Das GOUT!

Dr. Grace Frankel (BScPharm, PharmD, BCPS, EPPh)

Faculty/Presenter Disclosure

Faculty: Grace Frankel

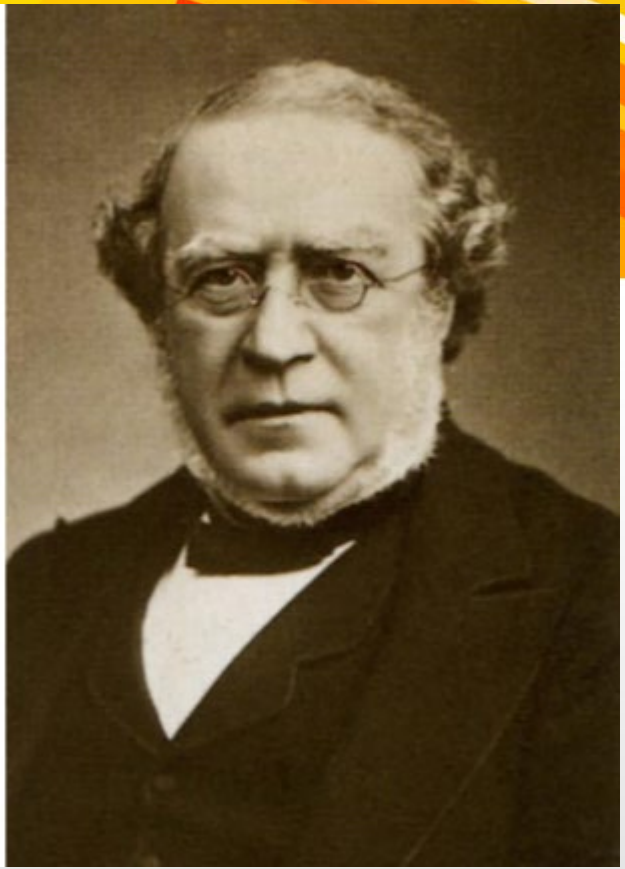
Relationships with commercial interest: None

- Occasional expert reviewer for Elsevier (pharmacy related textbooks)

Learning Objectives

1. Review epidemiology, pathophysiology and risk factors for gout
2. Discuss discrepancies in guideline recommendations for gout treatment and monitoring of uric acid levels
3. Analyze and discuss 2 patient cases to identify most appropriate pharmacotherapy for gout based on patient history and comorbid conditions
4. Summarize a common-sense approach to gout management using an evidence-based approach

Henry William Bunbury 1815



Sir Alfred Baring Garrod “the High Priest of Gout” 1819-1917

Z Rheumatol 2009 · 68:851–856

Epidemiology

- **Male sex** and **>60 years old**
  - SUA >340umol/L females
  - SUA > 404umol/L males
- 20% of males and females affected by *hyperuricemia* but gout affects men > women (6% vs 3% respectively)
- Genetics/Ethnicity plays a large role
  - Polynesian women, indigenous Pacific races like Maori and Taiwanese (genetic defects in renal handling of urate)
  - African Americans, Japanese and Hmong (Southern China)

Pathophysiology and drug targets

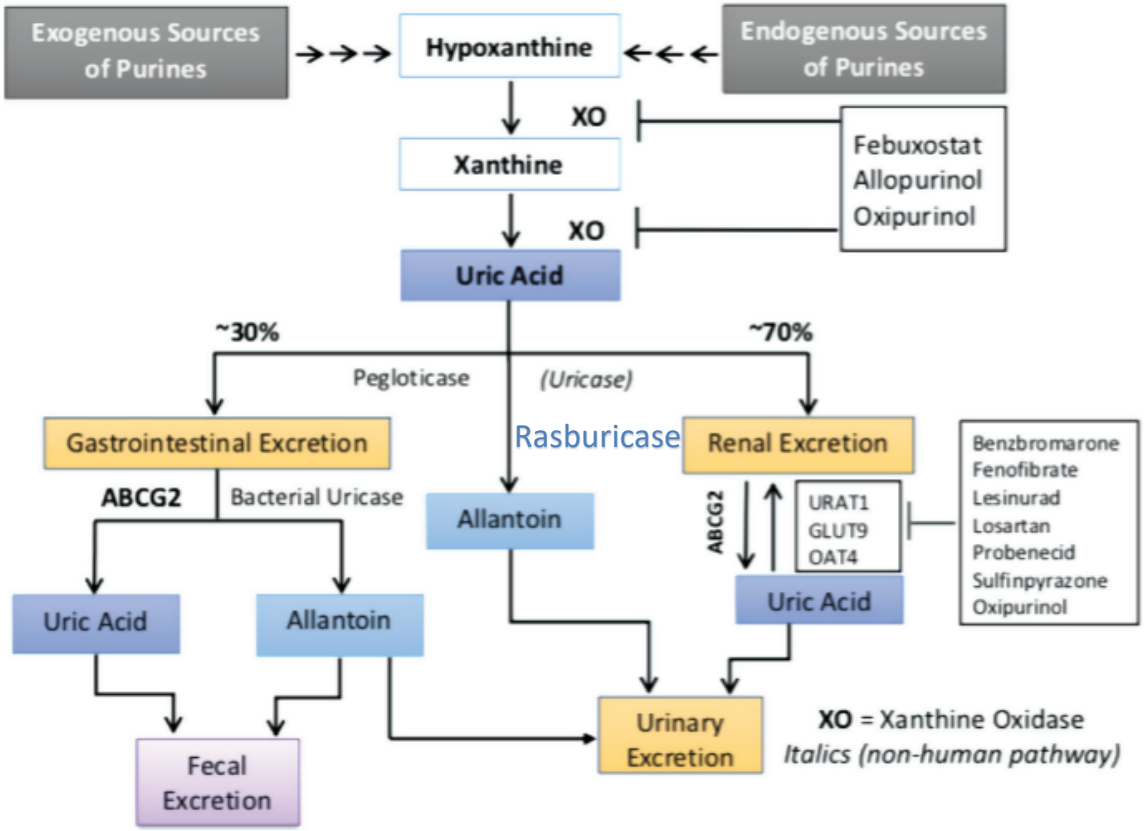


Figure 1. Schematic diagram for purine metabolism and urate-lowering therapy mechanisms of action.

Adapted with permission from: Roman YM. The Daniel K. Inouye College of Pharmacy scripts: perspectives on the epidemiology of gout and hyperuricemia. Hawaii J Med Public Health 2019;78:71-6.

Roman YR and Shah NR. Chapter: Hyperuricemia and Gout. ACSAP 2021 Book 1: Endocrinology and Rheumatology Care. [Accessed Sept 27, 2021]

slido

Which one of the following reduces the risk of gout?

