RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Second Annual National Conference

September 30 – October 2, 2021

Phoenix, AZ

RhAPP
RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Impact of renal or hepatic dysfunction on medication management of rheumatologic disorders

Beth H. Resman-Targoff, Pharm.D., FCCP
Clinical Professor, University of Oklahoma College of Pharmacy

Disclosure

All faculty and staff involved in the planning or presentation of continuing education activities provided by the Annenberg Center for Health Sciences at Eisenhower (ACHS) are required to disclose to the audience any real or apparent commercial financial affiliations related to the content of the presentation or enduring material. Full disclosure of all commercial relationships must be made in writing to the audience prior to the activity. All staff at the Annenberg Center for Health Sciences at Eisenhower and Rheumatology Advanced Practice Providers (RhAPP) have no relationships to disclose.

Faculty Disclosure

Beth H. Resman-Targoff, Pharm.D., FCCP

- There are no financial relationships to disclose

Learning Objectives

- Describe drugs used to treat rheumatologic diseases that can affect kidney or liver function
- Evaluate consequences of those effects
- Assess need for drug dosage adjustments in patients with renal or hepatic impairment

Kidney Disease

- Affects 31 million in US
  - Can be result of rheumatologic diseases
    - Specific disease involvement of kidneys
    - Consequence of inflammation
  - Drug nephrotoxic effects (#3 cause acute kidney injury)
- Considerations when dosing rheumatologic drugs
  - Drug accumulation can ↑ risk for other toxicities
  - Little guidance provided in product information or published literature for most drugs

https://nephcure.org/livingwithkidneydisease/what-is-kidney-disease-2/

Sales GTM, et al. Rev Assoc Med Bras 2020;66(suppl1):S82-90.

Chronic Kidney Disease (CKD)

- Stages
  - 1: GFR ≥90 mL/min, normal
  - 2: GFR 60-89 mL/min, mild CKD
  - 3A: GFR 45-59 mL/min, mild to moderate CKD
  - 3B: GFR 30-44 mL/min, moderate to severe CKD
  - 4: GFR 15-29 mL/min, severe CKD
  - 5: GFR <15 mL/min, end stage CKD

Stamp LK, et al. Nat Rev Rheumatol 2021;https://doi.org/10.1038/s41584-021-00657-4.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Most common prescribed drugs
- 2.5 million in US/year have NSAID-related renal issues
  - Up to 15% of acute kidney injury associated with NSAIDs
  - >25% incidence in those over 65 years old
    - Elderly often have osteoarthritis, gout, chronic inflammation

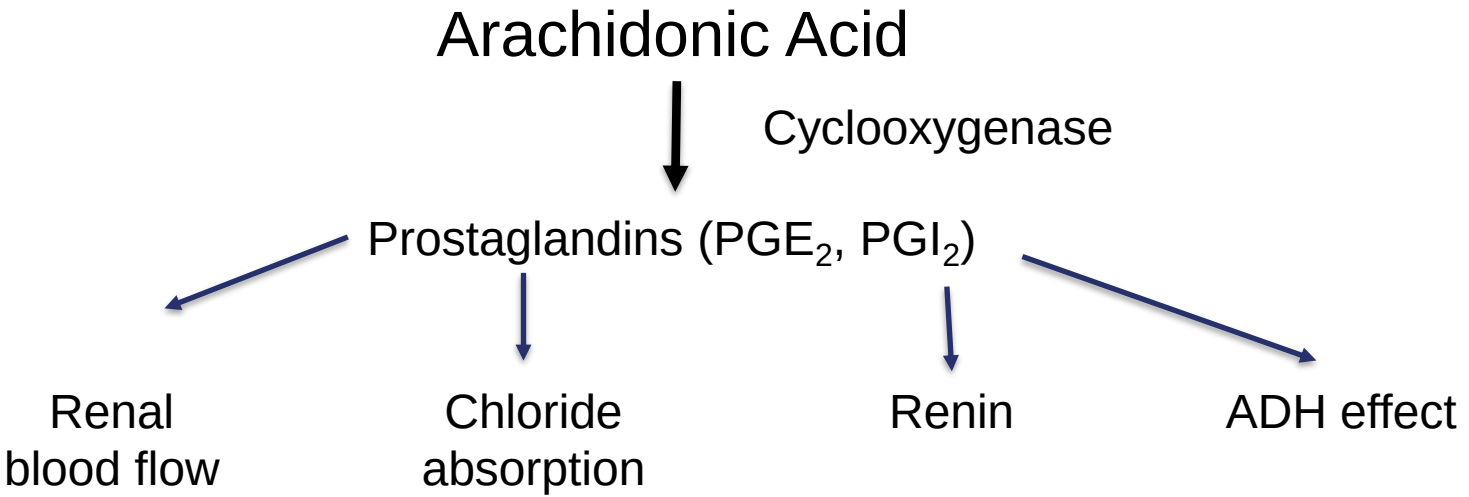
Bindu S, et al. Biochem Pharmacol 2020;180:114147.

Adverse NSAID Effects on Kidneys

- Acute kidney injury
- Chronic kidney disease
  - Renal papillary necrosis
  - Interstitial nephritis
  - Glomerulonephritis
  - Electrolyte imbalance: hyperkalemia, hyponatremia
  - Renal tubular acidosis
  - Fluid-retention-induced hypertension

Bindu S, et al. Biochem Pharmacol 2020;180:114147.

