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Rheumatologic Drug Dosing and the Kidney

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Disclosure

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Faculty Disclosure

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

- Research, Consultant: Oklahoma Medical Research Foundation Immunology Lab Consultant (spouse)

Learning Objectives

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

Kidney Disease

- Affects 31 million in US
  - Can be result of rheumatologic diseases
    - Specific disease involvement of kidneys
    - Consequence of inflammation
  - Nephrotoxic effects of drugs
- 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/

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, moderate CKD
  - 3B: GFR 30-44 mL/min, moderate CKD
  - 4: GFR 15-29 mL/min, severe CKD
  - 5: GFR <15 mL/min, end stage CKD

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

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

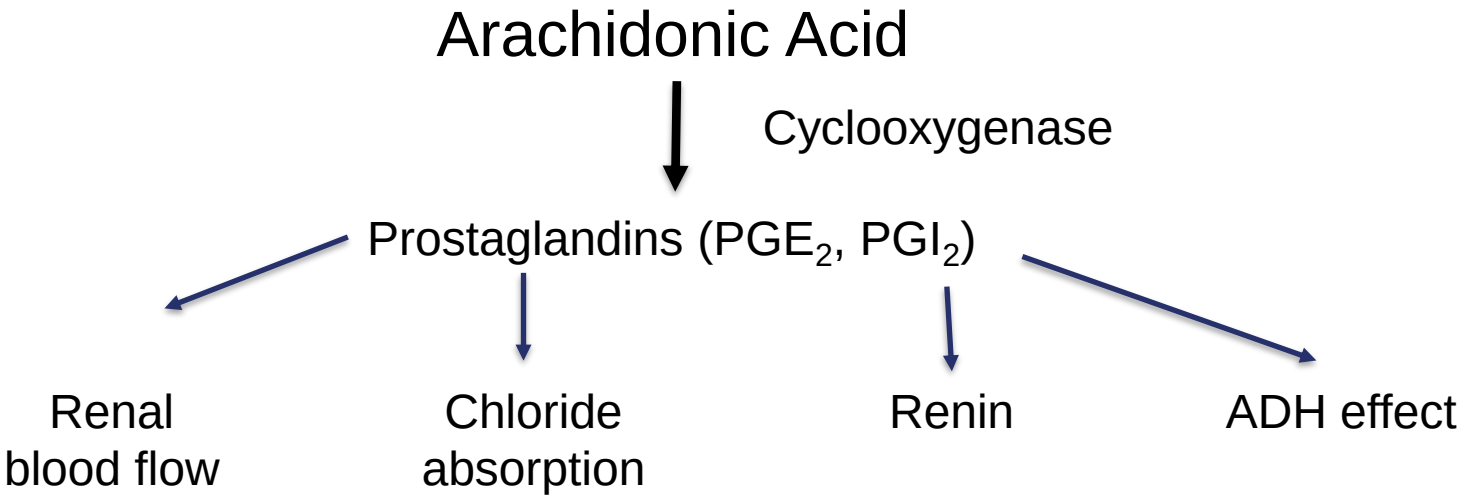
Bindu S, et al. Biochem Pharmacol 2020;180:114147.