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Slido Question #1

Which one of the following *reduces* the risk of gout?

a) A diet rich in red meat and seafood
b) High alcohol intake
c) Smoking
d) Consumption of high fructose corn syrup
e) Obesity

Risk Factors for Gout

	Urate overproduction	Urate Underexcretion	Combined
Primary	• Genetics • Ideopathic • Lesch-Hyhan syndrome • Kelley-Seegmiller syndrome • PRPP synthetase super-activity	• Genetics • Ideopathic • Familial juvenile gouty nephropathy	N/A
Secondary	• Purine-rich diet • Increased cell turnover • Tumor lysis syndrome • Glycogen storage disease	• Drugs • Volume depletion • Renal insufficiency • Hypertension • Lactic acidosis/ketoacidosis • Lead poisoning • Hypothyroidism • Hyperparathyroidism • Sarcoidosis • Down syndrome	• Alcohol • Exercise • Septic shock • Glycogenesis type 1 • Aldolase-B deficiency

Table 2: in Roman YR and Shah NR. Chapter: Hyperuricemia and Gout. ACSAP 2021 Book 1: Endocrinology and Rheumatology Care. [Accessed Sept 27, 2021]

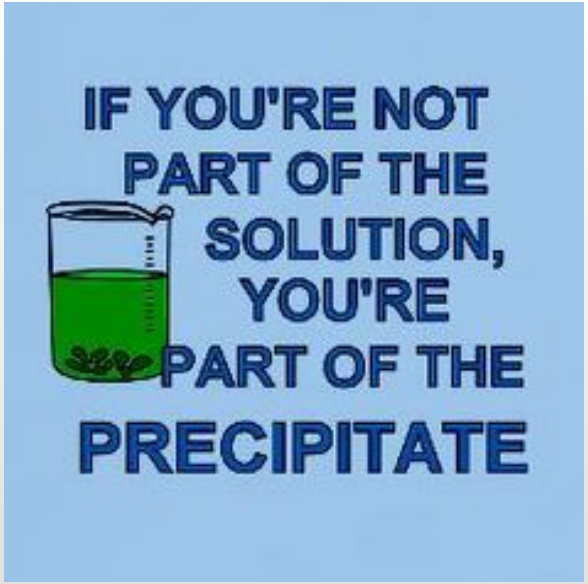
Drug-Induced Hyperuricemia

Reduced secretion	Increased Production	Combined Mechanisms
• Aspirin (<2g/day) • B-blockers • Cyclosporine • Tacrolimus • Diuretics** • Ethambutol • Pyrazinamide • L-Dopa • Nicotinic Acid • Ritonavir	• Cytotoxic chemotherapy • Fructose • Theophylline • Xylitol	• Testosterone • Ticagrelor

What patient population uses several of these therapies concomitantly?

Uric Acid and MSU formation

- Monosodium urate (MSU) crystal formation facts:
  - Depends on solubility/saturation levels
  - **MSU formation is associated with SUA levels >405 umol/L** (saturation point)
  - Shedding of the MSU crystals results in monocyte activation → cryopyrin activation → IL-1B + other cytokines
    = INFLAMMATION (heat, erythema, swelling) and/or interstitial nephritis/nephrolithiasis



J Clin Rheumatol . 2008 Oct;14(5 Suppl):S55-62

Diagnosis of Gout

Clinical Characteristics

- Sudden onset, often nocturnal
- First MTP (podagra), severe pain redness, swelling
- Episodic in nature, resolution in <15 days
- Tophus formation (chronic gout)

Joint Fluid Analysis

- Gold standard (presence of MSU crystals)
- Rule out infection (culture negative) but inflammatory in nature

Labs

- High SUA (but diagnosis not based solely on lab values, can be normal)

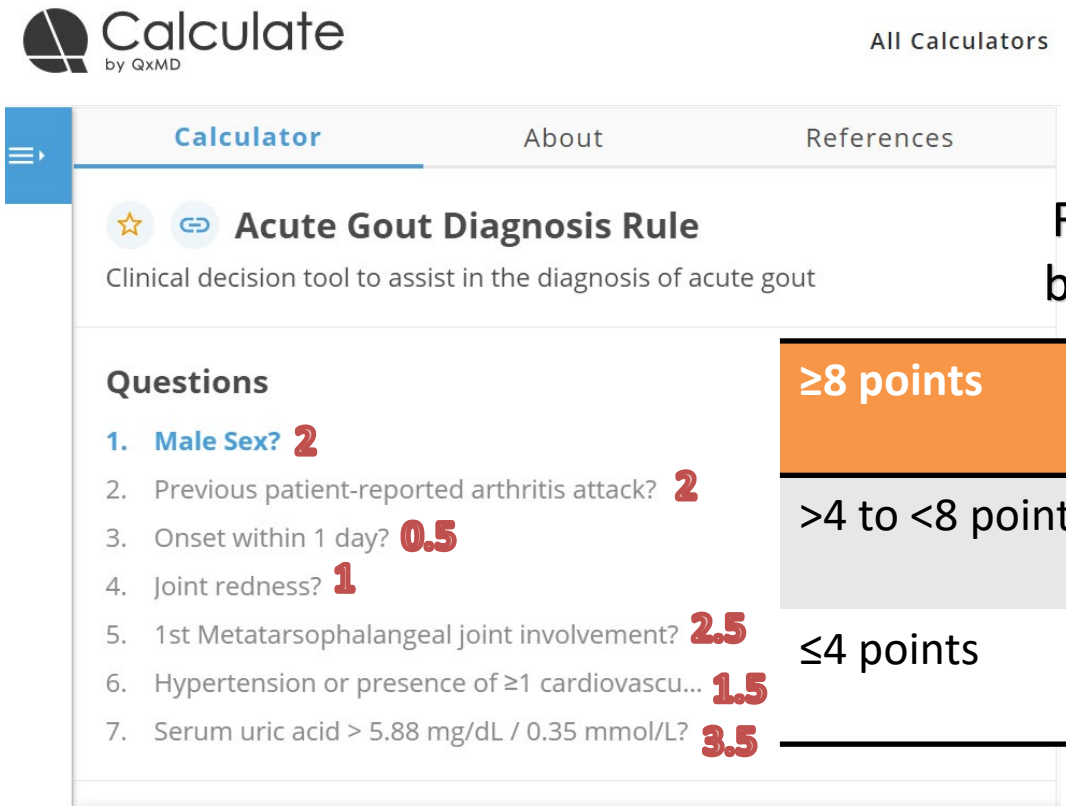
Imaging

- Asymmetric swelling, evidence of gout erosion
- Presence of gout tophus/double contour sign (US)
- Gout crystals (dual-energy CT)

Risk Factors

- >60, male sex
- Family history/genetics
- Chronic disease: CKD, HTN, CVD, Obesity, HTN,
- Meds

There's an app for that!