Arachidonic Acid Pathway

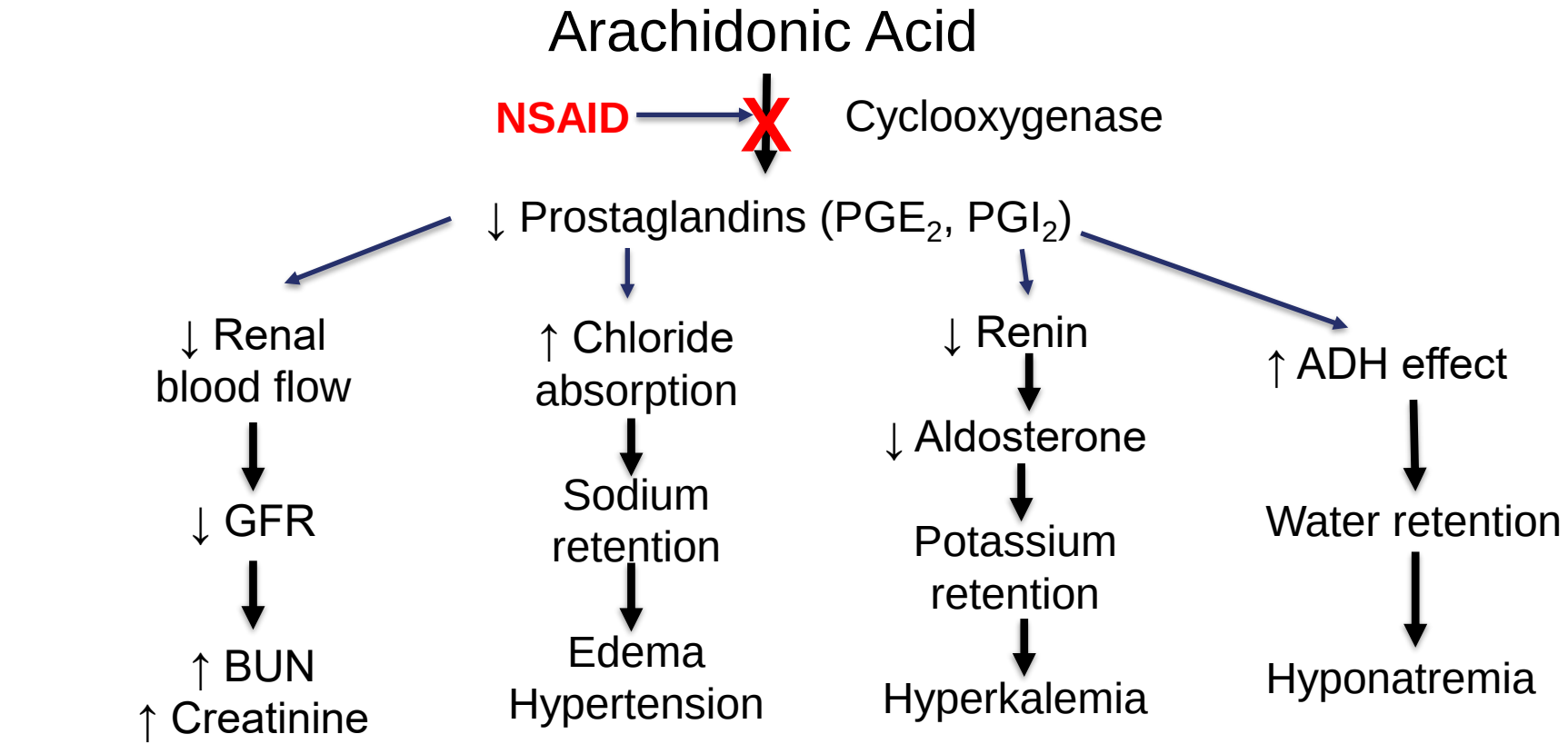


White WB. Am J Med 2009;122:S3-9.

Cyclooxygenase

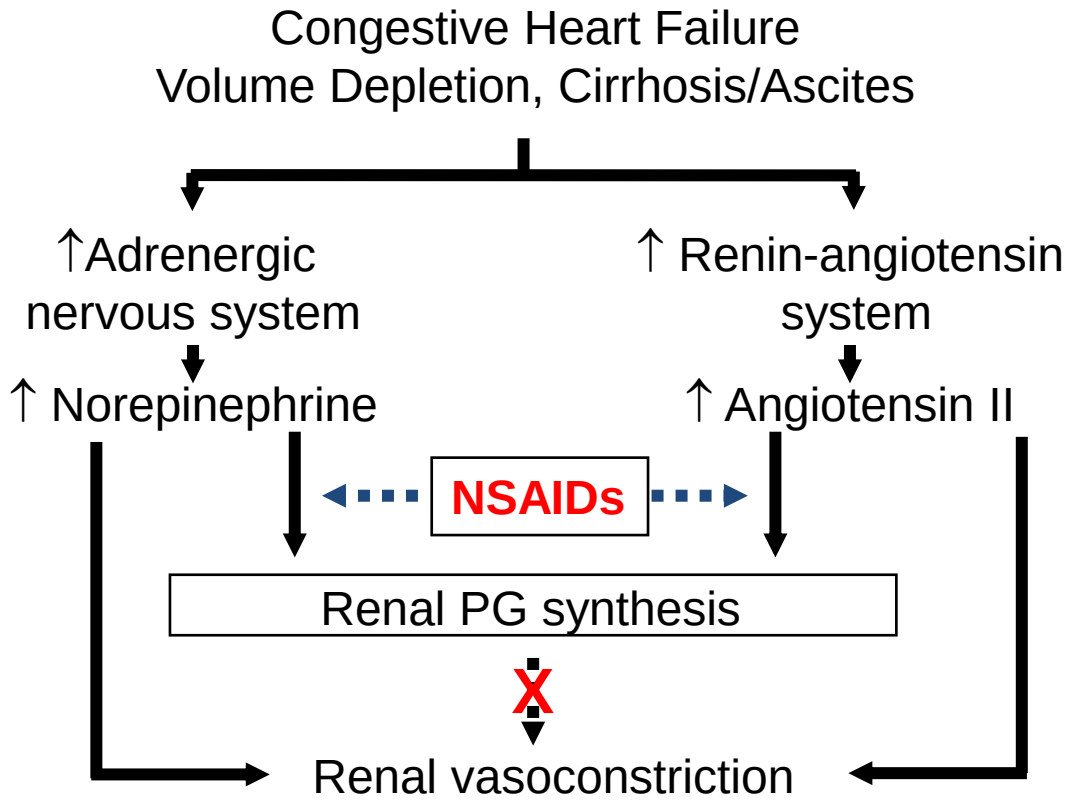
- Inhibited by all NSAIDs
- Mediates most NSAID effects
- Aspirin – irreversible effect