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

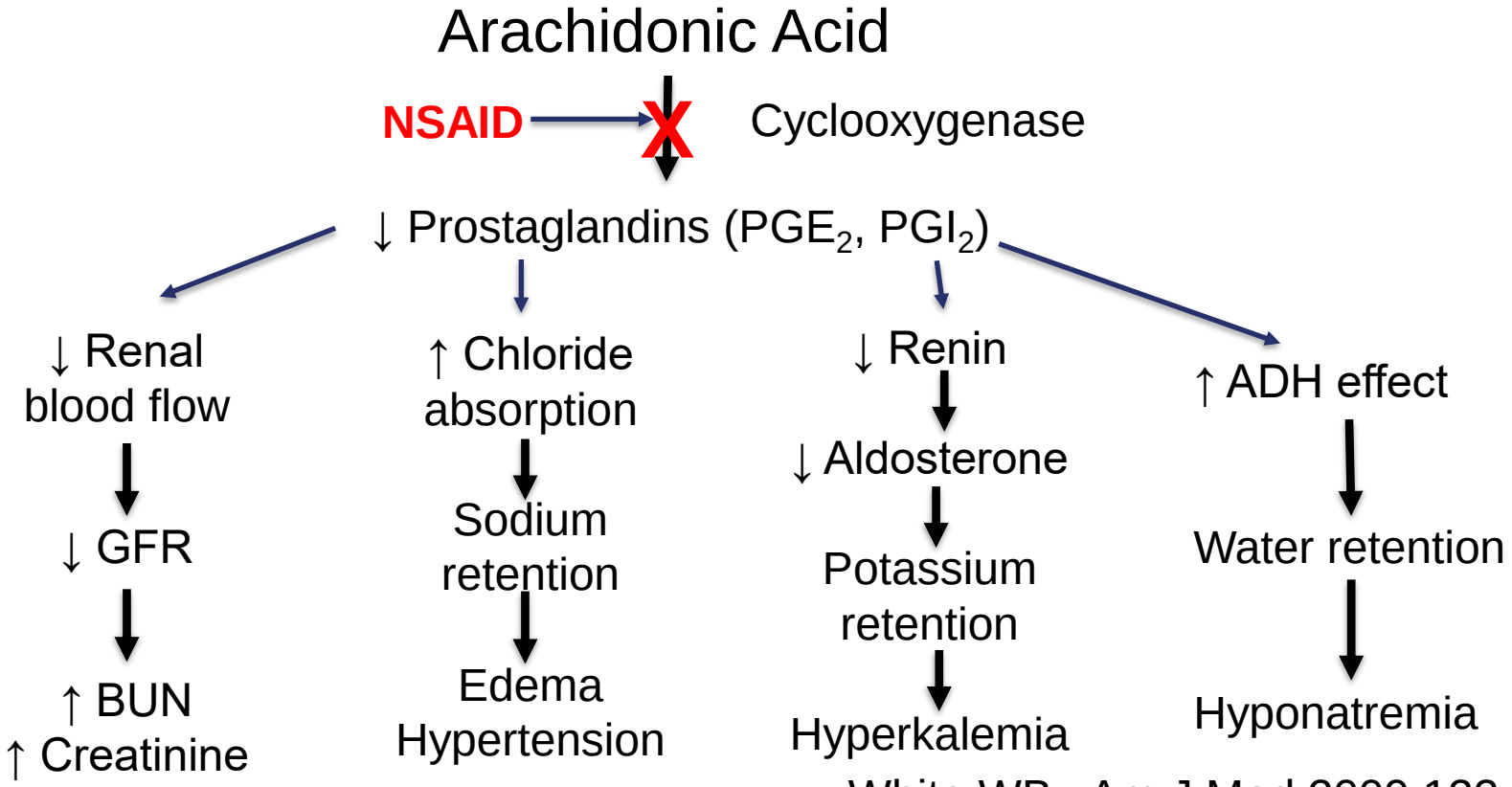


White WB. Am J Med 2009;122:S3-9.