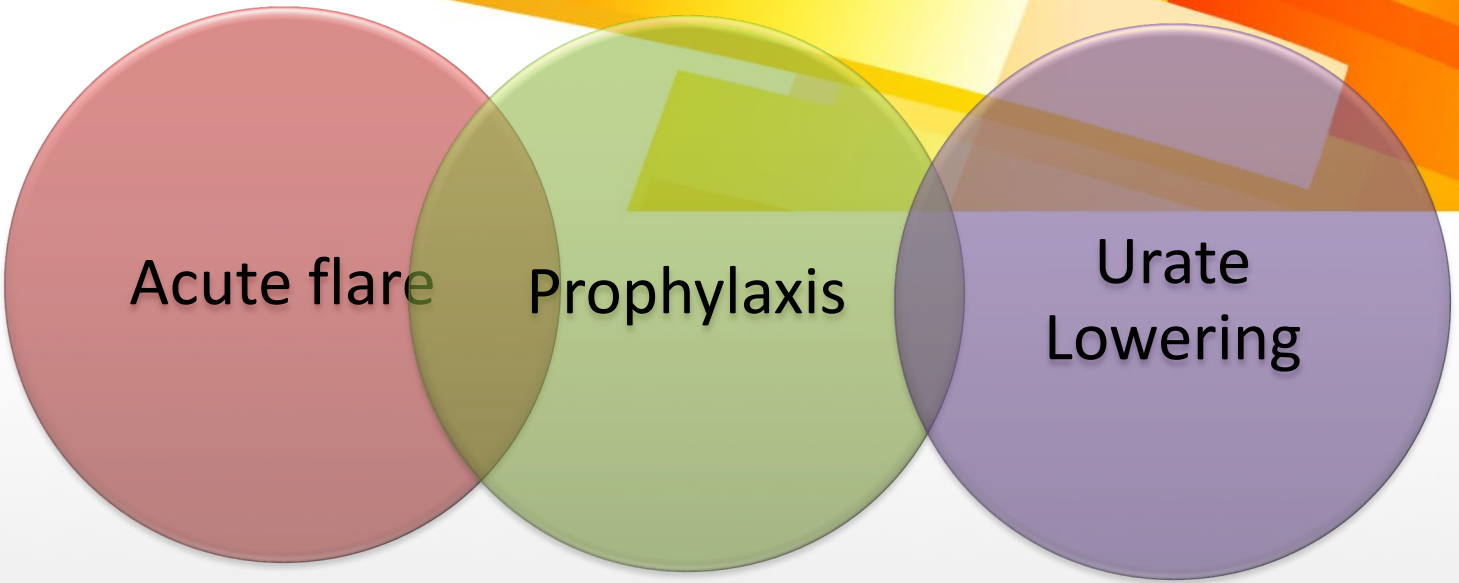


Family practice based calculator

≥8 points	High probability of gout
>4 to <8 points	Intermediate probability of gout
≤4 points	Low probability of gout

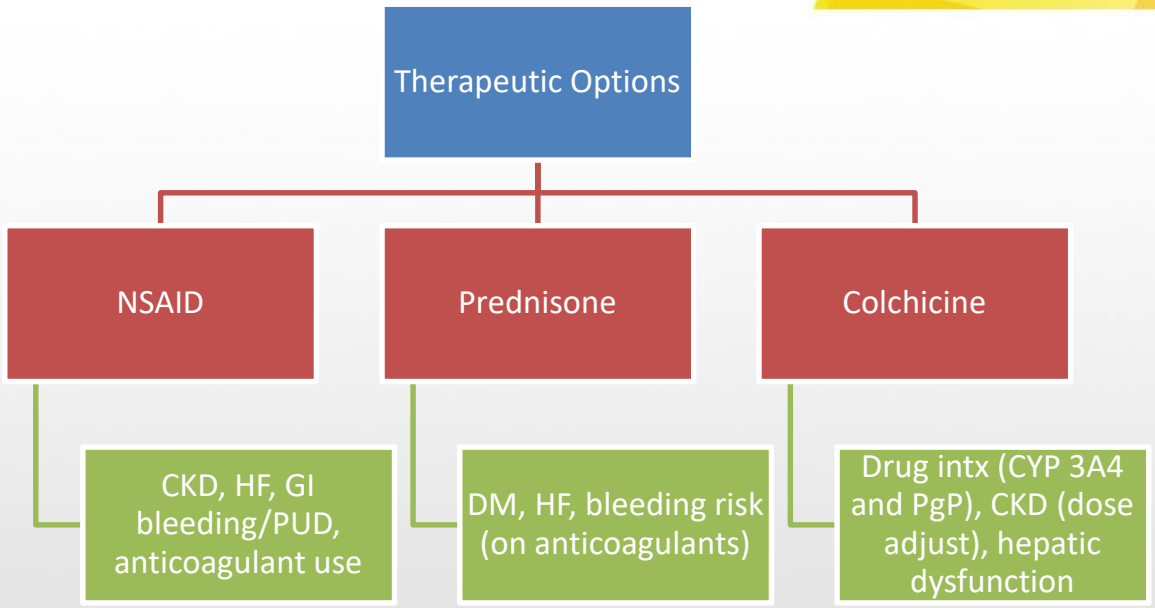
Consider joint aspiration

Original publication: Arch Intern Med 2010;170(13):1120



TREATMENT AND MANAGEMENT OF GOUT

Acute Gouty Arthritis (FLARE)



IL-1 inhibitors: Anakinra (for severe gout, increased infection risks/inj site reactions)

Acute Therapy PEARLS

- **NSAIDs**
  - Appropriate for younger patients without comorbid disease burden
  - CKD, HF, recent MI, PUD/Hx GI bleed and current use of anticoagulants/antiplatelets are relative contraindications for use (weigh risks/benefits)

- **Prednisone**
  - 0.5mg/kg/day (usually 30-40mg/day)
  - Taper dose over 7-10 days
  - Consider intra-articular injection if 2 or less joints affected and infection is ruled out

- **Colchicine**
  - Initiate within **36 hours of presentation**
  - **FLARE DOSE: 1.2mg** at onset followed by **0.6mg 1 hour later, then 0.6mg BID**
  - **Renally eliminated!!!!! (but not contraindicated - ADJUST)**
    - **CrCl 30-80mL/min – no dose adjustment needed**
    - **(conservative) CrCl 30-60mL/min 0.6mg daily max**
    - **CrCl<30mL/min – same dose for flare, but cannot repeat for 14 days**

- **IL-1 inhibitors**
  - Anakinra: injection site reactions and increased risk of infection
  - For refractory patients (high cost)

- **Combination therapy?**
  - Colchicine and NSAIDs if severe flare
  - AVOID NSAID + Steroids (high risk of GI bleed)

Prophylaxis therapy (3-6 months)

- **NSAIDs**
  - Appropriate for younger patients without comorbid disease burden
  - Conflicting evidence regarding “safest” NSAID
    - J Am Coll Cardiol . 2020 Aug 4;76(5):518-529 → celecoxib (seriously)
- **Prednisone**
  - 0.5mg/kg/day (usually 30-40mg/day)
  - Taper dose over 7-10 days
  - Consider intra-articular injection if 2 or less joints affected and infection is ruled out
- **Colchicine**
  - Dose is **DIFFERENT** than in acute flare
  - 0.6mg daily-BID (choose 0.6mg **once daily** if CrCl 30-60mL/min)
  - WATCH for GI intolerance

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Which one of the following patients would you consider initiating allopurinol therapy in?

ⓘ Start presenting to display the poll results on this slide.