NSAID Renal Effects



White WB. Am J Med 2009;122:S3-9.

Effects of Decreased Circulating Volume



Risk Factors for NSAID-Induced Kidney Injury with Cr ≥ 2

- Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)
  - eGFR 30-59 mL/min/1.73m^2: caution or avoid
  - eGFR <30 mL/min/1.73m^2: relative contraindication
- Age ≥60 years
- Volume depletion
- Hypertension
- Hypercalcemia
- Renal artery stenosis
- ACE inhibitors, ARBs, calcineurin inhibitors, aminoglycosides

Rahman S, et al. Prim Care Clin Office Pract 2014;41:803-21.

Kielstein JT, et al. Curr Hypertens Rep 2020;22:102

Patients at Mild-Moderate Risk for NSAID Nephrotoxicity

- Use analgesics only and/or topical products
- If NSAIDs, use low dose
- Laboratory monitoring
  - Creatinine, urinalysis
- Clinical monitoring
  - Weight, edema
- Follow-up within 1-2 weeks
- Counsel patients about use of OTC NSAIDs

Rheumatoid Arthritis

- Kidney involvement common in RA
  - Inflammation vs. drugs
  - Kidney amyloidosis, interstitial disease
  - Mesangial proliferative glomerulonephritis most common (34-36%)
  - Nephrotoxic: cyclosporine, penicillamine, gold, NSAIDs
  - Little nephrotoxicity: methotrexate, azathioprine, sulfasalazine, hydroxychloroquine, leflunomide

Wu CL, et al. Clin J Am Soc Nephrol 2018;13:702-9.

Methotrexate (Otrexup, Rasuvo, Trexall, Rheumatrex)

- >80% excreted unchanged in urine
  - 25% by glomerular filtration
  - 75% by active tubular secretion
- Accumulates in third space fluids
  - Prolonged toxicity with ascites or pleural or pericardial effusions or with peritoneal dialysis
  - May not be reflected by serum concentrations
    - MTX polyglutamate metabolites half-life 1-4 weeks

Svanström H, et al. Pharmacoepidemiol Drug Saf 2018;17:885-93.
Iwaki M, et al. Biol Pharm Bull 2017;40:926-31.
Shively R, et al. Rheumatology 2020;59:e93-4.

Methotrexate (MTX)

- Close monitoring if impaired renal function (or elderly); consider dose reduction
  - No specific dosage adjustment in product information
  - Lexicomp: CrCl >50 mL/min: no adjustment
  - CrCl 10-50 mL/min: 50% of dose
  - CrCl <10 mL/min: avoid use
- Nephrotoxicity more common with higher doses than those used in rheumatology

Lexicomp – methotrexate 8/10/21.

Sales GTM, et al. Rev Assoc Med Bras 2020;66(suppl1):S82-90.

Methotrexate and NSAIDs

- Increased risk adverse events with combination vs. low-dose MTX alone
  - Mechanism
    - Decreased renal perfusion (prostaglandin effect)?
    - Plasma protein displacement of MTX?
    - Competition for renal tubular secretion?
    - Inhibition of renal uptake of MTX?
    - Additive pharmacodynamics effect?

Svanström H, et al. Pharmacoepidemiol Drug Saf 2018;17:885-93.
Iwaki M, et al. Biol Pharm Bull 2017;40:926-31.

Methotrexate and NSAIDs

- Register-based cohort study in Denmark
  - Patients with rheumatoid arthritis
  - MTX alone (n=21,536) vs. MTX/NSAID (n=21,536)
  - Composite endpoint: serious adverse event
    (liver toxicity, acute renal failure, cytopenia)
    - Weighted hazard ratio 1.40 (95% CI, 1.07-1.82)
  - Combination increased risk for acute renal failure by 104%
- Counsel patients taking MTX about NSAID use

Svanström H, et al. Pharmacoepidemiol Drug Saf 2018;17:885-93.

Sulfasalazine (Azulfidine)

- No specific dosage adjustments – use with extreme caution
- 90% of sulfasalazine and metabolites cleared by kidneys
- Case report of renal failure associated with sulfasalazine metabolite stones
  - Volume depletion and low urine pH are risk factors
- Counsel about adequate hydration

Durando M, et al. Am J Kidney Dis 2017;70:869-73.

Lexicomp – sulfasalazine 8/10/21.

Leflunomide (Arava)

- No dosage adjustments (has not been studied)
  - Use with caution
  - Canadian labeling: moderate/severe impairment – contraindicated
- Converted to active metabolite, teriflunomide
  - Normal renal function: 48% eliminated in feces; 43% kidneys as metabolites

Russo PAG, et al. Ann Pharmacother 2013;47:e15.

Lexicomp – leflunomide 8/10/21.