Cyclooxygenase

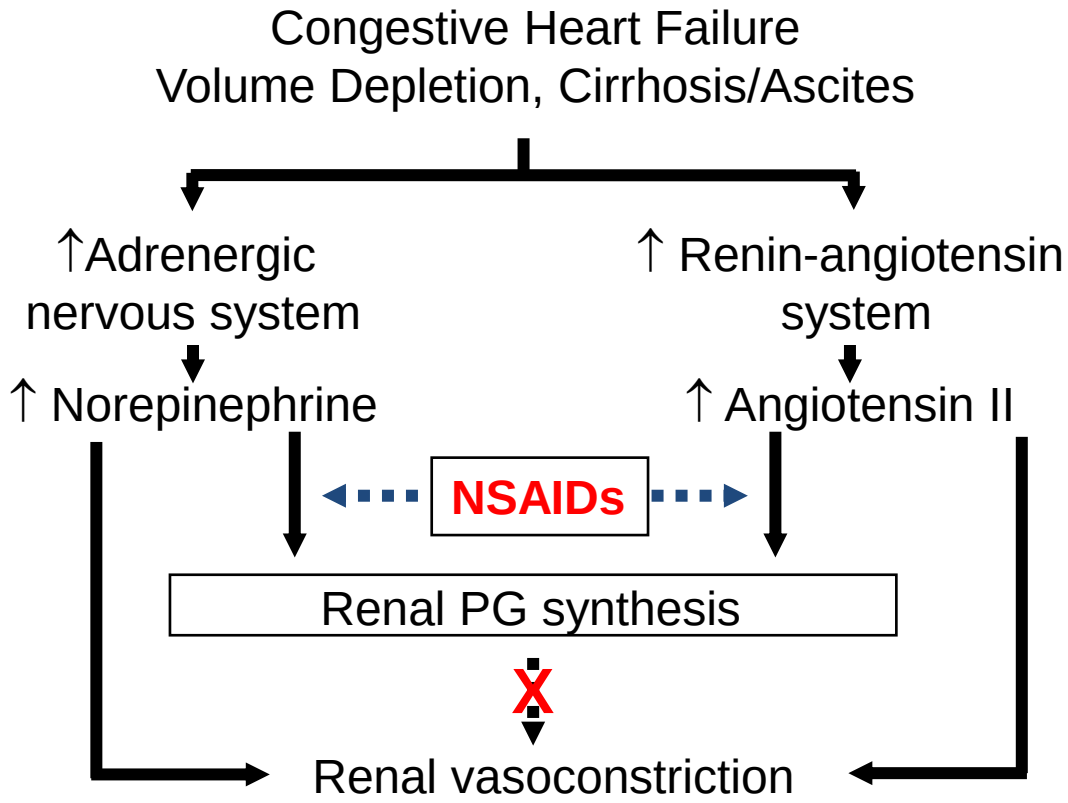
- Inhibited by all NSAIDs
- Mediates most NSAID effects
- Aspirin – irreversible effect

NSAID Renal Effects



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

Effects of Decreased Circulating Volume



Risk Factors for NSAID-Induced Kidney Injury

- Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)
- 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.

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
- Nephrotoxicity more common with higher doses than those used in rheumatology

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

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

Lexicomp – methotrexate 11/12/20.

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 11/11/20.

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 11/08/20.

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
  - May need ↓ dose with prolonged use
  - Consider using 50% dose reduction if GFR <10 mL/min/1.72 m^2 or dialysis

Moura-Neto JA, et al. Braz J Nephrol 2020;42(2 Supl 1):49-50.
Lexicomp – hydroxychloroquine 11/20/20

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

Lexicomp – tofacitinib 11/20/20.

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 11/20/20.

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 11/20/20.
Mohamed MF, et al. J Clin Pharmacol 2019;59:856-62.

Gout/Hyperuricemia

- Gout affects 3.9% of adults in US
- It can be associated with chronic kidney disease
  - 10-39% have gout; 71% with gout have stage ≥2 CKD (<90 mL/min)
  - Hyperuricemia very common in CKD
- Important to consider CKD when using drugs to treat gout and hyperuricemia
- Most large trials excluded subjects with eGFR < 30 mL/min

Abhishek A. Curr Opin Rheumatol 2020;32:134-9.
Stamp LS, et al. Rheumatology 2018;57:i35-41. www.kidney fund.org.
Juge PA, et al. Joint Bone Spine 2017;84:595-8.
Saag KG, et al. Arthritis Rheum 2016;68:2035-43.

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.