Slido Question #2

Which one of the following patients would you consider initiating allopurinol therapy in?

a) 67 YO M, CKD (eGFR 31mL/min), DMII, UA 550 umol/L, first ever gout flare
b) 62 YO F, HTN, UA 610 umol/L with no gout symptoms
c) 47 YO M, no comorbidities, UA 490 umol/L, first ever gout flare
d) 59 YO M, HTN, DMII, UA 310 umol/L on losartan, metformin and febuxostat

Uric Acid Lowering Therapy (ULT)

- Who qualifies for therapy? [ACR 2020 Guidelines]
  - **Strong recommendation**
    - ≥ 2 gout flares per year
    - Tophaceous gout (presence of subcutaneous tophi)
    - Radiologic evidence of joint damage as a result of gout
  - **Conditional recommendation**
    - Patients in first gout flare with CKD Stage 3 or greater, SUA >535umol/L and/or urolithiasis
    - Patients in a gout flare with infrequent symptoms (<2 flares per year)

Arthritis & Rheumatology Vol. 72, No. 6, June 2020, pp 879–895

ULT Therapeutic Choices

- **Allopurinol** (xanthine oxidase inhibitor – inhibits production)
  - Dose: Initial 50-100mg daily (Max 800mg/day)
  - PEARLS: Can use in renal disease but MORE CONSERVATIVE with dosing and titration. **RISK OF SCARS (severe cutaneous adverse reactions) = SJS, TENS, DRESS**

- **Febuxostat** (xanthine oxidase inhibitor – inhibits production)
  - Dose: Initial 40mg daily (Max 80mg daily)
  - PEARLS: AVOID in CV disease (increased risk heart failure, CV death and all-cause death), CI in liver disease (get LFTs before starting), indicated for patients with a true allopurinol allergy. Achieves better uric acid lowering than allopurinol (higher potency)

- **Probenecid** (uricosuric agent – increases excretion, blocks absorption)
  - Dose: Initial: 250mg twice daily (Max 4g daily)
  - PEARLS: dramatic uric acid excretion (1-2g/day) increases risk of UA nephropathy, nephrolithiasis/urolithiasis. Renally eliminated (CI CrCl<30mL/min). Can inhibit excretion of other drugs.

ULT Therapeutic Choices (refractory disease)

- **Pegloticase (US only)** – recombinant pegylated uricase (breaks up uric acid to allantoin for excretion)
  - Dose: 8mg IV Q2weeks
  - PEARLS: drug antibodies can form, infusion reactions (pre-treatment required), must stop all other ULT before starting therapy
- **Rasburicase – used only in oncology**
  - Dose: 0.05-0.2mg/kg IV once daily
  - PEARLS: primarily for prevention/treatment tumor lysis syndrome in oncology (very costly) – triggers gout flares (thus why it's not used in gout)

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True or False: Uric acid lowering therapy (ULT) should be titrated to a target of <360 umol/L in patients with gout? (and even lower, <300 umol/L in those with tophi)

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Slido Question #3

True or False: Uric acid lowering therapy (ULT) should be titrated to a target of <360 umol/L in patients with gout? (and even lower, <300 umol/L in those with tophi)

a) True
b) False
c) It’s controversial

Uric acid controversies

CLINICAL GUIDELINE

ACP American College of Physicians

Leading Internal Medicine, Improving Lives

Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Russell P. Harris, MD, MPH; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Evidence was insufficient to conclude whether the benefits of escalating urate-lowering therapy to reach a serum urate target ("treat to target") outweigh the harms associated with repeated monitoring and medication escalation.

ACR GUIDELINE FOR MANAGEMENT OF GOUT

2020 American College of Rheumatology Guideline for the Management of Gout

Arthritis & Rheumatology

Vol. 72, No. 6, June 2020, pp 879–895

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

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

Studies used to support this statement include several multidisciplinary interventions by pharmacist and nurses in a treat-to-target approach but also lifestyle counselling

Uric acid controversies

TOOLS FOR PRACTICE

Targeting uric acid levels in treating gout

Joey Ton BScPharm PharmD Michael R. Kolber MD CCFP MSc

Clinical question

To prevent gout recurrence, should we prescribe urate-lowering therapies (eg, allopurinol) to target uric acid levels?

Bottom line

Best evidence finds that increasing the dosage of allopurinol to achieve a serum urate target (eg, <360 µmol/L) does not reduce gout flares, pain, or function compared with standard allopurinol dosage. Febuxostat increases cardiovascular death and overall mortality and should not be used in most patients with gout.

Can Fam Physician.

A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout

Lisa K Stamp,[1,2] Peter T Chapman,[2] Murray L Barclay,[1] Anne Horne,[3] Christopher Frampton,[1] Paul Tan,[3] Jill Drake,[1] Nicola Dalbeth[3]

Ann Rheum Dis 2017 Sep;76(9):1522-1528

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	RCT, parallel-group – follow-up 12 months
P	N=183, gout with CrCl-based allopurinol therapy for 1 month or more and SUA >6mg/dL (357umol/L). Mean SUA 7.15 and mean allopurinol dose 269mg/day at baseline
I	Dose escalation of allopurinol
C	Continue current dose of allopurinol
O	Serum uric acid, gout flares and safety measures (LFT/renal outcomes, side effects)

- SUA -0.34mg/dL (20 umol/L) control vs -1.5mg/dL (89umol/L) intervention group
- 32% control and 69% intervention had SUA <6mg/dL (<357umol/L)
- No difference in gout flares between groups: 59% control, 54% intervention had ≥1 gout flare over 12 month period
- No real differences in side effects between groups, some LFT changes in dose escalation group

Ann Rheum Dis 2017 Sep;76(9):1522-1528

Episode 457: Who let the Gout Out? Targeting Uric Acid Levels in Treating Gout

August 28, 2020

In episode 457, James and Mike yet again invite Joey Ton to go through the evidence around reaching a target serum urate level in patients with gout. As with many arbitrary thresholds determined from observational studies (sometimes), or just made up, when you properly study if there is a benefit to achieving these levels the theory really crumbles under the weight of the evidence. We also briefly talk about the febuxostat vs allopurinol data and the outcomes that matter.

Case Study 1

JL is a 50 YO M (BMI 27 kg/m^2, Japanese) with a history of MSU proven gout with infrequent flares (1 per year). He takes celecoxib 100mg PO BID for 5 days during a flare. His most recent lab work 4 weeks ago showed SUA 452 umol/L, sCr 106 umol/L, K+ 3.2. He has HTN (recent BP 136/80) and dyslipidemia. He smokes 2-3 cigarettes per day and consumes 2-3 drinks per week (wine). His father also had gout.

- HCTZ 50mg daily
- Amlodipine 2.5mg daily
- Atorvastatin 20mg daily
- Acetaminophen 325mg PRN for headaches

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Case Study 1, #1 - Which one of the following most increases JL’s risk of having gout?

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Case Study 1

JL is a 50 YO M (BMI 27 kg/m^2, Japanese) with a history of MSU proven gout with infrequent flares (1 per year). He takes celecoxib 100mg PO BID for 5 days during a flare. His most recent lab work 4 weeks ago showed SUA 452 umol/L, sCr 106 umol/L, K+ 3.2. He has HTN (recent BP 136/80) and dyslipidemia. He smokes 2-3 cigarettes per day and consumes 2-3 drinks per week (wine).

- HCTZ 50mg daily
- Amlodipine 2.5mg daily
- Atorvastatin 20mg daily
- Acetaminophen 325mg PRN for headaches

Question #1:

Which one of the following most increases JL's risk of having gout?

a) Smoking
b) Alcohol use
c) Race/ethnicity
d) Obesity

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Case Study 1, #2 - Given his medication history, which one of the following is most likely adversely contributing to his SUA concentrations?