Leflunomide

- Case report – end stage renal disease & peritoneal dialysis
- Rheumatoid arthritis responded moderately well
- Low teriflunomide plasma concentrations
  - Higher unbound fraction in ESRD
  - Genetic factors:
    - CYP2C19 loss-of-function allele (↓ conversion of leflunomide to teriflunomide)
    - Wild-type ABCG2 (↑ enterohepatic recycling & fecal elimination)

Russo PAG, et al. Ann Pharmacother 2013;47:e15.

Hydroxychloroquine (Plaquenil)

- No dosage adjustments; use with caution
  - Long half-life up to 40-50 days
  - May need ↓ dose with prolonged use
  - Consider using 50% dose reduction if

    GFR <10 mL/min/1.72 m^2 or dialysis
  - Not dialyzable – no additional post-dialysis dose

Moura-Neto JA, et al. J Bras Nefrol 2020;42(2 suppl 1):49-50.
Lexicomp – hydroxychloroquine 8/10/21.

Hydroxychloroquine (HCQ)

- Observational cohort study – newly diagnosed RA; no history of chronic kidney disease (CKD)
- Association of HCQ use with risk of CKD
  - Mean follow-up 4-6.5 years
  - 36% lower incidence CKD with HCQ users vs. nonusers
  - Lower rate with higher HCQ doses
- Prevent kidney damage in lupus nephritis

Wu CL, et al. Clin J Am Soc Nephrol 2018;13:702-9.

Janus Kinase Inhibitors

- Tofacitinib (Xeljanz)
  - Mild impairment: no dosage adjustment
  - Moderate/severe or ESRD with hemodialysis
    - IR tablet: if 10 mg BID→5 mg BID; if 5 mg BID→5 mg QD
    - ER tablet: if 22 mg QD→11 mg QD; if 11 mg QD→5 mg QD IR
    - If hemodialysis day, administer after session
  - Immune mediated glomerular disorders reported with tofacitinib and biologics (not baricitinib)

IR = immediate release; ER = extended release

Lexicomp – tofacitinib 8/10/21.

Chessa E, et al. BioDrugs 2021;35:175-86.

Janus Kinase Inhibitors

- Baricitinib (Olumiant)
  - GFR >60 mL/min/1.73 m^2: No adjustment
  - GFR 30-60 mL/min/m^2: 1 mg QD
  - GFR < 30 mL/min/1.73 m^2: use not recommended

Lexicomp – baricitinib 8/10/21.

Janus Kinase Inhibitors

- Upadacitinib (Rinvoq)
  - eGFR 15-89 mL/min: No adjustment
  - eGFR <15 mL/min/1.73 m^2: not studied
- Single dose pharmacokinetic study
  - Mild-moderate-severe renal impairment (non-RA)
  - 20% eliminated unchanged in urine (minor role)
  - Limited impact of renal impairment on upadacitinib exposure

Lexicomp – upadacitinib 8/10/21.
Mohamed MF, et al. J Clin Pharmacol 2019;59:856-62.

Gout/Hyperuricemia

- Gout affects 0.1-10% of adults in US
- It can be associated with chronic kidney disease
  - 19.9-70% with gout have CKD ≥ stage 3 (eGFR <60 mL/min/1.73 m^2) and 20-24% have eGFR <30 mL/min/1.73 m^2
  - ~25% with CKD ≥ stage 3 have gout
  - ↑ urate very common in CKD (64% with stage 3 & 50% with stage 4 or 5)
- Important to consider CKD when using drugs to treat gout and hyperuricemia
- Most large trials excluded subjects with eGFR <30 mL/min
  - FDA & EMA restrict inclusion of study participants with CKD ≥ stage 3
  - Most publications are case reports or case series

Abhishek A. Curr Opin Rheumatol 2020;32:134-9.
Stamp LK, et al. Nat Rev Rheumatol 2021;https://doi.org/10.1038/s41584-021-00657-4.
Pisaniello HL, et al. Arthritis Res Ther 2021;23:130.

Colchicine (Colcrys, Mitigare, Gloperba)

- Up to 20% excreted unchanged by kidneys
- In renal failure, half-life can be 2-3x longer
- Not removed by dialysis
- Toxicity risk factors (further ↑ if multiple present)
  - Renal impairment/transplantation
  - Liver disease
  - Advanced age
  - Drug interactions

Abdellatif A. Am J Ther 2014;21:523-34.
Medani S, et al. Clin Nephrol 2016;86:100-5.
Pisaniello HL, et al. Arthritis Res Ther 2021;23:130.

Colchicine

- Examples of drug interactions
  - P-glycoprotein/strong cytochrome P450 3A4 inhibitors
    - Clarithromycin, ketoconazole, itraconazole, protease inhibitors
  - P-glycoprotein/moderate CYP3A4 inhibitors
    - Verapamil, diltiazem, erythromycin
  - P-glycoprotein/weak CYP3A4 inhibitors
    - Cyclosporine, amiodarone, ranolazine
  - Statins (CYP3A4 inhibitors), fibrates, hepatitis C treatment (sofosbuvir/ledipasvir)
  - ↑ adverse events & deaths reported with these and colchicine, esp in CKD

Medani S, et al. Clin Nephrol 2016;86:100-5.
Mullins M, et al. Clin Toxicol 2011;49:648-52.
Pisaniello HL, et al. Arthritis Res Ther 2021;23:130.

Colchicine

- Major toxicities
  - Gastrointestinal (vomiting, diarrhea)
  - Neuromuscular (myopathy, rhabdomyolysis)
  - Central nervous system (fatigue, headache, seizures)
  - Renal (acute kidney injury, volume depletion)
  - Hematological (pancytopenia, coagulopathy)
  - Skin (rash, alopecia)
  - Liver (↑ liver enzymes)

Medani S, et al. Clin Nephrol 2016;86:100-5.