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, fibrates
  - ↑ adverse events & deaths reported with these and colchicine, esp in CKD

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

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 11/18/20.

Gout

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

Lexicomp – anakinra 11/09/20, canakinumab 11/08/20.

Allopurinol (Aloprim, Zyloprim)

- Hypersensitivity reactions/severe cutaneous adverse reactions (SCAR)/drug reaction with eosinophilia and systemic symptoms (DRESS)
  - Rare but serious
  - 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: 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.

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:
    - Start 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 11/08/20.
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
- 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 11/08/20; pegloticase, canakinumab 10/24/20.

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 10-30 mL/min: 75-100% of usual dose
- CrCl ≤10 mL/min: 50-75% of usual dose
- Hemodialysis: Administer dose after with ≥12 h before next session
- Maintain hydration and consider mesna to prevent hemorrhagic cystitis

Lexicomp – cyclophosphamide 11/20/20
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 11/17/20.

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 11/12/20.

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 11/13/20.

Calcineurin Inhibitors (CNI)

- Tacrolimus (Prograf, Astagraf XL, Envarsus XR)
  - Elimination not affected by renal impairment but nephrotoxicity may require dose reduction

Lexicomp – tacrolimus 11/23/20.
Yap DYH, et al. Rheumatology 2014;53:2232-7.

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

Lexicomp

Osteoporosis (OP)

- 50% with osteoporosis have stage 2/3 CKD
  - CrCl <35 mL/min in >80% women & 50% men with OP
- Both osteoporosis & CKD increase with age
- Rheumatologic drugs (e.g., corticosteroids)

  ↑ osteoporosis risk
- Presence of CKD mineral and bone disease (CKD-MBD) may affect safety of drugs – limited data

Cesini J, et al. Joint Bone Spine 2012;79:S104-9.
Khairallah P, et al. Clin J Soc Nephrol 2018;13:962-9.

Bisphosphonates

- Concern: adynamic bone disease, mineralization defects (CKD-MBD)
- Alendronate (Fosamax), ibandronate (Boniva), risedronate (Actonel, Atelvia)
- CrCl ≥30 mL/min: no dose adjustment
  - ≥35 mL/min for alendronate but some data that if no CKD-BMD, may be okay for CrCl >25 to <35 mL/min
  - Others not recommended for CrCl < 30 mL/min

Khairallah P, et al. Clin J Soc Nephrol 2018;13:962-9.

Denosumab (Prolia)/Romosozumab (Evenity)

- Concern: mild to severe hypocalcemia
  - 15% of patients in denosumab study
  - Especially if CrCl <30 mL/min and/or on dialysis
  - Prevent with adequate calcium & vitamin D intake
  - Monitor closely
- No dosage adjustment needed

Lexicomp – denosumab 11/13/20; romosozumab 10/24/20.
Khairallah P, et al. Clin J Soc Nephrol 2018;13:962-9.

Teriparatide (forteo)/Abaloparatide (Tymlos)

- Concerns
  - Hypercalcemia (teriparatide: 11% females, 6% males, abaloparatide: 3%)
  - Hyperuricemia (teriparatide: 3%, abaloparatide: 25%)
- No dosage adjustment needed

Lexicomp – teriparatide 11/05/20; abaloparatide 11/06/20.
Khairallah P, et al. Clin J Soc Nephrol 2018;13:962-9.

Zoledronic Acid (Reclast)

- Caution if CrCl <80 mL/min (manufacturer)
- CrCl ≥35 mL/min: no dosage adjustment needed
- CrCl <35 mL/min: use contraindicated
  - ↑ risk nephrotoxicity
    - Case report severe AKI in elderly patient taking telmisartan, celecoxib, rosuvastatin
  - Lack of efficacy & safety data
  - CKD-BMD: may ↑ risk fracture & vascular calcification

Lexicomp – zoledronic acid 11/23/20.
Im H, et al. Am J Ther 2018;25:e289-90.

Conclusion

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

Questions?