase sUA and induce flares

Management of lifestyle factors

Regardless of disease activity-

- *Limiting alcohol intake is* ***conditionally recommended***
- *Limiting purine intake is* ***conditionally recommended***
- *Limiting high-fructose corn syrup intake is* ***conditionally recommended***
- *Using weight loss program (no specific program endorsed) is* ***conditionally recommended*** *for pt who are overweight/ obese*
- *Adding vitamin C supplementation is* ***conditionally recommended against***

Diet and Gout

- Obesity and genetic factors are important determinants of hyperuricemia and gout.
- Consumption of alcohol, purine rich diet, and high fructose corn syrup increases the risk of gout flares
- Dairy, cherry extract and possibly omega 3 fatty acids reduce the flare risk.
- Although certain food items may impact gout flares, their effects on tophi are not known.

Danve, Sehra and Neogi Best Practice & Research Clinical Rheumatology 35 (2021) 101723

Clinicians be mindful when soliciting information regarding the dietary habits of patients and ensure that discussions are not misinterpreted as “patient blaming,” as patients frequently feel stigmatized when discussing gout with their providers.

Karen Spencer et al. Ann Rheum Dis 2012;71:1490-1495

Management of concurrent medications

Regardless of disease activity-

- *Switching HCTZ to an alternate antihypertensive when feasible is* ***conditionally recommended***
- *Choosing losartan preferentially as an antihypertensive agent when feasible is* ***conditionally recommended***
- *Stopping low-dose aspirin (for patients taking this medication for appropriate indications) is* ***conditionally recommended against***
- *Adding or switching cholesterol-lowering agents to fenofibrate is* ***conditionally recommended against*** *for patients with gout*

Summary

- Gout is the most common inflammatory arthritis in the world
- It is possible to control the gout and prevent complications by using the available medications methodically
- Treat the acute flare with either colchicine/NSAIDs/Steroids
- Always use prophylaxis with colchicine (or NSAIDs) in the initial 3 to 6 months of starting ULT
- Start low dose allopurinol (100 mg) and adjust the dose to achieve sUA <6 mg/dl
- Optimize other medications that could contribute to hyperuricemia
- Encourage lifestyle modifications but avoid patient blaming
- When in doubt, find a rheumatologist!

Thank you

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