Colchicine

- Major toxicities
  - Cardiovascular (pulmonary edema, cardiogenic shock)
  - Respiratory (failure, ARDS, bronchopneumonia)
  - Reproductive (oligospermia)
  - Multiorgan failure (above + lactic acidosis, sepsis, DEATH)

Medani S, et al. Clin Nephrol 2016;86:100-5.

Colchicine

- Dosing
  - Gout flare
    - CrCl 30-80 mL/min: No change
    - CrCl <30 mL/min: Consider alternative
      - Or 1.2 mg, then 0.6 mg in 1 h; do not repeat treatment <14 d
      - Or 0.3 mg without repeat for ≥3-7 d
  - Flare prophylaxis
    - CrCl 30-80 mL/min: No change or 0.6 mg/d if 30-60 mL/min
    - CrCl <30 mL/min: Consider alternative
      - Or 0.3 mg/d or 0.6 mg every other day
      - Maximum 0.6 mg/d

Lexicomp – colchicine 8/10/21.

Gout

- NSAIDs – as discussed
- Corticosteroids – no renal concern
  - Might exacerbate tophaceous gout disease???
- Anakinra (Kineret) [off-label use]
  - CrCl ≥30 mL/min: no dose adjustment
  - CrCl <30 mL/min: consider every other day dosing (e.g., 100 mg)
- Canakinumab (Ilaris)
  - No adjustment (has not been studied)
  - Approved for gout flares by EMA, not FDA

Lexicomp – anakinra 8/10/10, canakinumab 8/10/21
Kielstein JT, et al. Curr Hypertens Rep 2020;22:102.
Pisaniello HL, et al. Arthritis Res Ther 2021;23:130.

Allopurinol (Aloprim, Zyloprim)

- Hypersensitivity reactions/severe cutaneous adverse reactions (SCAR)/drug reaction with eosinophilia and systemic symptoms (DRESS)
  - Rare but serious
    - Related to ↑ oxypurinol concentrations??
  - Risks:
    - First 8-9 wk after starting Genetic factors: HLA-B*5801 (test if at risk: Han Chinese, Koreans, Thai, African Americans); if homozygous & eGFR <30 mL/min/1.73 m^2, odds ratio = 1269.45; 95% CI: 192.3, 15,260.1
    - ↑ drug concentrations with starting dose (>1.5 mg/per mL/min of eGFR), chronic kidney disease, diuretics (e.g., furosemide)

Stamp LK, et al. Rheumatology 2018;57:i35-41.
Kielstein JT, et al. Curr Hypertens Rep 2020;22:102.
Stamp LK, et al. Baillieres Best Pract Res Clin Rheumatol 2020;34:101501

Allopurinol vs. Febuxostat Hypersensitivity

- Medicare claims data 2006-12; age ≥65 years
  - Assess hypersensitivity reaction risks
  - New prescriptions: allopurinol, febuxostat, colchicine
  - Hazard ratio for hypersensitivity reaction vs. colchicine:
    - Allopurinol 1.32 (95% CI, 1.10-1.60)
    - Febuxostat 1.54 (95% CI, 1.12-2.12)
    - Febuxostat + colchicine 2.17 (95% CI, 1.18-3.99)
  - Risks for allopurinol hypersensitivity:
    - Starting dose >300 mg/d, diabetes, female sex

Singh JA, et al. Ann Rheum Dis 2020;79:529-35.

Febuxostat (Uloric)

- Renal dysfunction
  - CrCl 30-89 mL/min: no dose adjustment
  - CrCl <30 mL/min: maximum dose 40 mg/d
- 49% excreted in urine; 45% in feces

Lexicomp – febuxostat 8/10/21.
Bardin T, et al. Curr Opin Rheumatol 2019;31:152-8.

Febuxostat

- Retrospective study in 73 patients with gout & CKD stage 4/5 eGFR ≤30 mL/min/1.73 m^2

  [mean follow-up 68.5 ± 64.8 wk]

  - Daily dose 40-120 mg/day
  - 82.2% stage 4 CKD & 17.8% stage 5; 24.7% renal transplantation
  - Renal function improved in 24.7%, stable in 32.9%, ↓ in 42.5%
  - 40% stage 4 & 53.8% stage 5 worsened (↓ eGFR >10%) over 1.3 ± 1.2 y

Juge PA, et al. Joint Bone Spine 2017;84:595-8.

Febuxostat

- Randomized, double-blind, placebo-controlled 12-month study with 96 patients with gout
- GFR 15-50 mL/min/1.73 m^2
  - Daily dose 30 mg BID, 40/80 mg QD, or placebo
  - All received colchicine 0.6 mg QOD or prednisone ≤10 mg/d x 6 mo
  - Primary endpoint: change in creatinine from baseline to month 12
  - Severe renal impairment at baseline: (53% placebo vs. ~30% febux)
  - No significant ↓ renal function with febuxostat over 12 mo
  - Renal failure/impairment in 3.1 % (febuxostat 30 mg BID), 12.5% (febuxostat 40/80 mg QD), 25% placebo

Saag KG, et al. Arthritis Rheum 2016;68:2035-43.

Other Urate-Lowering Drugs

- Probenecid
  - Avoid use if CrCl <30 mL/min (↓ efficacy, nephrolithiasis risk)
- Uricases
  - Pegloticase (Krystexxa)
  - Rasburicase (Elitek)
  - No necessary dosage adjustments

Lexicomp – febuxostat, probenecid 8/10/21; pegloticase, canakinumab 8/10/21.