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Case Study 1

JL is a 50 YO M (BMI 27 kg/m^2, Japanese) with a history of MSU proven gout with infrequent flares (1 per year). He takes celecoxib 100mg PO BID for 5 days during a flare. His most recent lab work 4 weeks ago showed SUA 452 umol/L, sCr 106 umol/L, K+ 3.2. He has HTN (recent BP 136/80) and dyslipidemia. He smokes 2-3 cigarettes per day and consumes 2-3 drinks per week (wine).

- HCTZ 50mg daily
- Atorvastatin 20mg daily
- Acetaminophen 325mg PRN for headaches

Question #2:

Given his medication history, which one of the following is most likely adversely contributing to his SUA concentrations?

a) Celecoxib
b) Acetaminophen
c) HCTZ
d) Atorvastatin

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Case Study 1, #3 - What would be the best therapeutic management for JM’s gout?

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Case Study 1

JL is a 50 YO M (BMI 27 kg/m^2, Japanese) with a history of MSU proven gout with infrequent flares (1 per year). He takes celecoxib 100mg PO BID for 5 days during a flare. His most recent lab work 4 weeks ago showed SUA 452 umol/L, sCr 106 umol/L, K+ 3.2. He has HTN (recent BP 136/80) and dyslipidemia. He smokes 2-3 cigarettes per day and consumes 2-3 drinks per week (wine).

- HCTZ 50mg daily
- Atorvastatin 20mg daily
- Acetaminophen 325mg PRN for headaches

Question #3:

What would be the best therapeutic management for JM's gout?

a) Discontinue celecoxib and initiate colchicine

b) Discontinue acetaminophen and initiate aspirin

c) Discontinue atorvastatin and initiate fenofibrate

d) Discontinue HCTZ and initiate losartan

Drugs that can lower SUA (other than ULT)

- **Antihypertensives**
  - Losartan (↓6% SUA overall, 23% in genetically predisposed)
  - Amlodipine (↓ gout by 37% - ALLHAT trial)
- **SGLT2i's**
  - Canagliflozin (↓13% SUA)
- **Lipid-lowering agents**
  - Fenofibrate (↓20% SUA in DMII)
  - Pravastatin/Atorvastatin (variable)

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Case Study 1, #4 - JM asks if there are any natural products that could help with his gout. Which of the following has evidence to lower the risk of gout flares?

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Case Study 1

JL is a 50 YO M (BMI 27 kg/m^2, Japanese) with a history of MSU proven gout with infrequent flares (1 per year). He takes celecoxib 100mg PO BID for 5 days during a flare. His most recent lab work 4 weeks ago showed SUA 452 umol/L, sCr 106 umol/L, K+ 3.2. He has HTN (recent BP 136/80) and dyslipidemia. He smokes 2-3 cigarettes per day and consumes 2-3 drinks per week (wine).

- HCTZ 50mg daily
- Atorvastatin 20mg daily
- Acetaminophen 325mg PRN for headaches

Question #4:

JM asks if there are any natural products that could help with his gout. Which of the following has evidence to lower the risk of gout flares?

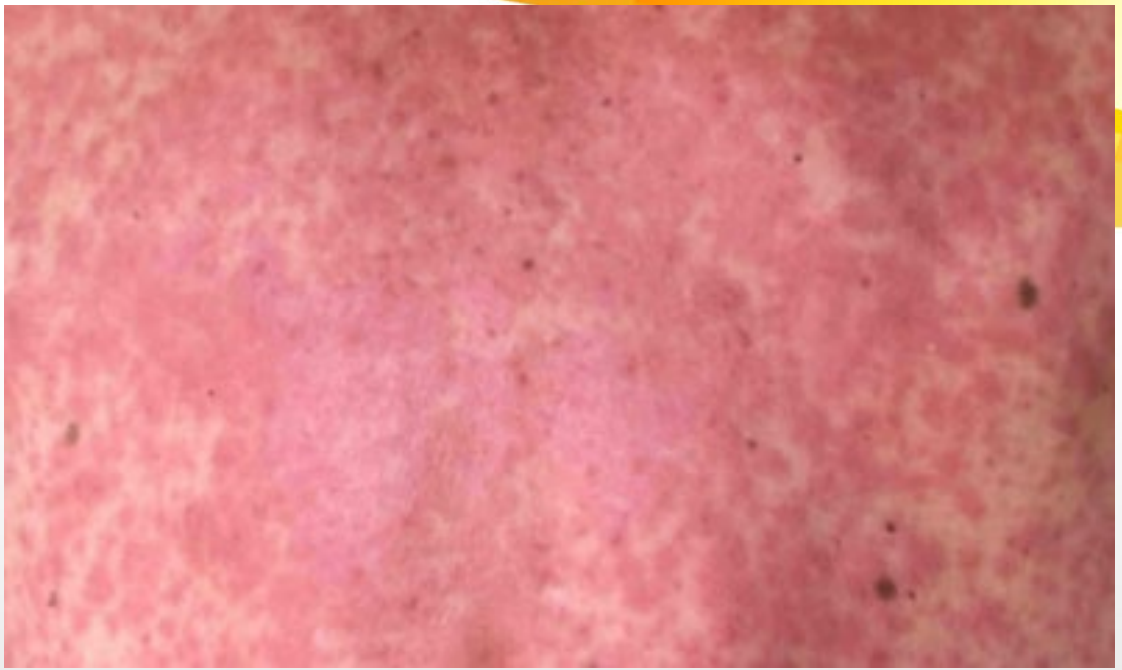
a) Cherries
b) Garlic
c) Willow Bark
d) Coffee

Evidence-Based Complementary and Alternative Medicine 2019 Dec 4;2019:9896757

Case Study 2

MW, a 60 YO F (Filipino ethnicity), presents to her primary care provider for her first visit subsequent to an ER visit 3 weeks ago for a severe gout flare (SUA in the ER was 6. She has a history of MI, CKD (eGFR 45mL/min), DMII (last A1c 6.1%), urolithiasis and tophaceous gout. Today, she shows you a rash she developed 2 days ago.

- Bisoprolol 5mg daily
- Ramipril 10mg daily
- ASA 81 mg daily
- Rosuvastatin 40mg daily
- Ferrous fumarate 300mg HS
- Metformin 500mg BID
- Allopurinol 200mg daily (new, ER D/C)
- Naproxen 500mg BID (New, ER D/C)



Picture from patient’s back (morbilliform)
Started on her stomach yesterday, spread to back (wrapped around).
Arms and legs spared

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Case Study 2, #1 - What advice would you give this patient?

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Case Study 2

MW, A 60 YO F (Filipino ethnicity), presents to her primary care provider for her first visit subsequent to an ER visit 3 weeks ago for a severe gout flare (SUA in the ER was 650. She has a history of MI, CKD (eGFR 45mL/min), DMII (last A1c 6.1%), urolithiasis and tophaceous gout. Today, she shows you a rash she developed 2 days ago.