ACR 2020 Gout Guideline

- Allopurinol preferred first line, even if CKD stage ≥3
  - Febuxostat also preferred over probenecid if stage ≥3
  - Start allopurinol at ≤100 mg/d; ≤50 mg/d if CKD stage ≥3
  - Titrate allopurinol doses by 50-100 mg/d every 2-≥4 wk to achieve serum urate target <6 mg/dL
  - Start febuxostat ≤40 mg/d
  - Conditionally, start probenecid 500 mg 1-2x/d
- Initiate urate-lowering therapy for 1st flare IF

  CKD stage ≥3, serum urate >9 mg/dL, or urolithiasis

FitzGerald JA, et al. Arthritis Care Res 2020;72:744-60.

Systemic Lupus Erythematosus (SLE)

- Lupus nephritis is a common complication of SLE
  - Prevalence 20% in African Americans & 52% in Asian/Pacific Islanders vs. 13-14% in other groups
  - Risk is greatest in first year after disease onset
- There are renal concerns with drugs used to treat lupus nephritis

Maningding E, et al. Arthritis Care Res 2020;72:622-9.

Cyclophosphamide (Cytoxan)

- CrCl ≥30 mL/min: No dose adjustment
- CrCl 10-29 mL/min: 75-100% of usual dose
- CrCl <10 mL/min: 50-75% of usual dose
- Hemodialysis: Administer 50-75% of usual dose after with ≥12 h before next session
- Maintain hydration and consider mesna to prevent hemorrhagic cystitis

Lexicomp – cyclophosphamide 8/10/21
Monach PA, et al. Arthritis Rheum 2010;62:9-21.

Mycophenolate (Cellcept, Myfortic)

- No specific recommendations
- May need lower doses
- Monitor closely for adverse events
- Mycophenolate mofetil is hydrolyzed to active mycophenolic acid which is glucuronidated to an inactive metabolite 87% excreted in urine

Lexicomp – mycophenolate 8/10/21.

Azathioprine (Imuran)

- CrCl >50 mL/min: No adjustment
- CrCl 10-50 mL/min: 75% of usual dose
- CrCl <10 mL/min: 50% of usual dose

Lexicomp – azathioprine 8/10/21.

Calcineurin Inhibitors (CNI)

- Acute & chronic nephrotoxicity
  - Acute form reversible
  - Chronic use – slow ↓ in renal function; can progress to end-stage renal disease
    - Extensive changes in renal architecture
    - Individual susceptibility may be based on genetic variability in:
      - Upregulation of transporter ABCB1 to extrude CNI from renal cells
      - Reduction of CYP3A5 metabolizing enzyme leading to reduced CNI intrarenal detoxification

Hesselink DA, et al. Ther Drug Monit 2010;32:387-93.

Calcineurin Inhibitors (CNI)

- Cyclosporine (Gengraf, Neoral, Sandimmune)
  - Abnormal renal function: use contraindicated
  - During treatment (indication-specific)
    - e.g., RA: Cr > 30% above pre-treatment - ↓ dose by 25-50%; D/C if ineffective in ↓Cr or if Cr ↑ is severe

Lexicomp – cyclosporine 8/10/21.

Calcineurin Inhibitors (CNI)

- Tacrolimus (Prograf, Astagraf XL, Envarsus XR)
  - Elimination not affected by renal impairment but nephrotoxicity may require dose reduction
- Voclosporin (Lupkynis)
  - eGFR ≥60 mL/min/1.73 m2 – no adjustment
  - >20%-<30% change from baseline ↓ dose by 1 capsule/d
    - After 2 wk, if still ↓ >20%, ↓ dose again by 1 capsule/d
  - ≥30% ↓, D/C, reassess in 2 wk
    - If eGFR back to ≥80% baseline, restart at lower dose

Lexicomp – tacrolimus 8/10/21.
Yap DYH, et al. Rheumatology 2014;53:2232-7.
https://lupkynispro.com/dosing/

Biologics

- For most, no adjustment provided by manufacturer
  - (For many, not studied (especially with CrCl <30 mL/min])

Etanercept	Belimumab	Guselkumab
Adalimumab	Rituximab	Ixekizumab
Certolizumab pegol	Sarilumab	Risankizumab
Golimumab	Tocilizumab	Secukinumab
Infliximab	Abatacept	Ustekinumab
		Anifrolumab-fnia

Lexicomp
Saphnelo prescribing information 8/21

Hepatic Disease

- Chronic liver disease
  - Adults in the U.S. with diagnosed liver disease: 1.8%
  - Accounted for 44,358 deaths last year

- Drug induced liver injury
  - Incidence: between 10 and 15 per 10,000 to 100,000 persons exposed to prescription medications
  - Accounts for approximately 10% of acute hepatitis cases
  - Many medications utilized for rheumatologic conditions can cause or potentiate liver injury
  - Dosing recommendations are often arbitrary as drug elimination is difficult to estimate and extent of elimination cannot be quantified

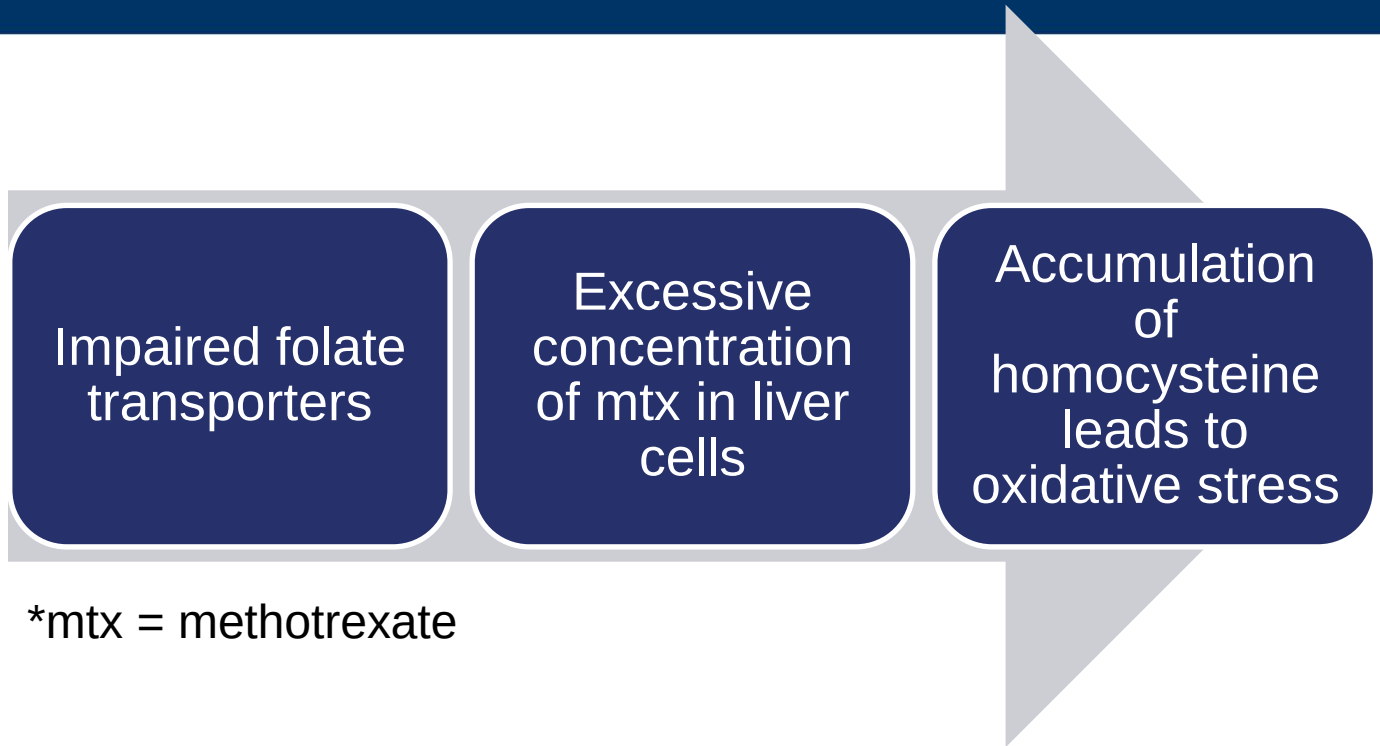
CDC Fast Stats – Chronic Liver Disease and Cirrhosis 8/14/21.
Larrey D, et al. Semin Liver Dis 2002;22:145-55.

Methotrexate

- Transient transaminase elevations
  - Can lead to chronic hepatotoxicity if therapy is not adjusted
- Fibrosis/cirrhosis reported after 2 years of treatment
  - May be asymptomatic (noted in patients with psoriasis)
- A total dose of 1.5 grams can be fatal
- Weekly doses ranging from 7.5 mg to 30 mg

Dubey L, et al. Indian J Pharmacol 2016;48:591-4.
Van Dooren-Greebe RJ, et al. Br J Dermatol 1994;130:204-20.
Aithal GP, et al. Aliment Pharmacol Ther. 2004;19:391-9.

Methotrexate – mechanism of damage



*mtx = methotrexate

Conway R, et al. World J Hepatol 2017;9:1092-1100.
Holmboe L, et al. Br J Clin Pharmacol 2012;73:106-14.
Cheng HS, et al. Psoriasis (Auckl) 2018;8:21-9.
Ezhilarasan D. Toxicology 2021;458:152840.

Methotrexate – risk factors for hepatotoxicity

- Alcohol
- Concomitant hepatotoxic medications
- Dose
- Duration (> 2 yrs)
- Female
- Older age
- Increased body mass index
- Preexisting renal disease
- Preexisting hepatic disease including hepatitis, non-alcoholic steatohepatitis/fatty liver disease

Lexicomp – methotrexate 8/14/21.
Ezhilarasan D. Toxicology 2021;458:152840.

Methotrexate – management

- Folic Acid 1 – 5 mg daily
  - 1 mg recommended for ALL patients
  - Up to 5 mg can be utilized for patients still experiencing limiting side effects on 1 mg of folic acid

- Leucovorin 5 mg daily
  - An option in patients for whom folic acid is insufficient
  - Concern for decreased methotrexate efficacy when used with leucovorin

Lexicomp – methotrexate 8/14/21.
Shiroky JB, et al. Arthritis Rheum 1993;36:795-803.

Methotrexate – management

- No dose adjustments recommended in package labeling for patients with liver disease
- Lexicomp:
  - Bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose
  - Bilirubin >5 mg/dL: Avoid use
- Consider holding therapy if hepatotoxicity on methotrexate
- Liver biopsies?

Lexicomp – methotrexate 8/14/21.
Floyd J, et al. Semin Oncol 2006;33:50-67.

Other Small Molecule Drugs

- Leflunomide
  - Hepatic metabolism to teriflunomide (active metabolite)
  - Not recommended for use in patients with preexisting liver disease or those with baseline ALT >2 times ULN
  - If ALT >3 times ULN, discontinue and consider cholestyramine
  - Consider avoiding use with methotrexate due to increased risk of hepatotoxicity
- Cyclophosphamide
  - No dose adjustments recommended in package labeling
  - Lexicomp:
    - Bilirubin 3.1 to 5 mg/dL or transaminases >3 times ULN: Administer 75% of dose.
    - Bilirubin >5 mg/dL: Avoid use

Lexicomp – leflunomide 8/14/21.
Lexicomp – cyclophosphamide 8/14/21.