- Bisoprolol 5mg daily
- Ramipril 10mg daily
- ASA 81 mg daily
- Rosuvastatin 40mg daily
- Ferrous fumarate 300mg HS
- Metformin 500mg BID
- Allopurinol 200mg daily (new, ER D/C)
- Naproxen 500mg BID (New, ER D/C)

Question #1:

What advice would you give this patient?

a) Prescribe prednisone 50mg PO daily x 5 days

b) Stop allopurinol therapy, prescribe topical corticosteroids

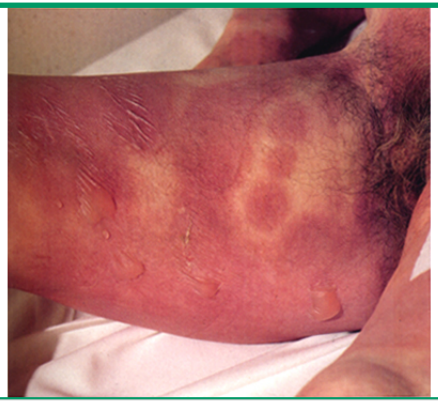
c) Stop ramipril, prescribe OTC 2nd generation antihistamine

d) Stop naproxen, prescribe prednisone 20mg PO daily x 7 days

Allopurinol and SCARS (severe cutaneous adverse reactions)

- Rare; 0.1-0.4% prevalence, however mortality is up to 25%
- Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TENs) and Drug reaction with eosinophilia and systemic symptoms (DRESS)
- **Risk factors:**
  - Genetic predisposition (HLA-B*5801) – Han Chinese
  - Higher starting doses
  - Shorter titration periods
  - Lower renal function
- STOP Medication IMMEDIATELY
  - May take ~3 weeks to resolve

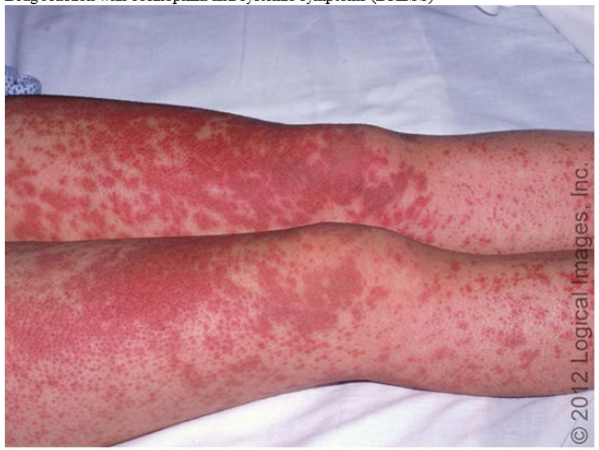
Cutaneous changes of Stevens-Johnson syndrome (SJS)



Generalized eruption of lesions that initially had a target-like appearance but then became confluent, brightly er[illegible] and bullous. The patient had extensive mucous me[illegible] involvement and tracheobronchitis.

Reproduced with permission from: Stevens-Johnson Syn[illegible] Epidermal Necrolysis. In: Color Atlas and Synopsis of Clin[illegible] Dermatology: Common and Serious Diseases, 3rd editio[illegible] Johnson RA, Wolff K, et al (Eds), McGraw-Hill, New York [illegible]. © 1997 McGraw-Hill.

Drug reaction with eosinophilia and systemic symptoms (DRESS)



Confluent morbilliform skin eruption with follicular accentuation in a patient with drug reaction with eosinophilia and systemic symptoms (DRESS).
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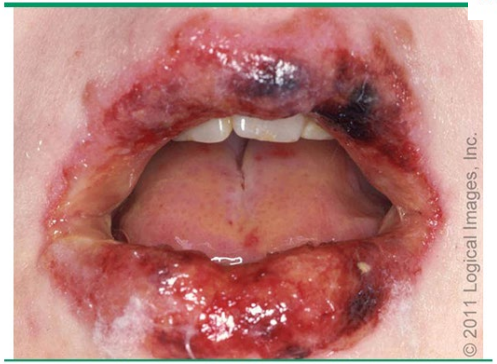
Mucosal changes in Stevens-Johnson syndrome/toxic epidermal necrolysis



Changes similar to those observed in SJS/TEN can also be observed in erythema multiforme majus.

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

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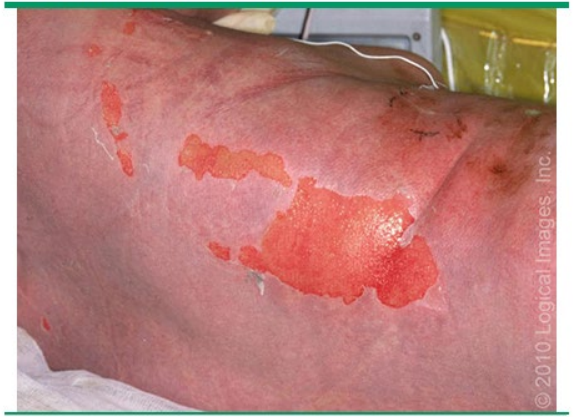
Toxic epidermal necrolysis



Diffuse erythema and large areas of denuded epidermis are present.

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Case Study 2, # 2 - What approach would you take now for MW’s ULT?

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Case Study 2

MW, A 60 YO F (Filipino ethnicity), presents to her primary care provider for her first visit subsequent to an ER visit 3 weeks ago for a severe gout flare (SUA in the ER was 750. She has a history of MI, CKD (eGFR 45mL/min), DMII (last A1c 6.1%), urolithiasis and tophaceous gout. Today, she shows you a rash she developed 2 days ago.

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- Metformin 500mg BID
- Allopurinol 200mg daily (new, ER D/C)
- Naproxen 500mg BID (New, ER D/C)

Question #2:

What approach would you take now for MW's ULT?

a) Change allopurinol to febuxostat

b) Change allopurinol to probenecid

c) Change allopurinol to prednisone

d) Refer to rheumatology

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Case Study 2, #3 - Considering her comorbid conditions, what is the safest NSAID to recommend for MW?

ⓘ Start presenting to display the poll results on this slide.

Case Study 2

MW, A 60 YO F (Filipino ethnicity), presents to her primary care provider for her first visit subsequent to an ER visit 3 weeks ago for a severe gout flare (SUA in the ER was 750. She has a history of MI, CKD (eGFR 45mL/min), DMII (last A1c 6.1%), urolithiasis and tophaceous gout. Today, she shows you a rash she developed 2 days ago.

- Bisoprolol 5mg daily
- Ramipril 10mg daily
- ASA 81 mg daily
- Rosuvastatin 40mg daily
- Ferrous fumarate 300mg HS
- Metformin 500mg BID
- Allopurinol 200mg daily (new, ER D/C)
- Naproxen 500mg BID *New, ER D/C)

Question #3:

Considering her comorbid conditions, what is the *safest* NSAID to recommend for MW?

a) Ketorolac
b) Indomethacin
c) Celecoxib
d) Naproxen

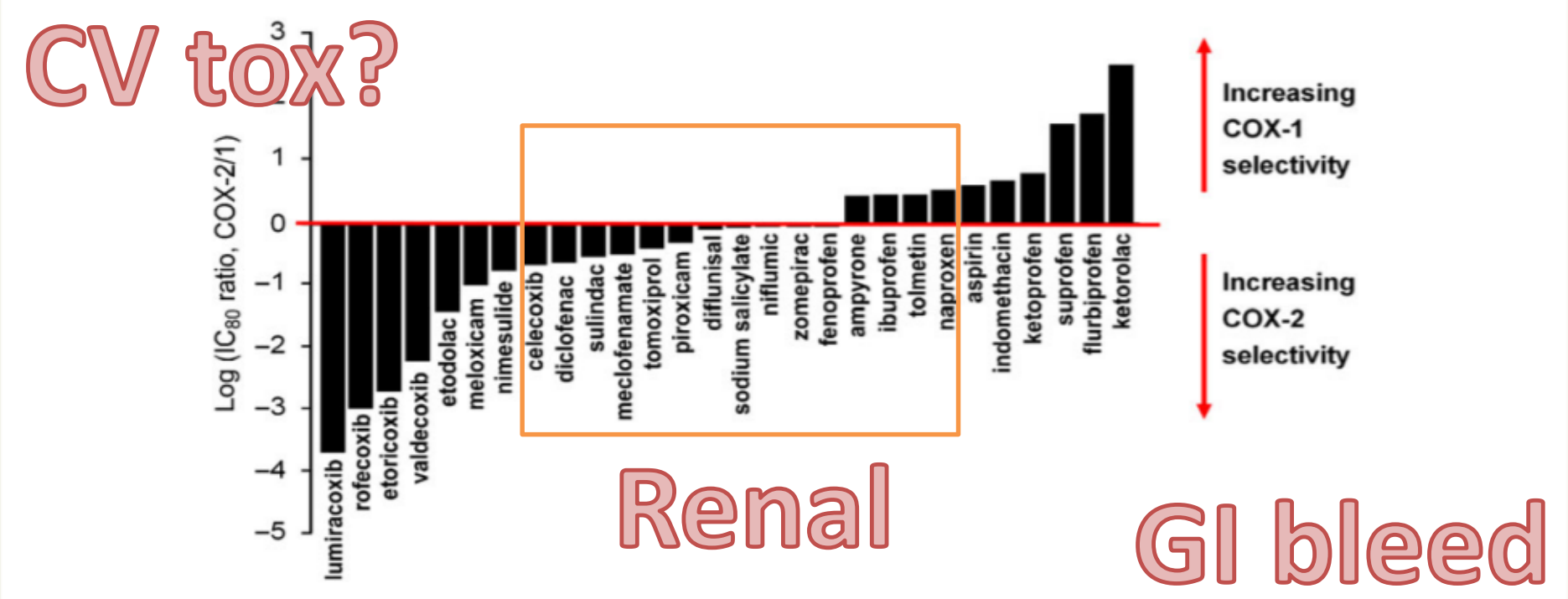
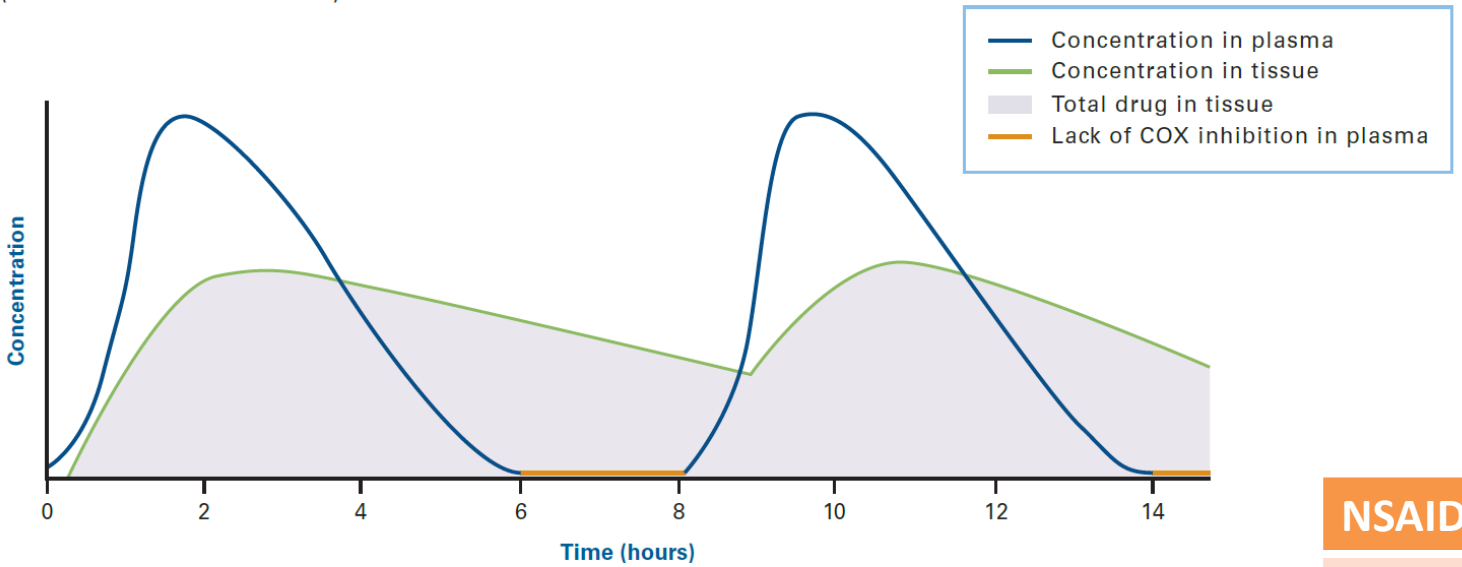


Figure 2 Relative COX selectivity of non-steroidal anti-inflammatory drugs displayed by the concentration of the drugs (IC_{80}) required to inhibit COX-1 and COX-2 activity by 80%.

European Heart Journal (2016) 37, 1015–

Figure 5. Typical Plasma and Tissue Concentration Profile of Acidic NSAIDs Such as Diclofenac and Ibuprofen (short elimination half-life)[47]



Plasma and tissue pharmacokinetics of multiple doses of an NSAID (such as diclofenac or ibuprofen) with a short half-life. As shown, period doses may permit recovery of COX enzyme function in the central compartment (ie, blood, vessel walls, and kidneys).
Adapted from Brune K. *Curr Med Res Opin.* 2007;12:2985-2995.