Other Small Molecule Drugs

- Hydroxychloroquine
  - No dose adjustments – use with caution
- Sulfasalazine
  - No dose adjustments – use with extreme caution
  - Cases of hepatic necrosis have been reported
- Azathioprine
  - No dose adjustments – use with caution
- Mycophenolate
  - No dose adjustment
  - Consider monitoring due to an increased concentration of MPA/MPAG free fraction

Lexicomp – hydroxychloroquine 8/14/21.
Lexicomp – sulfasalazine 8/14/21.
Lexicomp – azathioprine 8/14/21.
Lexicomp – mycophenolate 8/14/21.

**MPA = mycophenolic acid; MPAG = mycophenolic acid glucuronide*

Janus Kinase Inhibitors

- Tofacitinib
  - AUC (area under the curve) and C_{max} (maximum serum concentration) increased by 1.5 times in moderate impairment
  - Cases of hepatotoxicity have been reported
  - Dose adjustments for liver impairment
    - Mild impairment: No dosage adjustment necessary.
    - Moderate impairment:
      - IR tablet: if 10 mg BID→5 mg BID; if 5 mg BID→5 mg QD
      - ER tablet: if 22 mg QD→11 mg QD; if 11 mg QD→5 mg QD IR
    - Severe impairment: Use is not recommended

Lexicomp – tofacitinib 8/14/21.

Janus Kinase Inhibitors

- Upadacitinib and Baricitinib
  - Cases of elevated LFTs have been reported
  - Dose adjustments
    - Mild/Moderate impairment: No dosage adjustment necessary.
    - Severe impairment: Use is not recommended

Lexicomp – upadacitinib 8/14/21.
Lexicomp – baricitinib 8/14/21.

Biologics – IL-6 Inhibitors

- Tocilizumab (Actemra)
  - Avoid use in patients with ALT or AST > 1.5 x ULN

Hepatotoxicity During Therapy	
ALT/AST > 1 – 3 ULN	IV 8 mg/kg → 4 mg/kg IV 4 mg/kg → hold therapy SubQ 162 mg weekly → 162 mg every other week SubQ 162 mg every other week→ hold therapy
ALT/AST 3 – 5 ULN	Hold therapy and consider restarting when ALT/AST is 3 x ULN
ALT/AST > 5 ULN	Discontinue

Lexicomp – tocilizumab 8/14/21.

Biologics – IL-6 Inhibitors

- Sarilumab (Kevzara)
  - Avoid use in patients with active hepatic disease

Hepatotoxicity During Therapy	
ALT/AST > 1 – 3 ULN	Adjust concomitant DMARD therapy
ALT/AST 3 – 5 ULN	Hold therapy and consider restarting at 150 mg every 14 days
ALT/AST > 5 ULN	Discontinue

Lexicomp – sarilumab 8/14/21.

Biologics – TNF inhibitors

TNF Inhibitor	Effect
Adalimumab	Not studied in hepatic failure No dose adjustments necessary Cases of elevated LFTs have been reported
Certolizumab	
Golimumab	
Etanercept	
Infliximab	

Lexicomp 8/14/21.

Biologics – Others

Biologic	Effect
Secukinumab	Not studied in hepatic failure
Ixekizumab	No dose adjustments necessary
Abatacept	
Anakinra	Cases of elevated LFTs have been reported
Canakinumab	Cases of neonatal hepatic failure have been reported
Rituximab	
Belimumab	

Lexicomp 8/14/21.

General Management Principles

- Liver Function Monitoring
  - Baseline, 2-4 weeks, then 8-12 weeks, then every 12 weeks thereafter
  - More frequent testing needed (every 4-8 weeks) in patients with non-alcoholic fatty liver disease
- Hepatitis B
  - Obtain baseline status and retest if risk factors present
  - If positive (core antibody OR surface antigen), ensure prophylactic antiviral therapy is prescribed concomitantly
- Hepatitis C
  - Obtain baseline and retest every 5 years or earlier if risk factors present
  - Patients should not be treated differently than patients without Hepatitis C

Singh JA, et al. Arthritis Rheumatol 2016;68:1-26.
Fraenkel L, et al. Arthritis Care Res 2021;73:924-39.

Colchicine

- Clearance of colchicine is decreased in the setting of hepatic impairment
- Avoid use of P-gp or strong CYP3A4 inhibitors with colchicine in patients with preexisting hepatic disease due to fatal toxicities.
- Avoid use of colchicine to treat gout flares in patients with preexisting hepatic disease.
- No dose adjustments are recommended, but should be considered in patients with severe hepatic impairment
- Stewart, et al. reported adverse liver events in 1.9% of colchicine users versus 1.1% in the comparator groups (RR 1.6, 95% CI 0.9-3.0)

Lexicomp – colchicine 8/14/21.
Stewart S, et al. Arthritis Res Ther 2020;22:28.

Other Gout Medication – No Dose Adjustments

- Febuxostat
  - Cases of hepatic failure and transaminase elevation have been reported
  - Use with caution in severe hepatic impairment
- Allopurinol
- Probenecid
- Pegloticase and Rasburicase

Lexicomp – 8/14/21.

Conclusion

- Rheumatologic diseases can affect renal & hepatic function
  - Drugs used to treat them may have nephrotoxic or hepatotoxic effects or may accumulate in patients with ↓ renal or hepatic function
  - Always check patient's renal and hepatic function before ordering medications
- Check concurrent and new medications for potential drug interactions or similar toxicities with new drugs
- Counsel patients about OTC medication use

Questions?