NSAID	T ½ (hr)
Diclofenac	2 (IR)
Ibuprofen	2.4
Celecoxib	11
Naproxen	12-17

Am J Manag Care. 2015;21:S139-S147

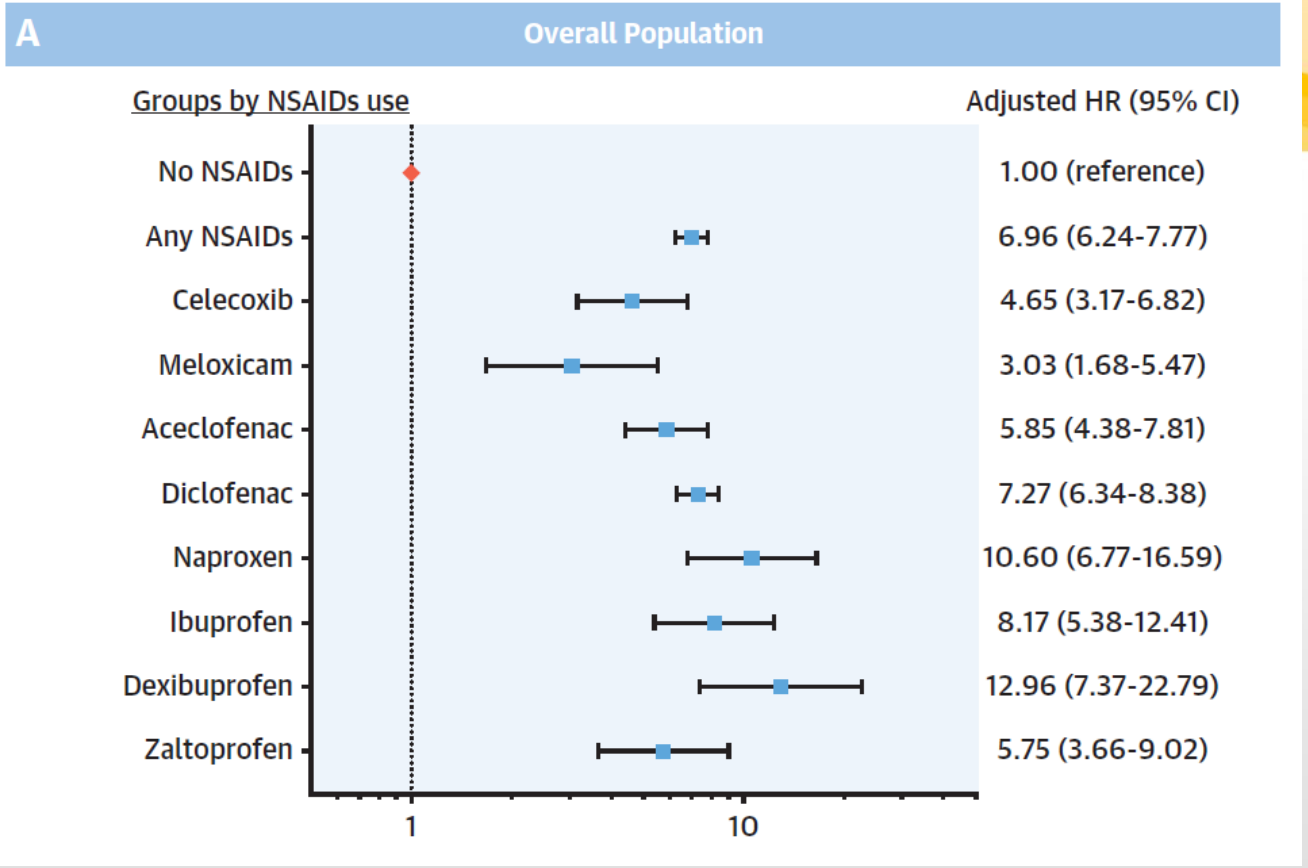
Naproxen least risk??
How about all have a risk....

Table 1. Summary of the numbers of studies and overall results.

Drug	Case-Control Studies		Cohort Studies		Total Number of Studies	Pooled RR (95% CI)	Heterogeneity		
	Number of Studies	Number of Exposed Cases/ Controls	Number of Studies	Number of Person-Years of Exposure			Cochran *Q*	*p*-Value	I^2
Naproxen	24	3,103/24,468	17	159,824	41	1.09 (1.02, 1.16)	143.1	<0.0001	70.70%
Ibuprofen	21	5,716/37,207	17	255,621	38	1.18 (1.11, 1.25)	226.7	<0.0001	81.90%
Celecoxib	20	1,496/12,755	15	179,479	35	1.17 (1.08, 1.27)	236.9	<0.0001	84.40%
Rofecoxib	19	1,662/10,827	15	126,219	34	1.45 (1.33, 1.59)	227.8	<0.0001	84.20%
Diclofenac	16	3,181/13,523	13	50,736	29	1.40 (1.27, 1.55)	224.4	<0.0001	86.60%
Indomethacin	11	788/4,406	3	9,350	14	1.30 (1.19, 1.41)	20.8	0.1	32.60%
Piroxicam	7	288/1,216	1	0[a]	8	1.08 (0.91, 1.30)	8.6	0.3	18.90%
Meloxicam	6	240/714	1	0[a]	7	1.20 (1.07, 1.33)	2.8	0.7	0%
Etodolac	4	464/4,115	1	8,994	5	1.55 (1.28, 1.87)	18.9	0.01	57.70%
Etoricoxib	4	60/116	0	0	4	2.05 (1.45, 2.88)	0.7	0.9	0%
Valdecoxib	1	2/2	4	5,629	5	1.05 (0.81, 1.36)	13.4	0.004	77.60%

PLoS Med . 2011 Sep;8(9):e1001098

Cardiovascular Risk of Concomitant NSAIDs Treatment After MI



	Cohort, database study (Korea)
P	N=108,332, mean age 64 years, 2.3 years f/up
I&C	Recent MI, followed for NSAID use
O	CV events and bleeding

J Am Coll Cardiol 2020;76:518–29)

Practical NSAID Tips:

- All NSAIDs increase CV and renal risks (some are better for GI – COX-2 selective)
- Consider short-acting, non-selective (ibuprofen, IR diclofenac) may allow for COX enzyme recovery in-between doses
- Lowest doses for relief (naproxen ≤500mg/day, ibuprofen ≤ 1200mg/day) to avoid adverse effects
- COX-2 inhibitors (specifically celecoxib) may not have the same CV risk as rofecoxib due to the fact it's les Cox-2 selective (more ?non-selective) – need to study this more

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Case Study 2, #4 - Which one of the following would be the best therapeutic strategy for this patient's overall gout management considering her comorbid conditions?

ⓘ Start presenting to display the poll results on this slide.

Case Study 2

MW, A 60 YO F (Filipino ethnicity), presents to her primary care provider for her first visit subsequent to an ER visit 3 weeks ago for a severe gout flare (SUA in the ER was 750. She has a history of MI, CKD (eGFR 45mL/min), DMII (last A1c 6.1%), urolithiasis and tophaceous gout. Today, she shows you a rash she developed 2 days ago.

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- Metformin 500mg BID
- Allopurinol 200mg daily (New, ER D/C)
- Naproxen 500mg BID (New, ER D/C)

Question #4

Which one of the following would be the best therapeutic strategy for this patient's overall gout management considering her comorbid conditions?

a) Colchicine 0.6mg daily for prophylaxis therapy, probenecid for ULT

b) Prednisone 40mg daily for prophylaxis therapy, febuxostat for ULT

c) Continue naproxen for prophylaxis therapy, probenecid for ULT

d) Stop NSAID therapy, initiate probenecid only for ULT

Summary of PEARLS

- Uric acid levels are a *tool* to individualize therapy, not a treat-to-target approach
- Give your patients 3-6 months of acute flare prophylaxis if deciding to start ULT; choose an agent based on comorbid conditions
- Don’t be afraid to use allopurinol in CKD; just start LOW, titrate SLOWLY (due to risk of SCARs)
- Colchicine is also appropriate in renal disease, adjust the dose!
- NSAIDs have harms (CV, renal, GI); use short-acting agents at lowest effective doses
- A multi-faceted, interprofessional approach (ULT, lifestyle changes) most effective

References

- Roman YR and Shah NR. Chapter: Hyperuricemia and Gout. ACSAP 2021 Book 1: Endocrinology and Rheumatology Care. [Accessed Sept 27, 2021]
- American College Rheumatology Guidelines 2020
- American College Physicians Guidelines 2017
- Gout. Lancet